Lifestyle Medicine

FOURTH EDITION

Edited by

James M. Rippe, MD

CRC Press
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Lifestyle Medicine

The fourth edition of Dr. James Rippe's classic *Lifestyle Medicine* Textbook continues to lead and inform the rapidly growing field of lifestyle medicine. This is the discipline that focuses on the impact of daily habits and actions on both short- and long-term health and quality of life.

The first edition of this comprehensive work named the field of lifestyle medicine in the academic medical literature. The fourth edition continues to span and expand the field and offers extensive evidence-based literature in virtually every aspect of lifestyle medicine. This textbook, edited by cardiologist Dr. James Rippe, who is a leading lifestyle medicine researcher, represents the combined wisdom and recommendations of over 325 experts in virtually every aspect of lifestyle medicine. Chapter authors have been chosen because of their background as leaders in various aspects of lifestyle medicine.

Lifestyle Medicine, Fourth Edition contains extensive sections on the treatment and prevention of coronary heart disease, stroke, cancer, diabetes, obesity, substance abuse, dementia, and many other clinical conditions. Key lifestyle modalities such as physical activity, nutrition, weight management, sleep, stress reduction, and positive connections with other humans are supported by detailed discussion and state-of-the-art evidence. The expanded section on behavioral medicine provides an important framework for these discussions. Every chapter has been completely revised and many new topics added, such as lifestyle medicine for nursing, psychiatry, and preventive neurology.

The fourth edition of this classic text continues to serve as the leading, comprehensive textbook in lifestyle medicine. The original has been called the "indispensable bible" of lifestyle medicine, and the fourth edition of this work continues to justify this designation.

There is no longer any serious doubt that daily habits and actions have a significant impact on multiple aspects of health. The fourth edition of *Lifestyle Medicine* provides the scientific evidence to support this assertion and will serve as an invaluable reference and guide, not only to lifestyle medicine practitioners but to all primary care physicians, subspecialty physicians, nurses, and other healthcare practitioners.



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Fourth Edition

Edited by
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Professor of Medicine
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To my magnificent wife, Stephanie Hart Rippe, and our wonderful children Hart, Jaelin, Devon, and Jamie—the greatest gifts of my life.



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Preface

The field of lifestyle medicine continues to rapidly expand offering the potential for enormous health benefits around the world. I am proud that I named this field in the academic literature with the first edition of this textbook which was published in 1999. Now with the fourth edition of *Lifestyle Medicine,* we continue to see how the field has grown in stature and expanded in scope.

There is no longer any serious doubt that daily habits and actions profoundly impact both short and long-term health and quality of life. An overwhelming medical and scientific literature underscores these concepts. Literally thousands of studies provide evidence that regular physical activity, maintenance of a healthy body weight, not smoking cigarettes, following sound nutritional practices, reducing stress, getting healthy sleep and other health promoting practices all profoundly impact health. Recent studies have deepened our understanding in all of these areas.

Conversely, an inactive lifestyle, obesity, high levels of stress and cigarette smoking or exposure to cigarette smoke and other pollutants as well as poor nutritional habits all significantly and negatively impact on health.

Since the publication of the third edition of *Lifestyle Medicine* (CRC Press, 2019) the positive literature about lifestyle choices and health has continued to grow stronger, and the scientific basis has deepened and broadened. The field of lifestyle medicine has continued to expand around the globe and multiple new initiatives such as the World Health Organization initiative to combat non-communicable diseases emphasizing key lifestyle habits and practices have sprung up over the last few years.

As the field of lifestyle medicine has grown and expanded, so has the *Lifestyle Medicine* text in order to serve the needs of an increasing number of individuals who are incorporating lifestyle medicine practices in various components of health care. The fields impacted by lifestyle medicine include not only practicing physicians but also public health officials and physicians in virtually every branch of medicine. Serving these diverse audiences remains the goal of the fourth edition of *Lifestyle Medicine.*

The devastating impact of COVID-19 has further underscored why lifestyle medicine modalities are so important. Individuals who have high blood pressure, who are obese, who smoke cigarettes, or who have significant risk factors for heart disease, all disproportionately suffered morbidity and mortality from COVID-19. This pandemic also underscored the vital importance of continuing to work to achieve health equity. Disadvantaged populations, particularly in minority populations such as Hispanics and Blacks suffered three to four times the mortality of Caucasians from COVID-19 in the United States. These underserved populations often do not have access to adequate medical care and often live in crowded inner-city environments. Major health organizations such as the American Heart Association, the American College of Physicians and the American College of Lifestyle Medicine have all articulated important initiatives to address and improve health equity.

The fourth edition of *Lifestyle Medicine* has been thoroughly rewritten and updated and also incorporates a number of new sections and chapters which address the needs and concerns of lifestyle medicine practitioners as well as a wide variety of other healthcare providers and physicians throughout the world.

As always, the fourth edition of *Lifestyle Medicine* focuses on the evidence-base for lifestyle medicine procedures and practices. This has been the goal since the first edition of this textbook. The enormous strength and literature are underscored by the incorporation of lifestyle recommendations in virtually all evidence-based guidelines addressing the prevention and treatment of metabolic diseases. For example, the following guidelines and consensus statements from various prestigious medical organizations all provide an emphasis on lifestyle medicine principles and practices as key components of the prevention and treatment of disease.

- JNC VIII Guidelines for Hypertension, Prevention and Treatment
- ACC/AHA Guidelines for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure 2018
- NCEP (ATP IV) Guidelines for Blood Cholesterol
- Institute of Medicine Guidelines for Obesity Treatment
- ACC/AHA Scientific Consensus Statement on the Treatment for Blood Cholesterol
- Guidelines from the American Diabetes Association for the Management of Diabetes
- Dietary Guidelines for Americans 2020–2025
- American Heart Association Nutrition Implementation Guidelines
- Guidelines from the American Academy of Pediatrics for the Prevention and Treatment of Childhood Obesity
- Guidelines from the American Academy of Pediatrics for the Treatment of Pediatric Blood Pressure
- Guidelines from the American Academy of Pediatrics for the Treatment of Lipids
- Guidelines from the American Heart Association and the American Academy of Pediatrics for the Prevention and Treatment of the Metabolic Syndrome
- American Heart Association Strategic Plan for 2020

- Joint Statement from the American Heart Association and American Cancer Society for the Prevention of Heart Disease and Cancer
- Presidential Advisory from the AHA and American Stroke Association
- AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults
- ACS/ADA/AHA Scientific Statement on Preventing Cancer, Cardiovascular Disease and Diabetes
- Physical Activity Guidelines Advisory Committee Report of 2018
- The AHA/ACC Guidelines for the Management of Blood Cholesterol
- Adult Treatment Panel from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adult
- 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk
- Recommendations for Cardiovascular Health and Disease Surveillance for 2030 and Beyond: A Policy Statement from the American Heart Association
- 2021 American Heart Association (AHA) Scientific Statement on Dietary Guidance to improve Cardiovascular Health
- The AHA Guidelines for Detection, Evaluation, and Treatment of High Blood Pressure
- World Health Organization Executive Summary for Non-Communicable Disease Initiative

Unfortunately, despite the widespread recognition of these evidence-based guidelines and consensus statements about the important role of lifestyle measures and practices in the prevention and treatment of metabolic diseases, progress in these areas has been frustratingly slow in populations around the world. In the United States, for example, consider the following:

- Cardiovascular disease remains the leading killer of both men and women in the United States, resulting in over 37% of all mortality every year and has multiple lifestyle factors as underlying risk factors.
- Over 75% of the adult population in the United States does not achieve enough physical activity to result in health benefits.
- Over 72% of the adult population in the United States is either overweight or obese
- The prevalence of pediatric obesity has tripled over the last 20 years.
- Only 12% of the adult population in the United States consume adequate levels of fruits and only 7% consume the recommended amount of vegetables.
- 15% of individuals still smoke cigarettes.
- Over 40% of the adult population in the United States has high blood pressure.

The difficulty of achieving healthy lifestyle habits and practices is a worldwide problem. The World Health Organization estimates that 71% of worldwide mortality comes from non-communicable diseases and most of the risk of these diseases comes from lifestyle habits and practices.

An enormous body of scientific evidence demonstrates that positive lifestyle factors dramatically lower risk factors for chronic disease. One good example involves the Nurses' Health Study, where it was reported that 80% of all heart disease and over 91% of all diabetes in women, could be eliminated if they adopted a cluster of positive lifestyle practices including maintenance of a healthy body weight (body mass index of 19–25 kg/m^2), regular physical activity (30 minutes or more on most days), not smoking cigarettes, and following a few simple nutritional practices such as increasing whole grains and consuming more fruits and vegetables. The same was true for men. The US Health Professionals Study showed similar dramatic reductions of risk in men from those with positive lifestyle factors. Even if individuals adopted only one of these positive factors, their risk of developing coronary artery disease and diabetes would be cut in half. Unfortunately, numerous studies have shown that fewer than 5% of adults in the United States follow most or all of these health promoting practices.

Large, randomized trials have also shown the power of daily habits and practices. For example, the Diabetes Prevention Program followed individuals with baseline glucose intolerance who increased their physical activity and lost 5% of their body weight. These individuals reduced their risk of developing diabetes by 58%.

In the LOOK AHEAD Trial, individuals who lost 7% of their body weight significantly reduced risk factors for heart disease and diabetes. In both of these large, randomized controlled trials, over 90% of initial weight loss was maintained over four years for individuals who continued to follow the program and received periodic follow up from health professionals.

The literature relating lifestyle practices and habits and their impact on health continues to grow deeper and more complex. This presents a challenge for physicians and other health care professionals trying to keep up to date on this ever-expanding field and incorporating these findings into modern medical practice. The literature is also complicated because it is spread over a wide variety of disciplines. This provides the rationale for why the need for a comprehensive, evidence-based textbook spanning the field of lifestyle medicine has become even more evident in the last four years since the publication of the third edition of this textbook which, is a major goal for the fourth edition of *Lifestyle Medicine*.

In the first edition of *Lifestyle Medicine* in 1999 we coined the term "lifestyle medicine" and summarized key findings across multiple disciplines that existed in the late 1990's. Since the publication of this first edition of *Lifestyle Medicine* a number of other initiatives have taken place, including the launch of a peer reviewed academic journal

in lifestyle medicine (the *American Journal of Lifestyle Medicine*; SAGE Publications). Consensus statements about the core principles of lifestyle medicine have also been published in the *Journal of the American Medicine Association* as well as in the *American Journal of Lifestyle Medicine*.

In addition, an academic medical society in lifestyle medicine, the American College of Lifestyle Medicine (ACLM), has been established for physicians and other health care workers. This organization currently has more than 11,000 members and is the most rapidly growing health care organization within academic medicine. ACLM has also launched numerous important initiatives in education and the practice of lifestyle medicine.

In addition to ACLM, other medical and professional groups have increasingly embraced the concept of lifestyle medicine. These include the American Heart Association which now has a changed the name of its council from the "Nutrition, Physical Activity and Metabolic Council" to the "Council on Lifestyle and Cardiometabolic Health." The American Academy of Family Practice and the American College of Preventive Medicine now also offer education tracks for individuals interested in adding lifestyle medicine as a key component of their medical practices.

The field of lifestyle medicine has now spread around the world. Over 40 countries have now established lifestyle medicine programs. These programs reflect the enormous interest and potential of lifestyle medicine to exert a positive impact on global healthcare. For example, I was pleased to give the opening keynote address for the third annual China Healthy Lifestyle Medicine conference held in 2023 in Shenzhen, China sponsored by the Fuwai Hospital in Beijing in conjunction with its newly established Center for Lifestyle Medicine. The interest in lifestyle medicine in China is staggering. Over 2.5 million individuals participated virtually in the plenary session and viewed my keynote address.

The international growth of lifestyle medicine coincides with the major initiative announced by the World Health Organization to combat non-communicable diseases (NCDs). As already indicated, the WHO states that over 71% of all mortality each year is caused by NCDs. The recommended modalities to ameliorate this worldwide pandemic involve multiple lifestyle medicine modalities such as increased physical activity, weight management, avoidance of cigarette smoking and reduction in excessive use of alcohol. It is clear that lifestyle medicine has now become a worldwide initiative with the potential to improve the health of every country on earth.

All of these advances are welcome and will enhance the likelihood of formal adoption of lifestyle medicine practices within the medical community. Unfortunately, at the current time, less than 40% of physicians routinely counsel their patients on such important habits and actions such as weight management, physical activity, and proper nutrition. This is a squandered opportunity since more than 75% of adults see their primary care physician at least once per year. This gap between evidence and application represents an enormous mandate and opportunity to underscore the links between lifestyle habits and practices and health outcomes.

So, what is "lifestyle medicine?" In the first edition of this textbook, I defined it as "the integration of lifestyle practices into the modern practice of medicine both to lower the risk factors for chronic disease and/or, if disease is already present, serve as an adjunct in its therapy. Lifestyle medicine brings together sound, scientific evidence in diverse health related fields to assist the clinician in the process of not only treating disease, but also promoting good health." This definition, while over two decades old, has largely stood the test of time. Other organizations that have entered the area of lifestyle medicine have offered very similar definitions of lifestyle medicine and these definitions serve as the defining principle behind the fourth edition of *Lifestyle Medicine*.

The fourth edition of *Lifestyle Medicine* is divided into 22 sections related to lifestyle medicine. Each section has been edited by a leader of that particular discipline and chapters have been rewritten by recognized leaders within the discipline. All chapters have been fundamentally rewritten or substantially revised and brought up to date with current evidence and understanding of practices. There are also many new chapters and three new sections which have been added to reflect modern understandings in particular areas that have emerged which are critically important to lifestyle medicine.

The fourth edition of *Lifestyle Medicine* opens with Part I on *Lifestyle Management and Prevention of Cardiovascular Disease*. This was chosen as the initial section for several reasons. First, I am a cardiologist and my initial interest in lifestyle medicine came through issues related to lowering the risk of cardiovascular disease. Secondly, the area of cardiovascular medicine has been one of the leaders in recommending positive lifestyle habits and practices to reduce the risk of disease. These concepts are articulated both in the AHA Strategic Goals for the Year 2020 and for the AHA Impact Goals for 2030. The council that I sit on within the AHA has changed its name from the "Council on Nutrition, Physical Activity and Metabolism" to the "Council on Lifestyle and Cardiometabolic Health." This represents a welcome recognition of the key role that lifestyle plays in the prevention and treatment of heart disease. In addition, the most recently developed practice guidelines for cardiologists as well as the evidence-based recommendations for lipid management and high blood pressure management all start with the strong recommendation to focus on lifestyle as the foundational recommendation to lower the risk of heart disease. The 2021 nutritional guidance from the American Heart Association furthers this cause.

Part II is on *Nutritional Aspects of Lifestyle Medicine.* Nutrition plays a very prominent role in healthy lifestyle habits and actions. This section has been entirely updated and includes such new chapters on the Dietary Guidelines for Americans 2020-2025 as well as important chapters on

nutrition for elderly individuals and an important chapter on nutrition and hydration.

Part III is an expanded section on *Physical Activity.* This section focuses on state-of-the-art chapters on exercise prescription for various populations emphasizing what physicians should know about prescribing exercise and physical activity. I hope that this section will encourage physicians to play a more active role in this area. Physical activity remains one of the most powerful tools we have to lower the risk of chronic disease. The Physical Activity Guidelines for 2018 Advisory Committee report documented an expanded list of health benefits of physical activity throughout every stage of life ranging from the age of two to older adults. A recent emphasis on the health risks of an inactive lifestyle is also the focus of a new chapter in this section.

Part IV is an expanded and updated section on *Behavioral Medicine*. Understandings of how to change behaviors are foundational for virtually every aspect of lifestyle medicine. This section includes chapters outlining theoretical frameworks for how to apply psychological theories to promote healthy lifestyles and also contains chapters on Motivational Interviewing, and the Transtheoretical Model of Change and Positive Psychology. An important chapter is also included on the "Intention- Behavior Gap" which offers suggestions of how to bridge the gap between what individuals know they should do and what they, in fact, are actually doing. The chapter on coaching remains an important aspect of this area.

Part V contains a fundamentally reworked chapter on Approaches to Dysglycemia. This section includes recommendations for prevention and treatment of diabetes but puts them in a broader context of an emerging framework of Dysglycemia Based Chronic Disease which emphasizes how lifestyle factors can play a key role in all stages of Dysglycemia. In the chapter on Adiposity-Based Chronic Disease, the authors argue that this framework is a much more action-oriented approach to weight gain and obesity than previous concepts in this area.

Part VI is an expanded section on *Lifestyle Issues in the Prevention and Treatment of Cancer.* This includes not only chapters on physical activity and nutrition and cancer, but also tobacco, vaccines and weight control. Cancer is the second leading cause of morbidity and mortality in the United States and lifestyle measures can a play critically important role at all stages of life to lower risk factors or serve as an adjunct to therapy. This section was admirably edited by Dr. Nathan Berger. I am sad to report that Dr. Berger suddenly passed away just prior to the publication of this book. He will be missed.

Part VII is a detailed section on *Obesity and Weight Management* which provides modern understandings, not only on the epidemiology of weight gain and obesity, but also important chapters on pharmaceutical and surgical treatments in addition to both exercise and nutrition.

Part VIII explores issues related to *Lifestyle and Immunology and Infectious Disease*. It has been well known that regular physical activity can improve immunity and this section documents the theories of why this occurs.

Part IX on *Pulmonary Medicine* contains updated and expanded chapters on such critically important topics as Asthma, Influenza, and Indoor Air Quality. The chapter on Lifestyle Measures and their Impact on COVID-19 represents a new and important addition to this section.

Part X represents a combined section on *Obstetrics, Gynecology and Women's Health* dealing with these important issues throughout the lifespan.

Part XI contains important new chapters on *Cardiac Rehabilitation and Secondary Prevention* and is updated to include recent advances in digital health as well as lipid management and the pros and cons of various supplements and vitamins in the prevention and treatment of cardiovascular disease.

Part XII on *Lifestyle Components of Pediatric Medicine* is written by recognized experts in this area. This section spells out in detail the importance of lifestyle measures at every stage of life, even prior to birth. Chapters in this section provide guidance for lifestyle medicine practitioners to help families explore, and if necessary, treat issues of childhood obesity and potential complications such as high blood pressure and dyslipidemia in children. This comes at an important time since the prevalence of obesity in children has tripled in the last 20 years.

Part XIII represents a fundamentally new and important section in lifestyle medicine on *Lifestyle Medicine and Nursing.* Nurses are often the front line healthcare professionals who interact with individuals while making recommendations about lifestyle habits and practices. There are over four million registered nurses in the United States, which makes nursing the largest healthcare profession within the United States. For all of these reasons, the expansion of lifestyle medicine as a component of nursing practice is an important expansion of the purview for the fourth edition of *Lifestyle Medicine.*

Part XIV also represents a new section and emphasis in lifestyle medicine entitled *Mental Health and Psychiatry Issues in Lifestyle Medicine*. A significant overlap exists between psychiatric issues and metabolic issues so a section in this area is highly welcomed and an important expansion of the field of lifestyle medicine. Included in this section are important chapters on the treatment of various psychiatric issues such as anxiety and depression. An important chapter on lifestyle and brain health emphasizes that many of the factors which have been incorporated into cardiovascular medicine are also of great importance in the area of maintaining a healthy brain throughout life.

Part XV also represents a new section in the fourth edition entitled *Preventive Neurology.* Multiple chapters in this section elucidate how lifestyle medicine habits and practices impact not only on the likelihood of developing Alzheimer's Disease and other dementias but also on stroke and Parkinson's Disease. The chapter on Sleep and Lifestyle Medicine in this section emphasizes that sleep carries multiple health related implications. It is particularly important to have a comprehensive chapter on sleep since it is clear that sleep also plays very significant roles in cardiovascular medicine and other aspects of lifestyle medicine.

An increasing number of individuals have begun to make lifestyle medicine a cornerstone of their medical practice. For this reason, we have greatly expanded the section on *The Practice of Lifestyle Medicine* (Part XVI) to provide guidance for principles and practices of lifestyle medicine, both for individuals who want to have this area be part of their practice and also those who want to make it the cornerstone of their practice. There is now an emerging trend in lifestyle medicine involving individuals who want to obtain advanced understandings of the field. An important chapter on high intensity lifestyle medicine has been included in this section.

Part XVII on *Substance Abuse and Addiction* reflects the fact that lifestyle medicine practitioners often end up treating individuals with these issues in the course of their regular practice. There is abundant information in this section about how lifestyle habits and practices impact on both the likelihood of abusing substances and how to treat addiction.

Positive lifestyle habits and actions are critically important at every stage of life. This is particularly important for individuals over the age of 65 who represent the fastest growing portion of the United States population. Individuals who reach the age of 65 have an 80% chance of reaching the age of 80. Individuals who reach the age of 80 live an average of 8-10 years longer. For all these reasons, it is important to emphasize the role of lifestyle medicine in geriatrics. This is core motivating principle behind the

greatly expanded section on "*Lifestyle Medicine in Geriatrics"* (Part XVIII). In addition to lifestyle issues related to the geriatric population valuable chapters include how to manage the stresses and strains of caregivers which are often underestimated. Issues related to loneliness, which is an increasing problem in the geriatric population, is also a focus of this section as well as the role of lifestyle medicine practices and habits to lower the risk of polypharmacy which occurs commonly in the geriatric population. All of these factors impact on the emerging concept of "successful aging" which underscores lifestyle and health benefits for individuals over the age of 65.

Part XIX on *Health Promotion* is an important and historically prominent component of lifestyle medicine. This section in the third edition of *Lifestyle Medicine* was under the able direction of Dr. Dee Edington, a pioneer in health promotion. Sadly, Dr. Edington passed away in the midst of editing this section and it was admirably completed by his colleague Dr. Jane Ellery. Diverse topics of health promotion and their role in both corporate America and for individuals are elucidated in chapters in this section.

The multiple psychological benefits of regular physical activity are well known. In fact, in one survey of regular exercisers 75% indicated that the major reason why they exercise is for stress reduction. I can say in my own life that while as a cardiologist I am very well aware of how my daily exercise sessions lower my risk of heart disease and helps me maintain a healthy body weight. I also view daily exercise as a powerful health promotion tool. Part XX on *Exercise Psychology* describes in detail the interactions between mind and body. In fact, in this section, the authors start with the conviction that the separation between mind and body is artificial and that we ought to be thinking of a unified whole. Important chapters on regular physical activity and its powerful effect on anxiety and depression are important. Perhaps most attractive about this section is the concept of cognitive reserve. Regular exercisers seem to delay the likelihood of dementia and increase regular cognitive performance through their long-term exercise habits.

Injuries are the leading cause of morbidity and mortality for individuals under the age of 40. Part XXI written largely by experts from the CDC provides detailed evidence on how to prevent or treat this common occurrence.

Lifestyle changes do not occur in isolation; thus, public policy issues play an important role either in the environment or policies which can support or undercut individuals' ability to improve their health through lifestyle measures. The final part of this book, Part XXII on *Public Policy and Environmental Supports for Lifestyle Medicine* makes critical linkages between how public health and environmental conditions can play an important role in supporting individuals' efforts to improve their life and health through regular habits and actions.

The daunting task of generating this comprehensive and up to date volume of *Lifestyle Medicine* involves the hard work, talent and expertise of 24 section editors who have devoted enormous energy and talent to the difficult tasks of organizing and editing each section of the fourth edition of *Lifestyle Medicine* to ensure that each chapter is scientifically accurate, up to date and clinically useful. These section editors have recruited and interacted with over 325 distinguished contributors to a textbook which I hope and believe is not only evidence-based but clinically useful and motivational for clinicians and other healthcare professionals at all levels of training. We have also sought to make the book practical by providing state of the art summaries and practical applications of modern science and medical understandings in each chapter.

We have further emphasized clinical utility in the fourth edition of *Lifestyle Medicine* by asking each author to list "key points" at the beginning of each chapter and "Clinical Applications" at the end of each chapter. These additions, I hope, will help introduce key concepts in each chapter and guide readers through practical applications of information with the hope that this will enhance its applicability in the daily practice of medicine. The overarching goal, of course, remains to help all of our patients lead happier, healthier, and more productive lives, while also lowering their risk of chronic diseases and enhancing their quality of life.

Over the two and a half decades since the publication of the first edition of *Lifestyle Medicine*, important and extensive new information has been developed to provide scientific links between daily habits and actions and their critical impact on short and long-term health and quality of life. What started out as an aspirational idea has now grown into a worldwide movement.

As always, a key consideration for those of us in the healthcare community remains applying these understandings to the modern practice of healthcare in general and medicine in particular. Making a positive impact on lifestyle habits and actions which are the cornerstone of lifestyle medicine is, in my view, the single, greatest opportunity that we have to improve health outcomes and lower cost. This is absolutely essential to underscore and advance the value proposition in the practice of medicine. Enhancing health continues to be the challenge and enormous opportunity for all of us who are entrusted and blessed as gatekeepers for the health of our patients of our country. I hope that the fourth edition of *Lifestyle Medicine* will continue to support the magnificent efforts of all who strive to enhance the health for themselves and their patients.

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Serendipity and Important Milestones

With the publication of the fourth edition of *Lifestyle Medicine*, we celebrate the 25th anniversary of the publication of the first edition of this textbook. This is also serendipitous since, also this year, we celebrate the 20th anniversary of the establishment of the American College of Lifestyle Medicine which was founded and inspired by the first edition of this textbook.

About the Editor

James M. Rippe, M.D., is a graduate of Harvard College and Harvard Medical School with postgraduate training at Massachusetts General Hospital and the University of Massachusetts Medical School. He is currently the Founder and Director of the Rippe Lifestyle Institute and Professor of Medicine at the UMass Chan Medical School.

Over the past 30 years, Dr. Rippe has established and run the largest research organization in the world exploring how daily habits and actions impact short- and long-term health and quality of life. This organization, Rippe Lifestyle Institute, has published hundreds of papers that form the scientific basis for the fields of lifestyle medicine, risk factor reduction, and high performance health. Rippe Lifestyle Institute also conducts numerous studies every year on physical activity, nutrition, and healthy weight management. Dr. Rippe has written over 500 academic papers and abstracts and written or edited 60 books, including 37 for health care professionals and 23 for the general public.

A lifelong and avid athlete, Dr. Rippe maintains his personal fitness with a regular walk, jog, swimming, and weight training program. He holds a black belt in karate and is an avid wind surfer, skier, and tennis player. He lives outside Boston with his wife, television news anchor Stephanie Hart, and their four children, Hart, Jaelin, Devon, and Jamie.

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Part I

Lifestyle Management and Prevention of Cardiovascular Disease



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1 The Rationale for Intervention to Reduce the Risk of Cardiovascular Disease

James M. Rippe, MD

KEY POINTS

- Cardiovascular disease (CVD) remains the leading cause of death and disability in the United States and worldwide.
- Multiple risk factors increase the risk of CVD. Many of these risk factors have a significant lifestyle component.
- There has been a significant decrease in CVD mortality over the past four decades. Half of this decrease is due to lower risk factors. Increases in several risk factors, however, including obesity and diabetes, threaten to wipe out gains in all other risk factors.
- If individuals followed the four positive daily lifestyle measures—maintain proper weight, do not smoke cigarettes, engage in regular physical activity, and follow sound nutritional patterns (more fruits and vegetables, whole grains and fish), the prevalence of CVD could be decreased over 80%, and the prevalence of diabetes could be decreased over 90%.
- The American Heart Association (AHA) has recommended an emphasis on "primordial prevention," which is lowering the likelihood of developing risk factors in the first place.
- Physician visits are an ideal opportunity to stress the importance of lifestyle habits and practices to reduce the risk of CVD.

1.1 INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death for both men and women in the United States each year[1]. Over 37% of all mortality in the United States comes from CVD.[1] Although knowledge of many factors contributing to CVD is incomplete, it is clear that many risk factors contribute in significant ways to the ongoing epidemic of CVD.

CVD is truly a pandemic and represents the most important cause of death worldwide. In 2020, CVD resulted in an estimated 17.9 million deaths and 293 million disability-adjusted life-years (DALYs) lost.[2] These represent approximately 32% of all deaths worldwide and 13% of all DALYs lost that year. The World Health Organization (WHO) lists CVD as the leading cause of death worldwide. This disease not only impacts high income countries but has become increasingly prevalent in both low and middle income countries, which have seen an alarming increase in CVD rates.

So prominent has been the role of certain lifestyle factors that it has been argued that the world is entering into a new epidemiologic transition. In the past four epidemiologic transitions, the predominant causes of death have been identified, starting with pestilence and famine, then receding pandemics, followed by degenerative and man-made diseases, and finally, delayed degenerative diseases. It has been argued that the modern world may be entering a fifth epidemiologic phase highlighted by inactivity and obesity/diabetes, both of which contribute in significant ways to CVD.[3]

Lifestyle habits and practices constitute a significant contributor to this ongoing epidemic. While progress has been made in some of these areas (e.g., hypertension, total cholesterol, smoking cessation, physical activity), unfortunately, regression has occurred in such areas as obesity and diabetes.[4,5] The increasing prevalence of these latter two conditions has the potential to wipe out progress made on all the other lifestyle related risk factors for CVD.[3]

In addition to its human cost, CVD also represents an enormous financial drain in the United States. It has been estimated that over $219 billion per year is spent on direct medical expenses and other associated costs related to CVD.[6,7]

Lifestyle factors play a particularly prominent role in the development and pathogenesis of CVD. Indeed, five of the major risk factors for developing CVD relate to lifestyle practices, including the following: the choice of whether or not to use tobacco products, level of physical activity, control of lipids, diabetes, and obesity.[8]

This chapter will focus on the rationale for intervening to reduce risk factors for CVD. The next chapter will discuss applications of lifestyle interventions in clinical practice to reduce the risk of CVD.

Deaths from CVD and stroke have been declining in the United States for the past four decades. For example,

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between 1963 and 1990, the mortality of coronary heart disease fell by more than 50%.[9] Nonetheless, CVD and stroke remain the leading causes of morbidity and mortality in the United States and in most other industrialized countries. The decline in CVD and stroke is a result of not only reduced prevalence of risk factors but also advances in treatment and therapies. Nonetheless, the increased prevalence of diabetes, obesity, and an aging population work against reductions in CVD and stroke prevalence and require expanded efforts to reduce lifestyle related risk factors in order to continue reducing the burden of CVD.

Between1980 and 2000, the decline in age related death for coronary heart disease (CHD) led to an estimated decrease of 341,745 deaths.[4] About half of this decline resulted from improvements and advances in treatment, while approximately 44% related to risk factor reduction. An estimated 149,635 fewer deaths from CVD came from improved treatment[4] of some of its risk factors, while an estimated 59,370 increase in deaths occurred from the higher rates of obesity and diabetes.[4] The increasing prevalence of obesity and diabetes has the potential to completely wipe out the advances in the reduction of other risk factors if the trends of these two lifestyle risk factors are not reversed.

Despite advances in reducing certain lifestyle related risk factors for CVD, these factors remain extremely common. For example, the prevalence of hypertension in the United States has continued to increase, with recent data suggesting that more than one-third of American adults have high blood pressure, as defined by systolic BP >140 and diastolic BP >90 mmHg or taking antihypertensive medicines.[9,10] The Surgeon General's Report on Physical Activity and Health documented that over 70% of the adult population in the United States fail to get enough regular physical activity to lower their risk of CVD,[11] despite the fact that the 2018 Physical Activity Guidelines for Americans demonstrate multiple health benefits for virtually every population group.[12] Overweight and obesity have continued to rise in the United States, with over 73% of the population showing one of these two conditions.[13]

The epidemic of diabetes (T2DM) in the United States continues to rise, with approximately 9% of the adult population currently suffering from this chronic condition—almost double the rate of 20 years ago.[14] After several decades of encouraging declines in cigarette smoking, progress unfortunately appears to have leveled off in this area, with about 15% of the overall adult population in the United States still smoking. Thus, some progress in reducing risk factors has occurred, but enormous challenges and opportunities remain for applying lifestyle measures, often in conjunction with pharmaceutical therapy, to reduce the risk of CVD.

1.2 THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

As knowledge of the pathophysiology of atherosclerosis has advanced, new understandings have provided crucial linkages to the role of various lifestyle interventions in reduction of the risk of CVD. For example, poor diet (e.g., elevated consumption of saturated fats and calories, etc.) and diminished physical activity have been known for years to contribute to atherogenesis.[16,17] However, only in the past decade has the significant role of inflammation as an initiating event in the process of atherosclerosis begun to be elucidated. Since multiple related entities such as CHD, obesity, diabetes, glucose intolerance, and the metabolic syndrome have significant overlap, it may indeed be a component of systemic inflammation that unites all of these processes.

Fundamental to the understanding of the interplay between lifestyle and atherosclerosis is the evolving concept of the role of various structures and the interaction of components of both normal and diseased arteries (e.g., endothelium, smooth muscle, and intima) as well as how various cells in these structures function both in health and in disease.[16,18]

The evolving understanding of the biology of atherosclerosis is beyond the scope of the current chapter. The reader is referred to several recent excellent reviews that discuss current understandings of the atherosclerotic process in detail.[19–21]

1.3 UNDERSTANDING RISK FACTORS

1.3.1 The Concept of Risk Factors

The concept of risk factors is relatively new in the history of medicine. In fact, until the initial findings from the Framingham study were published in the 1960s, the concept of risk factors for CVD did not formally exist.[22] Framingham data showed that factors such as diabetes,[23–26] dyslipidemia,[27–31] high blood pressure,[32–35] and cigarette smoking[36–39] each independently and significantly increased the risk of CVD. The concept of CVD risk factors has been expanded to include physical inactivity[40] and obesity.[41] Other emerging risk factors where lifestyle habits and practices may play a role are under active investigation.

Framingham data also demonstrated that risk factors act synergistically and tend to cluster with each other.[42] Thus, in the presence of two risk factors, an individual quadruples their chance of developing CVD compared with individuals having no risk factors. Individuals with three risk factors increase their risk of developing CHC between 8- and 20-fold compared with individuals having no risk factors.[43]

In addition to the lifestyle related risk factors identified by the Framingham study and other observational and interventional studies, other risk factors have been determined, including age, gender, family history of CVD, elevated C-reactive protein (CRP), hemostatic factors, excessive alcohol consumption, hypertriglyceridemia, elevated homocysteine levels, and perhaps stress and other psychological factors such as depression.

Numerous studies have demonstrated that reducing risk factors for CVD can significantly decrease its likelihood.[44–46] Lifestyle measures are a particularly powerful and effective way of lowering risk factors, since these

measures are low risk and many of them simultaneously affect multiple risk factors.

1.3.2 Evidence Based Alternatives to "Risk Based" Approaches to the Prevention of Cardiovascular Disease

With the widespread use of statin medications, the "risk based" approach to prevention has now been challenged by many cardiologists in the area of primary prevention. Since the data on safety for statins are now prevalent, even for individuals at the lower end of absolute vascular risk as determined by currently available risk profiles such as the Framingham Heart Risk Score, preventive cardiologists have recently focused more attention on establishing risk profiles based on what works and in whom as a more evidence based and simpler approach to the complex model of previously existing risk factor scales. Cardiologists in the United States, Canada, and Europe have suggested five recommendations for simple and easily understood guidelines for the use of statin therapy in the prevention of CVD. The recommended five components of guidelines for the use of statin therapy are as follows:

1. On the basis of a quality, randomized clinical trial data (RCT), statin therapy should be used as an adjunct to diet, exercise, and smoking cessation for secondary prevention in individuals with a previous history of myocardial infarction (MI), stroke, or clinically apparent atherosclerosis.
2. High quality RCTs support the use of statin therapy as an adjunct to diet, exercise, and smoking cessation as a component of primary prevention for individuals over the age of 50 with diabetes, elevated low density lipoprotein (LDL) cholesterol, low high density lipoprotein (HDL) cholesterol or elevated high sensitive C-reactive protein (hs-CRP), or multiple risk factors.
3. On the basis of high quality RCTs, in prescribing statin therapy, physicians should seek to maximize the intensity of the regimen and then focus efforts on compliance and long-term adherence.
4. On the basis of high quality RCTs, the use of non-statin lipid lowering agents for mono-therapy or in combination with a statin should be limited while awaiting evidence that such an approach further reduces cardiovascular event rates in specific patient groups.
5. Guidelines based on trial evidence (to determine what works) and on trial entry criteria (to ascertain in whom) are simple, practical, and consistent with evidence based principles and should, therefore, result in broad clinical acceptance.

This fundamentally different approach based on evidence based alternatives from RCTs, particularly as they relate to the use of statins, has been widely accepted now in the preventive cardiology community.

It has been argued that this approach will be more effective in providing appropriate statin therapy for individuals at lower to middle risk from previous risk assessments such as the Framingham Risk, the Reynold's Risk, or the European System Coronary Risk Evaluation (SCORE). Previously available scores have typically been more effective in targeting lifestyle interventions for individuals at the highest risk. New, evidence based guidelines are thought to be more effective in recognizing individuals at lower or intermediate risk and reserving aggressive, pharmacologic interventions to those with "higher" risk profiles. It should be noted that in this new approach to cardiovascular prevention, lifestyle therapies are still a key component in all of the recommendations.

1.3.3 Relative Risk versus Absolute Risk

It is important to differentiate between "relative" and "absolute" risk, since this distinction underlies treatment strategies for risk factor reduction in CVD. *Relative risk* is a comparison between different risk levels. This estimates the likelihood that an individual who possesses a specific risk factor will develop CVD in comparison to an individual without that risk factor. *Absolute risk* represents the likelihood of developing CVD over a specified period of time. Framingham risk scores, for example, typically assess the absolute risk of developing CVD over a ten year period.

The difference between relative and absolute risk is a critical factor in clinical decision making. For example, a young individual with abnormal lipids would be treated differently than an older individual with a similar lipid profile, all other things being equal, since while their increased relative risk may be the same, their absolute risk may be quite different.[47–49]

One way of viewing relative risk may be that it provides an indication of how rapidly an individual may move to absolute risk. Thus, a young individual with high relative risk would be at greater risk of ultimately developing high absolute risk, motivating the clinician to devise strategies for lowering risk as a means of slowing the early stages of developing CVD. Interventions such as lifestyle measures, which carry multiple benefits and relatively little risk and expense, are attractive means for lowering both relative and absolute risk of CVD.

1.3.4 Primary versus Secondary Prevention

It is also important to distinguish between "primary" and "secondary" prevention when approaching risk factor reduction. Primary prevention is based on the goal of preventing or delaying the development of CVD, while secondary prevention focuses on interventions designed to reduce the likelihood of repeat cardiovascular events and/or mortality in individuals who already have established CVD. More aggressive measures for risk factor reduction

are typically indicated in individuals when they are used in secondary prevention.

Guidelines for risk factor reduction in primary prevention are available from a variety of sources. The most widely used is still the Framingham Risk Scoring system.[50]. Guidelines for interventions for secondary prevention have also been published by the AHA and are discussed in detail in **Chapters 60 and 61** later in this book.

1.4 PRIMORDIAL PREVENTION AND "IDEAL" CARDIOVASCULAR HEALTH

In 2010, the AHA issued a strategic plan through the year 2020 and beyond.[51] New to this plan was a concept of "primordial" prevention. The goal of primordial prevention as articulated by the AHA is "by 2020 to improve the cardiovascular health of Americans by 20% while reducing deaths from cardiovascular and stroke by 20%." In issuing this statement, the AHA recognized and declared that "[h]ealth is a broader, more positive construct than just the absence of clinically evident disease." It defined "primordial" prevention as a process to avoid adverse levels of risk factors in the first place rather than trying to reduce risk factors when they are already present or treating already established disease. This broader risk factor reduction strategy is completely consistent with the goals and vision of lifestyle medicine and will require careful attention to daily lifestyle habits and actions and their impact on risk factors and overall health.

The AHA Strategic Plan[51] also defined a construct of "ideal" cardiovascular health, which was defined as the following:

> The simultaneous presence of four favorable health behaviors: absence of smoking within the last year, physical activity at goal, consumption of a "heart healthy" dietary pattern and an ideal body mass index (BMI).
>
> "Ideal" cardiovascular health included as well as four favorable health factors: untreated cholesterol less than 200 mg/dL, untreated blood pressure less than <120/<80 mm Hg, and the abstinence of diabetes mellitus, absence of clinical cardiovascular disease (including CVD, stroke, heart failure, etc.).

Clearly, this very welcome framework will result in an increased emphasis on physicians treating, and patients following, positive lifestyle behaviors to improve their cardiovascular health.

1.5 IMPLEMENTING RISK FACTOR REDUCTION GUIDELINES

Another welcome trend in the area of risk factor reduction comes from the Dietary Guidelines for Americans 2020–2025,[52] Physical Activity Guidelines for Americans 2018,[12] and American Heart Association Scientific Statement on Implementing Pediatric and Adult Nutrition Guidelines.[53] All three of these guidelines have emphasized real world, practical implementation of guidelines. This is an important and new emphasis from these three widely read and influential documents.

1.6 THE SCIENTIFIC BASIS FOR RISK FACTOR REDUCTION

Multiple observational and interventional studies, including the Framingham Study,[54] the Nurses Health Trial,[55] the US Male Professional Health Trial, and the Women's Health Initiative,[56] have all demonstrated the link between risk factors and developing CVD as well as the power of reducing risk factors to reduce the likelihood of developing CVD. Results from these and other studies form the basis for recommendations in the following sections of this chapter on specific risk factors.

1.7 EVIDENCE-BASED VERSUS RISK-BASED STRATEGIES FOR PREVENTION OF CARDIOVASCULAR DISEASE

As already indicated, as new evidence has become available over the last decade from large randomized trials, some have advocated that guidelines for strategies to prevent cardiovascular disease should be based on clinical trial evidence rather than epidemiologic evidence.[57,58] This has been particularly useful when thinking about when to use statin medications for prevention of cardiovascular disease. Preventive cardiologists in the United States, Canada, and Europe have combined a list of recommendations on clinical trial data concerning when to use statins in the prevention of cardiovascular disease.[59,60] This strategy has been memorized as "what works" and "in whom." These recommendations will be handled in more detail in Chapter 2.

1.8 MODIFIABLE RISK FACTORS

This section will focus on risk factor reduction for those risk factors that can be modified, while the next section will focus on those risk factors that cannot be modified. The modifiable risk factors represent a particularly important area for clinical intervention. Numerous studies have demonstrated that the use of lifestyle measures for reducing modifiable risk factors is an effective strategy for reducing the risk of developing CVD.

1.8.1 Tobacco Use

Cigarette smoking is the leading preventable cause of death from all causes in the United States and the single most prevalent modifiable risk factor for the development of CVD.[61] CVD causes 35–40% of smoking related deaths, and an additional 8% of deaths have been attributed to second hand smoke exposure.[62–64]

Unfortunately, following many years of decline in cigarette smoking prevalence in the United States, the percentage of adults who smoke has recently stabilized at about 15%.[15] Rates of tobacco use are actually increasing among adolescents, young adults, and women.[15]

The link between cigarette smoking and increased risk of CVD has been established in multiple studies. Individuals who consume 20 or more cigarettes per day have a two- to threefold increase in CVD. Framingham study data demonstrated that cardiovascular mortality increases by 31% in women and 18% in men for each ten cigarettes smoked per day.[65] Multiple observational studies have also shown that smokeless tobacco and low tar cigarettes do not reduce the risk of CVD.

Numerous studies have demonstrated that smoking cessation improves longevity and reduces the risk of CVD.[66] Thus, stopping cigarette smoking remains the single most important intervention in preventive cardiology and lifestyle medicine. Smoking cessation yields significant benefits in a relatively short period of time.[67] In one study comparing 1,282 cigarette smokers with 2,068 controls, the risk of developing CVD amongst those individuals stopping cigarette smoking approached the level of never smokers within three years.[66] In addition to contributing greatly to the risk of CVD, cigarette smoking also significantly increases the likelihood of developing lung cancer and chronic obstructive pulmonary disease.

Despite the important and powerful health benefits of cigarette smoking cessation, the medical community has not been active enough in this area. The Centers for Disease Control and Prevention (CDC) estimates that only slightly more than half of smokers who had at least one physician visit in the previous year reported they were advised to quit smoking cigarettes.[67,68] The impact of spouse, friends, and families on cigarette smoking cessation is also significant. Recent studies suggest that smoking cessation by a spouse decreases an individual's chance of smoking by 67%, while smoking cessation by a co-worker, sibling, or friend contributes to a decrease of 25–36% in a person's likelihood of smoking.[69]

1.8.2 Dyslipidemias

Numerous trials have demonstrated that a variety of dyslipidemias or a combination of dyslipidemias increase the risk of CVD.[45,70–80]

1.8.3 Elevated Low Density Lipoprotein Cholesterol and Hyperlipidemia

Hypercholesterolemia has been clearly associated with increased risk of CVD. In particular, increased plasma levels of LDL have been associated with increased incidence of CVD. Based on these data, the Nutrition Cholesterol Education Program Adult Treatment Panel Guidelines (ATP III) established LDL as the primary target for intervention.[74] Numerous observational trials, including the Framingham study, MRFIT, the Nurses' Health Study, and the US Male Health Professional follow up study, have all demonstrated an association between elevated blood cholesterol and increased risk of CVD. Numerous interventional studies have also established that elevated blood cholesterol and in particular, elevated LDL is associated with increased incidence of CVD.[70–80] Several lines of evidence have suggested that what are regarded as "normal" cholesterol levels in Western society are higher than is necessary for good health. Furthermore, cholesterol levels measured early in life influence long-term cardiovascular risk, suggesting that cholesterol should be routinely measured in children. These studies have become particularly robust since the development of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). These agents lower LDL cholesterol much more efficiently than previously available drugs. Numerous, large clinical trials where statins have been utilized to lower LDH cholesterol by 20–60% reduced coronary events by up to one third over a five-year period without evidence of increased non-vascular mortality.[44]

1.8.4 Low Levels of HDL Cholesterol

A number of prospective cohort studies have also demonstrated an inverse relationship between HDL cholesterol and risk of CVD. Conversely, low HDL increases the risk of CVD.[44] Each increase in HDL cholesterol by 1 mg/dL is associated with a 2–3% decrease in risk of total cardiovascular disease.[44,80] Low HDL cholesterol has been defined as an HDL lower than 40 mg/dL. Levels lower than this are defined as an independent risk factor for CVD in the National Cholesterol Education Program (NCEP) Guidelines. Moreover, the NCEP Adult Treatment Panel (ATP III) Guidelines support an HDL level of >60 mg/dL as a negative risk factor for CVD.[81] It should be noted that several recent trials of novel pharmaceutical agents designed to raise HDL have been somewhat disappointing and have resulted in untoward side effects such as hypertension. Trials such as the "AIM-HIGH" study, which randomly allocated high risk patients to niacin supplementation, increased HDL cholesterol and reduced triglycerides, yet did not yield reductions in clinical events.[82] Furthermore, in the Investigation of Lipid Level Management to Understand its Impact on Atherosclerotic Events (ILLUMINATE), individuals at higher vascular risk who were given the Cholesterylester Transfer Protein (CETP) inhibitor torcetrapib actually showed an unanticipated increase in all-cause mortality.[83] Despite these negative results, HDL cholesterol level as a "negative risk factor" for CVD is strongly supported by both cross-sectional and prospective studies, which support its continued use in guidelines worldwide.

1.8.5 Hypertriglyceridemia

Triglycerides tend to vary inversely with HDL. An association between elevated triglyceride levels and cardiovascular

disease has been known for many years.[84,85] However, the evidence supporting a direct linkage is less robust than that for elevated LDL or low HDL and CVD. Recent attention has been focused on elevated triglycerides as a risk for heart disease, given its association with obesity, insulin resistance, and diabetes. Statements from the AHA on Childhood and Adolescent Obesity and on Triglycerides and Cardiovascular Health emphasize the importance of lowering triglycerides through lifestyle measures as a means of lowering risk of CVD.[86] Current designations for triglyceride levels are as follows: 150–199 mg/dL borderline high, 200–499 mg/dL high, and >500 mg/dL very high. Overall, 31% of the adult population in the United States has a triglyceride level ≥150 mg/dL.[84,85]

1.8.6 Hypertension

High blood pressure constitutes a significant increased risk of CVD. The prevalence of hypertension has increased steadily in the United States over the past ten years.[87] According to the report of the Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure (JNC VII), more than one out of every three adults suffers from high blood pressure.[87] This means that more than 50 million individuals have high blood pressure.[87] A subsequent report based on data from a recent National Health and Nutrition Evaluation Survey (NHANES III) places the number even higher at 38% of the population (65 million individuals).[88] Even individuals who have normal blood pressure at the age of 55 have a 90% risk of developing hypertension during their lifetime, according to data from the Framingham Heart Study.[89]

The relationship between blood pressure and the risk of CVD events is independent of other risk factors for CVD. For every 10 mmHg rise in diastolic blood pressure or 20 mmHg rise in systolic blood pressure above 115/75 mm Hg, the increase in risk of CVD doubles.[87]

The JNC VII guidelines create a lower than previously established guideline for normal blood pressure (below 120/80 mmHg) and created a new category of "prehypertension" to replace the old category of "high normal." The JNC VII classification for blood pressure in adults is found in Table 1.1.[87]

High blood pressure is also frequently found co-existing with other risk factors for CVD.[88,89] For example, individuals with high blood pressure have a greater than 40% chance of having elevated blood cholesterol.[90–92] This is particularly important, since over half of heart disease occurs in individuals with two or more risk factors. JNC VII guidelines recommend a six month trial of lifestyle related measures such as weight loss, smoking cessation, regular exercise, and improved nutrition for individuals with Stage 1 hypertension before starting pharmacologic therapy.[87]

It should be noted that a commission was established to formulate JNC VIII guidelines and made somewhat different recommendations.[93] The JNC VIII guidelines contain the following statement:

> There is strong evidence to support treating hypertensive individuals aged 60 or older to a BP goal of less than 150/90 mmHg and hypertensive patients 30–59 years of age to a diastolic goal of less than 90 mmHg; however there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal or for those younger than 30 years for a diastolic goal. So the panel recommends a BP of less than 140/90 mmHg for those groups based on expert panel.

The attempt from the JNC VIII guidelines was to make the blood pressure control recommendations based on

TABLE 1.1
Classification of Management of Blood Pressure for Adults 18 Years or Older

BP classification	Systolic BP, mm Hg*		Diastolic BP, mm Hg*	Management*		
				Lifestyle modification	Initial drug therapy	
					Without compelling indication	With compelling indications
Normal	<120	and	<80	Encourage		
Prehypertension	120–139	or	80–89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications†
Stage 1 hypertension	140–159	or	90–99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications; other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)‡	Drug(s) for the compelling indications; other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker.
*Treatment determined by highest BP category.
†Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg.
‡Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

evidence from randomized control trials. However, these recommendations have not been widely adopted. The JNC VIII guidelines emphasize that while these targets have been articulated, people's judgement should still prevail in hypertensive therapy.[93] Of note, both JNC VII and JNC VIII recommend lifestyle interventions such as regular aerobic exercise, eliminating salt intake, maintenance of proper healthy weight, and not smoking cigarettes as the cornerstone of any antihypertensive regimen. The 2017 report from the AHA and American College of Cardiology (ACC) presents guidelines roughly similar to JNC VIII and will be discussed in the next chapter.[94]

1.8.7 Diabetes and Glucose Intolerance

The incidence of type 2 diabetes, which represents a major risk factor for CVD, has increased dramatically in both men and women in the United States over the past 30 years. Diabetes now affects over 9% of adults.[14] Perhaps of even greater importance is that an estimated 35–40% of adults have impaired glucose tolerance or impaired fasting glucose levels.[95] In one study, the prevalence of glucose intolerance in individuals over the age of 75 years was 80%. Diabetes is also one of the most common chronic diseases in the world, affecting an estimated 285 million adults in 2010 (6.4% of the global adult population).[95] It is estimated that the prevalence of diabetes will grow to more than 430 million individuals (7.7% of the global adult population) by the year 2030.[14] Diabetes represents a significant risk factor for CVD. Individuals with diabetes have between two and eight times higher rates of cardiovascular events compared with nondiabetic controls.[91] This risk factor is particularly potent in women with diabetes, who increase their risk of developing CVD three- to sevenfold compared with a two- to threefold increased risk in men. The increase in diabetes parallels the increase of obesity in the United States.[92] It has been estimated that individuals born in the United States in the year 2000 will have a 36% chance of developing diabetes in their lifetime.[95]

For all of these reasons, prevention, early detection, and treatment of diabetes assume great importance as a modality for reducing the risk of CVD. Typical treatment involves multiple components of lifestyle measures such as weight loss for individuals who are overweight or obese, proper diet using medical nutrition therapy, and regular physical activity.

1.8.8 Obesity

The prevalence of overweight and obesity has increased significantly in the United States and other developed countries over the past 30 years. It is estimated that over 73% of the adult population in the United States is now overweight or obese.[13] Increases have been particularly prominent in the area of Stage 1 obesity and severe obesity. Between 1980 and 2004, the prevalence of obesity amongst adults in the United States doubled. In 2018, it was estimated that 38% women and 35% of men in the United States were obese.[13] Numerous studies have demonstrated that obesity constitutes a strong and independent risk factor for CVD in addition to its association with other risk factors such as dyslipidemia, diabetes, and hypertension. The AHA classifies obesity as a major risk factor for CVD because of these associations.

The most practical and recognized way of assessing obesity in clinical practice is to determine an individual's BMI. BMI has also been shown in numerous studies to correlate with health risk. BMI classifications, according to the Institute of Medicine,[96] are listed in Table 1.2.

The linkages between obesity and CVD are not completely understood, although they are probably mediated

TABLE 1.2
Classification of Overweight and Obesity as Recommended by the National Heart, Lung, and Blood Institute Guidelines

	Disease risk[a] relative to normal weight and waist circumference			
			Waist circumference	
	BMI (kg/m²)	Obesity class	<102 cm (men)<88 cm (women)	>102 cm (men)>88 cm (women)
Underweight	<18.5		–	–
Normal[b]	18.5–24.9		–	–
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	1	High	Very high
	35.0–39.9	2	Very high	Very high
Extreme obesity	≥40.0	3	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.
[b]Increased waist can also be a marker for increased risk in normal weight individuals.
BMI, body mass index.
Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services. Bethesda, MD.

not only by direct effects on the cardiovascular system (a hyperdynamic state and increased blood flow) but also through systemic inflammation. Adipocytes used to be considered relatively inactive storage depots; however, recent studies have shown that in fact, adipocytes are very metabolically active and generate a variety of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF),[100] and C-reactive protein (CRP).[96–99] Excess weight is also associated with a variety of novel risk factors, including an atherogenic dyslipidemia (low HDL-C, elevated triglycerides, elevated apoprotein B, and elevated LDL). In addition, obesity is associated with elevations in thrombotic factors such as Plasminogen Activator Inhibitor I and increased levels of fibrinogen.[101,102]

The distribution of body fat is also strongly and independently associated with CVD over and above increased body weight. In particular, increased abdominal obesity has been demonstrated to increase the risk of CVD.[103–105] A practical way of estimating abdominal obesity is to measure waist circumference. A waist circumference of ≥40 inches in men and ≥35 inches in women confers a significantly increased risk of CVD compared with lower levels of abdominal fat.

Adult weight gain also confers additional risk of CVD. According to the Nurses' Health Study[106] and US Men's Health Professional Study,[10] individuals who gained 20 lbs or more during their adult life significantly increased their risk of type 2 diabetes and CVD.[108]

1.8.9 Inactive Lifestyle

Physical activity carries multiple health benefits.[12] Unfortunately, the population in the United States (both children and adults) has become increasingly inactive. Numerous studies have demonstrated that an inactive lifestyle significantly increases the risk of CVD. In one study, fitness level was more strongly associated with heart disease than any other risk factor, including cigarette smoking and hypertension.[109] The Physical Activity Guidelines for Americans 2018 (PAGA 2018) lists multiple significant benefits for increased physical activity,[12] as demonstrated in Table 1.3.

There is strong evidence that regular physical activity lowers the risk of high blood pressure, adverse lipid profiles, type 2 diabetes, the metabolic syndrome, and weight gain. In addition, regular physical activity also lowers the overall risk for CVD, risk for stroke, and all-cause mortality.

The Healthy People 2010 Initiative recommended the goal that at least 30% of the population over the age of six should engage in light to moderate physical activity of at least 30 minutes per day. This goal has been repeated in the Healthy People 2020 guidelines[110] and the 2030 guidelines.[111] Clearly, we are falling far short of these goals. The Surgeon General's Report on Physical Activity documented that 24% of individuals report no recent physical activity, 54% are active but fall short of the recommendations from Healthy People 2020, while only 22% of adults achieve this level of activity.[110]

It should be emphasized that even very small amounts of physical activity substantially reduced the risk of both all-cause mortality and heart disease. As depicted in Figure 1.1, steep decreases in the risk of overall mortality in cardiovascular mortality occur for individuals who engage in physical activity at even the level of 30 minutes per week.

Further reductions occur up to the recommended 150 minutes of moderate physical activity per week, while even further reductions in risk occur beyond this recommended level in the PAGA 2018. However, the benefits of substantial increases beyond 150 minutes per week are much smaller than those of the first 150 minutes per week. (These benefits are depicted graphically in Figure 1.1.)

According to the PAGA 2018, over half of all adults do not obtain enough physical activity, and almost 32% of adults are classed as "inactive." The levels of physical activity for adults are found in Figure 1.2.

Numerous guidelines, including those from the AHA, the American College of Sports Medicine (ACSM),[109] the Centers for Disease Control (CDC), and the PAGA 2018,[12] all consistently recommend that adults accumulate at least 30 minutes of moderate intensity physical activity on most, if not all, days. The Physical Activity Guidelines for Americans 2018 provides an alternative of 75 minutes per week of vigorous intensity physical activity.[12] Definitions of low, medium and high physical activity are found in Table 1.4.

Recently, a corollary to the physical activity issue has been raised, with studies suggesting that excessive time spent sitting, particularly watching television or screen time, correlates with increased risk of CVD. A meta-analysis of prospective cohort studies estimated that if every adult in the United States decreased sitting time to less than three hours per day, the life expectancy of the population would increase by 2.0 years. In addition, if every adult reduced television viewing time to less than two hours a day, life expectancy would increase by 1.4 years.[112]

Numerous studies have shown that physician recommendation is a powerful motivator to change lifestyle habits, including level of physical activity. Moreover, several studies support the finding that if the physician him- or herself is physically active, they are more likely to recommended physical activity to their patients.[113,114] The most common form of physical activity recommended by physicians (first choice of over 90% of physicians) is walking.[114]

1.8.10 Poor Nutritional Habits

A large body of research supports a linkage between nutritional habits and risk of CVD. The AHA Guidelines for Pediatric and Adult Nutrition,[115] the Dietary Guidelines for Americans 2020–2025,[52] and the AHA's Strategic Impact Goal Plan through 2020 and Beyond all recommend nutrition intervention to lower the risk of CVD. These guidelines are consistent in recommending lower fat, higher fiber, increased consumption of fruits and vegetables, and control of calories to maintain a healthy body weight.[115]

TABLE 1.3

Physical Activity-Related Health Benefits for the General Population and Selected Populations Documented by the 2018 Physical Activity Guidelines Advisory Committee

Children	
3 to <6 years of age	**Improved bone health and weight status**
6 to 17 years of age	**Improved cognitive function (ages 6 to 13 years)**
	Improved cardiorespiratory and muscular fitness
	Improved bone health
	Improved cardiovascular risk factor status
	Improved weight status or adiposity
	Fewer symptoms of depression
Adults, all ages	
All-cause mortality	Lower risk
Cardiometabolic conditions	Lower cardiovascular incidence and mortality (including heart disease and stroke)
	Lower incidence of hypertension
	Lower incidence of type 2 diabetes
Cancer	Lower incidence of **bladder**, breast, colon, **endometrium, esophagus, kidney, stomach, and lung cancers**
Brain health	**Reduced risk of dementia**
	Improved cognitive function
	Improved cognitive function following bouts of aerobic activity
	Improved quality of life
	Improved sleep
	Reduced feelings of anxiety and depression in healthy people and in people with existing clinical syndromes
	Reduced incidence of depression
Weight status	**Reduced risk of excessive weight gain**
	Weight loss and the prevention of weight regain following initial weight loss when a sufficient dose of moderate-to-vigorous physical activity is attained
	An additive effect on weight loss when combined with moderate dietary restriction
Older adults	
Falls	Reduced incidence of falls
	Reduced incidence of fall-related injuries
Physical function	**Improved physical function in older adults with and without frailty**
Women who are pregnant or postpartum	
During pregnancy	**Reduced risk of excessive weight gain**
	Reduced risk of gestational diabetes
	No risk to fetus from moderate-intensity physical activity
During postpartum	**Reduced risk of postpartum depression**
Individuals with pre-existing medical conditions	
Breast cancer	**Reduced risk of all-cause and breast cancer mortality**
Colorectal cancer	**Reduced risk of all-cause and colorectal cancer mortality**
Prostate cancer	**Reduced risk of prostate cancer mortality**
Osteoarthritis	**Decreased pain**
	Improved function and quality of life
Hypertension	**Reduced risk of progression of cardiovascular disease**
	Reduced risk of increased blood pressure over time
Type 2 diabetes	**Reduced risk of cardiovascular mortality**
	Reduced progression of disease indicators: hemoglobin A1c, blood pressure, blood lipids, and body mass index
Multiple sclerosis	**Improved walking**
	Improved physical fitness
Dementia	**Improved cognition**
Some conditions with impaired executive function (attention deficit hyperactivity disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke)	**Improved cognition**

Benefits in **bold** font are those added in 2018; benefits in normal font are those noted in the 2008 Scientific Report. Only outcomes with strong or moderate evidence of effect are included in the table.

Source: 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC. Part D: Integrating the Evidence. D5-6.

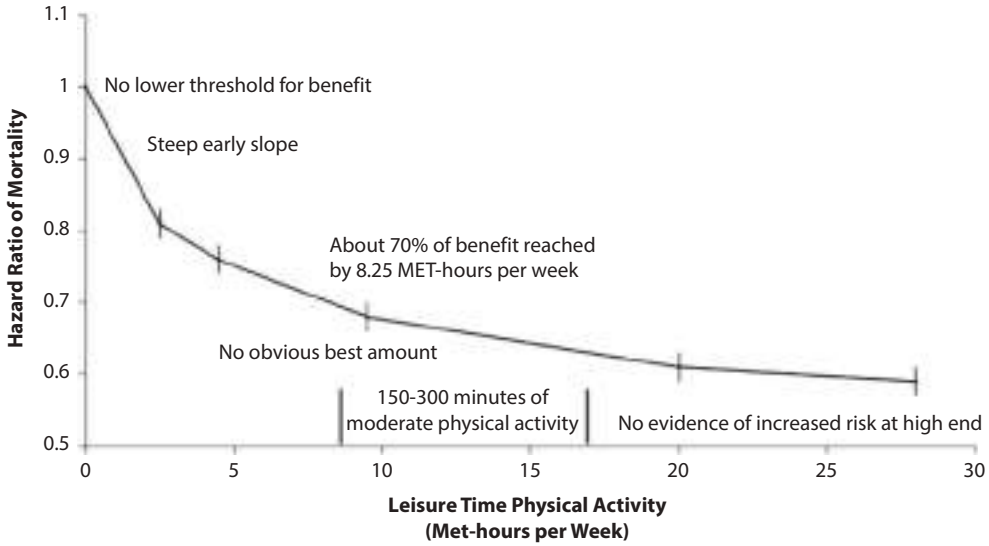


FIGURE 1.1 Relationship of moderate to vigorous physical activity to all-cause mortality with highlighted characteristics common to studies of this type. (From All-Cause Mortality. Cardiovascular Mortality and Incident Cardiovascular Disease. Part F. Chapter 6 in 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Committee Scientific Report. Washington, DC, U.S. Department of Health and Human Services, 2018.)

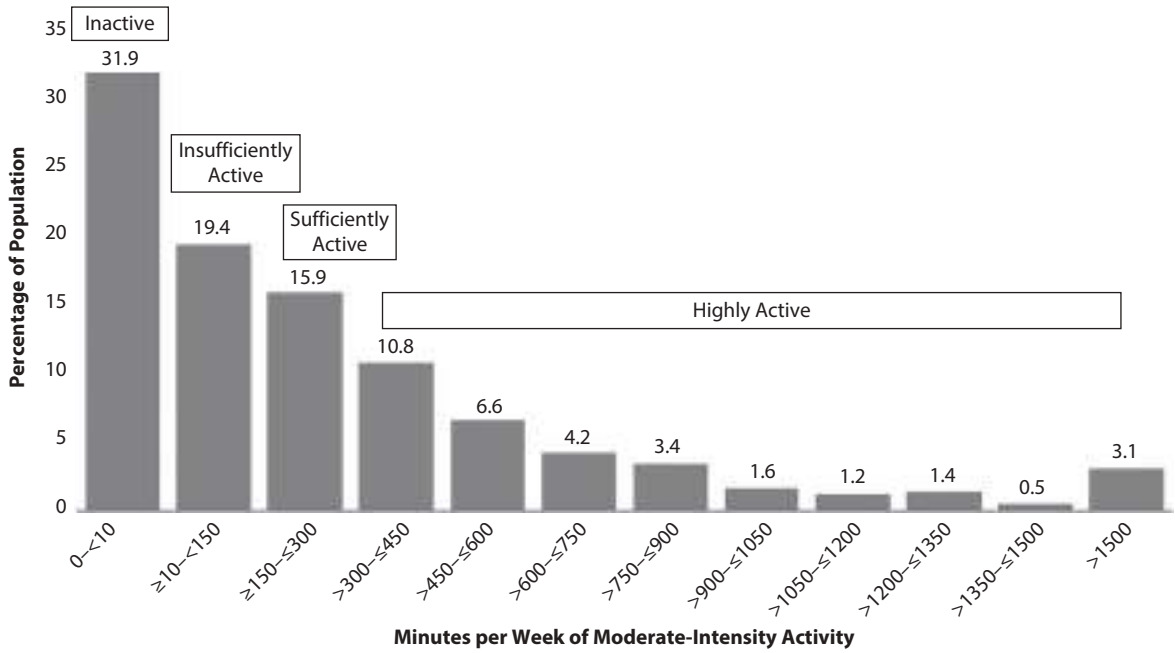


FIGURE 1.2 Distribution of self-reported volume of moderate-to-vigorous physical activity, 150 minutes per week increments, U.S. adults, 2015. (2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington DC: U.S. Department of Health and Human Services, 2018. Adapted from the data found in the National Health Interview Survey, 2015.)

The AHA Strategic Plan for 2020[51] establishes the following metric for nutrition goals to lower the risk of CVD and states:

> in the context of diet that is appropriate in energy balance pursing an overall dietary pattern that is consistent with a DASH (Dietary approaches to Systolic Hypertension) type eating plan including, but not limited to:
>
> - Fruits and vegetables: ≥ 5 cups per day
> - Fish: ≥ two 3.5 servings per week (preferably oily fish)

TABLE 1.4
Classification of Levels of Physical Activity

Classification of Total Weekly Amounts of Aerobic Physical Activity Into Four Categories (Levels of Physical Activity)	Range of Moderate-Intensity (Minutes a Week)	Summary of Overall Health Benefits	Comment
Inactive	No activity beyond baseline	None	Being inactive is unhealthy.
Low	Activity beyond baseline but fewer than 150 minutes a week	Some	Low levels of activity are clearly preferable to an inactive lifestyle.
Medium	150 minutes to 300 minutes a week	Substantial	Activity at the high end of this range has additional and more extensive health benefits than activity at the low end.
High	More than 300 minutes a week	Additional	Current science does not allow researchers to identify an upper limit of activity above which there are no additional health benefits.

- Fiber rich whole grains: ≥ 1.1 g of fiber per 10 g of carbohydrate (≥ three one oz equivalent servings per day)
- Sodium: < 1,500 mg per day
- Sugar sweetened beverages: ≤ 450 kcal (36 oz) per week

While these recommendations do not cover all aspects of a heart healthy diet, they represent a good starting point for physicians counseling patients about improved nutritional practices to lower the risk of CVD. These recommendations have been expanded upon in recent reviews.[116,117] Some recent evidence has suggested that diets adhering to the principles of a Mediterranean style diet supplemented with extra virgin olive oil or nuts reduced the incidence of major cardiovascular events in individuals with high cardiovascular risk.[118] Evidence based guidelines for overall dietary health are summarized in the Dietary Guidelines for 2020–2025 report.[52]

1.9 NONMODIFIABLE RISK FACTORS

The risk factors described in the previous section can all be reduced through appropriate lifestyle practices and habits in patients' daily lives. There are also a number of nonmodifiable risk factors for CVD, which will be discussed in this section.

Although this second group of risk factors cannot be altered through lifestyle habits, they play an important role as part of the overall patient risk factor profile. Specifically, individuals who have significant nonmodifiable risk factors should be even more strongly counseled to make appropriate lifestyle changes to alter those risk factors that are modifiable.

1.9.1 Age

Strong and consistent evidence associates increased age with increased risk of CVD. Approximately 80% of all fatal myocardial infarctions occur in individuals over the age of 65.[119] Thus, in the elderly population, control of modifiable risk factors assumes increasing importance. Regular physical activity, weight management, and control of lipids and blood pressure are all important areas for physicians to counsel patients over the age of 65.

1.9.2 Gender

More women than men die each year of heart disease, although CVD typically occurs at a younger age in men than in women.[120] Framingham study data demonstrate that men typically display the onset of symptoms of CVD ten years younger than women.[120] It is important to note that symptoms of CVD may present differently in women than in men. The AHA "Wear Red" program has provided an important emphasis on reducing risk factors for heart disease in women.[121]

1.9.3 Family History

A positive family history of CVD before the age of 65 in a first degree relative constitutes an independent risk factor for CVD.[119] Why CVD tends to aggregate in some families is not completely understood, although it may be mediated through genetics or through risk factors that relate to lifestyle components, such as levels of physical activity, nutritional habits, dyslipidemias, or weight.

1.10 THE METABOLIC SYNDROME AND THE CONCEPT OF MULTIPLE RISK FACTORS

Framingham data clearly support that clustering of risk factors is common.[40] One type of clustering of risk factors has been referred to as the "metabolic syndrome." While there is ongoing debate about the criteria for the metabolic syndrome,[122] and numerous different definitions exist, the

one most commonly employed (such as in the National Cholesterol Education Program ATP III Guidelines) includes the following criteria:

- Waist circumference >40 inches
- Blood pressure >135/85 mmHg
- Fasting blood glucose >110 mg/dL
- HDL cholesterol <40 mg/dL
- Fasting triglycerides >150 mg/dL

According to the ATP III Guidelines, if an individual has three or more of these five criteria, he or she is considered to have the metabolic syndrome.

Individuals with metabolic syndrome are at significantly higher risk for both CHD and diabetes than the general population. The ATP III Guidelines recommend that an individual with the metabolic syndrome should be treated as though they already have CVD. Data from the Framingham study demonstrate that 60% of CVD is found in individuals who possess two or more risk factors.

Debate is ongoing about the exact mechanism through which metabolic syndrome increases the risk of CVD. Some investigators maintain that the mechanism is through insulin resistance.[123] Others have emphasized underlying inflammatory processes as part of the metabolic syndrome that link to increased risk of CVD.[124] While the metabolic syndrome and obesity are not synonymous, they are strongly linked to each other. According to Framingham study data, obese individuals have approximately a 50% chance of having at least two other risk factors for CHD.[43]

The increased prevalence of obesity in children has drawn attention to its linkage to the increasing prevalence of both diabetes and the metabolic syndrome in children.[125] While considerable controversy exists about the criteria for the metabolic syndrome in children, the AHA has recommended careful exploration for other risk factors for CVD in children who are obese.

It should also be noted that recent data support that metabolic syndrome also results in a pro-inflammatory state. This is recognized by the most recent definition of the metabolic syndrome by the National Heart, Lung and Blood Institute.[125] This observation is important, since a pro-inflammatory state also occurs in diabetes, hypertension and obesity.

1.10.1 Low Dose Aspirin Therapy

Low dose aspirin therapy has been demonstrated to clearly and consistently provide substantial net benefits for persons at high risk for subsequent events secondary to existing CVD.[126] Thus, for secondary prevention, anti-platelet therapy with aspirin yields substantial net benefits, and the use of low dose aspirin is recommended, unless there are major contraindications. The use of other anti-platelet agents with demonstrated efficacies, such as clopidogrel, should be limited to patients who have aspirin allergy or intolerance.

For the primary prevention of CVD, however, the role of aspirin is not straightforward.[127] This is because individuals without established CVD have a lower absolute risk of cardiovascular events and thus, less absolute benefit, despite the fact that the risk of major adverse effects, such as bleeding, remains the same. In 2016, the United States Preventative Services Task Force (USPSTF) supported a statistically significant 22% reduction in non-fatal MI and a borderline significant 6% benefit in total mortality, a non-significant 5% benefit for non-fatal stroke, and a 6% benefit for cardiovascular mortality with low dose aspirin therapy.[128] Bleeding is the major known liability of aspirin use and an important consideration in assessing the likely risk to benefit ratio of aspirin in primary prevention. Thus, the benefit of low dose aspirin in secondary prevention in individuals for CVD is established, and use of low dose aspirin for primary prevention remains in debate. Several large studies are addressing this concern.

1.11 EMERGING RISK FACTORS

Recent research has identified a variety of other risk factors that are associated to a greater or lesser degree with CVD. These risk factors are discussed in this section.

1.11.1 High Sensitivity C-Reactive Protein (hs-CRP)

Inflammation has been identified as a key component of atherosclerothrombosis and provides an important link between plaque formation and acute rupture.[129] CRP, which is a marker of inflammation, has been identified as a significant cardiovascular CVD risk marker.[130] Numerous prospective studies have demonstrated that hs-CRP independently predicts the risk of CVD.[131–136] These data also apply not only to individuals with existing CVD but also to healthy individuals, including both men and women at all age levels. Elevated hs-CRP is not only associated with obesity and diabetes but also found in increased prevalence in individuals who lead sedentary lifestyles or are cigarette smokers.[130] These findings carry significant practical implications for counseling individuals concerning a variety of lifestyle measures. Comprehensive meta-analyses of the hazard associated with CVD associated with hs-CRP have demonstrated that it may exceed the risks associated with either elevated blood pressure or cholesterol.[137] The Emerging Risk Factor Collaboration study showed that hs-CRP is as accurate as total HDL cholesterol in predicting future CHD events.[138] Individuals with elevated hs-CRP and low levels of LDL cholesterol have higher absolute risk of vascular disease than those with low levels of hs-CRP and elevated levels of LDL. For all these reasons, it appears clinically wise to include hs-CRP measurement along with lipid evaluation as a strategy for lowering the risk of CVD.[139]

Several of the statin medications have been demonstrated to lower CRP in additional to lowering LDL cholesterol, which carries significant implications for combining pharmaceutical therapies along with lifestyle measures.[140,141]

1.11.2 Other Markers of Inflammation

The relationship between CVD and inflammation is an area of active research. A variety of other markers of inflammation in addition to CRP have emerged as potential risk factors for CVD. Most prominently TNF-α and Interleukin-6 (IL-6) have been associated with increased risk of CVD, but the data supporting these relationships are not as advanced as with CRP.[44]

1.11.3 Hemostatic Factors

Factors that may contribute to thrombogenesis have also been associated with increased risk of CVD. Factors currently under investigation that may contribute to thrombogenesis include Plasminogen Activator Inhibitor I (PAI-1), fibrinogen,[141–143] and coagulation Factor VII.

1.11.4 Homocysteine

Elevated levels of homocysteine, an amino acid derived from the degradation of methionine, have been associated with increased risk of CVD. Although the epidemiologic evidence is somewhat diverse, on average a 25% lower homocysteine level appears to be associated with approximately 11% lower risk of CHD in the general population. Homocysteine elevations are typically found in diets that are low in folate. In countries such as the United States where folate supplementation occurs, the prevalence of elevated homocysteine is significantly reduced. While laboratory tests are available to assess homocysteine, studies attempting to reduce the risk of CVD by reducing homocysteine levels have not yielded promising results.[144,145] Thus, homocysteine is not currently included as part of a risk factor profile.

1.11.5 LDL Subclasses and Particle Size

Laboratory tests are available to determine the amount of cholesterol carried by individual lipoprotein particles, which are characterized by their particle size. Some studies have suggested that small, dense LDL particles may be more atherogenic than larger LDL particles.[146,147] Of note, small, dense LDL particles have been associated more frequently with obese individuals and individuals with abdominal obesity than normal weight individuals. The data have not established the association between LDL particle size and CVD risk at a level that is useful for risk factor reduction strategies.

1.11.5.1 Lipoprotein (a)

Lipoprotein (a) is an LDL particle linked to a protein by a disulfide bridge. A number of studies have supported the role of LP(a) as a determinant of vascular risk.[148] However, it remains uncertain that LP(a) contributes further sensitivity or specificity to standard risk factor reduction strategies.[149]

1.12 OTHER RISK FACTORS

A variety of other risk factors for CVD have been either identified or postulated to potentially influence the likelihood of its development.

1.12.1 Levels of Antioxidants

Initial observational studies including the Health Professional Follow-up Study[150] and the Nurses' Health Trial[151] showed an association between high levels of vitamin E and other antioxidants and reduced risk of CVD. Subsequent interventional trials, however, have not corroborated these findings.[152] The AHA does not currently advocate antioxidant supplementation as a means of reducing CVD risk.

1.12.2 Alcohol

Alcohol consumption exerts a variety of effects on the overall cardiovascular system. A number of studies have demonstrated that moderate alcohol consumption reduces the overall risk of CVD.[153] "Moderate" alcohol consumption is typically defined as no more than one to two beers, one to two glasses of wine, or one to two "shots" of distilled spirits daily. Men are typically able to drink higher amounts of alcohol within the moderate range than women because of higher levels of alcohol dehydrogenase—the enzyme in the liver that breaks down alcohol. The mechanism by which moderate alcohol consumption may reduce the risk of CHD is attributed to either increasing HDL or decreasing platelet aggregation.[154] In contrast, alcohol consumption of three alcoholic drinks per day or more has been associated with increased risk of hypertension, overall risk of heart disease, congestive heart failure, a variety of gastrointestinal cancers, and motor vehicle accidents. Thus, a U-Shaped Curve[155] relationship exists relating the risk of CVD and alcohol consumption. Any individual or population wide recommendation for levels of alcohol consumption must consider the complexity of this relationship.[156]

1.12.3 Stress and Type A Personality

Some studies have supported the concept that personality type may contribute to the risk of CVD; however, these data remain controversial and inconclusive.[157,158] In particular, the anger element of Type A personality (a Type A personality is often found in individuals who are highly competitive and ambitious and perceive a constant struggle with their environment) may increase the risk of CVD. The mechanism by which stress may lead to increased risk of vascular disease is not completely understood but is possibly related to platelet and endothelial dysfunction as well as the induction of ventricular arrhythmias.

1.12.4 Depression

Depression has been demonstrated in a number of studies to predict CVD.[159,160] This association appears to be an independent one, although depression is also associated with lack of physical activity, hypertension, and smoking.[159,160] The mechanism through which depression may increase the risk of CVD includes elevated levels of hs-CRP, increased platelet activation, and decreased heart rate variability. Depression occurs in one out of three patients with heart failure and one out of five patients with CHD. Whether therapy for depression lowers the risk for CVD is uncertain.

1.13 FUTURE TRENDS IN RISK FACTOR ASSESSMENT

Some technologic enhancements, in both imaging techniques and genomics, have provided opportunities that may yield more precise and individualized characterizations of atherosclerotic plaque and risk of CVD.

1.13.1 Direct Plaque Imaging

High speed computed tomography (CT scanning) of the coronary arteries has been demonstrated in several studies to detect pre-clinical atherosclerosis.[161] Advances such as volume CT scanning (VCT) may further enhance the precision and predictive value of these technologies. At the current time, these technologies remain investigational. Concern has also been raised about the potential to overinterpret predictive values from imaging techniques such as coronary calcium scoring. In one study, 41% of all future vascular events occurred in individuals with a coronary calcium score lower than 100, and 17% occurred with a coronary calcium score of zero.[162] In this study, individuals with high risk scores by Framingham criteria, but low coronary calcium scores, still remained at high risk of CVD. Another imaging test that has been employed to attempt to assess the risk of CVD is ultrasound measurement of the common carotid intima-media thickness (CIMT). With regard to CIMT, a meta-analysis of 14 population based cohorts reported a consistent and strategically significant 9% increase of future vascular risk for each 0.1 mm increase in CIMT thickness.[163] This same analysis, however, found that CIMT measurement did not improve clinical accuracy once risk estimates and re-classification were utilized to adjust for usual risk factors.[164] In addition, Framingham investigators have reported limited usefulness for CIMT in this prediction.[165]

1.13.2 Genomic Approaches

Heritability accounts for up to one half of susceptibility to CHD. However, genetic risk factors have proven difficult to quantify. Advances continue to be made in genetic determinants of atherothrombosis. Although this field remains in its early stages of development, progress continues to be made.[166–168] Challenges exist because of multiple gene–environment interactions. Although this remains an area of active research, no genetic markers for atherothrombosis have yet achieved clinical utility. A recent study involving over 55,000 individuals, including 7,814 participants in the Atherosclerosis Risk in Community (ARIC) study, 21,222 in the Women's Genome Health Study (WGHS), 22,389 in the Malmö Diet and Cancer Study (MDCS), and 4,260 participants in the cross-sectional BioImage, assessed the risk of pulmonary events in individuals who had high genetic risk (top quintile of polygenic scores) compared with low risk (bottom quintile of polygenic scores). Coronary events were 91% higher in the high genetic risk group. Importantly, among participants in the high genetic risk profile, a favorable lifestyle (defined by no current smoking, no obesity, regular physical activity, and a healthy diet) resulted in a 46% lower relative risk of coronary events than those who had an unfavorable lifestyle. While this type of research[169] is in its infancy, it suggests that healthy lifestyle practices play an important role in individuals who are at high genetic risk of CVD.

1.13.3 New Risk Factor Scoring Systems

The Framingham Risk Scoring System has contributed in substantial ways to the ability to predict the risk of CVD; however, it is limited by not incorporating such risk factors as level of physical activity and obesity. One particularly attractive system has emerged from the New Zealand Guidelines Group, which provides useful information on the five- and ten-year risk of atherosclerosis. This area remains one of active research. Another attractive scoring system is the Reynolds Risk Score (www.reynoldsriskscore.com), which has the advantage of including both hs-CRP and family history as part of global risk assessment.[170]

1.13.4 Implementation of Risk Factor Reduction Strategies

One encouraging trend in risk factor reduction is an increased emphasis on more sophisticated and comprehensive approaches to the implementation of currently existing risk factor reduction guidelines.[52,54,114] Both the Dietary Guidelines for Americans 2020–2025[52] and the Nutrition Guidelines from the American Heart Association[54] make a substantial effort to focus on strategies for implementing existing guidelines.

1.14 CONCLUSIONS

The identification of risk factors for CHD continues to evolve and is an area of great practical relevance to clinicians. Particularly given the high level of modifiable risk factors for CVD, an enormous opportunity exists for physicians and other healthcare workers to counsel patients on lifestyle medicine concepts to lower their risk of CVD. Specific concepts for how to integrate lifestyle measures into clinical practice will be the topic of the next chapter.

CLINICAL APPLICATIONS

Action	Available Tools	Comment
Determine risk of CVD in all patients	Multiple risk factor scoring systems are available	See Chapter 2 for more details
Determine "vital signs" of positive lifestyle	Include body mass index (BMI), level of physical activity, nutritional practices, and smoking status in all initial assessments	These are key determinants of lifestyle CVD risk
Discuss smoking cessation with all smokers	Multiple tools available from many sources	Over one third of smokers are never counseled about cigarette smoking
Counsel all patients on weight management	Obtain weight and BMI on all patients	Forty percent of overweight and obese patients are never counseled on weight management
Counsel all patients on physical activity	U.S. Physical Activity for Americans Guidelines, 2018	Become familiar with these guidelines, utilize them, and counsel
Counsel all patients on nutrition	Dietary Guidelines for Americans 2020–2025, also multiple materials from the American Heart Association	Improved nutrition is a key in reducing the CVD risk

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2 Lifestyle Strategies for Risk Factor Reduction and Treatment of Cardiovascular Disease

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KEY POINTS

- Lifestyle strategies play a significant role in reducing risk factors for cardiovascular disease (CVD).
- Lifestyle interventions are key components of the American Heart Association (AHA)'s strategic plan for 2020 to lower the burden of cardiovascular disease in the United States and the 2030 AHA impact goals.
- Lifestyle strategies are a key component for both the prevention and treatment of metabolic diseases and are recognized as such by virtually every major national, evidence based guideline in metabolic diseases.
- In addition to annual fasting lipid profile, high sensitive C-reactive protein (hs-CRP) should be obtained, since levels of hs-CRP are the equivalent risk of lower density lipoprotein (LDL) cholesterol.
- Assessment and counseling for factors for CVD should be a part of every healthcare visit.

2.1 INTRODUCTION

Cardiovascular disease (CVD) remains the leading killer of men and women in the United States.[1] CVD also represents one of the quintessential lifestyle related diseases, since many of the risk factors for it, including cigarette smoking,[2] elevated cholesterol,[3] high blood pressure,[4] obesity,[5] and an inactive lifestyle[6] have significant lifestyle related components.

Lifestyle strategies can play a significant role in the reduction of risk factors for CVD as well as its prevention and effective treatment. In Chapter 1, we focused on the rationale for employing lifestyle strategies for risk factor reduction. The current chapter provides practical strategies for employing these modalities in clinical practice for the prevention and treatment of CVD.

Lifestyle interventions also represent an important strategy for physicians and other healthcare workers to assist patients in lowering their risk factors as well as preventing CVD and treating individuals with established CVD. These lifestyle related strategies are particularly valuable since they carry very little risk and may simultaneously reduce multiple risk factors for CVD. Furthermore, the AHA has articulated a vision to pursue "primordial" risk factors, meaning the prevention of risk factors in the first place. Lifestyle measures will be key components of this strategy.[7]

The AHA Impact Goal for 2030 articulates the goal of expanding health associated life expectancy while increasing lifespan, wellbeing, and health equity by Year 2030. The concept of Health Adjusted Life Expectancy (HALE) is defined as the number of years in good health, for years lived with disease or disability, for years lost to premature death. As articulated by the AHA, HALE can be increased by improving health and wellbeing, preventing or delaying the onset and manifestations of disease, and increasing life expectancy. All of these represent concepts that are very familiar to practitioners of lifestyle medicine.

The concept of wellbeing broadens the AHA vision from simply health to additionally encompassing mental status and aspects of life such as "security, prosperity, sense of connection and purpose." This broadens the mission of both CVD specialists and lifestyle specialists into the areas of neurobiological, behavioral, emotional, socioeconomic, and cultural wellbeing. Good data are available showing that how people feel about their overall life satisfaction strongly predicts how healthy they are, how long they will live, and their future healthcare needs *per se*.

The AHA 2030 Impact Goal continues the evolution from the AHA to incorporate lifestyle into the practice of cardiovascular medicine.[8] The AHA further articulated the importance of lifestyle in cardiovascular disease with the AHA/Adult Treatment Panel (ATP) Guidelines for Lifestyle Management to Reduce Cardiovascular Risk, published in 2014.[9]

Lifestyle measures are already incorporated as key recommended early intervention steps in most of the major, evidence based guidelines either prior to or in conjunction with pharmaceutical therapy to help patients lower the risk of CVD.[3,4,8–17] Unfortunately, many healthcare workers still do not properly emphasize these measures in their daily clinical practices. In addition, reimbursement models currently provide disincentives for using these strategies, since lifestyle interventions are typically not covered by health insurance plans. Aspects of the Health Care Reform Act,[18]

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particularly the Accountable Care Organizations provision, provide financial models to encourage these low cost, potentially high yield lifestyle measures. The challenge for healthcare professionals will be to understand and utilize these models to aggressively incorporate lifestyle measures into the prevention and treatment of CVD and other lifestyle related disease.

In addition to the financial disincentives, lack of time may represent another hurdle. Delivery of those measures related to prevention of CVD recommended by the U.S. Preventive Health Services Task Force has been estimated to take the typical clinician a minimum of 1.5 hours per day in non-reimbursable time.[19] Thus, it will be important in clinical practice to find ways to deliver proven lifestyle interventions with efficient strategies that are time sensitive.

A representative listing of national guidelines that incorporate lifestyle medicine emphasis in the treatment of CVD or as a strategy for lowering risk factors for related metabolic conditions is found in Table 2.1.

Healthcare professionals can be enormously influential in helping patients take positive lifestyle actions to lower their risk of CVD. Healthcare providers' recommendations to make changes in behaviors, such as cigarette smoking cessation, weight loss, or improved nutrition, have all been demonstrated to play important roles in lowering risk factors for CVD. Numerous studies have shown that the public perceives medical professionals as a reliable and credible source of information concerning health related behaviors.[20–27] Often, however, healthcare workers underestimate how powerful their role as health counselors can be. For example, fewer than 50% of smokers report receiving advice to quit from their physician,[22] and fewer than 40% of obese individuals report receiving advice about weight loss.[28] This is unfortunate, since the average adult in the United States visits a physician's office more than five times per year, and it has been estimated that physicians come in contact with over 75% of adults in the United States in any given year.[29] In addition to physicians, nutritionists, nurses with an interest and background in preventive cardiology or diabetes education, and other healthcare professionals can play critically important roles in counseling patients on positive lifestyle behaviors to lower their risk of coronary heart disease (CHD).

It should also be noted that the majority of patients who make lifestyle behavior changes do this without formal participation in an organized program. For example, over 90% of individuals who have stopped smoking have done this without formal smoking cessation programs.[30] Furthermore, the majority of patients who lose weight also do this on their own. Nonetheless, healthcare professional recommendations and support can be very valuable to motivate patients to start and maintain the process of behavioral change.

It is particularly important that physicians play a proactive role in this area. At the current time, physician office visits represent a missed opportunity to promote behavioral changes. It is hoped that the advent of such organizations as the American College of Lifestyle Medicine[31] and the lifestyle medicine track of the American College of Preventive Medicine[32] will help physicians build the knowledge, basic skills, and confidence needed to make these recommendations. A "blue ribbon" panel of physicians representing most major medical organizations has urged physicians to become involved in lifestyle medicine and outlined a series of competencies in this area.[33] The American College of Lifestyle Medicine, a professional organization dedicated to advancing the field of lifestyle medicine, has doubled its membership each year for the past five years. Since 2003, membership in this organization has increased over 1,200%, making it the fastest growing medical specialty in the United States.[34] In 2016, this organization outlined a series of topics and offered certification for those interested in deepening their knowledge of lifestyle medicine and incorporating it into their clinical practices.[35]

Increasingly, medical organizations in various subspecialties are understanding the power of daily lifestyle habits and practices in both the prevention and treatment of various disease, including CVD. For example, in 2013, the AHA and the American College of Cardiology (ACC)[36] jointly issued guidelines for lifestyle management to reduce

TABLE 2.1

Evidence-Based Guidelines that Employ Lifestyle Measures to Reduce the Risk of CHD and Other Metabolic Conditions

- NCEP
- JNC VII Guidelines for Prevention and Management of Hypertension
- IOM Guidelines for Management of Obesity
- Guidelines for the American Heart Association for the Prevention and Management of Coronary Artery Disease
- Guidelines from the American Diabetes Association for the Management of Diabetes
- Dietary Guidelines for Americans 2020–2025
- American Heart Association Nutrition Implementation Guidelines
- Guidelines from the American Academy of Pediatrics for the Prevention and Treatment of Childhood Obesity
- Guidelines from the American Academy of Pediatrics for Heart Disease Risk Factor Reduction in Children
- Guidelines from the American Heart Association and American Academy of Pediatrics for the Prevention and Treatment of Metabolic Syndrome
- Joint statement from the American Heart Association and American Cancer Society on the prevention of heart disease and cancer

cardiovascular risk. In conjunction with this initiative, the study group within the AHA, which had previously been called "The Council on Nutrition, Physical Activity and Metabolism," changed its name to "The Council on Lifestyle and Cardiometabolic Health."[37] Along with these changes, a series of articles was published by the AHA in the journal *Circulation* entitled "Recent Advances in Preventive Cardiology and Lifestyle Medicine."[38] Furthermore, the Health Care Reform Act[16] including the Accountable Care Provision mandated that physicians become more active in this area.

The case for aggressive employment of lifestyle measures in clinical medicine has continued to grow. Multifactorial risk factor reduction programs have been clearly demonstrated to reduce each of these risk factors individually and in groups of risk factors treated together. Epidemiologic studies have shown that positive lifestyle measures, such as not smoking; engaging in at least 30 minutes of physical activity per day; consuming a diet of more fruits, whole grains, fish, and vegetables; and maintaining a healthy weight, can reduce the incidence of CVD by over 80% and diabetes by over 90%.[39,40] Of note, incorporating just one of these health promoting practices reduces the risk of developing CVD and diabetes by over 50%.[39,40]

2.2 PREDICTING RISK

A key first step prior to using lifestyle measures to lower risk factors for CVD involves predicting risk. Risk prediction involves understanding the type and strength of evidence underlying risk factor assessment strategies as well as clearly understanding the difference between relative risk and absolute risk (see Chapter 1).

Most currently employed, evidence based frameworks for lowering risk factors for CHD involve assessing absolute risk. For example, lowering absolute risk underlies the strategies for the National Cholesterol Education Program ATP III Guidelines[41] and ATP IV Guidelines,[3] the American Diabetes Association Guide of Managing Diabetes,[11] and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[42] as well as the 2018 AHA/ACC 2018 Practice Guidelines.[3]

2.3 ASSESSING RISK

Multiple frameworks are available for assessing the risk of CVD. The most widely used one is the framework developed by the Framingham Heart Study investigators. This framework is found in Figure 2.1 and Figure 2.2. Figure 2.1 is used to assess risk for men, and Figure 2.2 is used to assess risk for women. The Framingham framework is based on estimating an individual's ten-year risk of developing CVD.[43] The higher the ten-year risk, the more intensity of intervention is warranted.

It should be noted that there are alternatives to the Framingham score. For example, the Reynolds Risk Score provides a variation to the Framingham score by incorporating whether a parent suffered a myocardial infarction (MI) before the age of 60 years as well as high sensitivity CRP (hs-CRP) level.[44,45] The Reynolds Score appears to be a better predictor of individuals in the middle risk category and is comparable to the Framingham Risk Score for individuals with low or high risk.

Other available risk scores include Systematic Coronary Risk Evaluation Project (SCORE), developed by the European Joint Task Force utilizing studies in 12 European countries involving 250,000 individuals.[46] A more recent set of guidelines was developed by the New Zealand Guidelines Committee, which assesses absolute cardiovascular risk during five years instead of ten.[47]

In 2013, the American College of Cardiology (ACC) and the AHA released new Guidelines for the Treatment of High Blood Cholesterol.[48] These guidelines were designed to update the previous Adult Treatment Panel III (ATP III) Report of the National Cholesterol Education Program.[41] These guidelines also followed a new paradigm for cholesterol management. The guideline process for this panel followed the "Rules" for Guideline Development published by the Committee for the Institute of Medicine (IOM).[49] The IOM report emphasized the necessity for "evidence based medicine" in guideline development, which basically outlines that recommendation should be made mainly on evidence obtained from randomized clinical trials (RCTs). Since other types of evidence, such as epidemiologic evidence, were no longer utilized, guidelines left many clinicians in the position of having to use their own clinical judgement to arrive at many clinical decisions, instead of having science based guidance to inform these clinical choices. It should be emphasized that both ATP III and the ACC/AHA Guidelines emphasize the value of lifestyle medicine. This emphasis, despite the fact that the ACC/AHA Guidelines, did not provide RCT evidence.

While ATP III identified LDL as a major cause for atherosclerotic coronary vascular disease (CVD), the ACC/AHA Guidelines *do not* make LDL the centerpiece of the guidelines. While they note that lowering LDL would be beneficial, by adhering to the ACC/AHA paradigm, LDL is basically irrelevant to guideline development. Instead, statin therapy became the lynchpin for recommendations. Thus, the ACC/AHA Guidelines (also called ATP IV) make cholesterol management different from the ATP III.

The ATP III Guidelines set a goal for LDL-C as less than 100 mg/dL for high risk patients, especially those with established atherosclerotic cardiovascular disease (ASCVD), and patients with a diabetes risk of >20% were further counted as high risk patients. Those considered at very high risk (i.e. established ASCVD), plus multiple risk factors, resulted in ATP III guidance of lowering cholesterol to <70 mg/dL. This LDL-C goal of <70 mg/dL is also based on RCTs outlined in ATP IV. In ATP III, if a patient at very high risk did not achieve an LDL-C of <70 mg/dL, the addition of a second LDL lowering drug was allowed to attain greater reduction of LDL-C. The ATP IV

Step 1

Age		
Years	LDL Pts	Chol Pts
30–34	–1	[–1]
35–39	0	[0]
40–44	1	[1]
45–49	2	[2]
50–54	3	[3]
55–59	4	[4]
60–64	5	[5]
65–69	6	[6]
70–74	7	[7]

Step 2

LDL-C		
(mg/dl)	(mmol/L)	LDL Pts
< 100	< 2.59	–3
100–129	2.60–3.36	0
130–159	3.37–4.14	0
160–190	4.15–4.92	1
≥ 190	≥ 4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
< 160	< 4.14	[–3]
160–199	4.15–5.17	[0]
200–239	5.18–6.21	[1]
240–279	6.22–7.24	[2]
≥ 280	≥ 7.25	[3]

Step 3

HDL-C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
< 35	< 0.90	2	[2]
35–44	0.91–1.16	1	[1]
45–49	1.17–1.29	0	[0]
50–59	1.30–1.55	0	[0]
≥ 60	≥ 1.56	–1	[–2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) < 80	80–84	85–89	90–99	≥ 100
< 120	0 [0] pts	0 [0] pts	1 [1] pts	2 [2] pts	3 [3] pts
120–129					
130–139					
140–159					
≥ 160					

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1–6)

Adding up the point	
Age	_____
LDL-C or Chol	_____
HDL-C	_____
Blood Pressure	_____
Diabeles	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10-Yr CHD Risk	Chol Pts Total	10-Yr CHD Risk
< –3	1%		
–2	2%		
–1	2%	[< –1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥ 14	≥ 56%	[≥ 14]	[≥ 53%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10-Yr CHD Risk	Average 10-Yr Hard* CHD Risk	Low† 10-Yr CHD Risk
30–34	3%	1%	2%
35–39	5%	4%	3%
40–44	7%	4%	4%
45–49	11%	8%	4%
50–54	14%	10%	6%
55–59	16%	13%	7%
60–64	21%	20%	9%
65–69	25%	22%	11%
70–74	30%	25%	14%

Relative Risk
- Very low
- Low
- Moderate
- High
- Very High

* Hard CHD events exclude angina pectoris

† Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100–129 mg/dl or cholesterol 160-199 mg/dl, HDL-C 45 mg/dl for men or 55 mg/dl for women, nonsmoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

FIGURE 2.1 Coronary heart disease (CHD) score sheet for calculating 10-year CHD risk according to age, total cholesterol (TC) (or low- density lipoprotein cholesterol [LDL-C]), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking. Score sheet for men based on the Framingham experience in men 30 to 74 years at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 (or LDL-C of 100 to 129 mg/dL), no diabetes, and no smoking.

Step 1

Age		
Years	LDL Pts	Chol Pts
30–34	–9	[–9]
35–39	–4	[–4]
40–44	0	[0]
45–49	3	[3]
50–54	6	[6]
55–59	7	[7]
60–64	8	[8]
65–69	8	[8]
70–74	8	[8]

Step 2

LDL-C		
(mg/dl)	(mmol/L)	LDL Pts
< 100	< 2.59	–2
100–129	2.60–3.36	0
130–159	3.37–4.14	0
160–190	4.15–4.92	2
≥ 190	≥ 4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
< 160	< 4.14	[–2]
160–199	4.15–5.17	[0]
200–239	5.18–6.21	[1]
240–279	6.22–7.24	[1]
≥ 280	≥ 7.25	[3]

Step 3

HDL-C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
< 35	< 0.90	5	[5]
35–44	0.91–1.16	2	[2]
45–49	1.17–1.29	1	[1]
50–59	1.30–1.55	0	[0]
≥ 60	≥ 1.56	–2	[–3]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) < 80	80–84	85–89	90–99	≥ 100
< 120	–3 [–3] pts	0 [0] pts			
120–129			0 [0] pts		
130–139				2 [2] pts	
140–159					3 [3] pts
≥ 160					

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	4	[4]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1–6)

Adding up the point	
Age	_____
LDL-C or Chol	_____
HDL-C	_____
Blood Pressure	_____
Diabeles	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10-Yr CHD Risk	Chol Pts Total	10-Yr CHD Risk
< –2	1%	[≤ –2]	[1%]
–1	2%	[–1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥ 17	≥ 32%	[≥ 17]	[≥ 27%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10-Yr CHD Risk	Average 10-Yr Hard* CHD Risk	Low† 10-Yr CHD Risk
30–34	< 1%	< 1%	< 1%
35–39	< 1%	< 1%	< 1%
40–44	2%	1%	2%
45–49	5%	2%	3%
50–54	8%	3%	5%
55–59	12%	7%	7%
60–64	12%	8%	8%
65–69	13%	8%	8%
70–74	14%	11%	8%

Relative Risk
- Very low
- Low
- Moderate
- High
- Very High

* Hard CHD events exclude angina pectoris

† Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100–129 mg/dl or cholesterol 160-199 mg/dl, HDL-C 45 mg/dl for men or 55 mg/dl for women, nonsmoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

FIGURE 2.2 Score sheet for women based on Framingham experience in women 20 to 74 years of age at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of Idealized risk are based on optimal blood pressure, total cholesterol (TC) of 160 to 199 mg/dL (or low-density lipoprotein cholesterol [LDL-C of 100 to 129 mg/dL), high-density lipoprotein cholesterol (HDL-C) of 55 mg.' dL. no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fast ng LDL-C measurements are available. Pts. points. (From Wilson PW: D' Agostino RD, Levy D, et al. Predication of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847.)

Guidelines also recommended that individuals with ≥5% risk could also receive statin therapy. ATP III allowed statin therapy for patients with 10% risk and an LDL >100 mg/dL, whereas ACC/AHA allowed statin at an LDL-C >70 mg/dL. This value is justified by the recent results from the JUPITER Trial,[50] which showed efficacy in patients with LDL-C <100 mg/dL. Controversy has arisen about whether or not to use the ATP III criteria or the ATP IV criteria. At the time of this writing, this controversy remains unresolved.

Since the risk of ASCVD increases with age, in the ATP IV Guidelines, there will be an increased number of people over the age of 65 who are eligible for statin therapy. This would include most men in their 60s and more women in their 70s. This increased use of statin medicine is also controversial, and the debate concerning this has not been resolved as of this writing.

For middle aged persons, the ACC/AHA Guidelines are similar to each other, although lower risk and lower LDL-C qualify for statin therapy in the ATP IV (ACC/AHA guidelines). With regard to young adults, the ACC/AHA Guidelines make no recommendations in this area, whereas the ATP III Guidelines recommended testing for lipoproteins every five years, starting at age 20. Other risk factors, likewise, should be measured in young adults. Risk factors clearly associate with the development of atherosclerosis in the age range of 20–39 years.[51] The ATP III Guidelines stress the importance of early intervention and risk factors, while the ACC/AHA Guidelines do not. It is important to emphasize that in both the ATP III and the ATP IV Guidelines, lifestyle modalities play essential roles.

2.4 CLASSIFYING INTERVENTIONS FOR MODIFIABLE RISK FACTORS

As outlined in Chapter 1, risk factors for CHD can be conveniently divided into "modifiable" and "non-modifiable." This framework also carries practical implications and is a commonly employed classification strategy.[52] In addition, classifications employed by the ACC and the AHA divide intervention to reduce risk factors into four categories based on the level of evidence that modifying a particular risk factor will result in lower risk of CHD. The following four classifications are typically employed:

- Class 1 Interventions: These interventions involve risk factor reduction strategies that have been proven to reduce risk when used.
- Class 2 Interventions: This classification includes risk factors where interventions are likely to lower the incidence of events but proof is less strong than Class 1 interventions.
- Class 3 Interventions: This classification includes risk factors that have been clearly associated with increased risk of CHD and which, if modified, might lower the likelihood of a coronary event.
- Class 4 Interventions: This classification includes risk factors that have been associated with increased risk of CHD and which, if modified, are not likely to decrease the risk of CHD or cannot be modified.

This framework for classifications is summarized in Table 2.2.

TABLE 2.2
Framework for Risk Factor Reduction Interventions

Class 1 Interventions
- Cigarette smoking cessation
- Management of dyslipidemias
- Management of hypertension
- Pharmaceutical measures for cardiac protection

Class 2 Interventions
- Obesity prevention and management
- Diabetes/glucose intolerance management
- Physical inactivity

Class 3 Interventions
- Nutritional counseling
- Psychological risk factors/counseling
- No alcohol consumption

Class 4
- Age
- Male gender
- Low socioeconomic status
- Family history of early onset CVD

See text for details.

2.5 CLASS 1 INTERVENTIONS

2.5.1 Lifestyle Approach to Cigarette Smoking Cessation

Cigarette smoking is the leading cause of preventable death in the United States each year, resulting in an estimated 480,000 deaths.[53] More than 32% of deaths from cigarette smoking result from CVD.[53] It has been estimated that over 49,000 of the smoking related deaths are the result of secondhand smoke exposure. Smoking also has an enormous economic impact on the United States economy.[54] It has been estimated that the United States incurs $96 billion in direct medical expenses and $97 billion in lost productivity annually as a result of cigarette smoking. Smokers lose at least one decade of life expectancy compared with never-smokers. The risk of death from cigarette smoking has continued to increase among women,[55] and the increased risks are now identical between men and women.[56] The 2004 Surgeon General's Report showed that smoking doubles the risk of CVD and increases CVD mortality by 50%.[54] Both of these risks increase with age and the number of cigarettes smoked. Worldwide, more than one million more deaths were attributable to tobacco in the year 2000 than in 1990.[56] Tobacco use is estimated to be responsible for five

million deaths worldwide per year.[57] In the United States, cigarette smoking peaked in 1955, when 55% of men were smokers. The peak for women came ten years later, with more than 33% smoking. Since that time, cigarette smoking has substantially declined; however, the rate of decline has slowed substantially in the past decade.

Currently, in the United States, 15.5% of adults smoke.[53] Slightly more of these individuals are men than women. Approximately 13.5% of women over the age of 18, and approximately 17.5% of men over the age of 18, smoke.[53] If individuals do not smoke cigarettes by the time they graduate from high school, it is highly unlikely that they will adopt this habit as adults. Smoking rates among high school seniors are slightly above 30%, with a slightly higher number of female smokers than males.[57] Smoking also tracks with socioeconomic status. Thirty-two percent of individuals living below the federal poverty line are smokers.[58]

The U.S. Public Health Service has published clinical practice guidelines classifying tobacco dependency as a chronic condition requiring repeated intervention.[56] These guidelines recommend that healthcare professionals ask every patient about tobacco use at every clinic visit.[59] Counseling and behavior therapies are based on the following:

1. securing social support
2. providing problem solving skills
3. social support outside treatment

According to the U.S. Public Health Service guidelines, which support a combination of counseling and pharmaceutical therapy, seven pharmacotherapies reliably increase long-term smoking abstinence, including bupropion hydrochloride,[60] Varenicline, and five nicotine replacement therapies (nasal spray, gum, patch, inhaler, and lozenges).[61] The efficacy of smoking cessation programs, in terms of success for one year, ranges from 6% with physician counseling alone to 18% with self-help programs and 20–40% with counseling plus pharmacologic intervention.[62] All individuals who smoke should, of course, be counseled to cease this potentially deadly habit. A particularly appropriate time to encourage patients to make this effort is after a cardiac event or discovery of existing CVD.

The Healthy People 2020 Initiative has established a goal of the United States reducing the national prevalence of cigarette smoking among adults to under 12%. Achieving this ambitious goal will require extensive implementation of evidence based tobacco control interventions. Some advances in tobacco control have occurred recently in the United States, including implementation of the 2009 Family Smoking Prevention and Tobacco Control Act, which granted the U.S. Food & Drug Administration (FDA) authority to regulate the manufacture, distribution, and marketing of tobacco products.[63] Other laws include the Children's Health Insurance Reauthorization Act, the Prevent All Cigarette Trafficking Act, and the Patient Protection and Affordable Care Act. These laws grant various federal agencies both authority and funding to regulate tobacco products and decrease access to tobacco among youth. In 2010, the U.S. Department of Health & Human Services entered a National Strategic Plan for Tobacco Control, including 21 Action Steps to accomplish this goal.

2.5.2 Lifestyle Approach to Management of Dyslipidemias

Average cholesterol levels among adult men and women in the United States have decreased to some degree since the 1960s but are still considered higher than good health requires. Agrarian societies have very low rates of CVD and exhibit total and LDL cholesterol levels well below those accepted as normal in Western societies.

Currently, approximately 45% of all American adults still have cholesterol levels greater than 200 mg/dL, and 16% have levels higher than 240 mg/dL.[64] In addition, both depressed high density lipoprotein (HDL) cholesterol levels and elevated triglyceride levels often occur together and result from different metabolic pathways than are typically involved in elevated LDL. These latter two lipid abnormalities are particularly associated with the metabolic syndrome.

Various organizations have listed somewhat different recommendations for cholesterol screenings. There is wide agreement that all patients with currently existing CVD should be periodically screened for serum cholesterol levels. The National Cholesterol Education Program (NCEP) ATP III Guidelines recommend that all adults older than 20 years should be routinely screened for serum cholesterol,[41] while the ATP IV Guidelines are silent on this issue. The American College of Physicians (ACP) provides less aggressive screening recommendations with advice that men between the ages of 35 and 65 and women between the ages of 45 and 65 be screened.[64] The U.S. Preventive Services Task Force advocates screening women over the age of 45 and men over the age of 35.[59]

It is important to understand that all of the above referenced guidelines advocate treatment based on assessment of the patient's overall risk. The ATP III Guidelines not only utilize LDL level but also recommend calculations based on the Framingham Risk Score (see Figure 2.1 and Figure 2.2). A guideline algorithm presented by the ATP III Guidelines is shown in Figure 2.3.

A variety of lifestyle recommendations are incorporated as first line treatment in the NCEP ATP III Guidelines. Nutritional intervention is recommended, including maintaining calories from fat between 25% and 35%, saturated fat counting for less than 7%, with cholesterol level intake limited to less than 200 mg/day. Complex carbohydrates are recommended at 50–60% of calories and protein at 15%. NCEP ATP III Guidelines recommend consumption of 20–30 grams of dietary fiber daily—an amount far more than the average American adult currently consumes.[41]

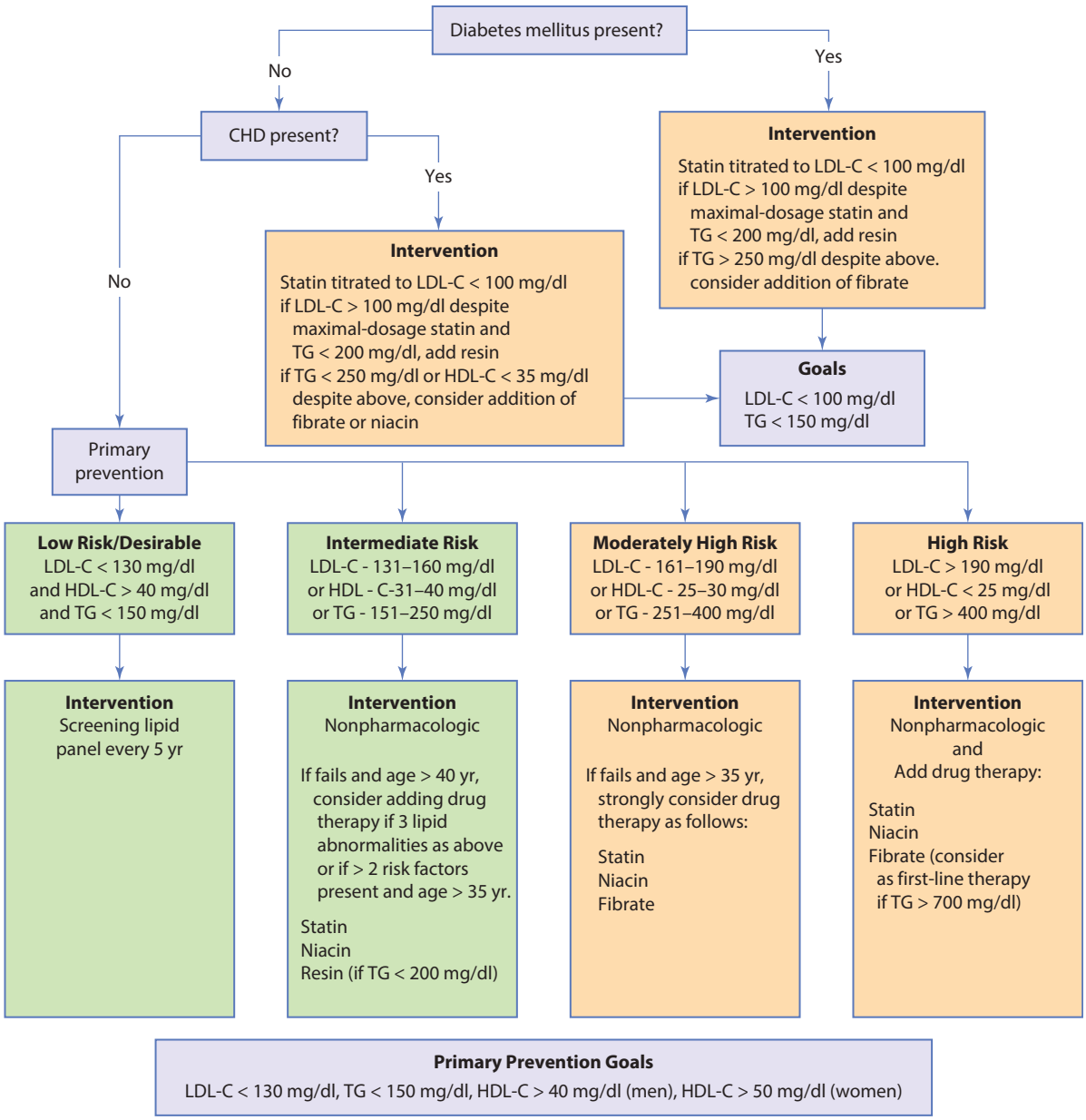


FIGURE 2.3 Algorithm for lipid-lowering therapy based on findings from intervention trials. CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. (From the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]: final report. *Circulation*. 2002;106:3143– 3421.)

In 2006, ACC and AHA updated their secondary prevention guidelines for lipid management, including most of the provisions in the NCEP guidelines but also strengthening them for individuals with established CHD. The AHA/ACC Guidelines extend the option of levels of less than 70 mg/dL for LDL for all patients with CHD, not just those at very high risk.[65] The guidelines also recommend that patients with triglyceride levels of 200–499 mg/dL should have non-HDL cholesterol level of less than 130 mg/dL and potentially further reduction to less than 100 mg/dL. Also in 2006, the AHA listed its nutritional and lifestyle recommendations.[66] A summary of these recommendations and their lifestyle interventions is found in Table 2.3. Within a clinical setting, it may be valuable for patients to receive the services of a registered dietitian to help them adhere to nutritional guidelines recommended by the AHA and NCEP ATP III.

In 2013, the ACC and AHA issued "Guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease in Adults." These Guidelines recommend increased use of statin medications to reduce ASCVD events in secondary and primary prevention and also recommend discontinuation of use of specific LDL and HDL treatment targets.[67] The four major statin benefit

TABLE 2.3

AHA 2008 Diet and Lifestyle Recommendations for Cardiovascular Disease Risk Reduction

1. Balance caloric intake and physical activity to achieve or maintain a healthy body weight
2. Eat a diet rich in vegetables and fruits
3. Choose and prepare foods with little or no salt
4. Minimize your intake of beverages and foods with added sugars
5. Consume oily fish at least twice a week
6. Limit your intake of saturated fat to <7% of energy, trans fat to <1% of energy, and cholesterol to <300 mg per day by choosing lean meats and vegetable alternatives; selecting fat free (skim), 1% fat and low fat dairy products and minimizing intake of partially hydrogenated fats
7. Choose whole grain, high fiber foods in your diet
8. If you consume alcohol, consume in moderation
9. When you eat food that is prepared outside of your home, follow the AHA Diet and Lifestyle Recommendations

Adapted from Lichtenstein AH, Appel LJ, Brands M, Carnethon M, et al. Diet and Lifestyle Recommendations Revision 2006. A Scientific Statement From the American Heart Association Nutrition Committee. *Circulation*, 114, 82–96, 2006.

groups where the use of statin medicines, according to this report, were indicated to reduce ASCVD risk were the following: Individuals 1) with clinical ASCVD, 2) primary elevations of LDL-C>190 mg/dL, 3) diabetics aged 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD, and 4) individuals without *clinical* ASCVD or diabetes with LDL-C 70 to 189 mg/dL who had a ten-year ASCVD risk >7.5%. These Guidelines were immediately criticized for recommending excessive use of statins, particularly in individuals with risk of >7.5%.[68,69] This controversy persists as of this writing.

A variety of pharmaceutical agents have been demonstrated to lower both total and LDL cholesterol as well as reduce morbidity and mortality from CHD. Most prominent amongst these medicines are the statins. While statins vary according to potency, they appear to be equally efficacious. Adherence is the key issue.

A recent approach to use of statins based on evidence from clinical trials has been suggested by preventive cardiologists in the United States, Canada, and Europe[68, 69]. It is based on the following five guidelines:

- Statin therapy should be used as an adjunct to diet, exercise, and smoking cessation for secondary prevention in patients with previous history of MI, stroke, or clinically apparent atherosclerosis.
- Statin therapy can be considered as an adjunct to diet, exercise, and smoking cessation as a component of primary prevention in those age 50 or over with either diabetes related lower HDL cholesterol or elevated hs-CRP.
- When prescribing statin therapy, physicians should seek to maximize the intensities of therapies and focus efforts on compliance and long-term adherence.
- The use of non-statins for lowering cholesterol agents for monotherapy or in combination with a statin should be limited until evidence is available that such an approach further reduces cardiovascular event rates in specific patient groups.
- A guideline based on prior evidence and on prior entry criteria must be simple, practical, and consistent with evidence based principles and should, therefore, result in broad clinical acceptance. New advances in prevention should be incorporated into these guidelines as quickly as possible.

It should be noted that these guidelines underscore the importance of lifestyle medicine principles of incorporating diet, exercise, and smoking cessation into the regimens that may also employ statin medicines.

Other agents available include niacin, fibrates, bile acid sequestrants, and cholesterol absorption inhibitors. A complete review of pharmaceutical therapies for the management of dyslipidemia is beyond the scope of this chapter and has been well treated in a variety of other publications. All the major cholesterol management guidelines advocate that lifestyle measures be combined if pharmaceutical agents are employed to produce the most favorable outcome (see also Chapter 4 on Clinical Strategies for Managing Dyslipidemias).

2.5.3 Lifestyle Management of Hypertension

According to the Joint National Committee (JNC) 7 Report, one out of every three American adults has high blood pressure, which represents more than 50 million Americans.[42] Another 25% fall into the "pre-hypertensive" category, which represents another 45 million Americans. The JNC 7 blood pressure classification is found is in Chapter 1.

A Commission was established to formulate JNC 8 Guidelines. However, the report of this Commission was never issued as formal guidelines. The intent was to change the approach to guidelines to a more evidence based rather than epidemiologic based approach.[70] The Commission issued a report that, as already indicated in Chapter 1, contained the following statement:

> There is strong evidence to support treating hypertensive patients age 60 or older to a BP goal of <150/90 mmHg and hypertensive patients 30-59 years of age to a diastolic goal of <90 mmHg. However, there is insufficient evidence in hypertensive persons under the age of 60 years for a systolic goal or in those under the age of 30 years for a diastolic goal, so the panel recommends a BP of <140/90 mmHg for those groups based on expert opinion.

As a practical matter, it should be noted that most organizations, including the AHA in their Clinical Guidelines for Establishing Goals for 2020, continue to use the cutoffs articulated in the JNC VII Guidelines.[42]

According to data from the Framingham Heart Study, individuals who have a normal blood pressure at the age of 55 still have a 90% chance of developing hypertension in their lifetime.[71] Control of high blood pressure in the United States remains abysmally low, with over two-thirds of individuals with hypertension not adequately controlled.[72]

A number of lifestyle measures are recommended by JNC 7 and can play significant roles in either reducing the likelihood of developing hypertension or treating it if it currently exists. These lifestyle measures include weight management, regular physical activity, proper nutrition, cessation of cigarette smoking, and moderation of alcohol—all of which represent first line lifestyle related measures in the treatment of high blood pressure within the JNC 7 framework.[42]

Increased body weight has clearly been associated with increased risk of high blood pressure.[73] Conversely, weight reduction in overweight or obese individuals represents a highly reliable way of lowering blood pressure. In most studies, individuals who are overweight or obese can anticipate reducing both systolic and diastolic blood pressure by 1 mmHg for every 2 lbs of weight loss.[74] The mechanism of blood pressure lowering resulting from weight loss is not completely understood. It may represent a decrease in blood volume, an initial diuresis, or reduction in systemic vascular resistance.[75]

Proper nutrition can also play a significant role in blood pressure control. Both the JNC VII Guidelines[42] and the AHA Nutrition Guidelines[66] recommend that individuals with hypertension should consume a diet with no more than 2,300 mg of sodium per day. Recently released Dietary Guidelines for Americans 2020–2025[76] recommends an even lower sodium consumption of 1,500 mg per day for individuals at increased risk for cardiovascular disease and all individuals over the age of 50.

Practical ways to lower salt consumption include removing the salt shaker from the table, reduction of salt in cooking, careful label reading of processed foods (a significant and often under-recognized source of sodium), and increased consumption of whole grains and fruits and vegetables. The Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes whole grains, fruits and vegetables, and low fat dairy products, has been shown to reliably lower high blood pressure.[77] An addition of further sodium restriction to the DASH diet results in further reduction in blood pressure.[78] Unfortunately, fewer than 20% of individuals with established high blood pressure are following a DASH type diet.[79]

Regular physical activity also helps prevent high blood pressure and lowers blood pressure in individuals with currently existing hypertension. Physically active individuals reduce their risk of hypertension by between 20% and 50%.[73] Individuals with established hypertension who start a physical activity program (emphasizing aerobic activities such as walking) may lower both systolic and diastolic blood pressure by 5-10 mmHg by participating in such moderate intensity physical activity.[80–82]

Excessive alcohol consumption is a risk factor for hypertension.[83] Moderation of this habit also can contribute significantly to controlling blood pressure. Cigarette smoking and use of other tobacco products has been repeatedly shown to raise blood pressure.[84,85] Cessation of this deadly habit should be recommended for multiple reasons.

Some evidence supports stress reduction as playing a role in lowering blood pressure, although this effect seems to be less prominent than the other lifestyle measures already discussed.[86] A beneficial aspect of lifestyle measures in relationship to blood pressure control is that they often act synergistically with each other. It should be noted that positive lifestyle measures when practiced simultaneously appear to have additive benefits. The PREMIER trial showed that a combination of weight loss, sodium restriction, increased physical activity, and limited alcohol consumption when practiced together resulted in substantial blood pressure reductions in individuals with above optimal blood pressure, including Stage 1 hypertension (140–159 mmHg systolic and 90–95 mmHg diastolic), and who were not taking antihypertensive medications.[87] Further benefits were achieved by individuals who implemented a DASH diet in addition to these other lifestyle modifications.

Some controversy has continued to exist related to whether or not lowering blood pressure to 140/90 mmHg is the optimum recommendation. The recently completed SPRINT (Systolic Blood Pressure Intervention Trial)[88] showed a benefit from reduced risk of kidney disease and heart failure in individuals who were at elevated risk for these conditions from lowering systolic blood pressure to 120 mmHg as compared with 140 mmHg. One negative aspect of this study is that it required an average of three pharmaceutical agents to obtain these further reductions. This would argue for a combination of fewer pharmaceutical agents plus lifestyle measures, which are likely to be synergistic with pharmaceutical therapy.

In late 2017, the ACC and the AHA issued new guidelines recommending more stringent control of blood pressure.[4] These guidelines lowered the definition of high blood pressure to any level higher than 120/80 mm Hg. These guidelines are intended to account for an increased risk of cardiovascular complications above these numbers.

As a practical matter, the new definition of high blood pressure resulted in nearly half of the United States population (46%) being categorized as having high blood pressure.

The greatest impact occurred in younger people. The prevalence of high blood pressure was expected to triple in men under the age of 45 and double among women under the age of 45 according to the new guidelines.

The ACC/AHA guidelines also recommended that high blood pressure should be treated earlier with lifestyle changes and in some instances with medication to reach levels of 130/80 mm Hg rather than 140/90 mm Hg in young, asymptomatic individuals. Abundant research suggests that increased physical activity and proper nutrition (including lower amounts of salt and fats in the diet and weight loss if necessary) can significantly lower blood pressure and act synergistically with each other and also with medications.

Categories in the new blood pressure guidelines are:

- Normal (less than 120/80 mmHg)
- Elevated: systolic between 120 and 129 and diastolic less than 80 mmHg
- Stage 1: Systolic between 130 and 139 or diastolic between 80 and 89 mmHg
- Stage 2: Systolic ≥140 or diastolic ≥90 mmHg

Hypertensive crisis was defined as systolic over 180 mmHg and/or diastolic over 120 mmHg. These patients need prompt changes in medication if there are no other indications of problems or need hospitalization if there are signs of organ damage. The guidelines also stressed the importance of using proper technique for measuring blood pressure and the use of home blood pressure monitoring using validated devices.[4] (See also Chapter 5.)

2.5.4 Pharmaceutical Measures for Cardiac Protection

A detailed review of pharmacologic interventions to lower the risk of heart disease is beyond the scope of this chapter. However, it is important to recognize that certain pharmacologic interventions have been demonstrated to be effective in either primary or secondary prevention of cardiovascular disease.

Aspirin has been demonstrated to lower the risk of subsequent events in individuals with existing CHD, where aspirin reduces the risk of subsequent events by 25%.[80] The AHA/ACC lowered the recommended prophylactic dose of aspirin in individuals with existing CHD from 75 to 325 mg/day to 75 to 162 mg/day, since anti-platelet trials had showed no difference in the reduction benefit and reduced risk of bleeding at this lower dosage range.[89] Other anti-platelet agents do not offer significant benefit over aspirin. These agents, such as Clopidogrel, should be limited to patients with aspirin allergy or intolerance.[90]

The picture of aspirin usage in primary prevention is less clear.[91] The AHA guidelines issued in 2007 for women recommend aspirin for high risk women whose ten-year risk of a coronary event, based on Framingham criteria, exceeds 20% and for all women over the age of 65 in whom blood pressure is controlled and the potential benefit for preventing MI or ischemic stroke outweighs the risk of bleeding or hemorrhagic stroke. The United States Preventive Health Services Task Force recommends aspirin for men 45–79 years of age and women 55–79 years of age for benefit in reduction of risk of MI in men and ischemic stroke in women if these benefits outweigh the risk of gastrointestinal bleeding.[92] It should be emphasized that most of the data on the use of aspirin in primary prevention predate concomitant use of statin therapy. Thus, many cardiologists consider utilizing statins as an adjunct to diet, exercise, and smoking cessation rather than aspirin in primary prevention.

Other potentially beneficial pharmaceutical agents include statins, beta adrenergic receptor blockers after MI, and angiotensin converting enzyme inhibitors in individuals at high risk for CHD events. Extensive reviews of all these medications may be found elsewhere.

2.6 CLASS 2 INTERVENTIONS

2.6.1 Obesity Prevention and Management

Obesity,[93] adult weight gain,[94] and increased abdominal fat[95] are all independently associated with increased risk for coronary heart disease.[95–99] Obesity also contributes to a variety of other risk factors for CHD, including hypertension, Type 2 diabetes (T2DM), and dyslipidemia. The AHA recognizes obesity as an independent risk factor over and above its association with other risk factors for CHD.[100]

Over the last 40 years, the percentage of the United States population considered to be overweight (body mass index [BMI] ≥25 ≤29.9) and obese (BMI ≥30.0) has risen steadily and substantially. As depicted in Figure 2.4, over 73% of the adult population in the United States are now considered overweight or obese.[101] The prevalence of obesity has risen particularly sharply, with the most dramatic increases in individuals who are extremely obese (BMI ≥40.0).[102]

The same trends have occurred in children,[103] as depicted in Figure 2.5. The prevalence of overweight has more than tripled amongst children in the United States in the past 40 years. ("Overweight" in children is defined by Centers for Disease Control [CDC] criteria as ≥95th percentile weight for height based on CDC 2000 tables).[104,105] Some criteria, such as those from the American Medical Association, also include a description of ≥85th percentile weight for height as "overweight" and ≥95th percentile of weight for height as an appropriate definition for "obese" in children.

Obese individuals are particularly likely to demonstrate clustering of risk factors.[96,106] Framingham data have demonstrated that over two-thirds of CHD is found in individuals with two or more risk factors.[96] Moreover, obesity is the major driver of the metabolic syndrome, which afflicts 25–35% of the adult population in the United States and represents a potent risk factor for both CHD and diabetes.[107]

Although the association between obesity and increased risk of CHD is well established, no large scale, randomized

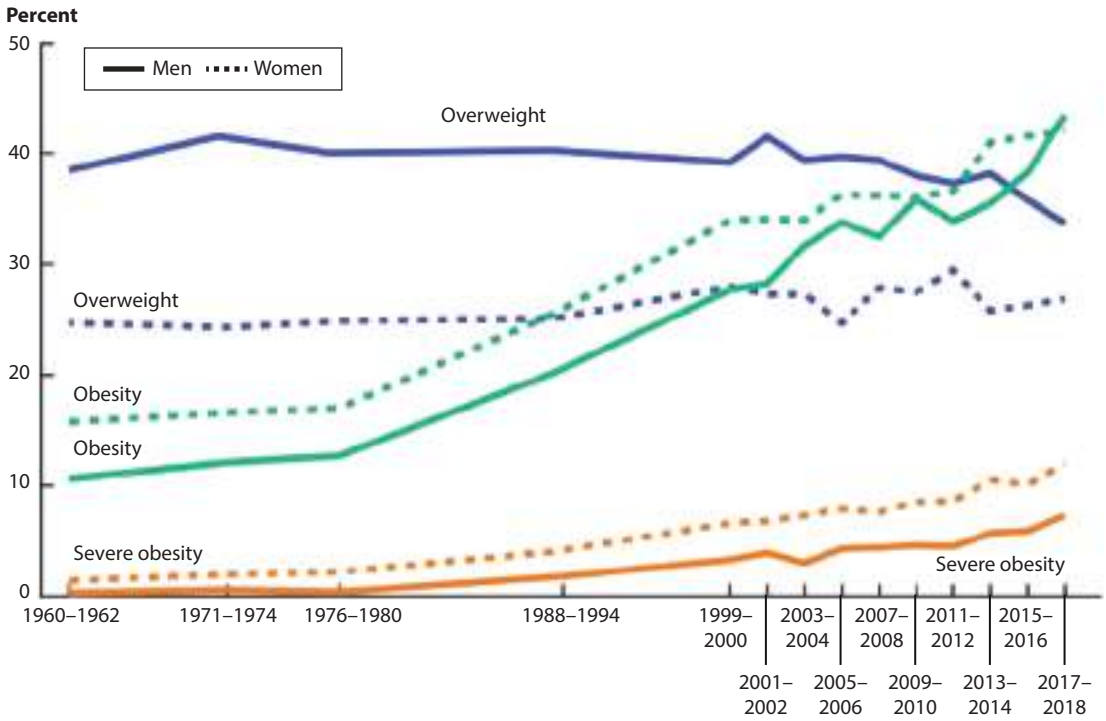
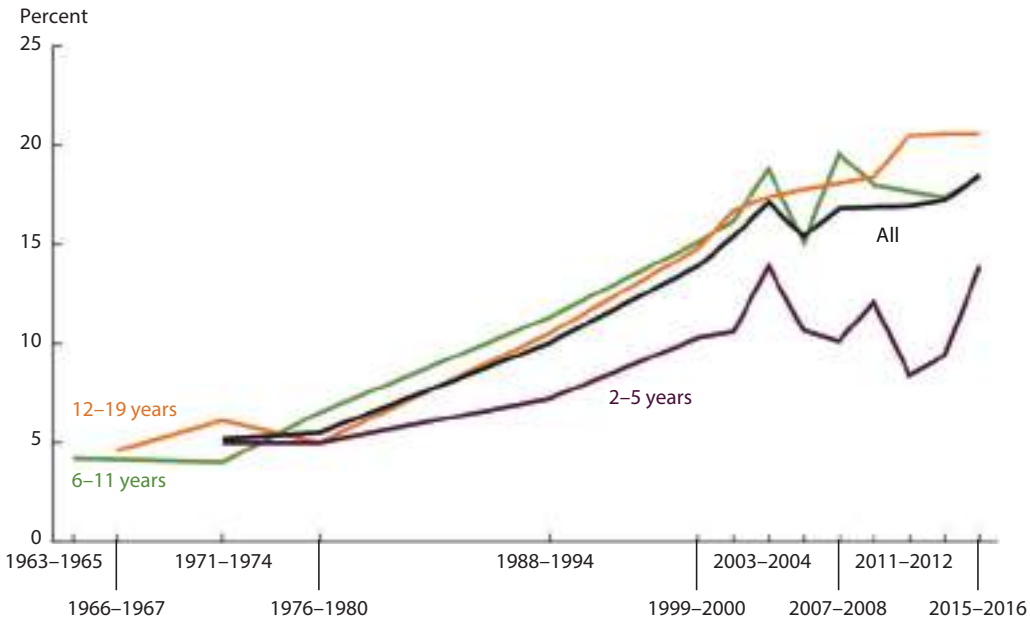


FIGURE 2.4 Trends in adult overweight and obesity ages 20 to 74 years. (From National Center for Health Statistics. No permission needed www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/overweight-obesity-adults-H.pdf)



NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: NCHS, National Health Examination Surveys II (ages 6–11) and III (ages 12–17); National Health and Nutrition Examination Surveys (NHANES) I–III; and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016.

FIGURE 2.5 Trends in childhood overweight. (From National Center for Health Statistics. www.cdc.gov/nchs/data/hestat/obesity-child1516/obesitychild1516.pdf)

trials of weight reduction as an intervention to lower the risk of CHD are available to estimate the benefits of weight loss. A number of trials, however, have shown that weight loss in obese individuals reduces risk factors for CHD and a variety of other chronic conditions. For example, in the Diabetes Prevention Program, individuals who were overweight and who lost 5–7% of their body weight and adopted a program of regular physical activity reduced their risk of

developing diabetes by 58%.[108] Nutritional strategies, with a particular emphasis on matching calorie intake to calorie output, have demonstrated effectiveness for weight loss. The Dietary Guidelines for Americans 2020–2025[76] list overconsumption of calories and overweight/obesity as the leading nutritional problems in the United States.

In addition, regular physical activity in conjunction with attention to caloric consumption has been found in numerous studies to help in the maintenance of long-term weight loss.[109–111] The preferred form of physical activity for most overweight or obese individuals is walking. Some studies have recommended 30–60 minutes of moderate intensity walking per day as a reasonable goal for individuals as a component of an effective and safe weight loss program.[110] The Dietary Guidelines for Americans 2020–2025 recommend 60 minutes or more of moderate physical activity as a component of weight management.[76]

Behavioral strategies and social support are also important as components of an overall strategy for long-term weight loss.[112] Support from an individual's family and friends or from groups (e.g. from an organization such as Weight Watchers International) has been demonstrated to be helpful in long-term maintenance of weight loss.[113]

A number of pharmaceutical therapies are currently available to assist in weight loss. These include Phentermine, the combination of topiramate/phentermine Qsymia, Supreza (phentermine), Lorcaserin, Orlistat (prescription), Orlistat (over-the-counter), Naltrexone, Bupropion, and Liraglutide. A description of the dosages and actions of these medications is beyond the scope of this chapter; they have been extensively reviewed elsewhere.[104] It should be noted that all of these medicines should be utilized in conjunction with positive lifestyle measures such as proper nutrition and regular physical activity.

It has been regularly shown that physician involvement in recommendations for weight loss represents an important predictor of both initial weight loss and maintenance of weight loss. A detailed description of available programs and therapies for weight loss is beyond the scope of the current chapter. The author has co-edited several textbooks on this topic, and the reader is referred to these textbooks for more detailed information in this area.[114,115]

2.6.2 Diabetes/Glucose Intolerance

The prevalence of diabetes in the United States has grown significantly over the past decade, which appears to reflect corresponding increases in the prevalence of overweight and obesity.[116] Currently, approximately 9% of the adult population in the United States—nearly 24 million people—have diabetes mellitus. The vast majority of these individuals (more than 90%) have T2DM.[117] Unfortunately, approximately one-quarter of individuals with diabetes are not aware they have this condition. Another significant problem is the recent increase in T2DM in children. It is now estimated that more new cases of T2DM than Type 1 diabetes are found in children each year.[118]

Diabetes represents a significant risk factor for CVD, which is the leading cause of death for both men and women with diabetes, resulting in 75% of all mortality.[116,117] A variety of lifestyle measures, such as weight loss in overweight or obese individuals and regular physical activity, play important roles in the management of diabetes.[119–121] These modalities are particularly important for blood sugar control in individuals with T2DM.

Because patients with diabetes often have other risk factors for CVD, aggressive treatment of these other risk factors is imperative. For example, guidelines from the American Diabetes Association for treating high blood pressure in individuals with diabetes recommend a target of BP at ≤130/80 mmHg for individuals with diabetes.[122,123] NCEP ATP III Guidelines treat diabetes as a CVD equivalent and recommend reduction of LDL cholesterol in diabetic individuals to a goal of less than 100 mg/dL[41].

Impaired glucose tolerance often proceeds overt diabetes and is particularly common in obese individuals. CDC data indicate that 35–40% of the adult population in the United States have glucose intolerance.[124] Recent studies have shown that overweight individuals with impaired glucose tolerance who lose weight, reduce total fat intake, and increase physical activity significantly decrease their risk of developing diabetes.[108,125] Thus, lifestyle measures are highly appropriate in both diabetic and pre-diabetic patients.

Few data are available to address appropriate strategies for long-term reduction in CVD mortality amongst patients with T2DM. To date, interventions to improve fitness and achieve weight loss as methods to reduce CVD morbidity and mortality have been disappointing. The Look AHEAD Trial randomized patients either to intensive lifestyle intervention, which promoted weight loss through increased physical activity and decreased caloric intake, or to a diabetes support and education program. The intent of the lifestyle intervention focused on weight loss but did not reduce the rate of cardiovascular events in this group during a median follow up period of almost ten years, despite the fact that beneficial effects occurred on levels of several biomarkers.[126] Thus, while this trial did not demonstrate a reduction in the risk of cardiovascular morbidity and mortality, it is important to note that patients in the intervention group had meaningful clinical improvement in multiple areas, including hemoglobin A1C, weight, physical fitness, and all other measured cardiovascular risk factors, except for LDL cholesterol levels. In addition, benefits to individuals in the intervention group included reduction in urinary incontinence, sleep apnea, and depression and improvements in quality of life, physical functioning, and mobility. All of these were accomplished with a high level of acceptance in the intervention group and low side effects. Thus, this trial suggests that the high intensity lifestyle intervention approach can be safely conducted and result in significant weight loss in diabetic patients. Application of these findings will depend on clinical judgement and individual patient characteristics for those physicians treating diabetes.

2.6.3 Physical Inactivity

The United States population has become increasingly sedentary.[81] Both the U.S. Surgeon General's Report on Physical Activity and Health[127] and data from the Behavior Risk Factor Surveillance System (BRFSS)[128] have suggested that more than 70% of the adult population in the United States do not achieve 30 minutes of moderate intensity physical activity on most, if not all, days. Multiple studies have demonstrated that an active lifestyle substantially decreases the risk of CVD. The AHA has listed the lack of physical activity as a major risk factor for CVD.[129]

The Physical Activity Guidelines for Americans 2018 provides a listing of known or anticipated health benefits from increased physical activity.[81] A listing of these known benefits and the strength of the evidence supporting these relationships are found in Table 2.4. As can be seen from this table, many of the known benefits from physical activity involve reduction of the risk of CHD.

The Physical Activity Guidelines for Americans 2018 recommend that individuals try to accumulate 150 minutes of moderate intensity activity or 75 minutes of vigorous activity on a weekly basis. Moderate intensity activities include such forms of physical activity as walking, jogging, cycling, or swimming at moderate intensity. A listing of physical activity guidelines is beyond the scope of this chapter. The reader is referred to the Physical Activity Guidelines for Americans 2018 for an excellent compendium of literature in this area.[81]

2.6.4 Moderate Alcohol Consumption

A number of studies have demonstrated that moderate alcohol consumption decreases the risk of vascular diseases such as heart attack, peripheral vascular disease, and sudden cardiac death.[83] It should be noted that these studies have also demonstrated that excessive alcohol consumption increases both all-cause mortality and cardiovascular disease mortality.[130,131] Moderate alcohol consumption has been defined as one drink per day for women and up to two drinks per day for men. The higher level allowed for men is a result of enhanced ability to metabolize alcohol due to more robust activity of the enzyme alcohol dehydrogenase in the liver in men. These levels of alcohol consumption have consistently corresponded to reduction of the risk for cardiovascular disease of approximately 20–40%. The most reasonable course in a clinical setting is to assess the

TABLE 2.4
Health Benefits Associated with Regular Physical Activity

Children and Adolescents

- Improved bone health (ages 3 through 17 years)
- Improved weight status (ages 3 through 17 years)
- Improved cardiorespiratory and muscular fitness (ages 6 through 17 years)
- Improved cardiometabolic health (ages 6 through 17 years)
- Improved cognition (ages 6 to 13 years)
- Reduced risk of depression (ages 6 to 13 years)

Adults and Older Adults

- Lower risk of all-cause mortality
- Lower risk of cardiovascular disease mortality
- Lower risk of cardiovascular disease (including heart disease and stroke)
- Lower risk of hypertension
- Lower risk of type 2 diabetes
- Lower risk of adverse blood lipid profile
- Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach
- Improved cognition
- Reduced risk of dementia (including Alzheimer's disease)
- Improved quality of life
- Reduced anxiety
- Reduced risk of depression
- Improved sleep
- Slowed or reduced weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain following initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)
- Lower risk of fall-related injuries (older adults)

Source: 2018 Physical Activity Guidelines for Americans. https://health.gov/our-work/nutrition-physical-activity/physical-activity-guidelines (page 32: Table 2-1. Health Benefits Associated with Regular Physical Activity). Accessed April 25, 2023.

risks and benefits of alcohol consumption on a case by case basis with each patient.

2.7 CLASS 3 INTERVENTIONS

2.7.1 Nutritional Counseling

Numerous studies have demonstrated that diet has an impact on CHD risk.[132–136] The U.S. Preventive Services Task Force listed nutritional counseling as having "moderate" evidence supporting its role in lowering the risk of CVD. Recent Scientific Statements from the AHA[59] as well as the Dietary Guidelines for Americans 2020–2025[76] both emphasize the important role of nutritional counseling to lower the risk of CVD. In particular, improved nutritional practices may help improve blood lipids, and strategies such as the DASH Diet[77,78] have been demonstrated to help control high blood pressure.

Numerous guidelines and resource materials are available in this area from the American Heart Association[137] as well as the American Dietetic Association[138] and the Preventive Cardiology Nurses Association[139] to assist patients in making nutritional choices to lower their risk of CVD. Additional guidelines are available from various professional societies providing key components of overall health and nutritional patterns. The guidelines are all very consistent with each other, so the individual healthcare professional is able to choose whichever one fits most conveniently into his/her practice.[140]

The complexity of recommending an optimal diet for cardiovascular health reduction has been recognized in all of these guidelines. Most recently, with this caveat in place, the 2020 Strategic Plan from the American Heart Association defined dietary goals as:

> in the context of a diet that is appropriate in energy balance, pursuing an overall dietary plan that is consistent with DASH including, but not limited to:
>
> - Fruits and vegetables ≥ 4.5 cups per day,
> - Fish ≥ 3.5 ounce servings per week (preferably oily fish),
> - Fiber rich whole grain (≥ 1.1g of fiber per 10g of carbohydrate: 3 one ounce equivalent servings per day),
> - Sodium <1500 milligrams per day,
> - Sugar sweetened beverages ≤ 450 kcals (36 ounce) per week.

These recommendations seem reasonable and have been expanded upon in recent reviews.[141,142] Some recent evidence has suggested that diets adhering to the principles of the Mediterranean style diet, which has been supplemented with extra virgin olive oil or nuts, can reduce the incidence of major cardiovascular effects amongst individuals with high cardiovascular risk. The Dietary Guidelines for Americans 2015 and 2020–2025 incorporate and expand upon these principles.[76]

2.7.2 Psychological Risk Factors/Counseling

A number of psychological factors, including depression, chronic hostility, social isolation, and lack of social support, have been linked to increased risk of CHD.[143] Some studies have suggested that improved psychological support systems may improve outcome following MI. For example, 1 meta-analysis of 37 smaller studies showed that stress management and health education in individuals with CHD reduced recurrent MI by 29% and cardiac mortality by 34%.[143] Office visits following MI clearly represent an excellent opportunity to assess levels of depression and social isolation in individuals who have suffered recent cardiac events.

2.8 POST MENOPAUSAL ESTROGEN THERAPY

It is well established that the risk of CVD in women increases significantly following menopause. Relatively few women experience CVD at younger than 45 years of age in the United States.[144] However, by the age of 60, CVD is the leading cause of death among women.

Multiple factors may explain the increased risk of CVD after menopause. For many years, the increase in CVD after menopause was attributed to the decline in endogenous estrogen that accompanies menopause. However, the Women's Health Initiative findings did not support this concept.[145–147] For this reason, hormone therapy is no longer recommended as an approach to prevention of CVD by the United States Preventive Services Task Force (USPSTF), the American Heart Association, or other scientific organizations.[146]

2.9 DETERMINANTS OF BEHAVIOR CHANGE

The belief that it is possible to change patient behavior provides the fundamental underpinnings to the concept of utilizing lifestyle measures to help patients adopt positive lifestyle behaviors to lower the risk of CHD or as an adjunct to the treatment of established CHD. A detailed review of the literature in this area is beyond the scope of the current chapter. However, this literature has been very well summarized in a variety of other publications.[148–150]

A variety of theoretical constructs provide the foundation for behavioral therapy.[148–150] These include:

- cognitive behavioral therapy (which assumes that behavior is learned and can, therefore, be unlearned through cognitive and behavioral strategies)
- social cognitive theory (this is based on the assumption that behavior is the result of interaction of personal and behavior factors as well as environmental influences)

- transtheoretical theory (stages of change; based on accurately placing an individual along the path of various stages of change)[149]

Familiarity with these theoretical constructs as well as the technique of motivational interviewing provides useful underpinnings and a practical framework for incorporating lifestyle change messages in clinical practice.

2.10 ESTABLISHING A LIFESTYLE MEDICINE EMPHASIS IN CLINICAL PRACTICE

As already indicated, physicians can play a particularly powerful role by recommending and monitoring lifestyle related changes for reduction in the risk of CVD. While challenges remain, including lack of time, inadequate reimbursement models, etc., it is clear that healthcare professionals need to move in this direction. Recent publications have suggested ways that interested physicians can incorporate more lifestyle medicine strategies into their daily practice of medicine.[150–154]

The evidence supporting lifestyle therapies for reduction of the risk of CVD is diverse and powerful. Moreover, an emphasis on the linkages between daily lifestyle habits and practices and the risk of CVD is incorporated in virtually all of the evidence based guidelines for treating CVD and its risk factors as well as reducing the risk of other metabolic diseases.[3–15] The AHA has also included positive lifestyle measures as a fundamental component of its strategic plan for 2020 for improving the cardiovascular health of the nation[7] as well as its Impact Goal for 2030[155] and its recommendations for Cardiovascular Health and Disease Surveillance 2030 and Beyond.[156] Finally, the Accountable Care Organization provision of the recent Affordable Health Care Act outlines that healthcare organizations and individual providers are mandated to increase involvement in this area.[142] The Guidelines for Physical Activity 2008[81,117] as well as the Dietary Guidelines for Americans 2015 and 2020–2025[69] provide fundamental, evidence based approaches to lifestyle related issues and should be the foundation for every healthcare worker's increasing emphasis on these strategies in their daily practice.

There has been a recent impetus toward incorporating models of Intensive Therapeutic Lifestyle Change (ITLC) into the practice of medicine. Several recent publications have provided guidance into the rationale for employing these strategies as well as methods for including them and potential outcomes.[157,158]

2.11 SUMMARY

An extensive body of scientific literature supports the concept that positive lifestyle measures are highly effective in lowering multiple risk factors for CHD as well as serving as components of therapy for individuals who already have established CHD. These interventions carry the substantial advantages of being low cost, carrying virtually no adverse side effects, and often simultaneously ameliorating multiple risk factors for CHD. The key imperative for physicians and other healthcare workers is to commit to learning how to incorporate counseling concerning these lifestyle measures in clinical practice and establishing strategies to bring this valuable body of information to their patients.

CLINICAL APPLICATIONS

Actions	Available Tools	Comments
Assess risk of CVD in all patients	Framingham Risk Scores or the equivalent are available for this purpose	Other risk scores including the Reynolds Risk Score are alternatives to the Framingham Risk Scores
Assess and counsel all patients who smoke on the importance of smoking cessation	Multiple tools are available from the American Heart Association, American Lung Association, etc.	Second hand smoke also poses danger and should be discussed with all patients
Assess and counsel related to dyslipidemias	Use the National Cholesterol Education Program (NCEP) criteria and tools or the equivalent	Lifestyle strategies including proper nutrition, weight management, and physical activity are a key component of managing dyslipidemias
Assess and counsel all patients related to blood pressure	Use JNC VII criteria to help individuals understand not only high blood pressure but also high normal and normal blood pressure and what can be done to treat them	Lifestyle strategies are a key component for individuals to maintain healthy blood pressure or lower blood pressure if they are in the pre-hypertension or hypertension categories
Assess and counsel all patients on obesity prevention and management	Obtain weight, body mass index (BMI), and waist circumference on all patients	Both BMI and waist circumference independently predict the risk of CVD
Assess and counsel all patients on physical activity	Utilize criteria from the U.S. Physical Activity Guidelines	These are very useful guidelines for all age groups, from children up to senior citizens

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3 Physical Activity and Fitness in the Prevention of Cardiovascular Disease

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KEY POINTS

- Cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, hypertension, and heart failure, is the leading cause of morbidity and mortality in the United States and around the world.
- Increased cardiovascular fitness and physical activity have both been shown to lower the risk of CVD and serve as an adjunct to its treatment.
- An inactive lifestyle, in contrast, increases the risk of CVD, particularly sedentary activities such as television watching and other forms of screen time.
- Assessment of physical activity and fitness should be a component of all physician visits.

3.1 INTRODUCTION

CVD, as defined by the Centers for Disease Control and Prevention (CDC), encompasses CHD, stroke, hypertension, and heart failure.[1] CVD accounts for nearly one in three deaths in the United States. Approximately 2,150 Americans die from some manifestation of CVD every day; roughly one every 40 seconds.[1] CVD has been the leading cause of death since 1900 and remains so despite a decades-long decline in CVD mortality.[1]

It's predicted that over 650,000 Americans will experience a first myocardial infarction (MI) this year, and approximately 300,000 will be the victim of a reinfarction.[1] It's estimated that another 155,000 infarctions will be "silent," with no symptoms or symptoms other than angina, which are missed or ignored.[1] Collectively, this means that an American experiences a coronary event every 34 seconds. Compared with those who are very physically active, the risk of CHD in sedentary individuals is 150–240% higher.[1] Unfortunately, only about a quarter of all Americans engage in enough exercise to meet the minimum standards of the Centers for Disease Control and Prevention (CDC): at least 150 minutes per week of moderate-intensity aerobic exercise or at least 75 minutes of vigorous exercise and muscle-strengthening activities at least 2 days per week.[2] Given that the greatest reduction in risk for CHD appears to be for those engaging in even modest amounts of physical activity compared with the most physically inactive,[3] even relatively small increases in physical activity could potentially result in a significant decrease in CHD for a large portion of the American population. For example, epidemiological data suggest that the estimated 2.3% decline in physical inactivity between 1980 and 2000 prevented or at least postponed 17,445 deaths due to CHD in the United States.[4]

In spite of the overwhelming evidence implicating physical inactivity as an important and significant risk factor for CHD, fewer than half of adults meet even the minimum recommendation for aerobic exercise.[5] Statistics for young people are even more alarming, with fewer than 20% of adolescents performing the recommended 60 minutes or more of daily physical activity.[6]

Despite the documented lack of physical activity in the United States, and the well-established benefits of regular exercise, many physicians are not encouraging their patients to exercise and lose weight.[7–9] Of equal importance, they do not appear to be adequately prepared to provide recommendations for exercise and physical activity. For example, a survey of 175 primary care physicians revealed that only 12% were aware of the recommendations of the American College of Sports Medicine (ACSM) for physical activity.[9] An evaluation of 51 internal medicine residents reported that while 88% were confident in their knowledge of the benefits of exercise, only about 25% demonstrated adequate knowledge useful for patient counseling.[10]

Healthcare professionals need to promote physical activity with all of their patients. In that regard, an understanding of the health benefits associated with physical fitness and regular physical activity is fundamental. This chapter reviews the evidence linking greater physical activity and fitness with primary prevention of cardiovascular and metabolic disease through effective risk factor management. Recommendations for exercise are also provided both in general terms and for specific conditions.

3.2 PHYSICAL FITNESS VERSUS PHYSICAL ACTIVITY

Physical fitness, specifically cardiorespiratory fitness, is defined here as the ability to deliver and utilize oxygen during sustained activity and typically quantified as maximal oxygen uptake (VO_{2max}). When respiratory gases are measured with a metabolic cart during a maximal graded exercise test, VO_{2max} is valid and reliable. However, submaximal tests or those relying on indirect measures such as time to

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exhaustion are subject to considerable error. Measures of physical activity, on the other hand, usually rely on retrospective self-reported data (i.e., physical activity questionnaires). Non-vocational or leisure-time physical activity (LTPA) is most commonly assessed. Vocational physical activity, household chores, and biking or walking to work are also sometimes quantified, but less often. The definitions of physical activity vary greatly from study to study, and the components of physical activity or exercise, such as intensity, duration, and frequency, are often not reported or inadequately assessed.

The categorization of physical activity (i.e., low, moderate, or high) also varies from study to study. Many studies use different criteria for moderate- and vigorous-intensity exercise or activity. The ACSM defines moderate physical activity as any activity requiring 50–70% of VO_{2max} or maximal heart rate.[11] Vigorous physical activity is anything greater than 70% VO_{2max} or maximal heart rate.[11] Walking or brisk walking is generally recommended as the type of exercise that meets the criteria for moderate physical activity. However, it is important to understand that the intensity of walking, or any exercise for that matter, is relative to an individual's age, physical condition, and fitness level. For example, based on the ACSM Guidelines for Exercise Testing and Prescription,[11] even brisk walking may not be of sufficient intensity to meet the minimum criteria for moderate physical activity in a normal, healthy individual of college age. Conversely, brisk walking might be considered vigorous activity for someone over the age of 65. As such, any exercise recommendations should be applied relative to the individual's capabilities and limitations.

Surprisingly, physical fitness has been shown to be only modestly correlated with physical activity, with correlations ranging from 0.09[12] to 0.60.[13] In a meta-analysis of 7 physical fitness and 16 physical activity cohorts cited in the 1996 Surgeon General's Report,[14] Williams[5] found that the risk of CHD or CVD decreased linearly with increasing percentiles of physical activity. He also found that the reduction in risk for CHD or CVD associated with increasing percentiles of physical fitness demonstrated a precipitous decrease occurring just before the 25th percentile of the physical fitness distribution. Further, at all percentiles ≥25th, the reduction in risk for CHD and CVD was significantly greater for physical fitness compared with physical activity, as illustrated in Figure 3.1.

These findings are supported in a more recent comparison of fitness versus physical activity in predicting all-cause mortality in a cohort of 842 men referred for exercise testing.[12] While both physical activity and fitness were strong predictors of all-cause mortality, physical fitness was a stronger predictor of mortality than activity level. A 1,000 kcal per week increase in physical activity was found to be similar to a 1 MET (metabolic equivalent; oxygen uptake of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) improvement in fitness, with both conferring a 15–20% reduction in mortality. Of equal, if not greater, interest, these data also demonstrated that 40% of the reduction in mortality occurred between the least active or fit and the next least fit or active groups, suggesting that even modest increases in physical activity or fitness, especially in those who are inactive, may result in a significant reduction in mortality.

It is important to emphasize that while the reduction in risk of CVD is greater when comparing levels of fitness with levels of physical activity, both the Physical Activity Guidelines for Americans 2018 (PAGA 2018) and the ACSM emphasize that in the area of physical activity, "some is better than none." It is also essential to note that it is often misunderstood that even a very small amount of physical activity substantially lowers the risk of mortality, in general, and from CVD, in particular. As illustrated in Figure 3.2, the highest part of the risk comes from individuals who were previously sedentary and begin to engage in physical activity for even as little as 30 minutes per week.

As evidenced from this graph taken from the PAGA 2018, there is no lower threshold for benefits. Increasing benefits occur for individuals who engage in approximately 150 minutes of regular physical activity, although meaningful benefits occur in individuals who engage in physical

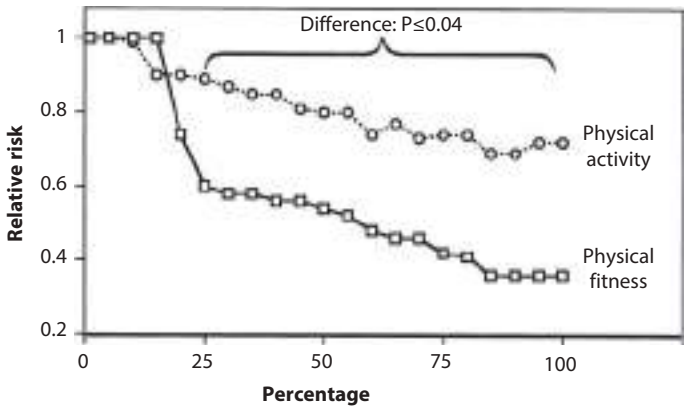


FIGURE 3.1 Estimated dose–response curve for the relative risk of either CHD or CVD by sample percentages of fitness and physical activity. Studies weighted by person-years of experience. (From Zoeller, R., Physical Activity and Fitness in the Prevention of Cardiovascular Disease. In Rippe, J.M. (ed), ***Lifestyle Medicine 3rd ed***. CRC Press, Boca Raton, 2019. With permission.)

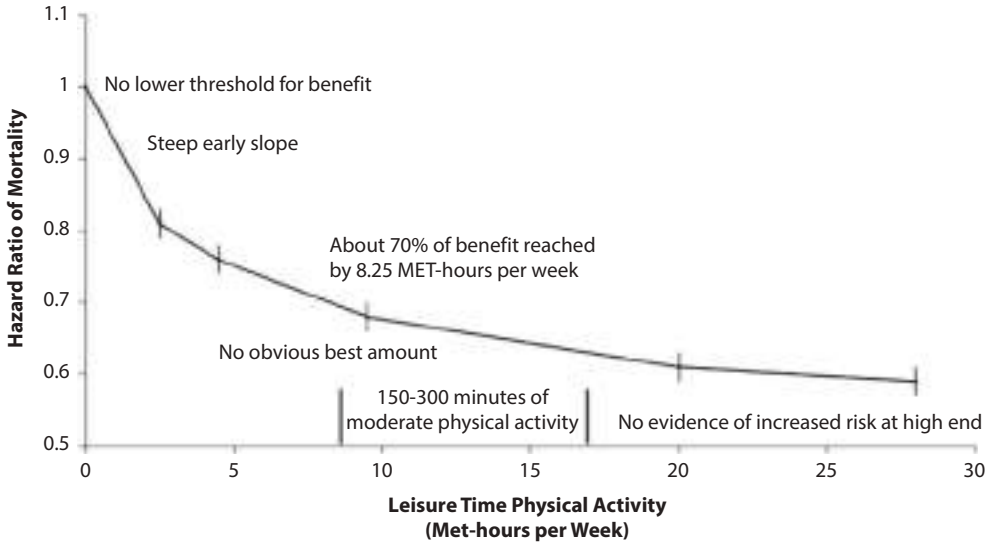


FIGURE 3.2 Relationship of moderate to vigorous physical activity to all-cause mortality, with highlighted characteristics common to studies of this type. (From the 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. US Department of Health and Human Services, Washington, DC, 2018.)

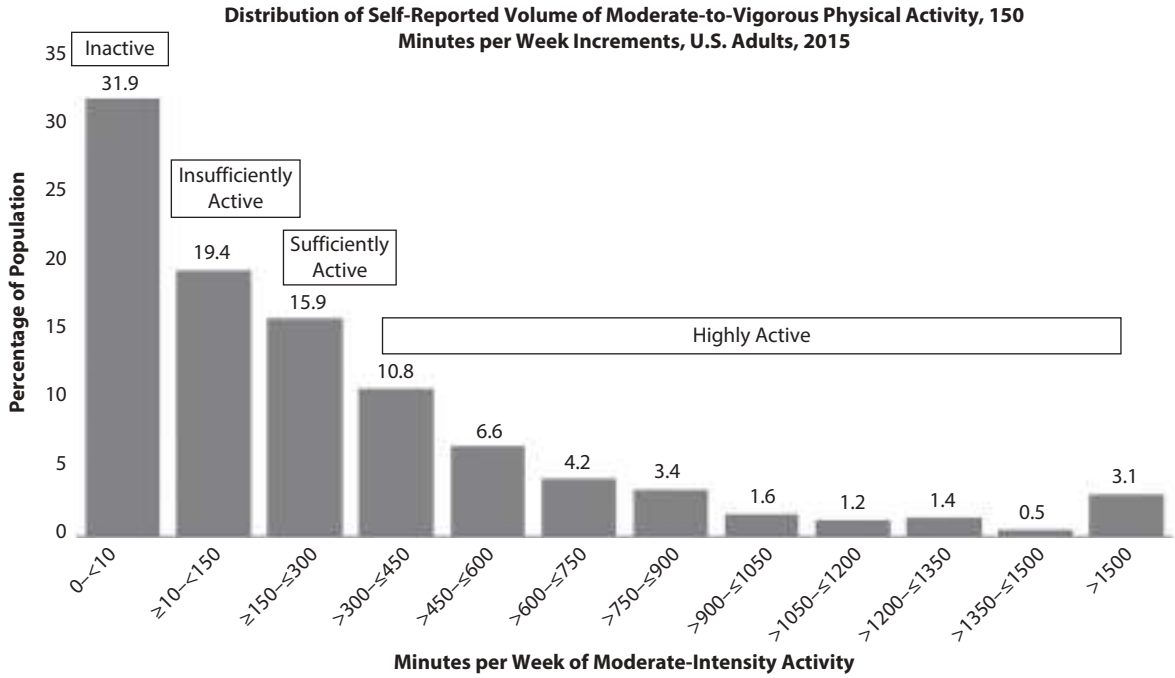


FIGURE 3.3 Minutes per week of moderate-intensity activity. (From the 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. US Department of Health and Human Services, Washington, DC, 2018.)

activity even substantially more than this. As illustrated in this figure, 70% of the benefit is achieved by individuals who engage in moderate physical activity, such as walking 30 minutes five times a week. However, 20% of the benefit comes for individuals who accumulate only 30 minutes per week!

While only approximately 25% of individuals achieve the chief guideline of 150 minutes of moderate-intensity physical activity on a weekly basis, according to the PAGA 2018 Guidelines, fewer than half of adults meet even minimum recommendations for physical activity, as illustrated in Figure 3.3.

3.3 GENERAL RECOMMENDATIONS FOR PHYSICAL ACTIVITY

In 1996, the Surgeon General's Report on Physical Activity and Health recommended:

people of all ages to include a minimum of 30 minutes of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week. It is also acknowledged that for most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or of longer duration.[14]

More recently, the 2018 Physical Activity Guidelines for Americans[15] provide updated and more specific recommendations for different age groups and some clinical populations. The following is a very brief summary of their recommendations.

3.3.1 Adults

- All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.
- For substantial health benefits, adults should do at least 150 minutes a week of moderate-intensity, or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on two or more days a week, as these activities provide additional health benefits.

3.3.2 Children and Adolescents

- Children and adolescents should do 60 minutes (one hour) or more of physical activity daily.
- Aerobic: Most of the 60 or more minutes a day should be either moderate- or vigorous-intensity aerobic physical activity, and should include vigorous-intensity physical activity at least three days a week.
- It is important to encourage young people to participate in physical activities that are appropriate for their age, that are enjoyable, and that offer variety.

3.3.3 Older Adults

- When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.
- Older adults should do exercises that maintain or improve balance if they are at risk of falling.
- Older adults should determine their level of effort for physical activity relative to their level of fitness.
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

The updated Physical Activity Guidelines for Americans are scheduled to be released in late 2018 and are likely to carry similar recommendations. They may be accessed at https://health.gov/news/blog-bayw/2018/03/2018-physical-activity-guidelines-advisory-committee-submits-scientific-report/.

3.4 WOMEN AND CHD

One in three women have some form of CVD; 6.6 million have been diagnosed with CHD.[1] In 2013 alone, 398,086 women died from CVD; about one death every 80 seconds.[1] Just over 40% of these deaths were attributable to CHD, including 50,742 from MI.[1] On average, new and recurrent MI as well as fatal CHD impact 405,000 women each year.[1] Because women typically have heart attacks at older ages than men do, they're more likely to die from them within a few weeks.[1]

Despite these overwhelming statistics, surveys indicate that some 44% of women still do not know that CHD is by far the number one killer of women in the United States.[1] And while regular physical activity has been demonstrated to significantly reduce the risk of CVD in women, they are on average less physically active than men, with only 46.1% of women compared with 54.2% of men engaging in moderate to vigorous activity on three or more days per week.[5]

Although a greater exercise volume and/or intensity appears to produce greater health benefits for most people, the literature examining the relationship between exercise intensity and risk for CHD is not unequivocal.[3] A meta-analysis of 16 gender-specific physical activity cohorts found that the risk for CHD decreased linearly with increasing percentiles of physical activity, but examination of the individual cohorts revealed considerable variation in the outcomes.[3] Specifically, there is evidence to suggest that the dose–response relationship between exercise intensity and risk for CHD or mortality may differ between men and women.[16–20] For example, based on data from the Nurses' Health Study, a cohort of 72,488 female nurses 40 to 65 years old, Manson et al.[17] concluded that "the reduction in risk for CHD for women who walked at a brisk pace three or more hours per week was similar to those women who engaged in regular vigorous ($\geq$ 6 MET) exercise." In 2001, data from the Women's Health Study[16] showed that walking 1 to 1.5 hours per week was associated with a 51% reduction in risk for CHD but walking $\geq$2 hours per week conferred no greater reduction in risk. More vigorous activity was not associated with a lower risk for CHD, comparing highest with lowest. Similarly, the relationship between walking pace and risk for CHD did not demonstrate a linear trend.

Other studies have not demonstrated an association between physical activity/inactivity and CHD and/or mortality in women, with 1 review reporting no relationship between physical inactivity and CHD in 10 of 14 studies.[18] More recently, Blair et al.[19] found that all-cause mortality rates in women did not differ across the range of physical activity levels. The Framingham Study also found no association

between physical activity level and mortality in women.[20] In contrast, a 2004 meta-analysis of 30 longitudinal studies examining the impact of physical activity on the risk for CVD in women showed a dose–response relationship, with a 20% to 40% reduction in risk for CVD in the most active women compared with those who were sedentary.[21]

This inconsistency in findings has been observed elsewhere[17] and may be the result of real gender differences or may reflect differences in study participants and/or design. For example, in the 16 studies he examined, Williams[3] found that the intervals (tertiles, quartiles, etc.) reported differed greatly, with 9 studies using 3 levels, 6 using 4 levels, and 1 study using 6 levels. In particular, the apparent gender differences in the response to physical activity may also be mediated by the physical activity levels of the study participants. As an example, in 2001, the most active 20% of women in the Women's Health Study expended ≥ 1,500 kcal per week in LTPA, whereas men in the highest quintile of physical activity in the Harvard Alumni Health Study reported expending ≥ 3,129 kcal per week in LTPA.[3] Interestingly, very recent physical activity data acquired by accelerometer from over 17,000 older women in the Women's Health Study showed a clear dose–response relationship with time engaged in "moderate to vigorous" physical activity.[22] Those women who exercised just over an hour per day at this intensity had mortality rates almost 65% lower than women who were sedentary.

The limited data on the relation between physical fitness and risk for CVD and/or mortality in women suggest a greater similarity with studies of men when compared with studies of physical activity. A relatively recent review of the literature revealed that low exercise capacity and slow recovery heart rate predicted CVD and mortality in both men and women.[23] Data from the St. James Women Take Heart Project demonstrated a 17% reduction in mortality in women for every 1 MET increase in exercise capacity.[21] As such, it would appear that women who engage in exercise vigorous enough to improve aerobic fitness gain health benefits comparable to those of their male counterparts.

3.5 STROKE

While the incidence of stroke and associated mortality rate has been declining since at least 2001, it is estimated that 795,000 people in the United States experience a new (~610,000) or recurrent (~185,000) stroke each year.[1] Of these, the large majority are ischemic (~87%) with the remainder being hemorrhagic in nature.[1] The risk of a stroke for African-Americans is nearly double that for Caucasians, and it tends to occur at a younger age.[1] Hispanics, particularly Mexican-Americans, have significantly higher rates of ischemic stroke and at a younger age.[1] Annually, 55,000 more women than men have a stroke, with the incidence in women aged 45 to 54 years being especially high.[1]

Some 200,000 to 500,000 transient ischemic attacks (TIAs) are estimated to occur in the United States each year, and the incidence is higher in men and in African- and Mexican-Americans.[1] The occurrence of a TIA increases the risk of a stroke in both the short term and the long term.[1] Approximately 15% of all strokes are preceded by a TIA, and about 12–13% of individuals will die within a year of a TIA.[1]

The most important risk factors for stroke include history of TIA, pre-existing CHD, age, hypertension, diabetes mellitus, cigarette smoking, and atrial fibrillation.[1] Physical inactivity has also been shown to increase the risk of a stroke and stroke mortality, but its relationship to cerebral events is less well understood than its relationship to CHD.[1] Meta-analyses have shown that the reduction in risk for stroke associated with aerobic exercise/activity ranges between 20% and 40% depending on the type of stroke and the study design.[22,23] The benefit for women is less clear and may not be as great as that for men.[22] It remains unresolved whether or not a dose–response relationship exists between level of physical activity and stroke risk. While those studies that looked at different levels of physical activity generally found a greater benefit for higher levels of physical activity, there was a real lack of consistency in their findings.[22] In addition, the criteria for different levels of physical activity are not uniform, varying from study to study and often poorly quantified. As such, an exercise prescription to optimize the reduction in risk for stroke remains undetermined. Currently, the American Heart Association recommends moderately intense aerobic physical activity for *at least* 30 minutes per day to reduce the risk of ischemic stroke.[24] While there is evidence that greater muscular strength in youth is associated with a modestly reduced risk (~5–10%) for stroke later in life,[25] the relationship between muscular strength, strength training, and stroke risk remains virtually unexplored.

3.6 HYPERTENSION

Based on data from the National Health and Nutrition Examination Survey (NHANES), it's estimated that some 80 million adults or almost 1 in 3 American adults suffer from hypertension (systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg).[1] The prevalence in African-American adults is amongst the highest in the world. Looking at all Americans with hypertension, 82.7% were aware of it, 76.5% were being treated, and only 54.1% had it under control. A meta-analysis of 61 studies involving more than 1 million individuals demonstrated that mortality associated with both ischemic heart disease (IHD) and stroke increases linearly from levels as low as 115 mmHg SBP and 75 mmHg DBP.[26] For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, there is a doubling of mortality from both IHD and stroke.[26] Those with hypertension have a shorter life expectancy and a shorter life expectancy free of CVD, and can expect to live more years with CVD compared with those who are normotensive.[1]

Regular physical activity has been shown to be an effective way to lower blood pressure in 75% of persons with

hypertension.[27,28] Compared with sedentary adults, those who are physically active have a lower incidence of hypertension,[29–31] with blood pressures that average 5 mmHg lower.[32] Higher levels of occupational and/or leisure-time physical activity are associated with lower blood pressure.[27,31,33] These data have led to recommendations for regular physical activity as lifestyle therapy for the prevention and management of hypertension.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)[34] recommends regular aerobic physical activity such as brisk walking at least 30 minutes per day, most days of the week, for the prevention and management of hypertension. In a meta-analysis of 44 trials of at least 4 weeks' duration and after controlling for other factors, increased physical activity was associated with a small but significant decrease of 3/2 mmHg in normotensive subjects and 7/6 mmHg in hypertensive subjects.[35] The training intensity in these studies averaged 65% of heart rate or VO_2 reserve. However, the characteristics of the training programs (intensity, duration, and frequency) explained less than 5% of the variance in blood pressure response. Weekly energy expenditure was not significantly related to the changes in SBP or DBP. Vigorous exercise was not found to be different from moderate-intensity exercise in its ability to reduce blood pressure, with some studies showing that exercise at 40% of VO_2 reserve produced a greater reduction in SBP than exercise at 65–75% of VO_2 reserve.[35,36] As such, and per JNC VII, regular moderate-intensity exercise is recommended for the prevention and management of hypertension.

The JNC VIII Guidelines made the same recommendations. Some significant changes were made in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults.[37] The 2017 ACC/AHA Guidelines established classification and treatment thresholds, found in Table 3.1. These guidelines also recommend a variety of non-pharmacologic interventions, prominently featuring physical activity consisting of 120–150 minutes per week of aerobic physical activity and 90–120 minutes per week of dynamic resistance exercise.

The guidelines for blood pressure in the 2017 ACC/AHA recommendations were significantly lower than previous recommendations and were based on the findings of the Systolic Blood Pressure Intervention Trial (SPRINT).[38] This study was conducted on over 9,000 individuals with a mean age of 67.9 years and a SBP of 130–180 mmHg who were at increased risk for cardiovascular events. Researchers compared targets of SBP <120 mmHg with standard targets of SBP <140 mmHg. The SPRINT Trial showed a 30% decrease in the composite outcome of MI, acute coronary syndrome, stroke, and heart failure or death compared with the standard target group. Unfortunately, in order to achieve these lower levels of blood pressure, three antihypertensive medicines were required in many participants, which may make it impractical in a normal clinical setting. It should be emphasized that many of the lifestyle modalities, such as weight management, weight loss, increased physical activity, and proper nutrition, can also significantly lower blood pressure, which may make these lower thresholds more achievable.

3.6.1 Resistance Exercise Training and Blood Pressure

Resistance training is generally recommended as an adjunct to aerobic activity. On average, studies have reported 3 mmHg reductions in resting SBP and DBP following progressive weight lifting programs.[30,37–39] Although this decrease may seem small, a 3 mmHg reduction lowers the risk of CHD, stroke, and all-cause mortality.[30] Two to three days per week of total body resistance training is generally recommended.[16,40–42] However, as with aerobic exercise, the "optimal" exercise prescription for strength training is not known. More specifically, low- to moderate-intensity strength training (30–40% of a 1 repetition maximum (1RM) for upper body exercises, and 50–60% 1RM for lower body exercises) is currently recommended by some for the prevention and management of high blood pressure.[27,42] Cornelissen et al.[43] showed that single bouts of either high- or low-intensity resistance exercise lowered SBP, but only low-intensity training lowered DBP. Other studies reported that high-intensity resistance training reduced neither SBP nor DBP, and actually raised SBP in some individuals.[44]

TABLE 3.1
Categories of Blood Pressure in Adults

BP classification	SBP (mmHg)	DBP (mmHg)	Lifestyle habits	Drug treatment
Normal BP	<120	<80	Promote	None
Elevated BP	120–129	<80	Yes	None
Stage 1 hypertension	130–139	80–89	Yes	May be indicated[a]
Stage 2 hypertension	≥140	≥90	Yes	Indicated[b]

Adapted from 2017ACC/AHA Categories of BP in Adults.
[a]Initiate pharmacological treatment if clinical atherosclerotic CVD or estimated ten-year CVD risk >10%.
[b]Consideration of two medications from two different classes.

The currently recommended strength training program to optimize blood pressure reduction is 1–3 sets of 10–15 repetitions for each of the major muscle groups (thighs [hamstrings and quadriceps], hips, back, chest, arms, and abdominals), on two to three days per week.[30,42,45–49]

3.7 HEART FAILURE

It's estimated that some 5.7 million Americans suffer from heart failure (HF, also known as congestive heart failure).[1] The risk of developing HF increases with age; by the age of 40, both men and women have a 1 in 5 risk of developing HF at some time in their lives.[1] Both the incidence and prevalence of HF are particularly high in minorities, especially African-Americans.[1] HF occurs earlier and mortality is higher in African-Americans compared with Caucasians.[1]

Surprisingly few studies have examined the relationship between physical activity and primary prevention of HF. Two large longitudinal studies exploring this association found that compared with sedentary individuals, those who engaged in regular vigorous exercise had a 15–35% lower risk for developing HF.[50,51] Vigorous activity was defined as activities "vigorous enough to work up a sweat,"[45] such as running, jogging, swimming, heavy gardening, or competitive sports.[50,51] The reduction in risk was correlated with the frequency of vigorous exercise in a dose–response manner.[45] Activity of a moderate intensity, defined as > four hours/week of walking, cycling, or light gardening, was associated with ~15% reduction in risk. Pooled data from three large cohort studies showed a strong and negative dose–response relationship between LTPA and risk for HF. Those individuals whose LTPA exceeded 1,000 MET/min/week had a risk for HF that was 19% lower than that of their sedentary counterparts.[52,53]

3.8 DIABETES

The latest available data from NHANES estimate that 12.8% of Americans over the age of 19 have diabetes mellitus (DM), of which >90% are classified as Type II (T2DM).[1] Insulin resistance often precedes the onset of T2DM and is prevalent in the pre-diabetic states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Over 35% of Americans are classified as pre-diabetic with IFG and/or IGT.[1] This means that more than 47% of all adults have some degree of abnormal glycoregulation![1] The prevalence of CHD has been estimated to be as high as 55% in adult diabetics, and T2DM is an independent risk factor for myocardial infarction and CVD in both men and women.[53] T2DM is a predictor of ischemic stroke and HF, and DM increases the overall CV risk in patients with pre-existing HF.[54,55] Compared with non-diabetics, mortality from CHD has been reported to be twice as great in diabetic men and four to five times greater in diabetic women.[52] CVD is responsible for at least two-thirds of deaths in adults with DM.[52]

3.8.1 The Metabolic Syndrome, CVD, and T2DM

The clustering of risk factors known as the metabolic syndrome (see following section for definition and more information) is predictive of both T2DM and CVD. It is associated with a twofold increase in the risk for cardiovascular events.[53] Abdominal obesity in particular is an independent risk factor for insulin resistance[54,55] and T2DM.[56] Much of the increased risk of CHD and CVD associated with T2DM can be attributed to the presence of the metabolic syndrome.[57] One study reported ten-year cardiovascular mortality to be 3.55 times greater in men with metabolic syndrome than in those without the condition.[58]

Numerous studies have demonstrated an inverse relationship between physical activity and/or fitness and the risk for developing T2DM.[59–6]. Men of low fitness have a two to three times greater risk of developing T2DM compared with those in the higher fitness categories.[59,60] Similarly, physical activity shares an inverse relationship with the risk for T2DM in a dose–response manner. Even just daily walking for more than 30 minutes has been shown to reduce the risk of developing T2DM by 20–45%.[66,69–72,69–7]. Brisk/faster walking was associated with a lower risk independent of time spent walking.[63,66,67] In an interventional trial involving 18 previously sedentary middle-aged men and women, six months of walking (minimum of three days per week for 30 minutes) resulted in improved insulin sensitivity.[70] Sedentary behaviors such as excessive television watching have been demonstrated to increase the risk for T2DM even after controlling for diet and physical activity levels. It has been estimated that 43% of new cases of diabetes could be prevented by watching TV for less than ten hours per week and engaging in brisk walking for 30 minutes or more per day.[68] Modest improvements in diet and exercise habits have been shown to reduce the incidence of T2DM even in those at highest risk for developing it—those with IFG and/or IGT.[71–73]

3.8.2 Glycemic Control

Studies of aerobic exercise training have shown significant but modest reductions in glycosylated hemoglobin (HbA_{1c}, long-term index of glycemic control) of about 8% from baseline.[79,80] The exercise intensity in these studies accounted for almost 83% of the differences in post-intervention HbA_{1c} compared with 21% determined by exercise volume. Those interventions with an intensity >65% of VO_{2max} demonstrated the greatest improvement in HbA_{1c}. As such, exercise interventions for glycemic control should include some vigorous exercise.[79]

3.8.3 Strength Training

Resistance training, especially in combination with aerobic exercise training, can significantly improve HbA_{1C} levels, fasting blood glucose, and insulin sensitivity.[80] Additionally, other risk factors, such as blood pressure, have been shown

to be significantly reduced in diabetics with a program combining strength and aerobic training compared with either aerobic or resistance training alone.[77] As such, The American Diabetes Association now recommends strength training, in addition to aerobic exercise training, as part of a program to prevent or manage T2DM.[81] Weight training has been found to be safe in persons with CVD, ST depression, myocardial ischemia, ventricular dysrhythmias, and other cardiovascular complications.[78] The myocardial demands of high-intensity weight training are comparable to activities such as stair-climbing, walking uphill, or carrying 20–30 lbs of groceries.[81]

The following are some of the specific recommendations from the American Diabetes Association Consensus Statement on Physical Activity/Exercise and Type II Diabetes:[81]

- People with IGT should begin and continue a program of weight control, including at least 150 minutes per week of moderate to vigorous physical activity and a healthful diet with modest energy restriction.
- To improve glycemic control, assist with weight maintenance, and reduce risk for CVD, the panel recommends 150 minutes per week or more of moderate-intensity aerobic physical activity, and/or 90 minutes per week or more of vigorous aerobic exercise. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.
- Compared with lower volumes of activity, performing at least 4 hours per week of moderate to vigorous aerobic and/or resistance exercise is associated with greater CVD risk reduction.
- For long-term maintenance of major weight loss (≥13.6 kg or 30 lbs), larger volumes of exercise (7 hours per week of moderate or vigorous aerobic physical activity) may be helpful.
- Unless contraindicated, people with type 2 diabetes should be encouraged to perform resistance exercise 3 times per week, targeting all major muscle groups. This should progress to 3 sets of 8 to 10 repetitions at a weight that cannot be lifted more than 8 to 10 times. Initial supervision and periodic reassessments by a qualified exercise specialist are recommended to ensure that resistance exercises are performed correctly, to maximize health benefits, and to minimize the risk of injury.

3.9 OBESITY

Based on the most recent data from the NHANES, and using body mass index (BMI, body weight in kg/height in meters^2) as the criterion measure, the prevalence of overweight and obesity in the United States has decreased among those of higher socioeconomic status but increased among those of lower socioeconomic status.[1] The overall prevalence of extreme obesity in U.S. youth continues to increase, especially among adolescent boys. In adults, overweight is defined as a BMI of 25–29.9 kg/m^2. Obesity is defined as a BMI ≥30; extreme (formerly morbid) obesity is defined as a BMI ≥40. Overall, 73% of U.S. adults were overweight or obese according to recent NHANES data.[82] Among men, non-Hispanic blacks were less likely to be overweight or obese (69%) compared with Hispanics (80%) and non-Hispanic whites (73%). In women, non-Hispanic blacks (82%) and Hispanics (76%) were much more likely to be overweight or obese compared with non-Hispanic whites (61%). Among all U.S. adults, 35% were obese (34% of men vs. 36% of women). Hispanic and non-Hispanic black males (38%) were more likely to be obese than non-Hispanic white men (34%). Among women, non-Hispanic blacks (58%) and Hispanics (43%) were more likely to be obese than non-Hispanic whites (33%).

Over the last two decades, it has become increasingly apparent that abdominal adipose tissue has unique metabolic properties and may be more predictive of CVD, the metabolic syndrome, and diabetes than BMI or measures of overall adiposity.[83–93] Abdominal or central obesity is most commonly assessed by measuring waist circumference or waist-to-hip ratio (WHR). From 1988–1994 to 1999–2000 (most recent data available), the mean waist circumference of adult Americans increased from 95.3 cm to 98.6 cm in males and from 88.7 cm to 92.2 cm in females.[85]

Despite these rather alarming trends, only 40.3% of obese patients were advised to lose weight by their family physician in 2004, down from 42.3% in 1994.[86] An evaluation of an academic pediatric hospital found that only a few more than half (53%) of the children who met the NHANES criteria for overweight (≥95th percentile for BMI) were identified as such by their primary care physician.[87] Interestingly, while a majority (69%) of the children's charts contained an "adequate" dietary history, only 15% included information regarding physical activity and/or television watching.

3.9.1 Central Adiposity, Inflammation, and CVD

Atherosclerosis has now come to be understood as an inflammatory disease.[94–98] A growing body of evidence further demonstrates that greater adipose tissue mass, especially visceral adipose tissue, directly contributes to systemic inflammation.[92–94] The pro-inflammatory state associated with abdominal obesity has been proposed as a common underlying condition linking CVD, insulin resistance/T2DM, and the metabolic syndrome.[95–97] While a complete discussion of the complex physiology and mechanisms of adipose-related inflammation is beyond the scope of this chapter, it is increasingly evident that visceral adipose tissue secretes a veritable host of pro-inflammatory cytokines. Greater levels of central adiposity have been shown to be associated with higher circulating levels of these pro-inflammatory proteins, such as interleukin-6 (IL-6), tumor necrosis factor–alpha (TNF-alpha), and C-reactive protein (CRP).[98–100]

A published review of lifestyle interventions and systemic inflammation observed that 9 of the 12 studies reviewed demonstrated an inverse relationship between physical activity or fitness and markers of inflammation, after controlling for BMI or other measures of adiposity.[101] For example, in a 20-year follow-up of 4,252 elderly men (aged 40–59 at baseline), Wisse et al.[102] found that physical activity level was inversely associated with levels of CRP and other inflammatory markers, even after adjusting for BMI and other covariates. In those men who went from "at least lightly active" to inactive, the levels of these markers were similar to those men who had been inactive throughout the follow-up period. Those who were inactive at baseline but increased their level of activity had levels similar to those men who had remained continuously active.

The HERITAGE Family Study examined the effects of 20 weeks of exercise training on CRP levels in 652 sedentary, but healthy, adults.[103] The training program was performed on cycle ergometers three days per week, progressing to 50 minutes at 75% of baseline VO_{2max}. This protocol resulted in a substantial (17.8%) increase in VO_{2max}. However, reduction in CRP levels only occurred in the individuals with high baseline levels of CRP. The positive relationship between baseline CRP levels and exercise-induced changes has been observed elsewhere[104] and may explain, at least in part, why some studies have not found that an exercise intervention reduces levels of inflammatory markers.[105–110]

3.9.2 The "Fitness vs. Fatness" Debate

While it is well established that both increased body fat and low levels of physical activity and/or fitness are associated with increased mortality, T2DM, and CVD, it is not precisely clear as to their relative importance or how they interact. An extensive review of the literature addressing the fitness vs. fatness debate as it pertains to CHD and/or CVD concluded: "physically active lifestyle and/or a moderately high fitness level (i.e., not in the bottom 20% of the population) reduces the risk of CVD/CHD in overweight or obese persons."[111] While they suggest that overweight or obese individuals who are physically fit or active have levels of risk that approach those associated with those of lean, unfit persons, they also concede that their risk is still greater than for those who are fit/active and of normal weight. The authors further observed that the risk reduction associated with increased fitness or activity is greater in those who are overweight or obese compared with those of normal weight. Finally, they recommend that physical activity should be encouraged regardless of whether or not that activity induces weight loss. This recommendation is supported by the majority of the studies reviewed that found physical activity/fitness to be independent risk factors for CHD/CVD.

Addressing obesity begins with the understanding that weight gain is caused by a cumulative positive energy balance where energy intake exceeds energy expenditure. As such, weight loss can *only* occur in the presence of a negative energy balance. Maintenance of body weight, therefore, requires that energy intake matches energy expenditure. While the concept of energy balance or imbalance is conceptually simple, the respective roles of diet and exercise in weight loss and management are less clear. There follows a brief summary of recent and relevant investigations of the role of physical activity in 1) preventing weight gain, 2) weight loss, and 3) weight loss maintenance.

3.9.3 Preventing Weight Gain

In 2003, the International Association for the Study of Obesity (IASO) released the following statement regarding physical activity and prevention of unhealthy weight gain:

> The current physical activity guideline for adults of 30 minutes of moderate intensity activity daily, preferably all days of the week, is of importance for limiting health risks for a number of chronic diseases including CHD and diabetes. However for preventing weight gain or regain this guideline is likely to be insufficient for many individuals in the current environment. There is compelling evidence that prevention of weight regain in formerly obese individuals requires 60–90 minutes of moderate intensity activity or lesser amounts of vigorous intensity activity … For children, even more activity time is recommended. A good approach for many individuals to obtain the recommended level of physical activity is to reduce sedentary behaviour by incorporating more incidental and leisure-time activity into the daily routine.[112]

3.9.4 Physical Activity and Sustained Weight Loss

Unfortunately, most studies do not support increasing physical activity, either alone or in combination with a calorie restrictive diet, to be an effective means to produce short-term weight loss.[116–118] However, physical activity appears to play a major role in long-term maintenance of weight loss.[113–116] An extensive review of the role of exercise in promoting weight loss combined data sets and used weighted mean differences (WMD) to explore the efficacy of exercise interventions.[116] The randomized clinical trials (RCTs) in this review only included studies that incorporated a follow-up of at least 12 months' duration to assess long-term maintenance of weight loss. A summary of their findings follows:

- Compared with diet alone, diet plus exercise produced significantly greater weight loss at 12 months (WMD = −1.95 kg),18 months (WMD = −7.83 kg), and 36 months (WMD = −8.22 kg). In addition, there were small but significantly greater differences/improvements in high-density lipoprotein (HDL) and triglycerides at 12 months. At 18 months, diet plus exercise demonstrated large and significantly greater reductions in SBP (WMD = −8.90 mmHg) and DBP (WMD = −12.10 mmHg).

- A separate analysis in this review compared diet plus behavior therapy with diet plus behavior therapy and exercise. The addition of exercise produced significantly greater weight loss at 12 months (WMD = −3.02 kg) and at 24 months (WMD = −2.16 kg). There were no significant differences between groups for cholesterol, blood pressure, or glucose.

These data suggest that regular physical activity is advantageous for sustained weight loss.

3.9.5 How Much Physical Activity Is Required for Sustained Weight Loss?

There is a general consensus that 2,500–2,800 kcal per week (60–90 minutes per day of moderate-intensity physical activity) is required for long-term weight loss, as reflected in the recommendations and consensus statements of the U.S. Department of Health,[117] ACSM, and IASO.[118] These recommendations are supported by data from the National Weight Control Registry (NWCR), a database of approximately 5,000 individuals who have minimally lost 30 lbs. for at least one year (average weight loss is about 30 kg for an average of 5.5 years).[119] Data collected on these "successful losers" indicate that more than 90% of participants expended ~2,800 kcal per week in physical activity.

3.9.6 Resistance Training and Weight Loss

Despite claims in the popular literature, strength training is not recommended as the primary mode of exercise for weight loss.[118] While strength/resistance training has been shown to preserve fat-free mass when coupled with a calorie-restrictive diet, it has not been shown to enhance weight loss either alone or in combination with a dietary intervention.[113,115,116,118] Despite the apparent ability of resistance training to maintain muscle mass in the presence of calorie deficit, it does not appear to be able to prevent the decrease in resting energy expenditure associated with weight loss.[118,120] In the absence of a dietary intervention, some studies have shown that high-intensity resistance training can significantly increase resting energy expenditure for 16 hours or more.[121–125] However, these findings are based on a very small number of subjects and are not supported by the results of other investigations.[126–128] As such, in the absence of stronger evidence, resistance training is not recommended as the primary form of exercise to promote or enhance weight loss.[118] However, weight training may provide an advantage in maintaining fat-free mass and enhancing body composition with a weight loss intervention.[120,129–131]

3.10 LIPIDS

The role of blood lipids in the pathology of atherosclerosis is well established, and dyslipidemia is understood to be an important contributing factor for CHD.[132] Dyslipidemia includes elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C).[132] In addition, newer lipid and lipoprotein measures such as lipoprotein particle size and number, apolipoproteins, and triglyceride-rich lipoproteins (TRL) are emerging as risk factors that may also increase CVD risk.[133] The National Cholesterol Education Program Adult Treatment Panel III has published guidelines establishing lipid and lipoprotein modification goals for both primary and secondary prevention.[132] However, data from NHANES indicate that many Americans have not achieved recommended levels for all lipids and lipoproteins.[134]

One of the proposed mechanisms by which regular physical activity reduces the risk for CHD is its effect on blood lipids, especially the increase in HDL-C and reduction in TG levels.[132–134] Cross-sectional studies have consistently shown a positive association between the volume and intensity of aerobic activities and HDL-C levels and a negative association with TG levels.[135] However, reviews of the literature reveal a surprisingly inconsistent response of other blood lipids to regular aerobic exercise.[135,136] These findings may be further confounded by concurrent changes in body weight or composition. In studies without a dietary intervention, the most commonly reported change in lipids was an increase in HDL averaging 4.6%, ranging from a decrease of 5.8% to an increase of 25%. Simultaneous reductions in TG (3.7%), LDL-C (5.0%), but not TC, were also observed.[135] Changes in TC and LDL-C are much less frequently reported, are modest when they do occur, and may be more attributable to weight loss than the exercise intervention per se. As such, regular exercise alone cannot be recommended as an effective strategy to lower TC or LDL-C.[134]

Relatively few studies have attempted to evaluate the effect of the exercise prescription (intensity, volume, etc.) on blood lipids, and as such, there is no consensus on the optimal exercise regime for improving cholesterol profile. In most of the studies reviewed, the exercise intervention was performed at moderate to high intensity, three to five times per week, for at least 30 minutes per session. Total caloric expenditure, as opposed to exercise intensity, has been proposed to be of greatest importance for blood lipids, and a threshold of between 1,200 and 2,500 kcal per week has been proposed.[137]

A meta-analysis of studies that explored the effect of strength training on blood lipids, dating back to 1955, found that strength training resulted in modest but significant improvements in blood lipid profiles (but not HDL-C).[138] However, while earlier studies generally demonstrated an improvement in blood lipid profile with resistance training, at least some suffered from design flaws, including no or poor dietary control,[139–142] no control group,[139–141] or no control for fat loss.[140–143] Better designed and/or more recent studies have not found an improvement in lipoprotein profiles with resistance/strength training.[144–148]

3.11 METABOLIC SYNDROME

The clustering of established risk factors for CVD and T2DM has been recognized for decades.[149–165] In 1988, Gerald Reaven drew immense attention to risk factor clustering and CVD in his now famous "Banting Lecture" at the annual meeting of the American Diabetes Association.[153] He described a constellation of risk factors leading to the development of T2DM and CVD, which he termed *Syndrome X*. Reaven postulated the etiology and clinical course of three major related diseases—T2DM, CVD, and hypertension—all having a common foundation of insulin resistance and hyperinsulinemia. However, at that time, adiposity was not considered a major etiological factor.

The metabolic syndrome has been recognized as a global public health problem that is strongly linked as a seminal cause of CVD and T2DM, both of which are responsible for premature mortality and morbidity worldwide.[166–169] The metabolic syndrome is characterized by the clustering of specific cardiovascular risk factors including insulin resistance (IR), central obesity, hypertension, and atherogenic dyslipidemia (specifically, elevated TG and low levels of HDL-C.[170–174] Also, depending on the medical society definition applied, microalbuminuria may also be considered another risk factor.[174]

3.11.1 Different Medical Society Definitions of the Metabolic Syndrome

In establishing an *official diagnosis* for the metabolic syndrome, the American Association of Clinical Endocrinologists (AACE) championed the creation of the International Classification of Disease 9th revision (ICD-9) Code 277.7 for the metabolic syndrome.[171] Currently, there are five working medical society definitions proposed for the diagnosis of the metabolic syndrome.[175,176] Table 3.2 summarizes the various definitions published by the following medical societies: 1) World Health Organization (WHO),[177] 2) European Group for the study of Insulin Resistance (EGIR),[173] 3) AHA and the National Heart, Lung and Blood Institute (NHLBI) definition,[178] which refers to the updated National Cholesterol Education Program (NCEP) 2001 definition, 4) the American College of Endocrinology (ACE) and AACE consensus definition for epidemiological research,[174] and 5) the International Diabetes Federation (IDF).[175]

The majority of the recent research focusing on the metabolic syndrome involved the use of the NCEP definition because of its clinical utility (see Table 3.2). The NCEP definition requires that three of the following five criteria be present for a diagnosis of the metabolic syndrome: IFG,

TABLE 3.2
Metabolic Syndrome Definitions Issued by Various Medical Societies

	WHO 1999	EGIR 1999	ACE/AACE 2003	IDF 2005	AHA/NHLBI 2005
Requisite Criteria	IGT,IFG, type 2 diabetes, insulin in top quartile of population	Insulin in top quartile of population	High risk[a] BMI >25 kg/m^2 or WC >102 cm(men) or >88 cm (women)	WC ≥94 cm (men) and ≥80 cm (women), and population specific for ethnic groups[b]	N/A
Other Criteria	Plus ≥2 of:	Plus ≥2 of:	Plus ≥2 of:	Plus ≥2 of:	Plus ≥2 of:
Glucose	N/A	≥100 mg/dL, 2-hour post OGTT ≥140 mg/dL but not diabetes	≥100 mg/dL, 2-hour post OGTT ≥140 mg/dL but not diabetes	≥100 mg/dL, diabetes	≥100 mg/dL, diabetes or Rx
Obesity	W:H ratio >0.9 (men) or >0.85 (women); BMI >30 kg/m^2	WC ≥94 cm (men) or ≥80 cm (women)	N/A	N/A	WC ≥102 cm (men) or ≥88 cm (women)
Lipids	TG ≥150 mg/dL and/or HDL-C <35 mg/dL (men) or <39 mg/dL (women)	TG >180 mg/dL and/or HDL-C <39 mg/dL in men or women or Rx	TG >150 mg/dL or HDL-C <40 mg/dL (men) or <50 mg/dL (women)	TG ≥150 mg/dL or Rx or HDL-C <40 mg/dL (men) or <50 mg/dL (women) or Rx	TG ≥150 mg/dL or HDL-C <40 mg/dL (men) or <50 mg/dL (women) or Rx
Hypertension	≥140/90 mmHg or Rx	≥140/90 mmHg or Rx	>130/85 mmHg or Rx	≥130/85 mmHg or Rx	≥130/85 mmHg or Rx
Other	Microalbuminuria ACR ≥30 mg/g				

WC, waist circumference; W:H, waist hip; TG, triglycerides; OGTT, oral glucose tolerance test; Rx, medication; ACR, albumin: creatinine ratio; others designated in text. WHO = World Health Organization; EGIR = European Group for the study of Insulin Resistance; AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute; ACE/AACE = American College of Endocrinology/American Association of Clinical Endocrinologists; IDF = International Diabetes Federation.

[a]Family history of type II or gestational diabetes, known CVD, polycystic ovary syndrome, physically inactive lifestyle, >40 years of age, and ethnic populations at high risk for type II diabetes.

[b]In this analysis, Mexican-American men were classified using a WC cut-off value of ≥90 cm and Mexican-American women ≥80 cm.[9]

represented by a fasting blood sugar ≥110 milligrams per deciliter (mg/dL), including T2DM; HDL-C <40 mg/dL in men and <50 mg/dL in women; triglycerides ≥150 mg/dL; an augmented waist circumference (WC) of ≥102 centimeters (cm) in men and ≥88 cm in women; or a blood pressure value of ≥130/85 millimeters of mercury (mmHg).

3.11.2 Current Prevalence Estimates

It is estimated that close to one billion people worldwide have the metabolic syndrome.[179] Global prevalence estimates of the metabolic syndrome vary considerably, depending on the population under study, definition applied, and study design utilized. Using the NCEP definition, the age-adjusted prevalence for the metabolic syndrome in the United States is estimated to be 34.6%. These data also showed a 10% increase in the prevalence of the metabolic syndrome in U.S. adults from 1988–2002. With the metabolic syndrome becoming more common in Westernized societies,[179] the prevalence and incidence are anticipated to increase in line with the prevalence and incidence of obesity[177] and T2DM.[178]

3.11.3 Physical Activity and Prevalence of the Metabolic Syndrome

The association between physical activity or inactivity and prevalence of the metabolic syndrome is not clear, at least based on cross-sectional studies.[179–188] In most studies, the initial analysis often shows a negative relationship between physical activity level and the prevalence or risk of metabolic syndrome, but this association typically disappears after controlling for other factors such as gender, age, education, and socioeconomic status or other risk factors (i.e., smoking).

Several longitudinal studies showed that increased levels of physical activity, especially of vigorous intensity, were associated with significantly and dramatically reduced risk for developing the metabolic syndrome in a dose–response manner. Interventional studies are fewer in number, but at least one study showed that 20 weeks of vigorous exercise performed for 30 minutes, three times per week, resulted in a decreased prevalence of the metabolic syndrome (from 16.9% to 11.8%) in 621 men and women aged from 17 to 65 years.[178] That is, of the 105 participants with the metabolic syndrome at baseline, 32 no longer had the syndrome at the end of the study.

3.11.4 Cardiorespiratory Fitness and the Metabolic Syndrome

The relationship between cardiorespiratory fitness, as measured by VO_{2max}, and the metabolic syndrome has not been studied as extensively as the relationship with physical activity.[189–191] However, cardiorespiratory fitness can be more objectively measured and may be more predictive of the metabolic syndrome than physical activity per se. Cardiorespiratory fitness has been shown to be predictive of the metabolic syndrome, with men of low fitness (VO_{2max} <29.1 $ml \cdot kg^{-1} \cdot min^{-1}$) being almost seven times more likely to have metabolic syndrome compared with those men with a VO_{2max} ≥35.5 $ml \cdot kg^{-1} \cdot min^{-1}$.[83] Over a four-year period, and after controlling for age, BMI, socioeconomic status, presence of CVD, smoking, and alcohol consumption, the incidence of metabolic syndrome was found to be 47% and 75% lower in middle-aged men with a VO_{2max} of 29.0–35.6 and ≥ 37.0 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, compared with those men whose VO_{2max} was less than 28.9 $ml \cdot kg^{-1} \cdot min^{-1}$.

The relationship between aerobic fitness and the prevalence of the metabolic syndrome appears to hold for women as well. Women with a VO_{2max} of 11 METs or greater had a prevalence of the metabolic syndrome that was one-third to one-fourth that of women of lower fitness.[192]

The precise amount and intensity of physical activity required to prevent or reverse the clustering of risk factors known as the metabolic syndrome has yet to be definitely determined. While there is evidence to suggest that regular, moderate-intensity physical activity (such as walking 30 minutes on most days, if not every day, of the week) may be preventive of the metabolic syndrome, other evidence suggests that activity of greater intensity may be required to optimally minimize risk. Greater cardiorespiratory fitness has demonstrated an even stronger negative association with the metabolic syndrome. Attainment of higher levels of fitness requires more vigorous physical activity.[11]

3.11.5 Muscular Strength and the Metabolic Syndrome

Evidence from the Aerobics Center Longitudinal Study (ACLS) suggests that even after controlling for age, examination date, smoking status, alcohol intake, number of metabolic syndrome risk factors at baseline, family history of diabetes, hypertension, and early onset coronary artery, men above the 75th percentile for muscular strength have a 24% lower risk for developing the metabolic syndrome compared with men in the lowest strength category.[190] Others have also illustrated the benefits of resistance training and increases in muscular strength for metabolic risk.[193–195] Muscular fitness appears to add another level of protection against the metabolic syndrome in men and may help with daily and long-term glycemic control. However, strength training is recommended as an adjunct to regular aerobic exercise, but not the sole or primary form of activity to prevent or manage the metabolic syndrome[196].

3.12 CONCLUSION

CVD, in all its forms, represents the greatest threat, by far, to health and longevity in the United States and the world. The major risk factors for CVD are well known, and their prevention and/or management are crucial in reducing the prevalence of CHD, stroke, hypertension, and HF. Greater physical activity and especially greater cardiovascular

fitness have been shown to significantly reduce the risk of CVD. The reduction in risk is largely mediated via the risk factors as described in this chapter. As such, an appropriate and individually prescribed program of regular physical activity or exercise should be a standard lifestyle intervention for individuals of all ages and abilities.

CLINICAL APPLICATIONS

- Increased levels of cardiovascular and physical activity lower the risk factors for CVD as well as multiple other factors such as obesity, metabolic syndrome, and diabetes.
- The higher the fitness levels, the lower the risk of CVD.
- Aerobic conditioning and physical activity provide more benefits in terms of lowering cardiovascular risk compared with strength training, although resistance strength training can also add additional benefits.
- Assessment of cardiovascular fitness should be part of all physician visits.
- Prescription for physical activity should be part of all physician visits.
- Guidelines for Physical Activity are available, including the Physical Activity Guidelines for Americans 2008 (to be updated in 2018) and guidelines from the American College of Sports Medicine. These guidelines can be used as a basis for exercise and physical activity prescription.

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4 Clinical Strategies for Managing Dyslipidemias

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KEY POINTS

1. Dyslipidemia, in the form of abnormalities in total cholesterol, low-density lipoprotein, triglycerides, and/or a reduced level of high-density lipoprotein, is a significant risk factor for cardiovascular disease.
2. Treatment of dyslipidemia is guided by cholesterol levels, cardiovascular risk, and patient-specific factors.
3. A heart-healthy lifestyle is the cornerstone of the treatment of dyslipidemia, including healthy diet, exercise, maintaining a healthy weight, avoidance of tobacco, and moderation of alcohol.
4. Pharmacologic therapy for dyslipidemia requires a multipronged approach with a focus on the utilization of 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase inhibitors (statins).
5. Lipoprotein (Lp-a) and apo B_{100} have a demonstrated relationship with CVD risk. There is the consideration of intensive pharmacological therapy for patients with diagnosed Lp-a.

4.1 BACKGROUND

Dyslipidemia is defined as abnormal levels of lipids in the blood and may include elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and/or triglycerides (TG), and/or a reduced level of high-density lipoprotein cholesterol (HDL-C), alone or in combination.[1] Dyslipidemia is a prevalent condition in the United States, with almost 28% of the U.S. population having elevated LDL-C levels.[2] Additionally, elevated serum lipoprotein(a) is a risk factor for atherosclerotic cardiovascular disease. Environment and lifestyle play a large role in dyslipidemias, with a polygenic mode of inheritance. Familial hypercholesterolemia, an inherited monogenic autosomal dominant form, is much less common.[3] Although lipids contribute to many vital functions in the body, abnormal levels of lipids and their lipoprotein carriers contribute significantly to atherosclerosis and the development and progression of CVD.

4.2 ELEVATED TOTAL AND LDL CHOLESTEROL

Dating back to the 1970s, large longitudinal observational studies have demonstrated an association between total cholesterol and risk of CVD, even in the presence of other major risk factors.[4–8] Other observational studies have found that apolipoprotein B_{100} (apo B_{100}) is a strong predictor of coronary artery disease (CAD).[9,10] There also have been studies that have shown an association between lipoprotein-a (Lp-a) with increased risk of CAD.[9,11,12] Lp-a has an additional glycoprotein attached to the apo B_{100} and is considered a prominent monogenetic lipid disorder. Lp-a has proatherogenic and proinflammatory properties contributing to atherosclerotic cardiovascular disease (ASCVD) and a prothrombotic environment.[13,14] A meta-analysis of 36 prospective cohort studies with 126,634 participants found that after adjusting for age and sex, a higher level of Lp-a (one standard deviation [SD] higher concentration) increased the risk of myocardial infarction and CAD by 13% and ischemic stroke by 10%.[15] Guidelines are cautious and do not recommend universal testing as of yet, but it may be reasonable to measure Lp-a in individuals with hypercholesterolemia or with a history of ASCVD (or in a first degree relative). Primary prevention includes aggressive lifestyle change and statin drugs.[16] For secondary prevention, higher statin drug dosages, PCSK9 inhibition, niacin, or consideration of apheresis may be suggested.[16] However, it should be mentioned that statins have no effect on reducing Lp-a levels.[17] To date, there is no pharmacotherapy that specifically reduces Lp-a, although several trials are investigating Apo-antisense nucleotide and antisense oligonucleotides (Mipomersen) for the reduction of Lp-a.[13] To date, niacin, Mipomersen, and PCSK9 inhibitor have been found to have a 20–30% Lp-a lowering effect on top of total LDL lowering effects.[18–20]

Randomized controlled trials (RCTs) using cholesterol-lowering drugs such as statins (HMG-coenzyme A reductase inhibitors), cholesterol absorption inhibitors, cholestyramine, niacin, and fibrates have been successful in reducing CAD risk.[11,12,21,22] A landmark meta-analysis of large-scale (>30,000 participants) placebo-controlled statin trials found that statins resulted in a mean reduction of 30% in initial or recurrent CAD events over an average of 5.4 years.[22] Further analysis indicated that this CAD reduction was primarily related to a 28% reduction in LDL-C, with some benefits being derived from a 20% reduction in TG and an increase of 5% in HDL-C. Additionally, statins have pleiotropic antiatherosclerotic effects, which can further contribute to the reduction in the development and progression of CAD.[23,24]

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4.3 HIGH-DENSITY LIPOPROTEIN

Low HDL-C also is associated with the development and progression of atherosclerosis.[25] Support for the protective role of HDL-C against CAD has been shown by numerous RCTs through several cardioprotective factors, including antioxidant effects, improved endothelial function, anti-inflammatory effects, reduction in endothelial-derived adhesive proteins, antithrombotic and profibrinolytic effects, reverse cholesterol transport from foam cells to the liver, and even regression of atherosclerotic plaques.[22,25–28] Conversely, in a meta-analysis of over 100 trials, it was found that increasing HDL-C alone does not reduce the risk of cardiovascular events.[29] Supporting this finding, a recent pooled analysis of 37 cohort studies involving 3,524,505 participants and more than 612,027 deaths found that the risk (hazard ratio) for all-cause mortality followed a J-shaped curve related to high and low HDL-C with an all-cause mortality hazard ratio of 1.03 (95% confidence interval [CI]: 1.01–1.05) for each 10 mg/dL increase in HDL-C level and 1.10 (95% CI: 1.09–1.12) for each 10 mg/dL decrease in HDL level.[30] These findings require further investigation to elucidate the physiological pathways.

HDL-C removes cholesterol from the cell membrane and transports it to the liver for disposal in the bile as cholesterol or as bile acids.[31] Cholesterol acyltransferase (LCAT), an enzyme carried by HDL and activated by HDL's apo A-I, acts by esterifying HDL's newly acquired cholesterol, and the resulting cholesterol ester (CE) is drawn into the core of HDL. Cholesterol ester transfer protein (CETP) is another enzyme involved in reversed cholesterol transfer by catalyzing the transfer of CE from HDL to other lipoproteins in exchange for TG. If CETP is inhibited via pharmacological measures or inherited mechanisms, there is a resultant increase in HDL-C levels, which is postulated to reduce atherogenesis. However, it appears that drugs that impair the function of CETP result in an increased level of HDL-C as designed, but in contrast to a hypothesized reduction in atherogenesis, this does not protect against CAD and may even promote progression of CAD and result in increased risk of morbidity and mortality.[32–35] These studies suggest that very high levels of large HDL particles laden with cholesterol may lose their cardioprotective properties and may even be atherogenic.[36] Interestingly, individuals who have a specific genetic variant of apo A-I (i.e., apo A-I Milano) have low levels of HDL-C and a very low risk of CAD, and vegetarians generally also have reduced levels of HDL-C (and LDL-C) and have a low risk of CAD.[37,38]

4.4 TRIGLYCERIDES

Triglyceride levels are elevated for about an hour following a meal, primarily as part of TG-rich chylomicron. In the fasting state, TGs are primarily carried by very low-density lipoprotein (VLDL). Apo C-II (carried by chylomicrons and VLDL) activates lipoprotein lipase (LPL), found in the capillaries of skeletal and heart muscle as well as the adipose tissue. Associated LPL then acts on the TG of the lipoproteins to release free fatty acids and glycerol.[31] The triglyceride-rich VLDL is the precursor for circulating LDL via intermediate-density lipoprotein (IDL), which (together with other apo B_{100}-containing remnants of VLDL) may be able to cross the arterial endothelium and contribute to atherogenesis.[39]

Hypertriglyceridemia is another concerning type of dyslipidemia. Primary hypertriglyceridemia was recently found to be associated with incident CAD events (hazard ratio [HR] 1.79, 95% CI: 1.32–2.43), although the relationship was attenuated when adjusted for other cardiovascular risk factors (HR 1.53, 95% CI: 1.06–2.20).[40] This relationship has not been consistently found, particularly in studies that adjusted for HDL-C and other CAD risk factors.[41,42] For example, a meta-analysis of 6 cohorts involving 46,000 men and 10,000 women found that each 1 mmol/l (88.5 mg/dl) increment in TG level was associated with increased risk of CAD by 76% in women and 32% in men, but reduced to 37% and 14% for women and men, respectively, after adjustment for HDL-C.[42] In a review, it was found that lowering TG levels was associated with lower risk of major vascular events, even after adjustment for LDL-C lowering.[43]

4.5 NON-HDL CHOLESTEROL AND APO B

Older and current guidelines recommend lowering cholesterol levels within all apo B-containing lipoprotein particles (i.e., non-HDL-C, TC minus HDL-C) as a secondary therapeutic goal, following primary targeting of LDL-C, in the presence of elevated TG.[42,44] In observational studies, non-HDL-C was found to be a predictor of CVD.[45] Since LDL and VLDL (and its remnants following TG lipolysis) each contain one molecule of apo B, it is postulated that the plasma level of apo B represents the total atherogenic particle number.[44,46,47] A strong correlation (0.8–0.9) exists between non-HDL-C and apo B, but they are only modestly concordant.[36]

4.6 LIPID CLASSIFICATION AND TREATMENT TARGETS

The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Management of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults emphasizes classification and treatment of hyperlipidemia (HLD) based on risk of atherosclerotic CVD (ASCVD) and the importance of a patient–clinician discussion about level of risk.[48] The Guideline recommends, prior to shared decision-making about initiating therapy for HLD, the assessment of risk for ASCVD, which includes evaluation of LDL-C levels and the assessment of other patient-specific factors that influence ASCVD risk.[48] The guidelines also recommend evaluating the influence of lifestyle changes and lipid lowering medications by assessing

a fasting lipid panel 4 to 12 weeks after initiation of statin therapy or dose adjustment, and then every 3 to 12 months thereafter.[48]

Specifically, the 2018 ACC/AHA guidelines recommended that statin therapy is started based on age, diabetes status, LDL-C level, presence of ASCVD, and ASCVD risk (Table 4.1). We refer the reader to these guidelines for full details. To estimate ASCVD risk, this guideline advocates for the use of the ASCVD Risk Predictor Plus.[48,49] The ACC/AHA guidelines emphasize monitoring the efficacy of statin therapy at lowering LDL-C to the desired intensity.[48] High-intensity treatment is considered to be >50% lowering of LDL-C, moderate intensity is considered to be lowering of LDL-C by 30–50%, and low intensity is considered to be lowering of LDL-C by <30%.[48] The intensity of statin treatment depends on the degree of ASCVD risk (Table 4.1).[48] The ACC/AHA guidelines do not strongly advocate for the use of pharmacotherapy other than statins for primary prevention, but ezetimibe and PCSK9-I are discussed in the recommendations for those with clinical ASCVD.[48] Although some studies have found cholesterol lowering from niacin, bile acid sequestrants, cholesterol absorption inhibitors, fibrates, or omega-3 fatty acids,[50] these therapies are not a part of the clinical treatment algorithms in the 2018 AHA/ACC guidelines.[48] The 2018 AHA/ACC guidelines emphasize the importance of clinician–patient discussion on pharmacologic therapy and risk reduction when adding non-statin therapies.[51] This guideline also provides clinicians with additional considerations and criteria for the management of HLD in specific populations; for example, when TG ≥500 mg/dl, it is recommended to evaluate for reversible causes and initiate statin therapy.[48] Of note, the 2020 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines have additional guidelines and recommendations for the treatment of dyslipidemia and prevention of CVD, to which we refer the reader for additional guidance.[52]

4.6.1 Non-Statin Pharmacologic Agents

In the last decades, new non-statin pharmacologic agents have become available to treat dyslipidemia, some of which

TABLE 4.1

Risk Category, Recommended Therapy Intensity, and Expected Response: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines[48]

Patient group	Therapy intensity
Primary prevention	
Age >75 years old	Clinical risk assessment and discussion#
40–75 years old	
40–75 years old with diabetes	Moderate-to-high-intensity statin
40–75 years old and LDL-C ≥70–<190 mg/dl without diabetes	*For all in this category, ASCVD ten-year risk percentage begins the risk discussion*
ASCVD low risk (<5%)	Emphasize lifestyle, reduce risk factors (class I)
ASCVD borderline risk (5–7.4%)	If risk enhancers*,discuss moderate-intensity statin therapy (class IIb)
ASCVD intermediate risk (7.5–<20%)	If risk estimate + risk enhancers* favor statin, initiate moderate-intensity statin to reduce LDL-C by 30–49% (class I)+
ASCVD high risk (≥20%)	Initiate statin to reduce LDL-C by ≥50% (class I)
Patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dl)	Begin high-intensity statin therapy If the LDL-C remains ≥100 mg/dl consider adding ezetimibe If the LDL-C remains ≥100 mg/dl when taking statin plus ezetimibe, and patients has factors that increase risk of ASCVD, a PCSK9 inhibitor may be considered
Have clinical ASCVD	
ASCVD, not at very high-risk and age ≤75 years old	High-intensity statin (goal: reduce LDL-C ≥50%) (class I)If on maximal statin therapy and LDL ≥70 mg/dl, adding ezetimibe may be reasonable
ASCVD, not at very high-risk and age >75	Moderate- or high-intensity statin is reasonable (class IIa)
Very high-risk ASCVD	High-intensity or maximal statin (class I) If on maximal statin therapy and LDL ≥70 mg/dl, adding ezetimibe may be reasonable** If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (class I)**

*Risk enhancers: family history of premature ASCVD, persistently elevated LDL-C ≥160 mg/dL, chronic kidney disease, metabolic syndrome, preeclampsia, premature menopause, inflammatory diseases, persistently elevated triglycerides (≥175 mg/dl), and if measured, hsCRP ≥2.0 mg/l, Lp(a) >50 mg/dl (>2.0 mmol/l), apo B ≥130 mg/dl, ankle brachial index <0.9.

**If on maximal statin therapy and LDL ≥70 mg/dl or non-HDL-C ≥100 mg/dl, adding PCSK9-I is reasonable (class IIa)

+If risk decision is uncertain: consider measuring CAC in selected adults → If CAC zero: lower risk, if CAC 1–99: favors statin (especially > 55 years old), and if CAC >100 and/or >=75th percentile, initiate statin therapy.

Consider risk reduction, benefits vs. adverse effects, drug–drug interactions, frailty, and patient preferences.

Adapted from Grundy, S.M. et al., *J. Am. Coll. Cardiol.*, 73(24), e285–e350, 2019.

are being used in practice, whereas some are still under investigation.

Ezetimibe is a selective cholesterol absorption inhibitor that works by inhibiting Niemann-Pick C1 like 1 (NPC1L1) protein and by reducing cholesterol absorption in the small intestine.[51] Ezetimibe targets the uptake of cholesterol absorption at the jejunal enterocyte brush border and can lower LDL-C and non-HDL-C.[53] The CAD IMPROVE-IT trial investigated ezetimibe plus statin therapy compared with statin therapy alone in 18,000 patients who had been hospitalized for acute coronary syndrome (ACS) and found a statistically significant difference in LDL-C levels and improved cardiovascular outcomes (absolute risk difference 2.0).[54] As previously described, ezetimibe is a component of the treatment algorithm to lower LDL-C in 2018 AHA/ACC guidelines.[48]

The PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are another class shown to be beneficial when used with a statin. PCSK9 inhibitors are human monoclonal antibodies to PCSK9, which bind to PCSK9 and increase LDL receptors by increasing recycling of receptors to the cell surface, which should decrease LDL-C.[51,53,55] Landmark trials have supported the use of PCSK9 inhibitors in decreasing CAD risk. The FOURIER trial, a placebo-controlled trial of over 27,000 patients, reported that the addition of evolocumab (PCSK9 inhibitor) to statin therapy lowered LDL-C by 59% and reduced the risk of cardiovascular events.[56] The ODYSSEY trial, which utilized the PCSK9 inhibitor alirocumab in over 2,000 patients over 24 weeks, reported that the difference in LDL-C between the placebo and alirocumab group was 62%, and this effect remained at 78 weeks.[57] The PCSK9 inhibitor bococizumab was evaluated in the SPIRE-1 and SPIRE-2 trials, which found a 56% reduction in LDL-C compared with the placebo group, which had a 2.9% increase in patients with high cardiovascular risk at 14 weeks.[58] Bococizumab further reduced the risk of cardiovascular events in the high-risk patients (HR: 0.79, p=0.02) but not the low-risk group (HR: 0.99, p=0.94). The trial was, however, stopped prematurely due to the finding of high rates of the development of antidrug antibodies.[58] Inclisiran was studied in over 1,500 participants in the ORION-11 trial, and it was found that LDL-C level was reduced by approximately 50% (−52.3%, 95% CI: −48.8, −57.7%; p < 0.001).[59] The ongoing ORION-4 trial will recruit a total of 15,000 participants aged >55 years old with ASCVD and elevated TC (>155 mg/dl) to evaluate the effect on cardiovascular outcomes.[60] As previously described, the PCSK9 inhibitors are a component of the treatment algorithm to lower LDL-C in 2018 AHA/ACC guidelines.[48]

Bempedoic acid, an adenosine triphosphate (ATP) citrate lyase inhibitor, is an approved non-statin medication.[61] The Clear HARMONY trial tested the safety and efficacy of bempedoic acid in 2,230 patients and found that at 12 weeks, bempedoic acid reduced the mean of LDL-C by 19.2 mg/dl (mean difference from placebo: −18.1%, 95% CI: −20.0, −16.1; p < 0.001).[62] A meta-analysis of seven RCTs similarly found that bempedoic acid therapy significantly reduced LDL-C by 17.1–23.5% (mean difference (MD): −20.3%, 95% CI: −23.5, −17.1; I^2: 43%).[63]

Evinacumab is an angiopoietin-like protein 3 inhibitor drug that was found to reduce LDL-C by 33.12% (MD: −33.12, 95% CI: −48.64, −17.61), triglycerides by 50.96% (MD: −50.96, 95% CI: −56.55, −45.36), and HDL−C by 12.77% (MD: −12.77%, 95% CI: −16.36, −9.19) compared with placebo.[64] This medication is approved and in use clinically.

4.7 ROLE OF LIFESTYLE IN THE MANAGEMENT OF DYSLIPIDEMIA

Lifestyle, including diet, body weight, physical activity, alcohol consumption, and smoking status, plays a role in blood lipid levels in the population, although heritability can make a substantial contribution as well. With this in mind, it is clear why lifestyle is a key aspect of the management of dyslipidemia, as supported by both the 2018 ACC/AHA Guideline on the management of blood cholesterol and the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[1,48]

4.7.1 Impact of Diet (See Also Chapter 7)

It has been established that eating patterns associated with reduced rates of dyslipidemia and CVD include:

- A diet emphasizing vegetables, fruits, legumes, nuts, whole grains, and fish[1]
- Vegetarian and near-vegetarian diets[65,66]
- Mediterranean-style diets[4,67–70]
- The Dietary Approach to Reduce Hypertension (DASH) diet[71–74]
- The "Prudent Heart Healthy Diet," advocated by the AHA (formerly the AHA Step II Diet), ATP III, and the U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services (DHHS), Dietary Guidelines for Americans 2005,[45,73,75,76] and the AHA diet[73]

Overall, when looking at these diets in summary, dietary patterns to improve blood lipids are characterized by (1) a low intake of saturated fat, trans fat, and dietary cholesterol through a reduction in the consumption of red meat, hard fats, and full-fat milk, (2) increased intake of whole grains, legumes, fruits, and vegetables, and (3) a moderate intake of fish, poultry, and low-fat or fat-free milk and dairy products.

The 2018 ACC/AHA Guideline on the management of blood cholesterol and the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease encourage a heart-healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, red meat

and processed red meats, refined carbohydrates, and sweetened beverages.[1,48] The guideline also supports a reduction in calories from trans fat and saturated fat, with only 5–6% of total calories coming from saturated fat, an adjustment to appropriate calorie requirements, and personal and cultural food preferences.[48] The 2017 Update to the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk similarly advocates that lifestyle modification is needed before and after initiation of cholesterol-lowering medications.[51]

Observational studies and RCTs have found that the variance in mean TC levels was related to the variation in mean percentage of energy from saturated fatty acids (SFAs).[4,38,67,68] Metabolic ward studies have shown that omega-6 polyunsaturated fatty acids (PUFAs), particularly linoleic acid (18:1, n-6), have a cholesterol-lowering effect, as illustrated by the Keys equation:[77] $\Delta TC = 1.3\ (2\Delta S - \Delta P) + 1.5\ \Delta Z$ (ΔTC is the change in total cholesterol; ΔS is the change in percent of total calories provided by SFAs; ΔP is the change in percentage of energy from omega-6 PUFAs; and ΔZ is the square root of the dietary cholesterol expressed in mg per 1,000 kcal of dietary energy). This equation shows that for every 1% reduction in SFAs, serum TC is expected to be reduced by 2%. The relatively small impact of dietary cholesterol on blood cholesterol is due to the limited absorption of dietary cholesterol, with about two-thirds of circulating cholesterol synthesized de novo by the liver from acetyl coenzyme A products of metabolism.[78] It should be noted that only three long-carbon-chain SFAs have been shown experimentally to be responsible for increasing TC (lauric [12:0], myristic [14:0], and palmitic [16:0] acid). These SFAs appear to markedly downregulate hepatic synthesis of LDL apo B/E cell receptors, which reduces the removal of circulating LDL as well as VLDL, IDL, and apo B_{100}-containing lipoprotein remnants and results in a significant increase in cholesterol level.[78,79] Stearic acid (18:0) and SFAs with 10 or fewer carbons have no effect on TC and are not included in the Keys equation.[77] Omega-6 PUFAs, in contrast, lower cholesterol levels by upregulating hepatic LDL receptors, increasing the removal of lipoproteins, and reducing the rate of conversion of VLDL to LDL. The ATP III recommendation is to keep intake of omega-6 PUFAs to 10% or less of daily energy intake, as higher intake appears to lower HDL-C levels. Linoleic acid (18:2, n-6), the parent compound for the omega-6 family of PUFAs, is found in sunflower, corn, and soybean oils, as well as in seeds and nuts. Linoleic acid forms arachidonic acid (AA; 20:4, n-6) via enzymatic stepwise elongation of its carbon chain. AA is the precursor of prostaglandins and eicosanoids via cyclooxygenase (COX) enzyme activity and is essential for regulation of blood circulation, blood clotting, and inflammatory responses.[31]

Omega-3 PUFAs are a family of long-chained, essential fatty acids required in the diet. They have an initial double bond/unsaturated carbon atom at the third position from the methyl end of the molecule, rather than the sixth as for omega-6 PUFA. There has been increased interest in omega-3-PUFA due to its importance for eye and brain health, and its postulated contribution to primary and secondary prevention of CAD.[79–81] The parent compound of this family is α-linolenic acid (ALA;18:3, n-3). Its carbon chain is enzymatically converted to longer chains, and it eventually becomes the more unsaturated fatty acids, eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:5, n-3). It should be noted that DHA competes with AA for conversion via COX enzyme to alternative eicosanoids and prostaglandins, which are believed to be cardioprotective (Table 4.2) Because of the limited conversion of ALA to EPA and DHA, all three are currently considered essential dietary nutrients; however, DHA appears to be the most biologically active form of the omega-3 PUFAs.[82] ALA is primarily present in vegetable oils, particularly canola and soybean oils, whereas fatty fish such as salmon, mackerel, herring, and sardines are rich sources of EPA and DHA. The apparent relationship between omega-3 fatty acids and cardiovascular health was first observed during studies of the unique dietary habits of the Greenland Inuit.[83] Despite a diet consisting primarily of very fatty meat from sea mammals, they had a surprisingly low rate of CVD. This was eventually attributed to their high intake of EPA and DHA from these food sources. Other epidemiological observational studies have reported an inverse association of fish or fish oil supplement consumption with morbidity and mortality from CVD.[84] The cardioprotective effects of these fatty acids has further been confirmed in animal models and by primary and secondary CAD prevention trials,

TABLE 4.2

Experimentally Identified Mechanisms Postulated to Contribute to the Apparent Cardioprotective Effects of Omega-3 PUFAs [85, 86, 88]

- Reduced dyslipidemia (decreased TG and VLDL-C, and increased HDL-C)
- A moderate reduction in elevated blood pressure
- Improved endothelial function and endothelial-dependent and independent vasoreactivity
- Anti-inflammatory effects, inhibiting progression of atherosclerosis
- Antithrombotic effects
- Increased parasympathetic activity, as evidenced by increased heart rate variability
- Improved myocardial electrical stability, reducing risk of a fatal ventricular arrhythmia

indicating a 20–30% reduction in fatal and nonfatal CAD events.[85,86] It appears that a modest intake (e.g., one to two portions per week) of fatty fish that contains high amounts of omega-3 fatty acids may reduce the risk of CAD and is suggested as part of a healthy diet.[87]

DHA and EPA fish oil–based supplements have been found in older epidemiological studies to reduce TG (6% to 10% per gram of EPA and DHA), VLDL-C, VLDL-TG, and non-HDL-C, and increase HDL-C.[89] Additionally, intake of fatty acids from fish or fish oil supplements has been found by some studies to reduce rates of all-cause mortality, cardiac death, and sudden death,[90] but this has not been consistently found, and controversy still lingers. A recent Cochrane Review found that increasing EPA and DHA intake has minimal effect on cardiovascular health.[91] However, a meta-analysis from 2019 involving 127,477 participants found a significantly lower risk of ischemic CVD events and mortality with marine omega-3 supplementation (rate ratio [RR] = 0.92).[144] These findings were supported in a meta-analysis by Khan et al. in 2021 in 149,051 participants, indicating that EPA mono-therapy is more effective compared with EPA+DHA therapy, and overall CVD events and mortality were significantly reduced.[81] Additionally, Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels and reduced CVD morbidity and mortality in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT, HR = 0.75 with 2 g supplement vs. placebo), suggesting that purified EPA is beneficial.[92] Since over-the-counter fish oil supplements are not controlled by the Food and Drug Administration (FDA), they are not recommended for treating dyslipidemia, and current guidelines recommend eating two servings of fatty fish per week, such as salmon, sardine, mackerel, herring, trout, tuna, and anchovies, for primary and secondary CVD prevention as described earlier. However, prescription grade or purified EPA and DHA may be considered for patients with hypertriglyceridemia. For example, clinicians may consider prescribing icosapent ethyl (ethyl ester of EPA) for individuals with high levels of triglycerides who are already on a statin and who are at high cardiovascular risk.[52,92,93] The ongoing RESPECT-EPA trial should provide further clarification on the efficacy of EPA and ASCVD.[94]

The Seven Countries Study was one of the first to explore the benign relationship of monounsaturated fatty acids (MUFAs) in the diet to risk of CAD.[5] Approximately 80% of the fatty acids contained in olive oil are MUFAs, particularly oleic acid (18:1, n-9). Oleic acid either has no effect on blood lipids or reduces TC, but it appears to have no effect on HDL-C or TG.[95] However, the presence of MUFAs in LDL makes it less susceptible to oxidation. MUFAs are plentiful in olive oil, canola and peanut oil, avocados, nuts, and fish.

Trans fatty acids (TFAs) have attracted attention in recent years due to their adverse effects on blood lipids. The FDA mandates inclusion of quantities of TFAs on food labels along with those of SFAs and PUSFs, and an FDA ruling deemed hydrogenated oils as not safe for use in human food.[96] It should be noted that only a limited quantity of TFAs occurs naturally in meat and dairy products, while the 2.6% of daily energy intake of TFAs results from intake of margarines and shortenings used in food preparation. This is due to the formation of TFAs by the partial hydrogenation of the double bonds of unsaturated fatty acids in liquid vegetable oils to solidify them in order to make products more heat-stable and increase shelf life.[97] TFAs appear to promote cholesterol synthesis and a concomitant increase in LDL-C levels. But more importantly, in contrast to SFAs, they increase LP(a) and lower HDL-C levels.[98]

A diet high in non-digestible fiber, particularly β-glycans and pectin, may have a modest beneficial effect on TC and LDL-C levels.[38,99] Soluble fibers are found in whole grains (especially oats), fruits and vegetables, and beans and legumes. Soluble fibers prevent reabsorption of bile salts in the small intestine, which results in upregulation of hepatic LDL receptors, thereby enhancing LDL removal and reducing LDL-C levels. An intake of 30 g/day of soluble fiber has been associated with a 5 mg/dl reduction in total LDL-C levels, particularly the smaller, dense, atherogenic LDL particles, thereby reducing fatal and nonfatal CAD events.[38,100–103] Dietary fiber also slows gastric emptying and glucose absorption, and this decreases insulin response, which reduces hepatic lipogenesis and promotes satiety. The 2018 AHA/ACC Guidelines on the Management of Blood Cholesterol do not include a discussion or recommendation regarding fiber intake.[48]

Plant steroids and stanols (when esterified with a fatty acid, or when emulsified) are plentiful in vegetable oils, seeds, and nuts.[104] Past research found that PUFA margarines with or without the addition of 2 g/day of sterols/stanols to the diet may result in a reduction of 21 mg/dl in LDL-C (a 9–27% reduction) and non-HDL-C levels.[104,105] LDL-C removal is enhanced via an upregulation of LDL receptors in the liver, in part due to competitive inhibition of dietary and biliary cholesterol uptake in the small intestine.[38] The 2018 AHA/ACC Guidelines do not discuss or include recommendations regarding these products.[48] The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines from 2019 recommend supplementation with 2 g plant sterols (phytosterols) as a therapeutic strategy to reduce cholesterol in patients with dyslipidemia as adjunct pharmacotherapy in addition to statins if the treatment goal is not achieved.[106] This is in contrast to several other organizations, including the National Institute for Health and Care (NICE) in the United Kingdom, which cautions against the use of plant sterols/stanols due to their genetic association with atherogenesis in some studies.[107,108] Thus, despite the apparent cholesterol lowering capability of plant sterols/stanols, there have been no studies indicating CVD risk reduction and some studies indicating higher CVD risk. Therefore, much additional research is needed in this area, and no recommendations can currently be made.

Plant-derived antioxidants including vitamin E and β, other carotenes, water-soluble vitamin C, and a large variety of non-nutrient phytochemicals are postulated to reduce the development and progression of CAD by preventing oxidative stress and reducing LDL oxidation and endothelial dysfunction.[99,109] Vitamin E, which is found in vegetable oil, nuts, and seeds, is transported by LDL and has been associated with reduced CAD risk and reduction of oxidized LDL.[99,109] However, it should be noted that numerous large-scale randomized controlled clinical trials and meta-analyses have failed to demonstrate any protective effect against CVD mortality by supplementation of antioxidant vitamins (vitamin E, vitamin C, or beta carotene).[99,109–111] Flavonoids are a type of plant chemical (phytochemicals) found in fruits, vegetables, tea, red wine (and grape juice, from which wine is derived), and cocoa bean products. *In vitro* studies have shown phytochemicals to be potent inhibitors of LDL oxidation.[99] In a prospective cohort study, flavonoid consumption was associated with lower risk of death from CAD.[112] However, there have been inconsistent results from clinical trials, and evidence does not clearly support their use in a clinical setting.[99,113]

Moderate alcohol intake of one to two drinks per day has been associated with an approximately one-third lower risk of mortality from CAD when compared with either no or heavy alcohol consumption, possibly due to both antithrombotic effects and ethanol-involved increased HDL-C levels (by ~12%).[99,114] However, it should be noted that alcohol also produces a concomitant increase in TG and VLDL production and therefore raises non-HDL-C levels. Moreover, excessive use of alcohol has other harmful effects. Thus, it is considered unethical to encourage non-drinkers to start using alcohol for prevention of CAD.

4.8 WEIGHT MANAGEMENT

Health consequences associated with excess body weight include dyslipidemia, metabolic syndrome, and thereby an increased risk of type 2 diabetes and CAD.[115] Thus, weight reduction is a critical component in the management of dyslipidemia. The 2018 AHA/ACC Guidelines on the Management of Blood Cholesterol recommend caloric intake to avoid gaining weight or to lose weight in those who are overweight or obese.[48] Of note, if exercise is combined with reduced energy intake, fat-free mass is generally better preserved during weight reduction, and weight regain appears to be less likely.[96–98] It is essential to include behavioral modification related to diet and physical activity to successfully achieve and maintain an ideal body weight.[115–117]

A 10% loss in weight may result in a significant decrease in TC of 30.5 mg/dl (–13.2%), LDL–C 15.1 mg/dl (–11.3%), VLDL–C 15.5 mg/dl (–36.5%), and TG 58.4 mg/dl (–32.2%); HDL-C initially declines during the active weight loss phase and then increases by 5.5 mg/dl (+12.6%) after weight stabilization.[118] In a meta-analysis, Nordmann et al.[119] compared the effects of a reduced-fat diet (to 25–35% [current recommendation] of daily energy in four of these studies and to 10% in one study) with a low-carbohydrate diet (unlimited in protein and fat) in five studies on weight loss and cardiovascular risk factors. The mean weight loss at six months was significantly greater on the low-carbohydrate diet, while at 12 months there was no statistically significant difference between the low-carbohydrate and the reduced-fat diets. However, the reduction in TC and LDL-C was more favorable on the low-fat compared with the low-carbohydrate diets (mean difference in LDL-C between diets was –5.4 mg/dl). Interestingly, changes in HDL-C (+4.6 mg/dl) and TG (–22.1 mg/dl) were significantly more favorable on the low-carbohydrate diets. A meta-analysis by Hu and colleagues of 23 trials found that patients who followed low-carbohydrate diets compared with low-fat diets experienced a small but statistically significant lower reduction in TC (2.7 mg/dl) and LDL-C (3.7 mg/dl) but a greater increase in HDL-C (3.3 mg/dl) and a greater decrease in TG (–4 mg/dl), but these findings were not examined for long-term effects.[120]

A randomized study investigated the effects of weight loss and blood lipid changes in three diets—a low-carbohydrate, non-restricted-calorie diet with reduced fat (<35% of daily energy); a restricted-calorie diet, following AHA guidelines; and a restricted-calorie Mediterranean-type diet.[121] The mean weight loss after the two-year follow-up was 2.9 kg for the AHA diet, 4.4 kg for the Mediterranean diet, and 4.7 kg for the low-carbohydrate diet. There was a mean increase in HDL-C of 8.4 (+22.4%), 6.3, and 6.4 (+16%) mg/dl for the low-carbohydrate, AHA, and Mediterranean diets, respectively. TG reduction (23.7 mg/dl) was more favorable with the low-carbohydrate diet. Surprisingly, in this study there were no significant changes in LDL-C in any group.

The combination of dietary modification and regular exercise has consistently been shown to be effective for achieving and maintaining long-term weight reduction (~1 kg/week greater weight loss than dieting alone).[115–117] Aerobic exercise (as well as resistance exercise) may attenuate the fat-free mass loss that will occur with weight loss.[117] Regular aerobic exercise for 60–90 minutes per day is critical for preventing weight regain.[122,123] However, exercise alone is generally not effective for inducing sizable weight loss, unless one performs supervised, large-volume, prolonged aerobic exercise on five to seven days per week.[117]

4.8.1 Exercise Effects

It has been well established that increased physical activity and exercise training reduce morbidity and mortality from CAD through multiple cardioprotective effects, including improving dyslipidemia.[124–127] Studies have consistently shown that aerobic exercise training results in an increase in HDL-C of 2–3 mg/dl, or about 4–5%, with an associated increase in apo A-I and LPL activity.[128–131] However, it should be noted that there is a great deal of variability in the response of HDL-C following exercise training[132] that

appears to be related to genetic factors as well as weight change.[133–137] Exercise-induced reductions in LDL-C and TG appear to be rare in the absence of an associated weight loss.[128–131] The majority of controlled studies on the effect of exercise on blood lipids have used a standard exercise prescription of moderate-to high-intensity aerobic exercise for 30–60 minutes three times per week, with a weekly energy expenditure of 900–2,000 kcal (or about 10–20 MET hours) for at least 12 weeks (~15–20 miles/week of walking).[128–131] Of note, a recent meta-analysis study compared the effectiveness of 5 exercise types on cardiometabolic health in obese and overweight adults and found that among 81 RCTs, combined treatment (endurance training and resistance training) reduced TC significantly more than control (mean difference: –21.35, 95% CI: –33.36, –9.34).[138] The 2018 AHA/ACC Guideline advises that adults should participate in physical activity three to four times per week and that the activity should be 40 minutes in length and at a moderate-to-vigorous intensity.[48]

4.8.2 Cigarette Smoking

Cigarette smoking has been associated with reduced apo A-I and HDL-C levels by about 4 to 6 mg/dl, or 11–14% lower than in non-smokers.[139–141] More importantly, smoking cessation appears to result in a rapid improvement in HDL-C (an average 6–8 mg/dl increase).[142] In addition, smokers have been reported to have slightly higher LDL-C levels than non-smokers. These adverse effects of smoking on blood lipids are postulated to be due both to nicotine and to carbon monoxide exposure.[143]

4.9 CONCLUSIONS AND RECOMMENDATIONS

Lifestyle, particularly diet and physical activity, is a major contributor to dyslipidemia and resulting CVD. Table 4.3 summarizes the effects on dyslipidemia of specific dietary components and other aspects of lifestyle reviewed in this chapter.

CLINICAL APPLICATIONS

- Dietary patterns to improve blood lipids are characterized by (1) a low intake of saturated fat, trans fat, and dietary cholesterol through a reduction in the consumption of red meat, hard fats, and full-fat milk, (2) increased intake of whole grains, legumes, fruits, and vegetables, and (3) a moderate intake of fish and poultry and low-fat or fat-free milk and dairy products.
- To improve lipid profile, decrease SFAs, trans fats, and total cholesterol, moderate alcohol intake, and increase omega-6 PUFAs, omega-3 PUFAs, MUFA, and soluble fiber.
- Weight reduction, exercise, and smoking cessation are essential.
- Pharmacotherapy to treat dyslipidemia includes the use of statin drugs based on degree of ASCVD risk with consideration of the addition of PCSK9-I and ezetimibe to achieve desired LDL-C levels.

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TABLE 4.3
Impact of Lifestyle Changes on Lipids

Dietary component or TLC change	TC	LDL-C	HDL-C	TG (Non-HDL-C)
Decrease SFAs, trans fats, and cholesterol	↓↓	↓↓	↓	↓
Increase omega-6 PUFAs	↓	↓	→ or ↓	→
Increase omega-3 PUFAs	→	→ or ↑	↑ or →	↓↓
Increase MUFAs	→ or ↓	→ or ↓	↑ or →	↓
Increase soluble fiber	↓	↓	→	→
Moderate alcohol	→	→	↑↑	↑↑
Soy proteins	↓	↓	→	↓
Vitamin E (recycled by vitamin C)	_	↓ (OxLDL)	_	_
Negative energy balance (wt. loss)	↓	↓	↑	↓↓
Aerobic exercise	↓ or →	↓ or →	↑	→
Smoking cessation	→	→	↑	↓

↑ Increase, ↓ Decrease, → No change

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5 Lifestyle Management and Prevention of Hypertension

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KEY POINTS

1. Lifestyle interventions play a critical role in the management of hypertension.
2. Physical activity and exercise training can reduce blood pressure through a variety of beneficial physiological mechanisms.
3. A healthy diet consisting of high intake of fruits, vegetables, and whole grains is associated with lower blood pressure.
4. Weight loss and maintaining a healthy body weight through comprehensive lifestyle changes improve blood pressure.
5. Although pharmacotherapy is the mainstay for the treatment of hypertension, guidelines recommend that lifestyle interventions should be prescribed in conjunction with medications for patients with hypertension.

5.1 BACKGROUND

Hypertension is a well-established risk factor for cardiovascular disease (CVD) morbidity and mortality.[1] The global prevalence of hypertension has doubled in the last 30 years.[2] Despite major advances made in the understanding of hypertension physiology and pharmacological treatment of hypertension, blood pressure continues to be poorly controlled in the approximately 116 million U.S. adults diagnosed with hypertension.[3] Hypertension management guidelines highlight the critical role of lifestyle interventions in managing hypertension as a critical adjunctive therapy to pharmacologic treatment. In brief, some guidelines and their lifestyle intervention recommendations include:

- The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (henceforward referred to as the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults) advocates for non-pharmacologic interventions to prevent and treat hypertension, consisting of: (1) weight loss to ideal body weight, (2) the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, (3) sodium restriction to <1,500 mg/day, (4) increased intake of dietary potassium (3,500–5,000 mg/dl), (5) physical activity consisting of 90–150 minutes/week of aerobic or dynamic resistance exercise and three sessions/week of isometric resistance exercise, and (6) moderation of alcohol intake (≤2 drinks/day in men, ≤1 drink/day in women).[4] Of note, the guidelines also emphasize the need for team-based care models of management, including multidisciplinary care, for adults with hypertension to achieve optimal outcomes.[4,5]
- From a global perspective, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the management of arterial hypertension recommend lifestyle interventions for the control of blood pressure, which include smoking cessation, healthy diet, reduced salt intake, moderate alcohol intake, weight control, and regular exercise.[6] The 2020 International Society of Hypertension Global Hypertension Practice Guidelines recommend similar lifestyle interventions, as well as the integration of stress reduction and avoidance of air pollution.[7]

The 2017 AHA/ACC Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults has established classifications and treatment thresholds for hypertension (Table 5.1).[4] Treatment targets for blood pressure in those with hypertension were investigated through the Systolic Blood Pressure Intervention Trial (SPRINT) study with over 9,000 adults (mean age 67.9 years) who at baseline had a systolic blood pressure (SBP) >130–180 mmHg and increased risk of cardiovascular events.[8] The study compared intensive treatment to achieve blood pressure targets of SBP < 120 mmHg with standard targets of SBP < 140 mmHg.[8] The SPRINT trial was stopped early after approximately three years of follow-up due to a lower all-cause mortality (hazard ratio: 0.73, 95% confidence interval [CI] 0.6, 0.9) and a lower incidence (1.65%/year versus 2.19%/year) of the composite

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TABLE 5.1
Adapted from 2017 AHA/ACC Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure

Blood pressure category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	Lifestyle habits	Pharmacotherapy
Normal	<120	and	<80	Promote	None
Elevated	120–129	and	<80	Yes	None
Hypertension					
Stage 1 hypertension	130–139	or	80–89	Yes	May be indicated[a]
Stage 2 hypertension	≥140	or	≥90	Yes	Indicated

[a]Initiate pharmacotherapy if clinical atherosclerotic cardiovascular disease or estimated ten-year CVD risk ≥10%.
Source: Whelton, P.K., et al., *Hypertension* 71(6), e13–e115, 2018.

outcome of myocardial infarction, acute coronary syndrome (ACS), stroke, heart failure, or death in the intensive treatment group compared with the standard target group, but the intensive treatment-lowering target group had significantly higher rates of adverse events than the standard target group.[8] Although these results are promising, the study's measurement of blood pressure through research methods (the mean of three readings after five minutes of rest without a staff member present during readings) and the applicability of the results to populations excluded from the trial, including those with congestive heart failure, severe chronic kidney disease, secondary hypertension, institutionalized older adults, and those with low cardiovascular risk, have caused controversy.[9–11] Ideal blood pressure targets have continued to be investigated since the SPRINT trial. A Cochrane Review, which included 11 randomized trials involving over 38,000 participants, found that in adults with hypertension, there appears to be no additional benefit of lowering blood pressure to less than target levels of <140/90 mmHg.[12]

5.2 MEASUREMENT OF BLOOD PRESSURE

The 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults emphasizes proper blood pressure measurement technique (level IC recommendation) and highlights how differences may arise between blood pressure measured in different settings (please see the Guideline for an in-depth explanation of blood pressure measurement).[4] In brief, the Guideline recommends that blood pressure is measured according to six clearly defined steps: proper patient preparation, proper technique, proper measurements, proper documentation, averaging of readings, and providing readings to patients. The steps highlight the importance of five minutes of rest before measurement, the use of correct cuff size applied to the skin, arm placement, bilateral arm measurement, and utilizing the average of more than two readings obtained on at least two occasions. The Guideline also supports (level IA recommendation) that out-of-office blood pressure measurements are needed to confirm a diagnosis of hypertension and when titrating medications.[4] Of note, the U.S. Preventive Services Task Force recently released an evidence report highlighting that although office-based blood pressure screening has accuracy limitations, there are minimal direct harms of office-based blood pressure screening.[13]

5.3 ETIOLOGY OF HYPERTENSION AND RELATIONSHIP TO CARDIOVASCULAR DISEASE

Primary or essential hypertension, the most common type of hypertension in the United States (90–95%), has no specific known underlying cause, whereas secondary hypertension results from medical conditions such as kidney disease, renal artery stenosis, or adrenal tumors (e.g., pheochromocytoma, primary aldosteronism, and Cushing's disease).[14,15] There are modifiable risk factors associated with the development of essential hypertension, including high body mass index (BMI) (>25 kg/m^2), excess alcohol consumption, low levels of physical activity, and a diet rich in sodium as well as low in calcium, potassium, and magnesium.[14–20] Additionally, hypertension more commonly develops in those with a family history of hypertension, as well as in those who are older. Men are more commonly diagnosed with hypertension than women, possibly because there may be a need for sex-specific cut-off levels for hypertension diagnosis, but this is an area still under investigation.[21] There is increasing evidence that health inequity, institutional and structural racism, and social vulnerabilities may increase the risk of an individual developing hypertension. For example, having social vulnerabilities in the economic, education, health and health care, neighborhood and built environment, and social and community context domains was associated with a higher risk of developing hypertension (adjusted relative risk ratio 1.16 (95%CI 0.99, 1.36) for individuals with one vulnerability and 1.49 (95% CI 1.20, 1.85) for at least two vulnerabilities, compared with having no vulnerabilities) in the REGARDS study (Reasons for Geographic and Racial Differences in Stroke).[22] With this in mind, there is a great interest in developing multi-level interventions to promote health equity in the management of hypertension in the United States.[23] There is a critical need for further investigation in this area of research.

From a physiological perspective, any factor that increases cardiac output or total peripheral vascular resistance can increase blood pressure, since blood pressure is determined hemodynamically by the product of these two variables. Other contributing factors to an increase in blood pressure include endothelial dysfunction, increased sympathetic nervous system activation, and renin-angiotensin-aldosterone system (RAAS) activity. It is postulated that a sustained elevation in blood pressure can reset the baroreceptors, leading to hypertrophy of the arteriolar smooth muscle and increase in peripheral vascular resistance, which are the principal hemodynamic disturbances associated with essential hypertension.[14] Hypertension-induced left ventricular hypertrophy (LVH) is postulated to be related to an increase in both pre-load and after-load (i.e., chronic volume and pressure overload), resulting in eccentric or concentric volumetric ventricular changes associated with dysfunctional systolic contraction.[14,15,17,18] The reader is referred to a review on the topic by Rosendorff et al.[24]

5.4 PHYSICAL ACTIVITY, EXERCISE, AND HYPERTENSION

It is well established that physical activity and exercise influence blood pressure and hypertension. Observational studies have consistently reported an inverse association between leisure time physical activity, physical fitness, and the development and severity of hypertension, even after adjusting for other risk factors.[25–37] For example, Kokkinos et al. reported in a cross-sectional study an 8–9 mmHg lower systolic and 4–5 mmHg lower diastolic mean 24-hour ambulatory blood pressure in individuals with high and moderate physical fitness compared with persons with low fitness levels.[38] A review by Liu et al. found a dose-related relative risk reduction for hypertension of 6% for every ten MET hours per week of leisure time physical activity.[39]

The effect of exercise training on blood pressure has also been well established in countless randomized controlled trials (RCTs) and meta-analyses.[40–55] Overall, these studies have shown that moderate-intensity aerobic exercise training of 30–60 minutes/session three times/week for 12–16 weeks improves blood pressure.[56,57] Studies have found a mean reduction of 2.6–4.7 mmHg in SBP and 1.8–3.1 mmHg in diastolic blood pressure (DBP) in resting blood pressure levels in normotensive individuals and a reduction of 6–10 mmHg in SBP and 2.4–7.6 mmHg DBP in those with hypertension.[54] Differences in blood pressure reduction from exercise have been found to be related to the intensity of exercise training and based on participant BMI, sex, and age.[40–53,56–59] From these data, there is support that moderate-intensity (40–70% of maximal aerobic capacity) aerobic exercise training for 30–60 minutes on three to five days/week is effective for both prevention and management of hypertension. In a systematic review, the dose of exercise recommended for patients with hypertension based on the FITT (frequency, intensity, time, type) principle is aerobic exercise of any type on most, if not all, days per week at a moderate intensity (40 to <60% VO_2max) for 30–60 accumulated minutes/day as well as dynamic resistance exercise of any resistance type on 2–3 days per week at a moderate intensity for 10–12 repetitions of 8–10 exercises.[60] Interestingly, a recent Cochrane Review of 73 trials found that there is moderate-strength evidence that even moderate-intensity walking as physical activity probably reduces SBP.[61] Additional research is needed to establish blood pressure reduction in response to reducing sedentary time.

Immediately following cessation of a bout of aerobic exercise, there is a temporary reduction in SBP (5–15 mmHg) and DBP (4–6 mmHg) that appears to last for several hours (up to 24 hours).[57,62–64] It is postulated that the mechanisms of this acute blood pressure reduction include:

- Immediate decrease in sympathetic adrenergic stimulation of the precapillary vessels
- Attenuated response to alpha-adrenergic stimulation
- Laminar flow–mediated release of endothelial-derived vasodilatory chemicals (e.g., nitric oxide, prostacyclin, and adenosine)
- Resetting of the arterial and cardiopulmonary baroreceptor operating points
- Neural adaptations involving central vasopressin V_1 receptors and substance P receptors[63–68]

There have been inconsistent findings on the influence of resistance exercise training on reducing blood pressure.[56,57,69] Meta-analyses have reported a blood pressure reduction of approximately 3–5 mmHg SBP/3.5–3.9 mmHg DBP in normotensive individuals.[56,69,70] The recommendation for resistance exercise training is that it should only be used as a supplement and not a substitute for aerobic exercise training, and the strength of the evidence of these recommendations is weak overall.[60] The 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults discusses how 90–150 minutes/week of dynamic resistance exercise and three sessions/week of isometric resistance exercise are associated with beneficial effects on both SBP and DBP.[4] Additionally, the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommends, in addition to aerobic exercise, that individuals with borderline hypertension or hypertension participate in isometric resistance and dynamic resistance exercises.[71] The reader is referred to the American College of Sports Medicine's guidelines and contraindications to exercise testing and training in patients with hypertension.[72]

5.4.1 Mechanism

There have been many postulated and plausible mechanisms for the blood pressure–reducing effects of exercise training. Poiseuille's law explains that a small change in vessel diameter has a large effect on resistance to fluid

flow (i.e., inversely proportional to the fourth power of the vessel radius).[57] Therefore, a reduction in total peripheral vascular resistance, specifically by a change in small vessel diameter, may be responsible for at least one aspect of the blood pressure reduction with exercise training.[56] The exercise-induced reduction in peripheral vascular resistance is postulated to be mediated by several factors, including:

- Improved vascular endothelial function and arterial elasticity/compliance from increased nitric oxide (NO) synthase activity from exercise-induced laminar shear-stress and prolonged NO activity via reduced oxidative deactivation of NO, and reduction of collagen deposition on the media of the arteries
- Reduction in endothelial-derived endothelin-1
- Attenuation of alpha-adrenergic receptor response and reduced sympathetic tone
- Reduction in peripheral vascular resistance
- Improved baroreceptor reflex sensitivity
- Reduced circulating catecholamines[56,73–80]

The effects of exercise training on the RAAS are less well known. There have been a few reports of exercise training reducing renin activity and angiotensin-II activity in normotensive persons, but this has not been reported in hypertensive adults.[81,57] There is an improvement in insulin sensitivity with exercise training that has been associated with increased renal sodium excretion.[57,82] Exercise training–induced vascular adaptations also include an increase in the number of skeletal muscle precapillary and capillary vessels (i.e., angiogenesis) and adaptations in vascular structure, including vascular remodeling (arteriogenesis) resulting in a larger conduit artery lumen diameter, which further contributes to reduced vascular resistance.[57,83] The epigenetic impact on the exercise-induced reduction in blood pressure is less well known.

TABLE 5.2
DASH Diet

Nutrient	Percentage of total caloric intake
Total fat (% of total kcal)	25–35%
Saturated fat	<7%
Trans fats	<1%
Monounsaturated fats	15%
Polyunsaturated fats (with an Omega-6 to 3 ratio of 3 to 4 to 1)	≤10%
Cholesterol (% of total kcal)	≤200 mg/day
Protein (% of total kcal)	About 18%
Carbohydrates (% of total kcal)	50–60%
Dietary fiber (g/day)	31
Potassium (mg/day)	4,700
Calcium (mg/day)	500
Sodium (mg/day)	1,500–2,400
Number of servings per day based on 2,000 kcal diet	
	Daily servings[a] / **Servings per NIH DASH recommendations[b]**
Fruits	7–8 / 4–5
Vegetables	4–5 / 4–5
Grains	4–5 / 6–8
Low-fat dairy products:	2–3 / 2–3
Meats, poultry, fish	≤2 / ≤6
Nuts, seeds, dry beans	4–5 / 4–5/week
Fats, oils	2–3 / 2–3
Sweets	≤5/week / ≤5/week

[a]Adapted from Appel, L.J. et al., *Hypertension* 47(2), 296–308, 2006;
[b]Adapted from National Institutes of Health (NIH), DASH eating plan, 2021, www.nhlbi.nih.gov/education/dash-eating-plan, updated December 29, 2021, accessed June 4, 2022.

5.5 DIETARY MODIFICATIONS IN THE PREVENTION AND MANAGEMENT OF HYPERTENSION

Diet is well established to be associated with hypertension, with meta-analyses supporting that healthier diets are associated with a decreased likelihood of developing hypertension (odds ratio [OR] 0.81, 95% CI 0.67, 0.97).[84] A healthy diet is consistently recommended as part of the lifestyle treatment plan for adults with hypertension in the guidelines.[4,71] Reduced sodium intake and increased intake of potassium, calcium, and magnesium, as well as moderation of alcohol consumption, have been effective at reducing blood pressure.[85–88] Diets that have been shown to improve blood pressure include the DASH (summarized in Table 5.2), Mediterranean, low-carbohydrate, Paleolithic, high protein, low–glycemic index, low-sodium, and low-fat diets.[89] A systematic review and network meta-analysis compared the effect of different dietary approaches on blood pressure among hypertensive and pre-hypertensive patients and found that the DASH diet is the most effective diet in reducing both SBP and DBP based on high-quality evidence.[89] The total blood pressure reduction using the DASH diet is approximately 11/6 mmHg.[78] In a hallmark trial by Appel and colleagues, the DASH diet led to a reduction in blood pressure of ~11.4/5.5 mmHg in hypertensive participants and 3.5/2.2 mmHg in pre-hypertensive participants.[86]

Other dietary studies have reported that a diet high in fruits and plants resulted in blood pressure reductions of 6–10 mmHg in normotensive participants and 12–16 mmHg in those with hypertension.[85,88] Moreover, increased dietary fiber intake (11.5–14 g/day) was associated with a small reduction in SBP (1.1–1.6 mmHg) and DBP (1.3–2.0 mmHg).[91–93] In summary, a diet rich in fruits, vegetables, and whole grains is consistently recommended for blood pressure management.[4,90,94–96]

5.5.1 Effect of Sodium Restriction

Prospective studies, cross-sectional studies, animal studies, clinical trials, and meta-analyses have established a positive independent association between sodium intake and blood pressure.[46,97,98] Sodium restriction is consistently in the lifestyle recommendations of the guidelines, including the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, which recommends reducing sodium chloride intake to 1.5 g/day.[4] A hallmark dose–response sodium restriction–blood pressure trial was the DASH-Sodium Trial, which compared three levels of reduced sodium intake (150, 100, and 50 mmol/day) with changes in blood pressure and found a dose–response relationship between reduced sodium intake and SBP reduction.[87] A systematic review and network meta-analysis found that low-sodium dietary approaches were more effective to reduce SBP and DBP than low-fat diets (mean difference: −4.42, 95% CI: −7.12, −1.72, mean difference: −3.10, 95% CI: −4.52, −1.68, respectively).[89] Overall, sodium restriction has been found to reduce elevated SBP levels by 4.7–7 mmHg and elevated DBP levels by 2.5–2.7 mmHg, reduce the risk of progression of elevated blood pressure to hypertension, and potentiate the effects of pharmacological treatment.[46,85,97–102] It is important to note that there is a great inter-individual variability in blood pressure response to sodium restriction.[85,87,101,102]

5.5.2 Effects of Increased Dietary Potassium Intake

Fluid homeostasis and electrolytes influence blood pressure, with serum sodium levels promoting fluid retention in response to reduced serum potassium levels, whereas increased serum potassium levels lead to an increase in renal sodium excretion (natriuresis) and an associated diuresis.[103] Although clinical trials have reported mixed blood pressure responses to increased dietary potassium intake, increasing dietary potassium intake to 3.5–5.0 g/day has been associated with reduction of 3.49 mmHg (95% CI: 1.82, 5.15 mmHg) in SBP and 1.96 mmHg (0.86, 3.06 mmHg) in DBP in patients with hypertension.[96,104] However, the combination of a diet rich in potassium and low in sodium does not appear to be additive in its influence on blood pressure.[85] Currently, a dietary eating pattern similar to that of the DASH diet is recommended to consume 4.7 g/day of dietary potassium.[90] The 2017 AHA/ACC Guidelines recommend 3,500–5,000 mg/day of potassium via dietary intake.[4] Of note, patients with conditions associated with impaired urinary excretion of potassium (e.g., kidney disease) or who are using medications that reduce potassium excretion may need to consume a lower amounts of potassium as instructed by their healthcare provider.[16,85]

5.5.3 Effects of Alcohol Consumption

A J-shaped, dose-dependent association between alcohol consumption and blood pressure has been demonstrated in clinical trials. Relatively light (defined as blood alcohol concentration < 0.08% or < 0.08 g of alcohol/deciliter) alcohol consumption has been found to have no effect on blood pressure, whereas higher (defined as blood alcohol concentration ≥0.08% or ≥0.08 g of alcohol/deciliter) alcohol consumption increases blood pressure.[97,105–108] Controlled trials have demonstrated that a 50–70% reduction of alcohol consumption independently reduces blood pressure by approximately 3.5/3 mmHg, whereas a 10 g/day increase in alcohol consumption is associated with a blood pressure increase of 2/1 mmHg.[46,108] Additionally, when considering the acute effects of alcohol on blood pressure, a recent Cochrane Review of 32 trials, primarily conducted in men, found that high doses of alcohol (>30 g) decreased blood pressure for up to 12 hours after being consumed, but then increased blood pressure for 13 hours after being consumed.[109] Current recommendations are to limit alcohol intake (no more than two drinks/day for men and no more than one drink/day for women) for those with elevated blood pressure or hypertension, with a drink being defined as a serving of either 12 oz beer, 5 oz wine, or 1.5 oz of 80-proof distilled spirits.[4,16,85]

5.5.4 Effect of Omega-3 Polyunsaturated Fatty Acids

Fatty fish and fish oil supplements are rich in long-chain omega-3 polyunsaturated fatty acids, which are postulated to play a role in blood pressure regulation via the production of eicosanoids and prostaglandins. Small-scale studies in patients with hypertension using large doses of fish oil supplements (>3 g/day) have reported a blood pressure reduction of 2.3–4.0 mmHg in SBP and 2.2–2.5 mmHg in DBP.[46,110–112] In a recent meta-analysis, it was found that the optimal intake of omega-3 fatty acids for blood pressure lowering was 2–3 g per day, with potentially additional benefits on blood pressure lowering in those at high risk for CVD.[113] The evidence of omega-3 fatty acids as an adjunctive therapy to reduce high blood pressure or the risk for heart disease remains inconclusive. However, the Food and Drug Administration (FDA) does find that evidence is sufficiently credible to allow these claims on food and dietary supplements containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Overall, the evidence supports EPA and DHA omega-3 fatty acids reducing CVD risk by reducing blood pressure levels, albeit additional research is required.[114–117]

5.6 WEIGHT MANAGEMENT

The association between obesity and hypertension has been well established by both observational studies and clinical trials.[85,118] A reduction in body weight of 5–10 kg in overweight individuals reduces blood pressure by approximately 6–12/5–8 mmHg.[46,85,119–123] Exercise training remains an important part of a plan to manage weight, although exercise training alone generally results only in minimal (~2 kg) weight

loss.[124] Regular exercise training supports maintenance of lost weight and reduces the loss of lean body mass.[125–127] The combination of exercise and a reduction in energy intake generally results in a greater blood pressure reduction than either alone.[127,128] In a Cochrane Review, weight loss diets alone were found to reduce body weight, SBP (mean difference: –4.5 mmHg, 95% CI: –7.2, –1.8 mm Hg), and DBP (mean difference: –3.2 mmHg, 95% CI: –4.8, –1.5), but this review included a limited number of studies with a small number of participants.[129] In a recent update to the Cochrane Review on the long-term effects of weight-reducing diets on blood pressure, the authors found again that weight loss diets reduced blood pressure in individuals with primary hypertension.[130] The guidelines recommend that adults who are overweight or obese with elevated blood pressure or hypertension are counselled to achieve weight loss.[4]

5.7 COMPREHENSIVE LIFESTYLE MODIFICATION

Intervention trials that use comprehensive lifestyle modification to lower blood pressure have had encouraging results. The most notable large-scale trials are the PREMIER[131] and the Exercise and Nutritional Interventions for Cardiovascular Health (ENCORE)[132] studies. These RCTs have reported a mean reduction in blood pressure in hypertensive individuals of 11–16 in SBP and 6–10 mmHg in DBP following comprehensive lifestyle interventions (including weight reduction). In addition, the ENCORE trial reported a significant reduction in mean 24-hour ambulatory blood pressure in the comprehensive intervention group.[132] These studies support guidelines and the value of comprehensive therapeutic lifestyle interventions for the prevention and management of hypertension.[16,100]

5.8 COMPLEMENTARY THERAPIES

Complementary therapies also may have a role in the management of hypertension. We will be discussing some complementary therapies that have been evaluated. In meta-analysis, music-based interventions have found a trend towards decreased SBP from 144 mmHg (95% CI 137, 152) to 134 mmHg (95% CI 124, 144), and DBP from 84 mmHg (95% CI 78, 89) to 78 mmHg (95% CI 73, 84). [133] Meta-analysis comparing the effectiveness of three different traditional Chinese exercises (Tai Chi, Baduanjin Gigong, and Wuqinxi Gigong) combined with antihypertensive drugs found that Tai Chi plus drugs (weighted mean difference (MD) –12.42 mmHg, 95% CI –15.29, –9.55), and Baduanjin Gigong plus drugs (MD –7.03 mmHg, 95% CI –9.80, –4.26) were superior to antihypertensive drugs alone.[134] Yoga has also been found to have a significant but small effect on SBP (–4.17 mmHg, 95% CI –6.35, –1.99) and DBP (–3.62 mmHg, 95% CI –4.92, –1.60).[135] Transcendental meditation was similarly found to have a potentially small effect on lowering SBP levels (mean difference –4.26, 95% CI –6.09, –2.43) and DBP levels (mean difference –2.33, 95% CI –3.70, –0.97).[136] Garlic has also been explored as having a novel role in the reduction of blood pressure,[137–140] and the largest of these meta-analyses found that garlic reduced SBP by 3.75 mmHg (95% CI –5.04, –2.45) and DBP by 3.39 mmHg (95% CI –4.14, –2.65) compared with controls.[139] Although promising, much additional research is needed in this area before conclusive recommendations can be made.

5.9 PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION

Pharmacological management, alongside lifestyle modifications, continues to play a critical role in the management of hypertension. We recommend reviewing the guidelines for an in-depth review of pharmacologic management of hypertension. In brief, the 2017 ACC/AHA Guideline recommends initiating antihypertensive medications when the blood pressure is 130–139/80–89 if the patient has clinical atherosclerotic heart disease or an estimated ten-year cardiovascular disease risk of greater than 10%.[4] The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC-8) recommends initiating pharmacologic treatment when blood pressure is >150/90 in those over the age of 60 and >140/90 in those under the age of 60.[117] The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommends that pharmacologic management is initiated to achieve a goal of <130/80 for individuals with stage 1 hypertension and a 10% or higher atherosclerotic cardiovascular disease (ASCVD) risk for primary prevention of cardiovascular disease.[71] The AHA Statement on the Management of Stage 1 Hypertension in Adults With a Low 10-Year Risk for Cardiovascular Disease recommends that those with stage 1 hypertension and no atherosclerotic disease or a ten-year CVD risk <10% be initially managed with non-pharmacologic therapy, but with the consideration to start pharmacologic therapy if the blood pressure remains uncontrolled at three to six months.[141]

Patient-specific, multiple antihypertensive drugs are often required to achieve blood pressure goals, so it is imperative that the prescribing clinician pays particular attention to contraindications, drug interactions, and comorbidities when selecting antihypertensive drug therapy. The reader is referred to the guidelines for a more complete discussion of pharmacological therapy.[4,117] Numerous classes of antihypertensive drugs are available, including but not limited to thiazide and potassium-sparing diuretics, beta-adrenergic blockers, alpha-adrenergic blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), centrally acting drugs, and direct-acting vasodilators.[16,142] Of note, the 2017 ACC/AHA Guideline defines first-line agents as thiazide diuretics, CCBs, and ACE inhibitors or ARBs, but we refer the reader to the Guideline for a full discussion on this topic.[4] To potentiate the efficacy of pharmacotherapy, initiation of the previously described lifestyle modifications is strongly recommended throughout the guidelines.[4,117]

TABLE 5.3
Clinical Application/Lifestyle Modifications for Management of Hypertension

Modification	Recommendation	Approximate blood pressure reduction
Physical activity and exercise	Regular aerobic exercise 120–150 min/week or 60–90 min/day for weight reduction and maintenance Dynamic resistance exercise 90–150 min/week Isometric resistance exercise three sessions/week	2–9 mmHg
Healthy diet	Consume a diet rich in fruits, vegetables, and whole grains; moderate in fat-free or low-fat dairy products; reduced saturated fat and cholesterol, such as the DASH dietary pattern	8–11 mmHg
Reduced sodium/salt intake	Reduced sodium/salt intake (1.5 g/day of sodium or 3.8 g/day of sodium chloride or at least 1,000 mg reduction in current intake)	2–7 mmHg
Adequate potassium intake	Increase intake to 3,500–5,000 mg/day (level of DASH diet) from content from fruits, vegetables, and low-fat dairy products	2–5 mmHg
Limit alcohol consumption	≤2 drinks/day for men≤1 drink/day for women	2–4 mmHg
Healthy weight	Maintain a BMI between 18.5 and 24.9 kg/m^2	2–10 mmHg/10 kg weight loss

Adapted from Whelton, P.K. et al., *Hypertension* 71(6), e13–e115, 2018; Flack, J.M., Adekola, B., *Trends Cardiovasc. Med*., 30(3), 160–164, 2020; Williams, B., et al., *Eur. Heart J*., 39(33), 3021–3104, 2018.

5.10 SUMMARY OF CONCLUSIONS

The available evidence is robust in supporting therapeutic lifestyle changes for the prevention and management of hypertension and as adjuncts to pharmacotherapy of hypertension, as summarized in Table 5.3.

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Part II

Nutritional Aspects of Lifestyle Medicine



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6 Dietary Guidelines for Americans, 2020–2025: National Nutrition Guidance

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KEY POINTS

- The foods and beverages that people consume have a profound impact on their health.
- The *Dietary Guidelines for Americans* is updated every five years and reflects the current body of science related to what to eat and drink to meet nutrient needs, promote health, and reduce risk of chronic disease.
- More than half of all American adults have at least one chronic disease or condition that may be related to a poor quality diet and physical inactivity. A fundamental premise of the *Dietary Guidelines* is that just about everyone, no matter their health status, can benefit from shifting food and beverage choices to better support healthy dietary patterns.
- The ninth edition of the *Dietary Guidelines for Americans, 2020–2025* takes a lifespan approach, highlighting the importance of healthy dietary patterns at every stage of life from infancy through older adulthood.
- The *Dietary Guidelines* is a customizable framework that can be used to support healthy dietary patterns. Health professionals are vital to the translation of the *Dietary Guidelines* into programs and strategies and are uniquely positioned to support behavioral and systems change. The Federal government provides a number of free resources to assist them in these efforts.

6.1 INTRODUCTION

The scientific connection between food and health has been well documented for many decades, with substantial evidence showing that healthy dietary patterns can help people achieve and maintain good health and reduce the risk of chronic diseases throughout all stages of the lifespan. Yet, Federal data show that from the first edition of the *Dietary Guidelines for Americans* in 1980 through today, Americans have fallen far short of meeting its recommendations, and diet-related chronic disease rates have risen to pervasive levels and continue to be a major public health concern.

Table 6.1 describes the high rates of nutrition- and physical activity–related chronic diseases and their related risk factors. These diseases affect all ages—children, adolescents, adults, and older adults—though rates vary by several factors, including race/ethnicity, income status, and body weight status.

Given its aim to prevent further disease incidence by promoting health and reducing chronic disease risk, the *Dietary Guidelines for Americans, 2020–2025*[1] focuses on the general public, including healthy individuals, as well as those with overweight or obesity and those who are at risk of chronic disease. The importance of following the *Dietary Guidelines* across all life stages has been brought into focus even more with the emergence of COVID-19, as people living with diet-related chronic conditions and diseases are at an increased risk of severe illness from the novel coronavirus.

Grounded in the current body of scientific evidence on diet and health that is relevant to all Americans, the *Dietary Guidelines* is a critically important tool for health professionals, policymakers, and many other professionals. It is designed to help people make food and beverage choices all through life that are enjoyable and affordable and that also promote health and help prevent chronic disease.

6.2 BACKGROUND

Every five years since 1980, a new edition of the *Dietary Guidelines for Americans* has been published. The *Dietary Guidelines* is required under the 1990 National Nutrition Monitoring and Related Research Act, which states that every five years, the U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services (HHS) must jointly publish a report containing nutritional and dietary information and guidelines for the general public. The statute (Public Law 101-445, 7 U.S.C. 5341 et seq.) requires that the *Dietary Guidelines* be based on the preponderance of current scientific and medical knowledge. The 2020–2025 edition of the *Dietary Guidelines*

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TABLE 6.1

Facts about Nutrition-Related Health Conditions in the United States

Health Condition	Facts
Overweight and Obesity	• About 74% of adults are overweight or have obesity. • Adults ages 40 to 59 have the highest rate of obesity (43%) of any age group, with adults 60 years and older having a 41% rate of obesity. • About 40% of children and adolescents are overweight or have obesity; the rate of obesity increases throughout childhood and teen years.
Cardiovascular Disease (CVD) and Risk Factors: • Coronary heart disease • Hypertension • High LDL and total blood cholesterol • Stroke	• Heart disease is the leading cause of death. • About 18.2 million adults have coronary artery disease, the most common type of heart disease. • Stroke is the fifth leading cause of death. • Hypertension, high LDL cholesterol, and high total cholesterol are major risk factors in heart disease and stroke. • Rates of hypertension and high total cholesterol are higher in adults with obesity than those who are at a healthy weight. • About 45% of adults have hypertension.[a] • More Black adults (54%) than White adults (46%) have hypertension. • More adults ages 60 and older (75%) than adults ages 40 to 59 (55%) have hypertension. • Nearly 4% of adolescents have hypertension.[b] • More than 11% of adults have high total cholesterol, ≥240 mg/dL. • More women (12%) than men (10%) have high total cholesterol, ≥240 mg/dL. • 7% of children and adolescents have high total cholesterol, ≥200 mg/dL.
Diabetes	• Almost 11% of Americans have type 1 or type 2 diabetes. • Almost 35% of American adults have prediabetes, and people 65 years and older have the highest rate (48%) compared with other age groups. • Almost 90% of adults with diabetes also are overweight or have obesity. • About 210,000 children and adolescents have diabetes, including 187,000 with type 1 diabetes. • About 6–9% of pregnant women develop gestational diabetes.
Cancer[c] • Breast cancer • Colorectal cancer	• Colorectal cancer in men and breast cancer in women are among the most common types of cancer. • About 250,520 women will be diagnosed with breast cancer this year. • Close to 5% of men and women will be diagnosed with colorectal cancer at some point during their lifetime. • More than 1.3 million people are living with colorectal cancer. • The incidence and mortality rates are highest among those ages 65 and older for every cancer type.
Bone Health and Muscle Strength	• More women (17%) than men (5%) have osteoporosis. • 20% of older adults have reduced muscle strength. • Adults over 80 years, non-Hispanic Asians, and women are at the highest risk for reduced bone mass and muscle strength.

[a]For adults, hypertension is defined as systolic blood pressure (SBP) >130 mmHg and/or diastolic blood pressure (DBP) >90 mmHg.
[b]For children, hypertension was defined using the 2017 American Academy of Pediatrics (AAP) Clinical Practice Guideline.
[c]The types of cancer included here are not a complete list of all diet- and physical activity–related cancers.
LDL: low-density lipoprotein.

builds from the 2015 edition with revisions based on the *Scientific Report of the 2020 Dietary Guidelines Advisory Committee*[2] and consideration of input from Federal agencies and public comments.

The *Dietary Guidelines* is designed for policymakers and nutrition and health professionals to help all individuals and their families consume a healthy, nutritionally adequate diet. The information in the *Dietary Guidelines* is used to develop, implement, and evaluate Federal food, nutrition, and health policies and programs. It also is the basis for Federal nutrition education materials designed for the public and for the nutrition education components of USDA and HHS nutrition programs. State and local governments, schools, the food industry, other businesses, community groups, and media also use *Dietary Guidelines* information to develop programs, policies, and communication for the general public.

Although many recommendations have remained relatively consistent over time, the *Dietary Guidelines* also has built upon previous editions and evolved as scientific knowledge has grown. The *Dietary Guidelines for Americans, 2020–2025* reflects this in three important ways.

The first is its recognition that diet-related chronic diseases, such as cardiovascular disease, type 2 diabetes, obesity, and some types of cancer, are very prevalent among Americans and pose a major public health problem. Today,

more than half of adults have one or more diet-related chronic diseases or conditions. As a result, recent editions of the *Dietary Guidelines* have focused on healthy individuals, as well as those with overweight or obesity and those who are at risk of chronic disease. A fundamental premise of the *2020–2025 Dietary Guidelines* is that just about everyone, no matter their health status, can benefit from shifting food and beverage choices to better support healthy dietary patterns.

The second is its focus on dietary patterns. Researchers and public health experts, including registered dietitians, understand that nutrients and foods are not consumed in isolation. Rather, people consume them in various combinations over time—a dietary pattern—and these foods and beverages act synergistically to affect health. The *Dietary Guidelines for Americans, 2015–2020* puts this understanding into action by focusing its recommendations on consuming a healthy dietary pattern. The *2020–2025 Dietary Guidelines* carries forward this emphasis on the importance of a healthy dietary pattern as a whole—rather than on individual nutrients, foods, or food groups in isolation.

The third is its focus on a lifespan approach. This edition of the *Dietary Guidelines* highlights the importance of encouraging healthy dietary patterns at every life stage from infancy through older adulthood. It provides recommendations for healthy dietary patterns by life stage, identifying needs specific to each life stage and considering healthy dietary pattern characteristics that should be carried forward into the next stage of life. For the first time since the 1985 edition, the *2020–2025 Dietary Guidelines* includes recommendations for healthy dietary patterns for infants and toddlers.

6.3 OVERVIEW OF THE *DIETARY GUIDELINES FOR AMERICANS, 2020–2025*

The *2020-2025 Dietary Guidelines* provides four overarching Guidelines (Figure 6.1) that encourage healthy eating patterns at each stage of life and recognize that individuals will need to make shifts in their food and beverage choices to achieve a healthy pattern. The Guidelines also explicitly emphasize that a healthy dietary pattern is not a rigid prescription. Rather, the Guidelines are a customizable framework of core elements within which individuals make tailored and affordable choices that meet their personal, cultural, and traditional preferences. The Guidelines are supported by Key Recommendations that provide further guidance on healthy eating across the lifespan. Their call to action is "Make Every Bite Count with the Dietary Guidelines for Americans."

6.3.1 The Guidelines

1. **Follow a healthy dietary pattern at every life stage.** At every life stage—infancy, toddlerhood, childhood, adolescence, adulthood, pregnancy, lactation, and older adulthood—it is never too early or too late to eat healthfully.
   - For about the first 6 months of life, exclusively feed infants human milk. Continue to feed infants human milk through at least the first year of life, and longer if desired. Feed infants iron-fortified infant formula during the first year of life when human milk is unavailable. Provide infants with supplemental vitamin D beginning soon after birth.
   - At about 6 months, introduce infants to nutrient-dense complementary foods. Introduce infants to potentially allergenic foods along with other complementary foods. Encourage infants and toddlers to consume a variety of foods from all food groups. Include foods rich in iron and zinc, particularly for infants fed human milk.
   - From 12 months through older adulthood**,** follow a healthy dietary pattern across the lifespan to meet nutrient needs, help achieve a healthy body weight, and reduce the risk of chronic disease.
2. **Customize and enjoy nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.** A healthy dietary pattern can benefit all individuals regardless of age, race or ethnicity, or current health status. The *Dietary Guidelines* provides a framework intended to be customized to individual needs and preferences, as well as the foodways of the diverse cultures in the United States.
3. **Focus on meeting food group needs with nutrient-dense foods and beverages and stay within calorie limits.** An underlying premise of the *Dietary Guidelines* is that nutritional needs should be met primarily from foods and beverages—specifically, nutrient-dense foods and beverages. Nutrient-dense foods provide vitamins, minerals, and other health-promoting components and have no or little added sugars, saturated fat, and sodium. A healthy dietary pattern consists of nutrient-dense forms of foods and beverages across all food groups, in recommended amounts, and within calorie limits.

   The core elements that make up a healthy dietary pattern include:
   - Vegetables of all types—dark green; red and orange; beans, peas, and lentils; starchy; and other vegetables
   - Fruits, especially whole fruit
   - Grains, at least half of which are whole grain
   - Dairy, including fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverages and yogurt as alternatives



FIGURE 6.1 The Guidelines.

- Protein foods, including lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products
- Oils, including vegetable oils and oils in food, such as seafood and nuts

4. **Limit foods and beverages higher in added sugars, saturated fat, and sodium, and limit alcoholic beverages.** At every life stage, meeting food group recommendations—even with nutrient-dense choices—requires most of a person's daily calorie needs and sodium limits. A healthy dietary pattern doesn't have much room for extra added sugars, saturated fat, or sodium—or for alcoholic beverages. A small amount of added sugars, saturated fat, or sodium can be added to nutrient-dense foods and beverages to help meet food group

recommendations, but foods and beverages high in these components should be limited. The limits are:

- **Added sugars**—Less than 10 percent of calories per day starting at age 2. Avoid foods and beverages with added sugars for those younger than age 2.
- **Saturated fat**—Less than 10 percent of calories per day starting at age 2.
- **Sodium**—Less than 2,300 milligrams per day—and even less for children younger than age 14.
- **Alcoholic beverages**—Adults of legal drinking age can choose not to drink, or to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women, when alcohol is consumed. Drinking less is better for health than drinking more. There are some adults who should not drink alcohol, such as women who are pregnant.

6.3.2 Healthy Dietary Patterns

A dietary pattern represents the totality of what individuals habitually eat and drink, and parts of the pattern act synergistically to affect health. A healthy dietary pattern consists of nutrient-dense forms of foods and beverages across all food groups, in recommended amounts, and within calorie limits. Achieving a healthy dietary pattern at each life stage not only supports health at that point in time, but also supports health in the next life stage and possibly for future generations. If healthy dietary patterns can be established early in life and sustained thereafter, the impact on health could be significant. Establishing and maintaining a healthy dietary pattern can help minimize diet-related chronic disease risk. Conversely, consuming foods and beverages that are not nutrient-dense may lead to disease expression in later years. High intakes of such foods (i.e., an unhealthy dietary pattern) throughout the lifespan can increase the risk of developing chronic diseases.

The good news is that at any stage of life, individuals can make efforts to adopt a healthy dietary pattern and improve their health. The Healthy U.S.-Style Dietary Pattern, USDA's primary Dietary Pattern, provides a framework for healthy eating that all Americans can follow. It is based on the types and proportions of foods Americans of all ages, genders, races, and ethnicities typically consume, but in nutrient-dense forms and appropriate amounts. The Healthy Vegetarian Dietary Pattern and the Healthy Mediterranean-Style Dietary Pattern are variations that also exemplify a healthy dietary pattern. These USDA Dietary Patterns have 12 calorie levels to meet the needs of individuals across the lifespan ages 2 and older.

For the first time, the Healthy U.S.-Style and Healthy Vegetarian Dietary Patterns are provided for toddlers ages 12 through 23 months who are no longer receiving human milk or infant formula. These patterns are designed to meet nutrient needs while not exceeding calorie requirements and while staying within limits for overconsumed dietary components, such as added sugars, saturated fat, and sodium. These patterns are provided at four calorie levels.

The Healthy U.S.-Style Dietary Pattern is carried forward from the *2015–2020 Dietary Guidelines for Americans.* The 2,000-calorie level of the pattern is shown in Table 6.2. The USDA Dietary Patterns can be found in Appendix 3 of the *Dietary Guidelines for Americans, 2020–2025.*

The components of healthy dietary patterns recommended were developed by integrating findings from systematic reviews of scientific research, food pattern modeling, and analyses of current intake of the U.S. population:

- Systematic reviews of scientific research examine relationships between the overall diet and health outcomes.
- Food pattern modeling assesses how well various combinations and amounts of foods meet nutrient needs and accommodate limits.
- Analyses of current intakes identify areas of potential public health concern.

Together, these complementary approaches provide a robust evidence base for healthy dietary patterns that both reduce risk of diet-related chronic disease and promote nutrient adequacy.

6.3.3 Estimated Calorie Needs per Day

The amount of calories a person needs each day varies depending on a number of factors, including the person's age, sex, height, weight, level of physical activity, and pregnancy or lactation status. Due to reductions in basal metabolic rate that occur with aging, calorie needs generally decrease for adults as they age. In addition, a need to lose, maintain, or gain weight affects how many calories should be consumed. Estimated amounts of calories needed are provided in Appendix 2 of the *Dietary Guidelines for American, 2020–2025.* These estimates are based on the Estimated Energy Requirements (EER) equations[3] established by the National Academy of Sciences, Engineering and Medicine (NASEM) using reference heights (average) and reference weights (healthy) for each age-sex group.* These amounts are estimates. The best way to evaluate calorie intake, in comparison to calorie needs, is by measuring body weight status. After release of the 2020–2025 edition of the *Dietary Guidelines*, NASEM released updated *Dietary Reference Intakes for Energy*, which provide similar estimates.[4]

* For children and adolescents, reference height and weight vary. For adults, the reference man is 5 feet 10 inches tall and weighs 154 pounds. The reference woman is 5 feet 4 inches tall and weighs 126 pounds.

TABLE 6.2

Healthy U.S.-Style, Dietary Pattern at the 2,000-Calorie Level, with Daily or Weekly Amounts from Food Groups, Subgroups, and Components

Food Group[a]	Daily Amount[b] of Food From Each Group(vegetable and protein foods subgroup amounts are per week)
Vegetables	2½ c eq/day
--Dark green	1½ c eq/week
--Red and orange	5½ c eq/week
--Beans, peas, lentils	1½ c eq/week
--Starchy vegetables	5 c eq/week
--Other	4 c eq/week
Fruits	2 c eq/day
Grains	6 oz eq/day
--Whole grains	≥3 oz eq/day
--Refined grains	<3 oz eq/day
Dairy	3 c eq/day
Protein Foods	5½ oz eq/day
--Seafood	8 oz eq/week
--Meat, poultry, eggs	26 oz eq/week
--Nuts, seeds, soy products	5 oz eq/week
Oils	27 g/day
Limit on Calories for Other Uses (% of calories)[b]	240 kcal/day (12%)

[a]Definitions for each food group and subgroup are compiled in Appendix 3 of the *Dietary Guidelines for Americans, 2020–2025*.

[b]Food group amounts shown in cup (c) or ounce equivalents (oz eq). Oils are shown in grams (g). Amounts will vary for those who need <2,000 or >2,000 calories per day. Quantity equivalents for each food group are:

- Vegetables and fruits, 1 cup-equivalent is: 1 cup raw or cooked vegetable or fruit, 1 cup vegetable or fruit juice, 2 cups leafy salad greens, ½ cup dried fruit or vegetable.
- Grains, 1 ounce-equivalent is: ½ cup cooked rice, pasta, or cereal; 1 ounce dry pasta or rice; 1 medium (1 ounce) slice bread; 1 ounce of ready-to-eat cereal (about 1 cup of flaked cereal).
- Dairy, 1 cup-equivalent is: 1 cup milk, yogurt, or fortified soymilk; 1½ ounces natural cheese such as cheddar cheese or 2 ounces of processed cheese.
- Protein Foods, 1 ounce-equivalent is: 1 ounce lean meat, poultry, or seafood; 1 egg; ¼ cup cooked beans or tofu; 1 Tbsp peanut butter; ½ ounce nuts or seeds.

[c]Foods are assumed to be in nutrient-dense forms, lean or low-fat and prepared with minimal added sugars, refined starches, saturated fat, or sodium. If all food choices to meet food group recommendations are in nutrient-dense forms, a small number of calories remain within the overall limit of the pattern (i.e., limit on calories for other uses). The amount of calories depends on the total calorie level of the pattern and the amounts of food from each food group required to meet nutrient goals. Calories up to the specified limit can be used for added sugars, saturated fat, and/or alcohol, or to eat more than the recommended amount of food in a food group.

Note: The total dietary pattern should not exceed *Dietary Guidelines* limits for intake of added sugars, saturated fats, and alcohol; be within the Acceptable Macronutrient Distribution Ranges for protein, carbohydrate, and total fats; and stay within calorie limits. Values are rounded. See Appendix 3 in the *Dietary Guidelines, 2020–2025* for all 12 calorie levels of the Patterns.

6.3.4 Most Americans Do Not Follow a Healthy Dietary Pattern

The typical eating patterns currently consumed by many in the United States do not align with the *Dietary Guidelines* (Figure 6.2). For Americans ages 2 and older, Healthy Eating Index (HEI)-2015 scores indicate that intakes are not consistent with recommendations for a healthy dietary pattern. Average diet quality has slightly improved in the past ten years, but the average score of 59 (on a scale from 0 to 100) indicates that people have much room for improvement. Differences in overall HEI scores are seen across age, sex, race-ethnic, and income subgroups and by pregnancy and lactation status, though poor diet quality is observed across all groups. With each step closer to a diet that aligns with the core elements of a healthy dietary pattern, HEI scores will increase, and risk for chronic disease will decrease.*

When compared with the Healthy U.S.-Style Pattern, most Americans have substantial room for improvement:

* Data source for Healthy Eating Index 2015 scores: What We Eat in America, National Health and Nutrition Examination Survey (NHANES) 2015–2016, ages 2 and older, day 1 dietary intake data, weighted. For more information on the HEI, see: www.fns.usda.gov/healthy-eating-index-hei. Accessed April 20, 2023.

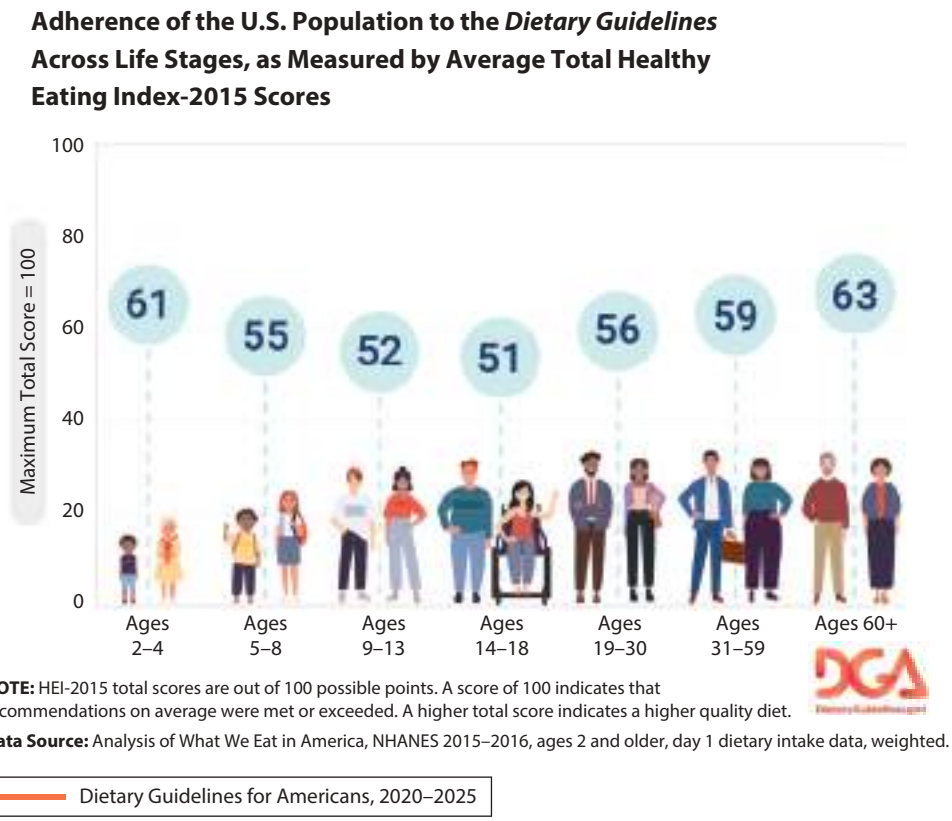


FIGURE 6.2 Healthy Eating Index scores by life stages.

- More than 80% have dietary patterns that are low in vegetables, fruits, and dairy.
- More than half of the population are meeting or exceeding total grain and total protein foods recommendations, but are not meeting the recommendations for the subgroups within each of these food groups.
- Most Americans exceed the recommendations for added sugars, saturated fats, and sodium.

Among nutrients, calcium, potassium, dietary fiber, and vitamin D are considered nutrients of public health concern because low intakes are associated with health concerns. For young children, individuals capable of becoming pregnant, and who are pregnant, low intake of iron also is of public health concern.

6.3.5 Key Dietary Principles

To help people meet the Dietary Guidelines and Key Recommendations, the following are important principles when making decisions about nutrient-dense food and beverage choices to achieve a healthy dietary pattern.

- Meet nutritional needs primarily from foods and beverages. The *Dietary Guidelines* are designed to meet the Recommended Dietary Allowances and Adequate Intakes for essential nutrients, as well as Acceptable Macronutrient Distribution Ranges, all set by NASEM. An underlying premise of the *Dietary Guidelines* is that nutritional needs should be met primarily from foods and beverages—specifically, nutrient-dense foods and beverages. In some cases, when meeting nutrient needs is not otherwise possible, fortified foods and nutrient-containing dietary supplements are useful. It is important to note that the nutrient density and healthfulness of what people eat and drink often is determined ultimately by how a food item, dish, or meal is prepared, at home and away from home or produced by a manufacturer. Based on the U.S. food supply and marketplace, healthy dietary patterns are achievable through thoughtful, informed choices one decision, one meal, one day at a time—and consistently over time.
- Choose a variety of options from each food group. Enjoy different foods and beverages within each food group. This can help meet nutrient needs—and also allows for flexibility so that the *Dietary Guidelines* can be tailored to meet cultural and personal preferences. All forms of foods, including fresh, canned, dried, frozen, and 100% juices, in nutrient-dense forms, can be included in healthy dietary patterns.
- Pay attention to portion size. Portion size is a term often used to describe the amount of a food or

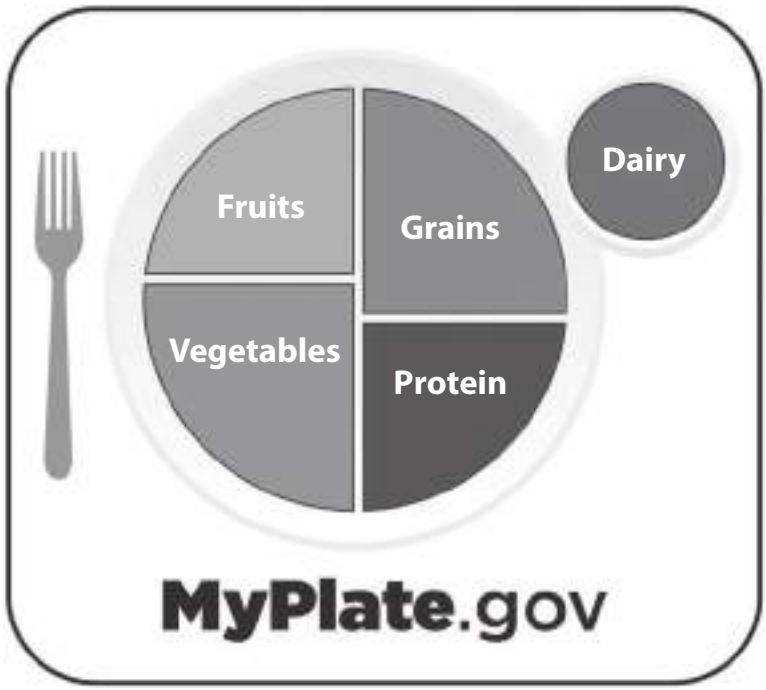


FIGURE 6.3 Federal nutrition symbol.

beverage served or consumed in one eating occasion. It is important to pay attention to portion size when making food and beverage choices, particularly for foods and beverages that are not nutrient-dense. A concept that can help people choose appropriate portions is serving size. This term is included on the Nutrition Facts label and refers to the amount of a food or beverage that is customarily consumed—it is not a recommendation of how much to eat or drink. Consuming less than the stated serving size results in consuming fewer calories and other nutrients or food components. Some products may have multiple servings per package.

For most individuals, no matter their age or health status, achieving a healthy dietary pattern will require changes in food and beverage choices. Some of these changes can be accomplished by making simple substitutions, while others will require greater effort to accomplish. The 2020–2025 edition of the *Dietary Guidelines* presents overall guidance on choosing nutrient-dense foods and beverages in place of less healthy choices and also discusses special nutrition considerations for individuals at each life stage—infants and toddlers, children and adolescents, adults, individuals who are pregnant or lactating, and older adults.

6.4 IMPLEMENTATION BY HEALTH PROFESSIONALS

Eating should be enjoyed, and a healthy dietary pattern can be enjoyable, from early life to older adulthood. The science reviewed to inform the *Dietary Guidelines* represents the diversity of Americans, including all ages and life stages, different racial and ethnic backgrounds, and a range of socioeconomic statuses. A healthy dietary pattern can benefit all individuals regardless of age, race or ethnicity, or current health status.

The *Dietary Guidelines* provides a framework intended to be customized to fit individual, household, and Federal program participants' preferences, as well as the foodways of the diverse cultures in the United States. The U.S. population is diverse in myriad ways. The *Dietary Guidelines* framework purposely provides recommendations by food groups and subgroups—not specific foods and beverages—to avoid being prescriptive. This framework approach ensures that people can "make it their own" by selecting healthy foods, beverages, meals, and snacks specific to their needs and preferences.

The food groups include a broad variety of nutrient-dense food and beverage choices. In every setting, across all cultures, and at any age or budget, there are foods and beverages that can fit within the *Dietary Guidelines* framework. Health professionals can support healthy dietary patterns by considering the following:

- Start with personal preferences: Exposure to different types of food is important early in life to better develop a child's interest and willingness to eat and enjoy a variety of foods. Through each life stage that follows, a key starting point for establishing and maintaining a healthy dietary pattern is to ensure that individual and/or family preferences—in nutrient-dense forms—are built into day-to-day choices.

- Incorporate cultural traditions: Cultural background can have significant influence on food and beverage choices. Customizing the *Dietary Guidelines* framework to reflect specific cultures and traditions is an important strategy to help communities across the country eat and enjoy a healthy dietary pattern. Nutrient-dense culturally relevant foods and beverages are part of all of the food groups. Spices and herbs can help flavor foods when reducing added sugars, saturated fat, and sodium, and they also can add to the enjoyment of nutrient-dense foods, dishes, and meals that reflect specific cultures. Relying on the expertise of professionals in nutrition and in specific cultural foodways can help people prepare foods healthfully while retaining heritage.
- Consider budget: Despite a common perception that eating healthfully is expensive, a healthy dietary pattern can be affordable and fit within budgetary constraints. There are a range of strategies that can be used to help individuals and families follow a healthy dietary pattern, including advanced planning; considering regional and seasonal food availability; and incorporating a variety of fresh, frozen, dried, and canned options.

6.4.1 Translating the *Dietary Guidelines* to Support Nutrition Education

The *Dietary Guidelines* is developed and written for a professional audience. Therefore, its translation into actionable consumer messages and resources is crucial to help individuals, families, and communities achieve healthy dietary patterns. With the needs of health professionals in mind, the USDA and HHS have developed a variety of tools that can help health professionals with disseminating food and nutrition messages based on the *Dietary Guidelines* to the public. These resources include MyPlate and a myriad of health professional resources available at DietaryGuidelines.gov.*

MyPlate (Figure 6.3). MyPlate† is the Federal nutrition symbol to help Americans make healthy food choices based on the *Dietary Guidelines for Americans*, which replaced the Food Pyramid in 2011. MyPlate serves as a visual reminder to build a healthy eating pattern by making healthy choices across the food groups. MyPlate is also used by professionals across multiple sectors and settings to help increase awareness about how to make healthy food and beverage choices over time. Created to be used in various settings and to be adaptable to support the needs of specific population groups, the MyPlate symbol and its supporting consumer resources bring together key elements of healthy dietary patterns. The MyPlate consumer messages can be used in a variety of educational materials for the public.

MYPLATE CONSUMER MESSAGES

A healthy eating routine is important at every stage of life and can have positive effects that add up over time. It's important to eat a variety of fruits, vegetables, grains, dairy or fortified soy alternatives, and protein foods. When deciding what to eat or drink, choose options that are full of nutrients. Make every bite count.

Think about how the following recommendations can come together over the course of your day or week to help you create a healthy eating routine:

- Make half your plate fruits and vegetables.
  - Focus on whole fruits.
  - Vary your veggies.
- Make half your grains whole grains.
- Vary your protein routine.
- Move to low-fat or fat-free dairy milk or yogurt (or lactose-free dairy or fortified soy versions).
- Choose foods and beverages with less added sugars, saturated fat, and sodium.

The benefits of healthy eating add up over time, bite by bite. Small changes matter. Start Simple with MyPlate.

Health Professional Resources Available at DietaryGuidelines.gov. USDA and HHS developed a variety of resources to help promote healthy eating across the lifespan from birth to older adulthood based on the *Dietary Guidelines for Americans, 2020–2025.* Many of the resources available on the website can be used in their entirety or adapted for different purposes to support and supplement nutrition education, programs, and policies. For example, a suite of print materials can be printed out and used directly with patients and clients. These print materials cover topics that are central to building a healthy dietary pattern, such as how to build a healthy eating routine, eating healthily for key life stages, including pregnancy and breastfeeding, birth to age 2, kids and teens, and older adults, and how to cut down on over-consumed nutrients such as added sugars, saturated fat, and sodium.

The Customizing the *Dietary Guidelines* Framework handout is especially useful in helping individuals with understanding the range of food and beverage options that are available within each food group. Effort was made to expand the list of food and beverage options within this handout to provide not only frequently consumed foods and beverages within each food group, but also less frequently consumed foods that may be more readily consumed among different population subgroups. In this way, this resource could be more reflective of the variety

* For more information, see: U.S. Department of Agriculture and U.S. Department of Health and Human Services, DietaryGuidelines.gov: www.dietaryguidelines.gov/. Accessed April 25, 2023.

† For more information, see: U.S. Department of Agriculture, MyPlate.gov: www.myplate.gov/. Accessed April 25, 2023.

of cultural foodways within the United States. Similarly, the food sources of select nutrients tables available on DietaryGuidelines.gov provide food sources of calcium, potassium, dietary fiber, and vitamin D, which as noted earlier, are considered dietary components of public health concern for the U.S. population. Iron is also a nutrient of concern for infants, particularly those receiving mostly human milk, and individuals of childbearing age. The food sources of select nutrients lists provide examples of a variety of nutrient-dense foods and beverages that are some of the highest sources of these dietary components. Health professionals are encouraged to use these lists to help individuals identify foods and beverages they enjoy—those that reflect their personal preferences and cultural traditions—and that also help meet their food group and nutrient needs. These food sources of select nutrients lists also reflect both frequently consumed sources and less frequently consumed sources with the goal of providing foods and beverages that better reflect the variety of cultural foodways within the U.S. population.

DietaryGuidelines.gov also offers resources that can be downloaded and adapted for a variety of purposes. Health professional presentation slides based on the *Dietary Guidelines* can be downloaded and used in their entirety, or single slides can be integrated into a different presentation. Health professionals are encouraged to use these slides to host their own presentation on healthy eating across life stages or for a specific life stage, including infants and toddlers, children and adolescents, adults, people who are pregnant or lactating, and older adults.

Figures from the *Dietary Guidelines for Americans* are also available to use. These figures can be used as a standalone handout, pulled into presentation slides as supporting data points, adapted and shared through social media channels, or used in flyers. Some key figures provided on DietaryGuidelines.gov include ones within this chapter that focus on how well Americans are doing at meeting dietary recommendations, as well as other figures that help to support education related to nutrient density and how nutrient-dense choices can be made at the food level, at a meal, and throughout the day.

Resources available on DietaryGuidelines.gov, including print handouts, figures, and graphics, are available in both English and Spanish.

6.5 SUPPORTING HEALTHY DIETARY PATTERNS FOR ALL AMERICANS

Everyone has a role to play to support access to healthy foods and beverages in multiple settings nationwide where people live, learn, work, play, and gather. Having access to healthy, safe, and affordable food is crucial for an individual to achieve a healthy dietary pattern. Concerted efforts within communities, businesses and industries, organizations, government, and other segments of society are needed to support individuals and families in making lifestyle choices that align with the *Dietary Guidelines*.

In 2019, 10.5% of households were food insecure at least some time during the year. Food insecurity occurs when access to nutritionally adequate and safe food is limited or uncertain. Food insecurity can be temporary or persist over time, preventing individuals and families from following a healthy dietary pattern that aligns with the *Dietary Guidelines*. The prevalence of food insecurity typically rises during times of economic downturn as households experience greater hardship. Government and nongovernment nutrition assistance programs help alleviate food insecurity and play an essential role by providing food, meals, and educational resources so that participants can make healthy food choices within their budget. Each of the life stage chapters within the *Dietary Guidelines* highlights examples of these programs, such as the Supplemental Nutrition Assistance Program (SNAP), that are available to alleviate food insecurity.

Food access is also important to consider. Food access is influenced by diverse factors, such as proximity to food retail outlets (e.g., the number and types of stores in an area), ability to prepare one's own meals or eat independently, and the availability of personal or public transportation. The underlying socioeconomic characteristics of a neighborhood also may influence an individual's ability to access foods to support healthy eating patterns.

Individuals may also need support in making healthy choices at home, at work, and in the community to build healthy dietary patterns. For some adults, preparing and consuming healthy meals at home will mean adopting a new habit and/or learning new skills, such as meal planning. For others, it may entail small changes to current routines. Planning meals and snacks in advance with food groups and nutrient-dense foods and beverages in mind can support healthy eating at home and improve dietary patterns of individuals and families. Preparing meals with family and friends also presents an opportunity for greater connection and enjoyment around food. For adults who are parents, guardians, or caregivers of children or adolescents, preparing meals also provides an opportunity to teach valuable cooking skills and model behaviors that support the adoption of healthy dietary patterns across younger life stages.

Health professionals play an important role in supporting healthy eating behaviors. Helping individuals become more aware of the foods and beverages that make up their typical dietary patterns and identifying areas for improvement can empower individuals to make changes to the types of foods they purchase or prepare. Teaching skills like cooking and meal planning and helping individuals understand how to read labels or make healthy menu substitutions also will support the adoption of a healthy dietary pattern. In settings where individuals spend their time, changing organizational practices, approaches, and/or policies to support improved dietary patterns also is needed. Strategies include offering healthy meals and snacks in cafeterias and vending machines, or implementing educational programs. Or, communities can support farmers' markets, community gardens, and related educational programming efforts.

6.6 THE DIETARY GUIDELINES LIFE STAGE APPROACH

This chapter has provided guidance about the fundamentals of a healthy dietary pattern described in the *Dietary Guidelines*. These fundamentals are remarkably consistent across life stages; however, the *Dietary Guidelines* also takes a closer look at each of the life stages. The *Dietary Guidelines* includes a chapter focused on the unique nutritional needs of infants and toddlers. Subsequent chapters present recommended dietary patterns, describe current nutrition intakes, and provide tailored nutrition information specific to children and adolescents, adults, individuals who are pregnant or lactating, and older adults, respectively.

6.7 ADDITIONAL RESOURCES

These resources are intended to complement existing Federal nutrition information and guidance that can be found at websites such as www.DietaryGuidelines.gov, www.healthfinder.gov, www.nutrition.gov, and www.MyPlate.gov. Additional information on vitamin, mineral, and macronutrient recommendations are available in the Dietary Reference Intakes, accessible at www.nal.usda.gov/fnic/dietary-reference-intakes. Finally, best practices that can be used to increase healthy and safe food options for employees can be found in the *Food Service Guidelines for Federal Facilities* at www.cdc.gov/obesity/strategies/food-serv-guide.html.

CLINICAL APPLICATIONS

- Communicate the value of a healthy lifestyle, including healthy eating, to your patients and clients and use resources available at DietaryGuidelines.gov and MyPlate.gov.
- Assist individuals with identifying a dietary pattern that is right for them based on their calorie needs; personal health; and cultural, ethnic, traditional, and personal preferences as well as an individual's budget and other issues of accessibility, such as access to healthy food.
- Encourage food and beverage choices that meet the Key Recommendations for food groups, subgroups, nutrients, and other components to contribute to overall healthy dietary patterns.
- Help individuals become more aware of the foods and beverages that make up their own or their family's eating patterns and identify areas, such as modifying recipes and/or food selections, where they can make shifts to align with the *Dietary Guidelines*.
- Establish and maintain sectors and settings that support healthy dietary patterns and encourage regular physical activity as part of a healthy lifestyle.

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7 Nutrition and Cardiovascular Disease

James M. Rippe, MD

KEY POINTS

- Cardiovascular disease (CVD) remains the leading killer of both men and women in the United States, resulting in over 37% of annual mortality.
- Nutritional practices play a pivotal role in the likelihood of developing CVD.
- Dietary patterns that include increases in fruits and vegetables, whole grains, seafood (particularly oily fish), legumes and nuts, and low or non-fat dairy products, and are lower in red meats and processed meats, and low in sugar sweetened beverages and refined grains have been repeatedly shown to lower the risk of CVD.
- Implementation of plant based diets such as those recommended by the American Heart Association and Dietary Guidelines for Americans will be a key mandate for clinicians to help their patients adopt healthier eating habits.

7.1 INTRODUCTION

Cardiovascular disease (CVD) is the largest source of morbidity and mortality in the United States and elsewhere in the developed world.[1] CVD accounts for over 37% of all mortality in the United States. There are hundreds, if not thousands, of studies to support the concept that daily lifestyle practices and habits exert profound effects on the likelihood of developing CVD. While many lifestyle practices are associated with positive benefits in both prevention and treatment of CVD, nutrition clearly plays a pivotal role.[2–6]

Multiple studies have demonstrated that a diet containing more fruits and vegetables, fish (particularly oily fish), whole grains and fiber, and also remaining in caloric balance, lowers the risk of CVD.[2–7] Other positive lifestyle decisions such as maintaining a proper body weight,[8,9] engaging in at least 30 minutes per day of physical activity,[10] and avoiding smoking and tobacco products[3] can also reduce the risk of CVD. These practices together can reduce the risk of CVD over 80% and diabetes by over 90% in both men and women. Indeed, participation in only one of these activities on a regular basis can reduce the risk of both CVD and diabetes by over 50%.[11,12]

Between 1980 and 2000, mortality rates from CVD fell by 40%[13]. Reductions in major lifestyle risk factors, such as increased physical activity, smoking cessation, and better control of cholesterol and blood pressure, accounted for approximately one-half of these reductions. Unfortunately, obesity and diabetes have moved in the opposite direction and have the potential to wipe out all the gains achieved by other lifestyle related risk factors, unless these negative trends can be reversed.[13] Between 1990 and 2013, deaths from CVD rose from 26% to 32% globally. This appears to be due to epidemiologic transitions that have occurred during this period of time.[2] Nutritional factors play a significant role in many of the components of either positive or negative lifestyle decisions or practices.

This chapter will focus on nutrition. Nutrition will be placed, however, in a broader lifestyle context with an emphasis on physical activity as well as energy balance and weight maintenance. This overall approach to lifestyle medicine is consistent with the approach taken by the American Heart Association (AHA) in multiple documents and scientific statements,[3–6], the Dietary Guidelines for Americans (DGA) 2020–2025 as well as multiple other resources,[8–14] and mission statements and position statements from the Academy of Nutrition and Dietetics.[15]

Nutritional guidelines offered by the AHA[3] and other evidence based documents, such as the 2013 AHA/American College of Cardiology (ACC) Guidelines on Lifestyle Management to Reduce Cardiovascular Risk[5] and the 2020 Strategic Plan for Improving Cardiovascular Health and Lowering Cardiovascular Risk from the AHA[4] as well as the report from the Dietary Guidelines Advisory Committee 2020–2025,[7] are very similar. All place an emphasis on not only nutrition but a broader approach toward positive lifestyle factors to improve cardiovascular health and reduce the risk of CVD.

7.2 BACKGROUND

Consensus statements and recommendations from a variety of organizations issued over the past ten years regarding nutritional strategies for improving cardiovascular health are very similar. Often, these recommendations have drawn upon the same database, in general, and in particular, large epidemiologic studies. These guidelines have often referred to each other. These published consensus statements form the basis of the recommendations made in this chapter and include the following:

- Diet and Lifestyle Recommendations Revision 2021: A Scientific Statement from the American Heart Association Nutrition Committee[3]
- Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction: American Heart Association Strategic Impact Goals through 2020 and beyond[4]

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- 2013 AHA/ACC Guidelines for Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[5]
- Dietary Guidelines 2020–2025 Advisory Committee Report
- Dietary Guidelines for Americans 2020–2025[7]

These consensus statements consistently recommend a dietary pattern higher in fruits and vegetables, whole grains (particularly high fiber), non-fat dairy, seafood, legumes, and nuts. The guidelines further recommend that those who consume alcohol (among adults) do so in moderation. The guidelines are also consistent in recommending diets lower in red and processed meats, refined grains, sugar sweetened foods, and saturated and trans fats. All of these guidelines have also emphasized the importance of balancing calories and physical activity as a strategy for maintaining healthy weight and thereby, further reducing the risk of CVD.[3–7]

The national guidelines on nutrition and cardiovascular health are also consistent with each other with regard to overall strategies for reducing cardiovascular health risk factors. For example, the AHA Strategic Goals for 2020 and beyond offer some specific guidance in the area of nutrition.[4] While recognizing that recommending an optimal pattern for CVD risk reduction is a complicated task, the 2020 Strategic Plan defines dietary goals as "in the context of a diet that is appropriate in energy balance pursuing and overall dietary plan consistent with DASH (Dietary Approaches to Stop Hypertension)." Eating plans recommended by the AHA include, but are not limited to, the following recommendations:

- Fruits and vegetables ≥4.5 cups/day
- Fish ≥ two 2½ ounce servings/week (preferably oily fish)
- Fiber rich/whole grain ≥1.1 grams fiber/10 grams carbohydrate, three 1 ounce equivalent servings/day
- Sodium ≤1,500 milligrams/day
- Sugar sweetened beverages ≤460 calories (36 ounces)/week

These recommendations represent a reasonable starting point and have been expanded upon in other guidelines and recent reviews.

Dietary guidance over the last 25 years has moved from specific foods and nutrients to a greater emphasis on dietary patterns. Thus, dietary patterns will be discussed in some detail in this chapter.

The emphasis in nutrition guidelines has also shifted to the critical aspect of implementing recommendations.[16,17] It is clear that nutrition plays a key role in many aspects of preventing CVD, but it is also recognized that despite consistent recommendations and guidelines for many decades, a distinct minority of Americans are following most of these guidelines. For example, with regard to nutrition and hypertension, fewer than 20% of individuals with high blood pressure currently follow the DASH diet.[18] It has also been estimated that fewer than 15% of adults in the United States consume the recommended number of fruits and vegetables.[19] The problem of how to encourage people to actually implement heart healthy guidelines in their daily lives remains an important topic, which will be discussed toward the end of this chapter.[20,21] There has also been an increased emphasis on how to incorporate behavioral medicine techniques into nutrition and other positive aspects of a positive lifestyle. This is another area of considerable ongoing research.

7.3 DIETARY PATTERNS

The 2020–2025 Dietary Guidelines for Americans focused on integrating available science and systematic reviews of scientific research, food pattern modeling, and analysis of the current intake of the U.S. population to develop the "Healthy U.S.-Style Eating Pattern."[7] This approach allowed the blending of the overall diet, including constituent foods, beverages, nutrients, and health outcomes. In addition, the food pattern modeling allowed more flexibility in amounts of foods from all food groups to establish healthy eating patterns that met nutrient needs and also accommodated limitations such as those for saturated fats, added sugars, and sodium. Finally, this approach allowed analysis of current intakes, identifying areas of potential public health concern. With this approach, the DGA 2020–2025 indicated the following:

- Within the body of evidence higher intakes of vegetables and fruits consistently have been identified as characteristic of healthy eating patterns; whole grains have been identified as well, although with slightly less consistently." Other characteristics of healthy eating patterns have been identified with less consistency including fat free or low fat dairy, seafood, legumes and nuts. Lower intakes of meats including processed meats, poultry; sugar sweetened foods, particularly beverages; and refined grains have also been identified as characteristics of healthy eating patterns.

Additionally, DGA 2020-2025 provided input on various dietary and health related components.

- Healthy U.S.-Style Eating Pattern
  Following the guidelines outlined in the preceding paragraph, the U.S. DGA 2020–2025 developed the U.S.-Style Healthy Eating Pattern for the 2,000 calorie level, including daily or weekly amounts from various food groups and components, which are found in Table 7.1.
  The DGA 2020–2025 Guidelines also emphasize that calories should be balanced and that intake

TABLE 7.1
Healthy U.S.-Style Eating Pattern at the 2,000 Calorie Level, with Daily or Weekly Amounts from Food Groups, Subgroups, and Components

Food Group	Amount in the 2,000-Calorie-Level Pattern
Vegetables	2½ c-eq/day
Dark green	1½ c-eq/wk
Red and orange	5½ c-eq/wk
Legumes (beans and peas)	1½ c-eq/wk
Starchy	5 c-eq/wk
Other	4 c-eq/wk
Fruits	2 c-eq/day
Grains	6 oz-eq/day
Whole grains	≥3 oz-eq/day
Refined grains	≤3 oz-eq/day
Dairy	3 c-eq/day
Protein Foods	5½ oz-eq/day
Seafood	8 oz-eq/wk
Meats, poultry, eggs	26 oz-eq/wk
Nuts, seeds, soy products	5 oz-eq/wk
Oils	27 g/day

of calories from added sugars, saturated fats, and alcohol should be limited so as to not exceed acceptable macronutrient distribution ranges for calories from protein, carbohydrates, or total fats. The Healthy U.S.-Style Eating Pattern is also designed to meet recommended daily allowances (RDA), adequate intakes of potential nutrients, as well as acceptable macronutrient distribution ranges (AMDR) set by the Food and Nutrition Board of the Institute of Medicine (IOM). Flexibility within the dietary pattern also allows minor modifications to enable the Mediterranean diet or DASH diet to be followed within these overall guidelines.

- Low Fat Diets
  Lower fat diet consumption has been generally accepted in clinical guidelines for CVD prevention.[3,5] This pattern forms the basis of numerous other diets to be discussed in this chapter.
  Briefly, low fat diets are based on total fat consumption of 25–35% of total calories, with saturated fat (SFA) no more than 7–10%, trans fat (TFA) less than 1%, and unsaturated fat, mainly monounsaturated fat (MUFA), and Omega 3 polyunsaturated fat (*N-3* PUFA) consisting of the rest of the calories from fat. This diet also calls for dietary cholesterol of less than 300 milligrams/day.[3,22,23]
  These recommendations can be met by emphasizing fruits and vegetables, low fat dairy products, including 1% milk, and low fat meat.[24] Some controversy remains about the type and amount of carbohydrates consumed. It should also be noted that the food matrix for SFAs has been an area of recent research, with some suggestion that SFAs coming from dairy products are less likely to cause an adverse increase in risk factors for CVD compared with other sources of SFAs.[25,26] The AHA/ACC Guidelines on Lifestyle Management recommend that consumption of SFAs should not exceed 6% of calories.[5]
- Low Carbohydrate Diet
  Low carbohydrate diets are typically defined as containing up to or less than 45% of total calories from carbohydrates (30–130 grams of carbohydrates/day). Studies of low carbohydrate diets have shown reduction in triglycerides (TG) and an increase in high-density lipoprotein (HDL) cholesterol (HDL-C).[27,28]
  One study that compared low carbohydrate with low fat and Mediterranean diets found greater weight loss in the low carbohydrate diet over the course of one year. A two-year dietary intervention, the randomized controlled DIRECT trial,[29] which involved 322 moderately obese participants comparing low fat with low carbohydrate and Mediterranean diets, found that the low carbohydrate diet was most effective in short-term weight loss, decreasing TG and increasing HDL-C levels. At four-year follow up, however, there were no significant differences among the three arms.
  There are insufficient data from long-term trials to demonstrate the benefits of a low carbohydrate diet compared with low fat and Mediterranean diets for reduction of the risk of CVD.
- Mediterranean Diet
  The Mediterranean diet was originally described as the one typically consumed in countries bordering the Mediterranean Sea.[30,31] It is characterized by relatively high fat intake (40–50% of total daily calories), of which SFA comprises ≤8% and MUFA 15–25% of calories. The Mediterranean diet is also characterized by high Omega 3 fatty acid intake from fish and plant sources and low Omega 6–Omega 3 ratios. It features seasonal, local fresh vegetables, fruits, whole bread, grains, legumes, nuts, and olive oil. Red meat is avoided. Moderate amounts of low fat dairy products as well as eggs, chicken, and fish are allowed. Small to moderate quantities of wine are encouraged with meals in non-Islamic countries.
  A recent, multi-center, randomized intervention study in Spain in individuals with high cardiovascular risk, but no overt evidence of cardiovascular disease at enrollment, were divided into three diets as follows: the Mediterranean diet supplemented with extra virgin olive oil, the Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce dietary fat).[32] The primary

endpoint was an incidence of major cardiovascular events such as myocardial infarction, stroke, or death from cardiovascular causes.

The two Mediterranean diets resulted in a decrease of approximately 30% in major cardiovascular events compared with the control diet, providing strong evidence that a Mediterranean diet supplemented with extra virgin olive oil or nuts reduces the risk of major CVD events.

- DASH Diet[17]

  The DASH diet, initially formulated in the 1990s,[18] has undergone several modifications and iterations since that time.[33,34] The initial goal was to lower blood pressure and CVD incidence by nutritional means. The DASH diet features vegetables and fruits as well as low fat dairy products, whole grains, chicken, fish, and nuts. It is low in fat, red meat, sweets, and soft drinks. The DASH diet provides more calcium, potassium, magnesium, and dietary fat and less fat and sodium than the typical Western diet.[34] The typical composition of the DASH diet is found in Table 7.2.

  Subsequent studies have substituted some of the carbohydrates with MUFAs and also have further decreased sodium in the diet. All of these modified DASH diets have significantly reduced both systolic and diastolic blood pressure by 7 to 9 mmHg compared with the typical Western diet.

  A study combining the DASH diet with a lifestyle program aiming to reduce overweight, increase physical activity, and restrict sodium and alcohol intake (the ENCORE Trial)[35] showed additional decreases in both systolic and diastolic blood pressure, which were reduced by 14.2 mmHg and 17.4 mmHg, respectively.

  Unfortunately, even in individuals with high blood pressure, fewer than 20% are currently following the DASH diet.[18]

- Vegetarian Diet

  A variety of vegetarian diets are available, including vegan (consuming no animal products), lacto-ovo vegetarian (consuming milk and eggs), and pesco vegetarian (individuals who consume fish along with a vegetarian diet).

  There are no data to suggest that one form of vegetarian diet is superior to others with regard to CVD risk.[36–39] Few randomized controlled trials (RCTs) have been performed on vegetarian diets, and they have typically been small. They have typically resulted in lower blood pressure compared with usual Western diets. Some observational studies have suggested that vegetarians experience improved health outcomes compared with non-vegetarians.[40] However, a variety of characteristics of vegetarian diets could account for these findings, including fewer meats and inclusion of plant based foods. Furthermore, vegetarians are often more health conscious than other individuals, although other factors could contribute to the lower reported incidence of CVD. It should be noted that vegetarian diets (and other low fat diets) can vary dramatically depending on the specific foods consumed.

- Japanese Diet

  There has been recent interest in Japanese diets, particularly those from Okinawa, which has among the lowest CVD rates in the world.[40,41] The traditional Japanese diets emphasize fish, soybean products, seaweed and vegetables, fruits, and green tea and are low in meat. It should be noted that Japanese diets often contain high sodium from soy sauce and have been linked to a higher risk of strokes.[42] There have been relatively few studies of Japanese diets, so many issues remain to be determined.

- Prudent Diet

  In a sense, the low fat diet, Mediterranean diet, DASH diet, and vegetarian diet all would fit in what has been called the "Prudent diet" category. A recent publication compared this diet pattern, which contains high levels of fruits, vegetables, legumes, fish, poultry, and whole grains, with a typical Western pattern, which contains higher intakes of red meat, processed meat, refined grains, French fries, and sweets/desserts.[43] In this study, the Western pattern was associated with a higher risk of mortality from cardiovascular disease (22% higher; 25% confidence interval [CI], 1–48), cancer (15%; 95% CI, 3–30), and all causes (21%; 95% CI, 12–32).

- Plant Based Diets

  There has been a recent surge in evidence and publications concerning "plant based" diets.[44] Essentially, these diets are defined by an emphasis on plants, including fruits and vegetables. Low fat diets and low carbohydrate diets can both be turned into plant based diets. The Mediterranean diet, DASH diet, vegetarian diets, and Japanese diets are all, in essence, plant based diets, since they emphasize fruits and vegetables, legumes, and nuts, and limit the amount of red meat, processed meat, sweets, and oils. It should be noted that the health benefits of plant based diets may vary according to the foods chosen. A recent article compared a "healthy" plant based diet with an "unhealthy" plant based diet.[45] The "healthy" plant based diet resulted in decreased risk of heart disease, while the "unhealthy" plant based diet did not.

7.4 INDIVIDUAL FOOD ITEMS

Numerous studies, including RCTs of risk factors for CVD as well as prospective cohort studies of disease endpoints,

TABLE 7.2
Following the DASH Eating Plan

Food Group	Servings Per Day			Serving Sizes	Examples and Notes	Significance of Each Food Group to the DASH Eating Plan
	1,600 Calories	2,000 Calories	2,600 Calories			
Grains*	6	6–8	10–11	1 slice bread 1 oz dry cerealt ½ cup cooked rice. pasta, or cereal	Whole wheat bread and rolls, whole wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice. unsalted pretzels and popcom	Major sources of energy and fiber
Vegetables	3–4	4–5	5–6	1 cup raw leafy vegetable ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice	Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4	4–5	5–6	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit ½ cup fruit juice	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Fat-free or low-fat milk and milk products	2–3	2–3	3	1 cup milk or yogurt 1½ oz cheese	Fat-free (skim) or low-fat (1%) milk or buttermilk; fat-free, low-fat, or reduced-fat cheese; fat-free or low-fat regular or frozen yogurt	Major sources of calcium and protein
Lean meats, poultry, and fish	3–6	6 or less	6	1 oz cooked meats, poultry, or fish 1 egg‡	Select only lean meats: trim away visible fat; broil, roast, or poach; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	3 per week	4–5 per week	1	½ cup or 1½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ cup cooked legumes (dry beans and peas)	Almonds, hazelnuts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas	Rich sources of energy, magnesium, protein, and fiber
Fats and oils§	2	2–3	3	1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing	Soft margarine, vegetable oil (such as canola, com, olive, or safflower), low-fat mayonnaise, light salad dressing	The DASH study had 27 percent of calories as fat, including fat in or added to foods
Sweets and added sugars	0	5 or less per week	≤2	1 Tbsp sugar 1 Tbsp jelly or jam ½ cup sorbet, gelatin 1 cup lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	Sweets should be low in fat

* Whole grains are recommended for most grain servings as a good source of fiber and nutrients.

† Serving sizes vary between ½ cup and 1¼ cups, depending on cereal type. Check the product's Nutrition Facts label.

‡ Because eggs are high in cholesterol, limit egg yolk intake to no more than four per week; two egg whites have the same protein content as 1 oz of meat.

§ Fat content changes serving amount for fats and oils. For example, 1 Tbsp of regular salad dressing equals one serving: 1 Tbsp of a low-fat dressing equals one-half serving; 1 Tbsp of a fat-free dressing equals zero servings.

Abbreviations: oz = ounce; Tbsp = tablespoon; tsp = teaspoon

provide consistent and strong evidence for cardiovascular effects of certain specific foods in contrast to individual nutrients. These studies represent the combined benefits of composite effects and interactions of multiple factors within foods rather than isolated nutrients. Most foods that fit into dietary patterns that have been demonstrated to lower the risk of CVD will be emphasized in this section.

7.4.1 Fruits and Vegetables

In RCTs, diets that emphasize the consumption of fruits and vegetables have been repeatedly shown to produce substantial improvements in risk factors for CVD, including lipid levels, blood pressure, insulin resistance, inflammatory biomarker levels, and weight control.[3,4,6,46] These same benefits have not been duplicated with supplements and are not dependent on dietary macronutrient composition (e.g. fat, protein, or carbohydrates). These benefits appear to result from phytochemicals and fiber found in fruits and vegetables as well as increased bioavailability of these nutrients in their natural state and replacement of less healthful food in the diet. Both cohort studies and RCTs together support strong evidence that fruit and vegetable consumption lowers CVD risk[3,4,6,46] Considerable research is currently underway to determine which specific types of fruits and vegetables are most beneficial to lower CVD risk.

7.4.2 Whole Grains and Dietary Fiber

Whole grains contain the endosperm, bran (the outer layer of the whole grain), and germ in relative proportions as they exist in the intact grain.[47] Refined grains, in contrast, retain only the endosperm. Dietary fiber consists of the remnants of edible plant lignin, polysaccharides, and associated substances that are resistant to digestion by the human gastrointestinal tract and enzymes.[48] Fiber includes the following: insoluble fiber (including cellulose and lignin), which is found in some vegetables, some fruits, and whole grains (including wheat germ); and soluble fiber, which includes pectin, fruits, guar gum, and mucilage.[49] Soluble fiber also is found in oat bran and legumes. Eating whole grains decreases total cholesterol by between 7 and 8 mg/dL and low-density lipoprotein cholesterol (LDL-C) levels by 6.9 mg/dL, according to a recent Cochrane analysis.[50]

The National Cholesterol Program (ATP III),[51] AHA, and Academy of Nutrition and Dietetics (AND)[52] all have guidelines that include recommendations to increase fiber intake. Whether or not added fiber when used as a food supplement can similarly lower risk factors for CVD is controversial.

The Food and Drug Administration (FDA) has approved a health claim for the soluble fiber from whole oats, whole grain barley products, and barley beta fiber.[53] The DRI recommends 25 grams of fiber for adult women and 38 grams for adult men per day. This corresponds to 14 grams of dietary fiber/1,000 kcal.[49]

7.4.3 Fish

Fish and other seafood contain a variety of healthful substances, including unsaturated fat, vitamin D, selenium, and long chain Omega 3 PUFAs. Some studies have suggested that fish oil has direct anti-arrhythmic effects, but studies in individuals with pre-existing arrhythmias have been inconsistent.[54] Fish oil has been shown to lower triglyceride levels, systolic and diastolic blood pressure, and resting heart rate. Based on these physiologic benefits, regular fish consumption is associated with lower incidence of CVD and risk of cardiac death.[55] For this reason, the AHA dietary recommendations include the consumption of two fish meals (preferably oily fish) per week.[2,3] It is not clear whether the benefits of eating fish can be reproduced by consuming fish oil supplements.

7.4.4 Nuts

Nuts, including tree nuts and peanuts, are nutrient dense foods that are high in unsaturated fats and other bioactive compounds as well as high quality vegetable protein, fiber, minerals, tocopherols, and phytosterols and phenolic compounds.[56] While peanuts are not technically tree nuts, and are typically considered ground nuts or legumes, they are widely identified in research and in the consumer mind as in the same grouping as tree nuts. Additionally, peanuts have a nutrient profile similar to tree nuts.

Epidemiologic studies have consistently shown a negative association between nut consumption and CVD risk.[57] Numerous research studies have shown that consumption of nuts can lower LDL-C concentration by approximately 10 mg/dL, while not significantly changing HDL-C levels. Triglycerides have also been shown to be reduced by >20 mg/dL in subjects with elevated blood cholesterol, though not in those with normal TG levels.

7.4.5 Meat

Dietary patterns that include lower consumption of red meat have been consistently demonstrated to lower CVD risk.[58,59] Various constituents of red meat, including SFAs, cholesterol, and in processed meat, high levels of salt, have been shown to increase factors for CVD. In one research study, both unprocessed and processed meat consumption was associated with higher CVD risk. Such consumption replaced foods with cardiac health benefits such as nuts, fish, and low fat dairy products. Consumption of red meat and processed meats has also been associated with weight gain, which may also increase the risk of CVD.

7.4.6 Dairy Products

Dairy products are rich in minerals such as calcium, potassium, and magnesium, protein (casein and whey), and vitamins (riboflavin and Vitamin B12) and may exert potential benefits by effectively lowering the risk for CVD. The

presence of saturated fat in full fat dairy products has raised concern related to potential adverse CVD effects.[60] For this reason, most dietary guidelines recommend low fat dairy products rather than full fat dairy products.

The inclusion of low fat dairy products as part of an overall heart healthy diet has been demonstrated to significantly lower blood pressure, lipid levels, and insulin resistance independent of changes in weight.[61,62] Due to the multi-component nature of such trials, however, it is difficult to sort out the specific benefits of dairy products.

Recent research has suggested that the matrix in dairy products may make the SFAs in them less hazardous in terms of CVD risk than other SFAs.[24,25] The DGAs 2020–2025 recommend that adults consume three cups of low fat milk or the equivalent on a daily basis.[7] This is far greater than the average serving of one cup per day consumed by adults in the United States. Children and adolescents also consume far below recommended levels.

The health effects of other dairy products such as yogurt, cheese, and butter are the subject of considerable research and require further study.

7.4.7 Soy

The protein found in soybeans is typically referred to as "soy" and is often used to replace animal protein in individual diets.[63] Soybeans contain no cholesterol, are low in saturated fat, and contain considerable protein. Soy is the only vegetable to contain all eight amino acids. The effect of soy on CVD risk has been inconsistent.

7.4.8 Sugar Sweetened Beverages (SSBs)

The effect of SSBs on cardiovascular disease risk is controversial. Some epidemiologic studies have suggested that increased consumption of SSBs increased the risk of heart disease, diabetes and obesity.[64–66] These studies, however, have not been supported by a number of RCTs.[67,6]. The AHA recommends that adult males consume no more than 150 kcal/day and adult females no more than 100 kcal/day in the form of SSBs.[69] The 2020 Strategic Plan from the AHA recommends no more than 460 kcal/week from SSBs.[4] The DGAs 2020–2025 recommend no more than 10% of calories from added sugars,[7] a recommendation also mirrored by the FDA.[70] This recommendation is exceeded by over 80% of the population in the United States.

It should be noted that while the consumption of added sugar has increased over the past 40 years in the United States,[71] this increase is relatively less than the increase in the consumption of fats and flour products. The consumption of all added sugars combined actually decreased from 19% of total calories in 1972 to 17% of total calories in 2010.[72]

SSBs may be an indication of an overall poor quality diet. For this reason, it seems reasonable to recommend no more than moderate consumption of SSBs in an overall cardiac healthy diet.

7.4.9 Alcohol

Alcohol consumption has been demonstrated in various studies to have both beneficial and adverse cardiovascular outcomes.[73–75] Heavy alcohol consumption (three alcoholic drinks/day or more for men and two or more alcoholic drinks/day for women) has been associated with increased risk of cardiomyopathy and higher risk rates of atrial fibrillation.[76] Heavy alcohol consumption is also associated with a variety of other non-cardiac, adverse health consequences such as motor vehicle accidents.[77] Conversely, moderate alcohol consumption (up to two drinks/per day for men and one drink/day for women) has been shown to result in a lower incidence of CVD and diabetes (DM).[78] These effects may be the result of moderate alcohol consumption raising HDL-C, reducing systematic inflammation, or improving insulin resistance.

7.4.10 Coffee and Caffeine

Coffee is consumed throughout the world and is a leading source of caffeine. Other sources of caffeine include primarily tea, cocoa products, cola beverages, and "energy drinks."[79] Caffeine is the best characterized compound in coffee. It has been estimated that 80–90% of adults regularly consume caffeine containing beverages and food. Coffee consumption has long been suspected of being a contributing factor to the development of CVD. Accumulating data over the past few years, however, have suggested no harmful relationship, and possibly even a protective association, between moderate coffee drinking and CVD mortality.[80] Furthermore, a recent study reported that the incidence of type 2 DM was lowered in individuals who consumed four or more cups of coffee a day compared with those who drank fewer than two cups per day.[81]

7.4.11 Tea

Tea is also widely consumed throughout the world. Numerous varieties of teas are available. Most of the tea consumed in Western countries (78%) is black tea, while 20% is green tea, which is the most commonly consumed tea in Asian countries, and Oolong tea (2%), which is mainly consumed in southern China. Several studies have suggested that tea consumption may protect against the incidence and progression of CVD.[82,83] These findings may result from improvement of endothelial function by the interaction between tea components and nitric oxide (NO).[84] This interaction appears to be the result of polyphenol-like flavonoids known as catechins in the tea resulting in the increased bioavailability of NO, which plays a significant role in endothelial function and arterial dilation.

7.4.12 Eggs

Over many years, the public were cautioned to limit egg consumption due to the high cholesterol content of egg yolks and the potential association with CVD.[85] However, subsequent

research has demonstrated that in contrast to SFAs and TFAs, dietary cholesterol, in general, and cholesterol in eggs, in particular, have minimal effects on blood cholesterol.[86] Eggs are also a good source of high value protein and a variety of vitamins and minerals. DGA Guidelines 2020–2025 have, nonetheless, continued to recommend restriction of dietary cholesterol to less than 300 milligrams/day.[7]

7.4.13 Garlic

Garlic preparations have been investigated for both prevention and treatment of CVD. Studies have included raw garlic, garlic powder tablets, oil of garlic, and aged garlic extract. Long-term observational studies, however, for garlic are not available. In view of short-term trials on the effect of garlic on factors for CVD showing modest effects,[87] it appears that garlic may reduce platelet aggregation, but its effect on other CVD risk factors is controversial.

7.4.14 Chocolate

Cocoa is similar to green teas with regard to the content of polyphenols. It is important to recognize that chocolate and cocoa are not the same thing.[88] While cocoa powder is used in the production of chocolate, fat and sugar are the major components of chocolate, creating a higher caloric content. Although the polyphenols from the cocoa may have some benefit for reducing risk factors for CVD, it is more appropriate to potentially recommend cocoa rather than chocolate due to the increased calories from sugar and fat in chocolate.

7.5 NUTRITIONAL SUPPLEMENTS

7.5.1 Salt and Sodium

Virtually every heart healthy dietary plan recommends a reduction in sodium.[3–5,7] Dietary sodium may come in a variety of forms, including processed food (a major source of sodium), table salt, snacks, etc. As dietary sodium intake increases, so does blood pressure.

A number of studies have shown that reduction in salt intake lowers the risk of CVD.[3–5,7,89–91] For this reason, the AHA established the interim goal of 2,300 mg/day of sodium and less than 1,500 mg/day in individuals with hypertension, African Americans, and middle or older age Americans.[92] However, the current average intake of sodium in the United States is 3.4 g/day. Several studies have suggested that lower intakes and higher intakes both increase the risk of CVD compared with the average amount currently being consumed by Americans.[93] Thus, considerable controversies remain in the area of sodium consumption and CVD risk.

7.5.2 Vitamin D

Vitamin D consumption is associated with decreased risk of bone disease based on well-designed studies. Vitamin D may also play a role in a variety of other health issues, including lowering the risk of CVD.[94] At the current time, however, there are insufficient data to recommend increased consumption of vitamin D as a strategy for lowering the risk of heart disease.

7.5.3 Antioxidant Vitamins E and C

Some observational studies initially suggested that antioxidant vitamins E and C were associated with lower risk of CVD. However, RCTs in this area have been largely disappointing. In fact, in several studies, increased mortality was found in individuals with pre-existing late stage atherosclerosis receiving antioxidant supplements with vitamin E or C.[95]

7.6 AHA/ACC DIET AND LIFESTYLE RECOMMENDATIONS

In 2021, the AHA summarized diet and lifestyle recommendations in a Scientific Statement from the AHA Nutrition Committee.[3] These recommendations were also included in 2013 with the AHA/ACC Guideline for Lifestyle Management to Reduce Cardiovascular Risk, which also provided specific clinical guidelines.[5] Numerous studies and research have supported these goals, but the basic framework from these two documents has stood the test of time and will be utilized in this chapter as a point of departure. Since many of the recommendations of these two documents have already been discussed in the sections on Dietary Patterns and Food, specific recommendations will be handled with brief summaries.

The AHA documents started from the fundamental premise that improving diet and lifestyle represents a critical component to an overall strategy to prevent CVD. Both documents differ from previous guidelines in recommending a broader approach to not just diet, but overall lifestyle. The combination of diet and physical activity, in particular, has been emphasized. Both documents emphasize both public health and clinical applications. With this in mind, the following goals have been outlined.

7.6.1 Consume an Overall Healthy Diet

This recommendation starts from the premise that we need to move from individual nutrients to overall dietary patterns such as already discussed in this chapter. It was recognized that RCTs of the whole diet are difficult and expensive to conduct. Numerous cohort and other epidemiologic studies support the concept that dietary patterns consisting of a variety of fruits and vegetables, whole grains, fat free and low fat dairy products, legumes, poultry, lean meats, and fish (preferably oily fish) consumed at least twice a week have been associated with lower risk of CVD.[3–5,94–97] This pattern is consistent with the U.S. Healthy Eating Plan, the Mediterranean diet, and the DASH diet, which have already been discussed in this chapter.

7.6.2 Aim for a Healthy Body Weight

The AHA Guidelines utilize the framework from the IOM establishing healthy body weight as defined as a body mass index (BMI) of 18.5–24.9 kg/m^2. Overweight is defined as a BMI between 25 and 29.9 kg/m^2, and obesity is defined as a BMI of ≥30 kg/m^2. This goal also recognizes that obesity is related to multiple other risk factors for CVD, such as dyslipidemias, high blood pressure, and diabetes, and that obesity in and of itself represents a risk factor for CVD.[98–102] Issues related to obesity management are handled in detail in Chapters 41–44.

7.6.3 Aim for a Desirable Lipid Profile

Elevations in total cholesterol as well as LDL cholesterol are established risk factors for CVD. As levels of LDL cholesterol increase, so does the risk of developing CVD. The following levels of LDL have been defined: optimal (less than 100 mg/dL); near or above optimal (100–129 mg/dL); borderline/high (130–159 mg/dL); high (160–189 mg/dL); very high (190 mg/dL or more).[52, 103, 104]. Several different guidelines have been published for managing LDL. However, dietary changes such as following an overall AHA Healthy Diet Plan are foundational to nutritional approaches to managing total cholesterol and LDL cholesterol.

Triglycerides and HDL cholesterol levels are also related to CVD risk and can be affected by both diet and body weight. Triglyceride levels of >150 mg/dL are considered abnormal.[105] Elevated triglycerides and low HDL are often seen together and are components of the metabolic syndrome.[106,107] Dietary recommendations for elevated triglycerides are virtually the same as those for low HDL cholesterol and elevated LDL cholesterol.

7.6.4 Aim for a Normal Blood Pressure

Elevated blood pressure represents a significant risk factor for both CVD and stroke. Nutrition clearly plays a significant role in blood pressure control. Issues related to optimum levels of blood pressure control have become somewhat controversial. Recommendations from the Joint National Commission VII (JNC VII) defined a normal blood pressure as <120/80 mmHg, and defined a diastolic blood pressure of 80–89 mmHg and 120–139 mmHg systolic as prehypertension, with >140/90 mmHg as "hypertension."[107] These were also the recommendations made by the AHA 2020 Strategic Plan.[4]

The committee appointed to develop the JNC VIII Guidelines made somewhat different recommendations. They issued the following statement:

> There is strong evidence to support treating hypertensive individuals aged 60 or older to a BP goal of <150/90 mmHg and hypertensive persons 30–59 years of age to a diastolic goal of <90 mmHg. However, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of <140/90 mmHg for those groups based on expert opinion.[108]

These guidelines also emphasize that clinical judgement should prevail when considering hypertensive therapy.

The guidelines for blood pressure were revised again in 2017 by the ACC and AHA and established a slightly lower threshold for blood pressure management. These guidelines are based on the findings from the Systolic Blood Pressure Intervention Trial (SPRINT). This trial was conducted in over 9,000 individuals with a mean age of 67.9 years and a systolic blood pressure of 130/180 mmHg and at increased risk of cardiovascular events. The researchers compared targets of SBP less than 120 mmHg with standard targets of SBP less than 140 mmHg. The SPRINT Trial showed a 30% decrease in the composite outcome of myocardial infarction, ischemic heart syndromes, stroke, and heart failure or death compared with the standard target group. These guidelines classify a normal blood pressure as systolic less than 120 mmHg and diastolic less than 80 mmHg. Elevated blood pressure was considered to be 120–129 mmHg and diastolic less than 80 mmHg. Stage 1 hypertension was considered to be 130–139 mmHg and diastolic 80–89 mmHg. Phase 2 hypertension is greater than or equal to 140 mmHg and diastolic greater than or equal to 90 mmHg. In all of these categories, the importance of positive lifestyle habits such as regular exercise and sound nutrition, as well as weight management, was emphasized. See Table 7.3.

It should be emphasized that both of these sets of recommendations support nutritional intervention as a key component of the overall prevention and treatment of high blood pressure. A nutritional pattern consistent with the DASH diet has been clearly demonstrated to help control blood pressure.[18] Unfortunately, a distinct minority of individuals who have high blood pressure actually follow the DASH diet. Other dietary modifications that have been shown to lower high blood pressure include reducing salt intake, establishing a caloric deficit to induce weight loss in overweight or obese individuals, moderate alcohol consumption

TABLE 7.3
Categories of BP in Adults[a]

BP Category	SBP (mmHg)		DBP (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
Hypertension			
Stage 1	130–139	or	80–89
Stage 2	≥	or	≥90

[a] Individuals with SBP and DBP in two categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥ occasions), DBP diastolic blood pressure, and SBP systolic blood pressure.

(among those who drink alcohol), and increased potassium intake. Physical activity is also an important recommendation and acts synergistically with diet to further lower blood pressure.

7.6.5 Be Physically Active

All of the major guidelines for nutritional intervention to reduce the risk of CVD also incorporate the recommendation to increase physical activity.[2,3,5]. Increased levels of moderate or vigorous physical activity have repeatedly been shown to lower the risk of CVD. Guidelines such as the AHA/ACC Lifestyle Recommendations and the DGA 2020–2025 as well as the 2006 Nutrition Guidelines from AHA and the Physical Activity Guidelines for Americans 2018[11] all recommend increased physical activity in addition to heart healthy nutritional plans. The best single source of information related to physical activity and reduced CVD and other chronic diseases may be found in the 2018 U.S. Department of Health and Human Services "Physical Activity Guidelines for Americans."[11] This document was designed to complement the Dietary Guidelines for Americans. More physical activity is associated not only with lowering the risk of CVD but also with specific CVD risk factors, including blood pressure, lipid profiles, and blood sugar.

7.6.6 Avoid Use of and Exposure to Tobacco Products

Overwhelming evidence exists from multiple sources that cigarette smoking and the use of tobacco products or exposure to cigarette smoke increase the risks for both CVD and stroke.[110] This evidence has been summarized in multiple other locations, including the AHA 2020 Strategic Plan[3] as well as the AHA/ACC Diet and Lifestyle Clinical Recommendations and Goals. Unfortunately, over 15.5% of U.S. adults still smoke cigarettes, and the rate of decline of cigarette smoking has significantly slowed over the past 20 years.[111] The risks of cigarette smoking for women are currently equivalent to those for men. Substantial benefits, however, in the reduction of risk of CVD accrue in the individual who stops smoking cigarettes. These benefits accrue over a very brief period of time.

7.7 IMPLEMENTING HEART HEALTHY NUTRITION PLANS

A recent emphasis at the AHA and other health oriented associations has been on implementing strategies to help individuals consume a more heart healthy diet. The AHA issued a Scientific Statement in 2009 entitled "Implementing American Heart Association Pediatric and Adult Nutrition Guidelines."[17] While this statement emphasized the complexity of factors that impact on nutritional choices, it also offered a multilevel framework to impact on these factors. This framework started with individual factors, which were then placed more broadly into family factors, environmental factors, the micro environmental, and finally, the macro environmental factors. Each of these interacting domains contains multiple influencers. Specific results related to these interactive factors are beyond the scope of this chapter. Readers are referred to this Scientific Statement for more detail.[17]

In order to positively impact on multiple factors that influence heart healthy nutrition, proven models of behavioral medicine will be required to help individuals adopt positive behavior, in general, and in the area of nutrition, in particular. Models of behavior change are beyond the scope of this chapter, but are found in Chapters 21–24 in this textbook.

7.8 CONCLUSIONS/SUMMARY

Overwhelming evidence exists to support the concept that nutritional practices strongly interact with the likelihood of developing CVD. Recent guidelines related to nutritional practices have placed them in the overall context of positive lifestyle habits and practices. Lifestyle medicine offers a promising framework for impacting on both nutritional practices and other lifestyle factors that impact on the risk of developing CVD. Evidence based guidelines from the Dietary Guidelines for Americans 2015–2020 and 2020–2025, the American College of Cardiology, and the American Heart Association Nutrition Guidelines 2021, as well as the AHA 2020 Strategic Plan, all emphasize that dietary patterns that include fruits and vegetables, whole grains, seafood, legumes and nuts, and non-fat dairy products and alcohol (among adults), and are lower in red meats and processed meats and low in SSBs and refined grains, all support reduced risk of CVD. While these patterns may be achieved in many different ways, it is important that they be tailored to individuals' cultural, biological, and medical needs.

Implementation of the guidelines from these scientific bodies remains the key challenge, which will require the recognition of multiple factors to interact with both individual and population-wide nutritional choices. A detailed and sophisticated understanding of not only the emerging science in nutrition and CVD, but also behavioral medicine, will be essential to accomplish the goal of helping individuals reduce their risk of heart disease through nutritional and other lifestyle practices.

CLINICAL APPLICATIONS

- Plant based diets from the American Heart Association, the American College of Cardiology, and the Dietary Guidelines for Americans are consistent with each other, so any of these can be followed to lower the risk of heart disease.
- The DASH diet has been shown to effectively lower blood pressure in individuals with hypertension.

- Nutrition plays a key role in lowering the risk of cardiovascular disease and should be placed in the context of an overall healthy approach to lowering the risk of CVD, including increased physical activity, weight management, and avoidance of tobacco products.
- Clinicians should routinely recommend that individuals follow diets that are high in fruits and vegetables, whole grains, seafood (particularly oily fish), legumes and nuts, and non-fat daily products, and lower in red meats, processed meats, SSBs, and refined grains to support reduction in the risk of CVD.

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8 Optimal Nutrition Guidance for Older Adults

Alice H. Lichtenstein

KEY POINTS

- Diet quality is directly related to optimal physical and cognitive function in older adults.
- Nutrient requirements either stay the same or increase with advancing years, whereas energy requirements decline, increasing the importance of making nutrient-dense food choices.
- Changes in sensory perception and the onset of chronic diseases may necessitate added attention to diet composition in older adults.
- Alterations in social environments and living situations make it important to monitor the ability and desire to obtain, prepare, and consume a high-quality diet.

8.1 INTRODUCTION

In 2015, approximately 46 million individuals living in the U.S. were over the age of 65 years. This number is expected to double to approximately 98 million by the year 2060, representing about 24% of the total population (Figure 8.1). Accompanying this increase, the older population is expected to become more racially and ethnically diverse. They are also expected to work longer and attain a higher level of education than prior generations. Current trends suggest a higher proportion of older adults than previously will be dealing with the challenges of obesity.

Accompanying this shift in the demographic makeup of the U.S. population is an ever-increasing need for specific nutrition guidance to achieve and maintain optimal physical and cognitive function with advancing years. Evidence suggests that within a population, older adults who score in the higher categories for diet quality[1–4] and physical activity measures[5,6] have the best survival rates.

8.2 CURRENT RECOMMENDATIONS

The revamp of the recommended dietary allowances (RDA) by the Food and Nutrition Board of the Institute of Medicine starting in the early 1990s brought about more precise recommendations for individuals above the age of 50 years.[7–14] The current recommendations, termed dietary reference intakes (DRI), include guidance for adults in categories of 31–50 years, 51–70 years, and greater than 70 years.[15] No further distinction is made for individuals aged 70 years and above. This lack of more precise guidance for those over 70 years is likely a consequence of limited information from the older-aged groups.[15] DRI values for most nutrients, including vitamin A, vitamin C, vitamin E, vitamin K, thiamin, riboflavin, niacin, folate, vitamin B_{12}, pantothenic acid, biotin, choline, chromium, copper, fluoride, iron, magnesium, manganese, molybdenum, phosphorus, selenium, and zinc, do not differ between adults above and below the age of 50 years. The nutrient recommendations for three nutrients, vitamin D, calcium, and vitamin B_6, are higher for older adults. The DRIs for vitamin D increased from 600 IU/day for females and males between 51 and 70 years of age to 800 IU/day for both females and males above 70 years of age.[16] The DRIs for calcium increased from 1200 and 1000 mg/day for females and males, respectively, between 51 and 70 years of age to 1200 mg/day for both females and males above 70 years of age.[16] The DRIs for vitamin B_6 increased from 1.3 mg/day and 1.4 mg/day for females and males, respectively, between 51 and 70 years of age to 1.5 mg/day and 1.7 mg/day, respectively, for both females and males above the age of 70 years.[9] Emerging evidence suggests future revisions in the DRIs for individuals over the age of 70 years may be necessary,[17] but any recommendations must await a thorough review of the new literature.

Although the DRIs for most nutrients do not increase with advancing age, with the exceptions of vitamin D, calcium, and vitamin B_6, it can become increasingly difficult to achieve the recommended intakes as individuals advance in years. In general, with increasing years, total energy needs decrease to compensate for diminished requirements associated with lower levels of physical activity, a higher proportion of fat mass relative to lean muscle mass, and a lower basal metabolic rate.[18,19] Similar or slightly higher nutrient needs must be met within the context of reduced food intake and commensurate with lower energy requirements. This can be accomplished by intentionally selecting nutrient-dense foods (high nutrient content per calorie). An icon summarizing salient points related to dietary modification for older adults has been developed to provide specific guidance, termed *MyPlate for Older Adults* (Figure 8.2). Differences from the *MyPlate Food Guide* for the general population include examples that emphasize nutrient-dense foods within each category, illustrations of foods that are particularly convenient for older adults (e.g., bags

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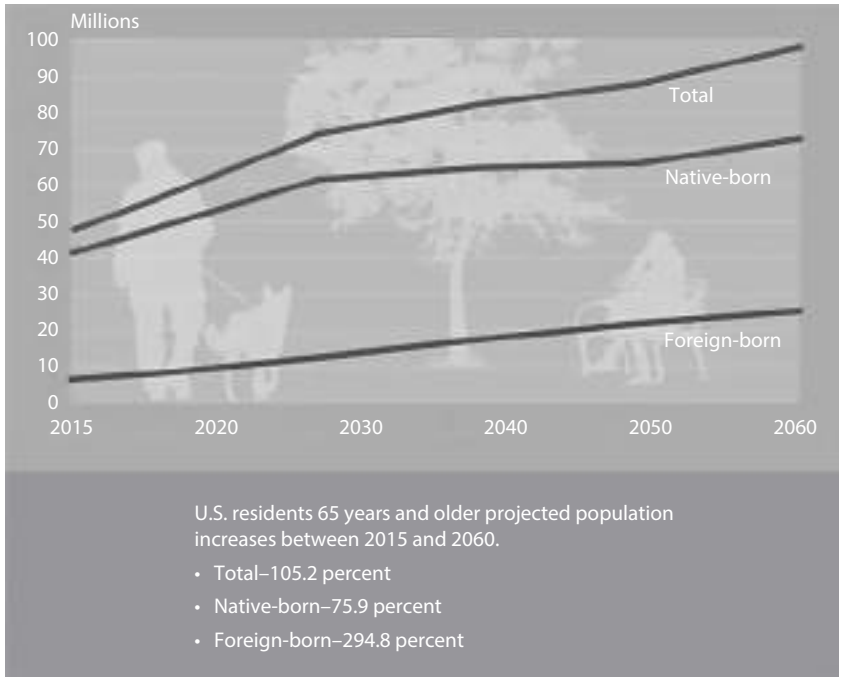


FIGURE 8.1 Projected number of U.S. residents 65 years and older.

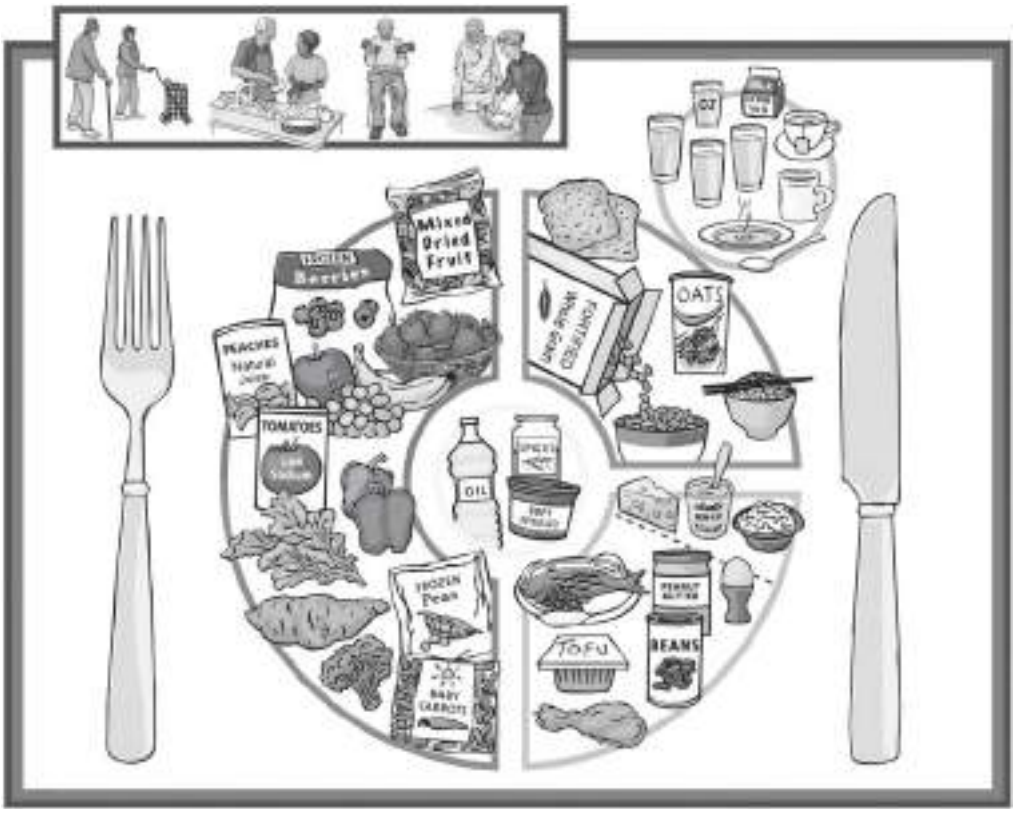


FIGURE 8.2 *MyPlate for Older Adults.*

of frozen vegetables), shift of the dairy group into the protein segment to provide a broader range of protein-rich food options, greater emphasis on fluid by depicting a variety of choices in a separate segment, incorporation of suggestions for regular physical activity as an integral part of the icon, addition of a segment at the center of the plate to emphasize the importance of including healthy oils in the diet and using seasonings (spices and herbs) as an alternative to salt,

and knife and fork on the side of the plate to encourage a focus on enjoying food when eating rather than focusing attention on a hand-held device.[20]

8.3 NUTRIENTS OF CONCERN

Adequacy of some nutrients can be a concern for all adults, particularly older adults. "Nutrients of public health concern" are divided into two categories—those of concern due to overconsumption and those of concern due to underconsumption. The criteria used by the 2020 Dietary Guidelines Advisory Committee to identify nutrients of public health concern include that population intakes are below or above the estimated average requirement or adequate intake, and there is corroborating evidence of adverse effects due to low or high intakes based on biochemical markers of nutrient status. Current nutrients of public health concern for underconsumption are vitamin D, calcium, potassium, fiber, and iron (not a concern for older adults); for overconsumption, nutrients of concern are sodium and saturated fat.

8.3.1 Vitamin D

Adequate vitamin D intake is of concern for older adults.[21] There are a number of factors that may compromise vitamin D status with advancing years. These include decreased efficiency of skin to synthesize vitamin D after exposure to sunlight and tendency to spend less time outdoors to accumulate sun exposure.[22] Limited sun exposure due to latitude or concern about sun exposure because of skin cancer risk can minimize endogenous vitamin D synthesis.[23,24] Additionally, overweight and obese individuals tend to have lower circulating vitamin D concentrations, potentially due to sequestration in the adipose tissue. As rates of overweight and obesity increase in the older population,[18,25] this factor may also contribute to compromised vitamin D status.[26] Up until recently, fluid milk was the only reliable food source of vitamin D in the U.S.[21] Recent changes to the vitamin D fortification regulation have resulted in an increased availability of vitamin D and calcium–fortified juices and juice drinks, and vitamin D-fortified dairy products other than fluid milk.[27,28]

8.3.2 Calcium

The vast majority of calcium in the body resides in bone and teeth. Much smaller but no less important amounts of calcium are critical for the regulation of cell signaling, blood clotting, muscle contraction, and nerve function. The richest naturally occurring and bioavailable source of calcium is dairy products. A wide range of low-fat and nonfat dairy products are currently available. There are two factors to take into consideration when recommending dairy products to older adults. The first is lactose intolerance. With increasing age, the rate of lactose intolerance increases.[29–31] Fortunately, a wide range of lactose-free and low-lactose dairy products are now available, as well as enzyme preparations (lactase) that can be taken when consuming foods containing lactose to decrease the symptoms of lactose intolerance. Although the prevalence of lactose intolerance increases with age, intolerance symptoms among lactose maldigesters tend to decrease with age, suggesting that as people get older, they may have more, rather than less, flexibility in their choice of calcium-rich dairy foods.[30] The second consideration with regard to dairy products is saturated fat. Dairy products can be a major source of saturated fat. Saturated fat intake is associated with an increased risk of developing cardiovascular disease.[32,33] Older adults should be encouraged to take advantage of reduced-fat versions of dairy foods and incorporate sources of unsaturated fat, such as soybean and canola oils, as alternative fats in their diets. Additional sources of dietary calcium are fortified drinks such as calcium-fortified orange juice and plant-based milks.

8.3.3 Potassium

Potassium functions as a critical electrolyte in the body, along with sodium, chloride, calcium, and magnesium. It is also involved with proper heart function, and skeletal and smooth muscle contraction. Rich dietary sources of potassium include fish and plant foods including legumes, vegetables, and fruits. Higher fruit and vegetable intakes have been associated with a number of positive health outcomes, including bone health, blood pressure, metabolic syndrome, stroke, and cardiovascular disease.[34–43]

8.3.4 Fiber

A major function of dietary fiber is its laxative effect in the gut. Whole vegetables and fruits are a good source of dietary fiber, as are whole grains and whole grain products. For this reason, older adults should be encouraged to consume fruits and vegetables in their natural state rather than the juice form. They should also be encouraged to choose whole grain products rather than refined and processed grain products such as those commonly available in large food markets. In general, fiber supplements are not routinely recommended because excessive fiber can decrease the bioavailability of calcium, iron, zinc, copper, and magnesium.[44]

8.3.5 Sodium

Under normal circumstances, small amounts of dietary sodium, along with potassium, help maintain normal blood pressure as well as muscle and nerve function. However, high amounts of dietary sodium are associated with hypertension.[34] Major sources of dietary sodium come from commercially prepared foods, with only a small percentage coming from salt added at the table.[39] There has been a dramatic increase in the availability of reduced-sodium products. Everyone, particularly older adults, should be encouraged to take notice and choose those products.

8.3.6 Saturated Fat

Higher intakes of saturated fat relative to unsaturated fat, both monounsaturated and polyunsaturated, are associated with higher risk of developing cardiovascular disease. Major sources of dietary saturated fat are fats of animal origin and tropical oils. Animal fats include meat and as indicated earlier, dairy fat. Tropical oils include palm, palm kernel, and coconut. Intake can be minimized by choosing lean cuts of meat, as well as limiting both frequency and portion size. Low- and fat-free dairy products are readily available. Ingredient labels can be used to determine whether commercially prepared foods contain tropical oils.

8.3.7 Added Sugar

High levels of added sugar intake have been associated with increased risk of developing obesity, heart disease, and type 2 diabetes, among other disorders.[39,45] Approximately 47% of added sugar in the U.S. diet comes from sugar-sweetened beverages, 31% comes from snacks and sweets, and the balance comes from a combination of other food categories, both obvious and less obvious.[39] The introduction of added sugars as a mandatory requirement of the revised Nutrition Facts labels has made it easier for individuals to compare items within categories so as to choose those with less added sugar, and has spawned the development of reduced-sugar options.

8.4 SPECIAL DIETARY CONSIDERATIONS FOR OLDER ADULTS

The area of maintaining optimal nutrient status in older adults must be considered in terms of physiological factors and psychological factors. Special attention to both of these factors is critical for ensuring optimal health outcomes.

8.4.1 Organ Systems

The way the body handles nutrients can change with advancing age. These changes are mostly due to changes in the functioning of organ systems, which can ultimately impact health outcomes (Table 8.1). Interestingly, few adverse nutritional consequences resulting from advancing years have been noted that are independent of ancillary biological changes. These exceptions include vitamin B_{12}, vitamin D, and calcium. With increasing years, many individuals experience a decline in gastric hydrochloric acid secretion.[46] The resulting hypochlorhydria causes a decline in the bioavailability of vitamin B_{12}. As previously noted, due to the diminished capacity to synthesize endogenous vitamin D, older adults may be at a compromised vitamin D status, and as a result, for calcium. Impairments or decreases in the function of the heart, blood vessels, and kidneys can stress the normal demands on everyday life. Changes in body composition (decreased lean muscle mass and increased fat mass) result in diminished basal metabolic rates, energy needs, and capacity for physical activity.[47] Increased use of prescription and nonprescription medications, chronic drug therapy, and decreased capacity of the liver to metabolize drugs can compromise nutrient utilization. These factors should be evaluated on a regular basis by the health care provider.

TABLE 8.1
Potential Biologic Changes Contributing to Altered Nutrient Status in Older Adults

System	Change
Digestive system	↓ Hydrochloric acid secretion
	↓ Digestive juice secretion (pancreas and small intestine)
	↓ Absorptive capacity (malabsorption)
	↓ Muscles tone large intestine (↓ gastrointestinal motility)
	↑ Chronic blood loss due to ulcers and hemorrhoids
Liver	↓ Hepatic and biliary function
	↓ Rate detoxification
Heart	↓ Cardiac output
	↓ Strength and flexibility of blood vessels
Kidneys	↓ Blood flow
	↓ Glomerular filtration
Senses	↓ Acuity vision and hearing
	↓ Taste (loss taste buds, mainly salt and sweet)
	↓ Smell
Skin	↓ Synthesis vitamin D
Body composition	↓ Lean muscle mass
	↑ Fat mass
	↓ Mobility
	↓ Dexterity
Immune system	↓ T cell-mediated function
	↑ Susceptibility to infection and malignancy
Pharmacokinetics	↑ Prescription and nonprescription drug use
	↑ Chronic drug therapy
	↓ Capacity to metabolize drugs
Mouth	↓ Salivary secretion
	↑ Altered bite pattern due to tooth loss

8.4.2 Taste and Smell

Retaining the desire to eat a variety of foods is integral to ensuring optimal nutrition for older adults. This issue is of particular concern because diminished taste and smelling acuity associated with aging can lead to poor appetite. This change includes loss of taste bud acuity, primarily with respect to salty and sweet food items, and a resulting greater sensitivity to acid and bitter food items.[48] Other changes frequently observed in older adults include a diminished sense of smell. Older adults with poor odor perception have lower nutrient intakes than those with good odor perception.[49–51]

8.4.3 Vision, Dexterity, and Mobility

Diminished vision, dexterity, and mobility can make food acquisition and preparation difficult, which can severely alter the variety and quality of foods consumed (Table 8.2).

TABLE 8.2
Activity of Daily Life Factors That May Contribute to Compromised Food Intake in Older Adults

Factor	Change
Oral cavity	↑ Peritoneal disease
↑ Ill-fitting dentures	
↓ Salivary gland secretions	Mobility
↓ Physical activity	
↓ Respiratory capacity	↓ Lean muscle mass (strength, physical disability)
↑ Physical isolation	Senses
↓ Acuity (taste, smell, sight)	Dexterity
↑ Arthritic involvement finger and hand joints	
↑ Tremor	↓ Manual dexterity
Energy needs	↓ Energy requirements
↓ Caloric intake	
	↓ Volume

TABLE 8.3
Psychosocial Factors Contributing to Compromised Food Intake in Older Adults

Factor	Change
Companionship	↑ Loss of spouse
↑ Social isolation	
↑ Loss of companions	↓ Social interaction secondary to ↓ mobility
Mental state	↑ Depression
↑ Mental deterioration (dementia)	
↑ Alcoholism	↑ Loneliness
↑ Chronic disease	Economic
↑ Fixed income (poverty)	
↓ Choice and availability	↓ Quantity needs
↓ Variety	Nutrition knowledge
↑ Susceptibility to food fads	↑ Susceptibility to nutrient supplement claims
Housing	↑ Change in status (loss of home)
↓ Independence	

Difficulty in opening jars, cans, or packaged foods due to arthritis or diminished strength can lead to decreased variety and ability to consume preferred foods. Small accommodations in an individual's environment, such as ergonomically designed kitchen aids (e.g., can openers and scissors), kitchen reorganization (e.g., eliminating clutter and moving frequently used items to most accessible places), and shifts to the use of partially prepared foods, can minimize a decline in diet quality. For example, resealable bags of frozen vegetables and fruits are particularly good choices for older adults because they allow easy apportioning of single or double servings, minimize pre-preparation (which can be difficult or even painful with advanced years), eliminate waste due to spoilage, reduce the need for frequent trips to the market, and provide variety during long periods of inclement weather. Likewise, purchasing boneless chicken breasts can decrease preparation and cooking times, and is adaptable to the preparation of individual small portions. Older adults may not automatically take advantage of newer forms of common food items (e.g., prewashed greens, precut fruit, shredded cheese) and require some regular guidance in this area.

8.4.4 Social Factors

In addition to declines in physical capacity associated with the aging process, there are also changes in the social environment of older adults that can have an impact on nutritional status (Table 8.3). With increasing years, the loss of a spouse or other family members with whom an individual shared and prepared meals is common. This can lead to social isolation, especially during mealtime, and diminished desire to prepare well-balanced and varied meals. Due to deterioration in mental or economic status, older adults are frequently faced with having to adapt to a new living environment. This can result in dramatic changes in mealtimes, food preparation, and foods available. The onset of chronic disease can further limit food choices and make older adults susceptible to the lures of food fads or dietary supplements promising a fountain of youth. Succumbing to these claims can drain scarce resources from food purchases and result in overconsumption of individual nutrients. The latter can interfere with prescription drug actions or utilization of essential nutrients. Depression frequently accompanies the aging process in individuals without adequate support to make the necessary adaptations that come with advancing age. Older adults are also at increased risk of alcohol abuse. All of these factors may contribute to poor food consumption patterns.[52]

8.5 PHYSIOLOGICAL CHANGES OF CONCERN IN OLDER ADULTS

Nutrient-related chronic diseases particularly prevalent in middle and later years include cardiovascular disease, cancer, type 2 diabetes, hypertension, osteoporosis, disorders of dentition and associated senses, and declines in immune function. In some cases, the goals of food and nutrient recommendations for older adults are aimed at delaying the onset of chronic disease, while in other cases they are intended to treat or accommodate the disorder.

8.5.1 Dentition and Associated Senses

Salivary secretions decrease with increasing age. Changes in bite pattern from partial or complete extraction/loss of teeth are common. Poorly fitted dentures can make eating painful and unpleasant. The prevalence of root canals is

higher in older than younger adults.[53,54] Increased incidence of tooth disease in older adults has been related, in part, to high levels of sugar consumption.[55] Any one or a combination of these factors can restrict the type and variety of foods consumed. For example, chewing and swallowing fibrous foods may be difficult due to poor dentition, resulting in a shift toward highly processed foods or juices that are low in fiber content.[56] It is critical when evaluating dietary intakes of older adults to consider possible concerns regarding food textures and preparation methods and to assess dentition.

8.5.2 Cardiovascular Disease

The risk of developing cardiovascular disease increases with age, especially after menopause in females.[57] Higher saturated fat coupled with lower polyunsaturated fat intake has consistently been associated with higher rates of cardiovascular disease.[58–60] The American Heart Association/American College of Cardiology[33] and the *2020–2025 Dietary Guidelines for Americans*[39] recommend dietary patterns that are rich in vegetables and fruits, whole grains, legumes (beans), fat-free and low-fat dairy products, fish, and lean meat. No specific recommendations for dietary change are made for adults as they age. The response to these recommendations in terms of plasma lipids appears consistent for both genders and all adult age groups.[32]

8.5.3 Osteoporosis

Age-related or type II osteoporosis (bone loss) is positively associated with the aging process. Osteoporosis is estimated to affect 200 million women worldwide—approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80, and two-thirds of women aged 90.[61] In men, it is estimated that the residual lifetime risk of experiencing an osteoporotic fracture over the age of 50 is 27%.[61] Age-associated bone loss is attributed to diminished estrogen production, decreased calcium absorption from the gastrointestinal tract, decreased calcium resorption by the kidney, decreased rates of physical activity, compromised vitamin D status, and decreased calcitriol production secondary to hyperparathyroidism.[61,62] In older adults, calcium balance is favorably affected by vitamin D intake and negatively affected by high sodium, protein, alcohol, and caffeine intakes.[62] Supplemental calcium and vitamin D in postmenopausal women living in northern latitudes (42°N) may minimize bone loss.[63] Because serum osteocalcin, calcidiol, and vitamin D fluctuate seasonally due to sun exposure, vitamin D intake is particularly important during the period of winter and spring in this group. These data strongly support routinely screening older adults for vitamin D status.

8.5.4 Glucose Intolerance/Type 2 Diabetes

The incidences of glucose intolerance and type 2 diabetes mellitus increase with age.[64,65] The increased incidence has been strongly associated with weight gain in later years. Lifestyle interventions have been demonstrated to be efficacious in preventing or delaying the onset of type 2 diabetes mellitus.[66–68] These include regular daily physical activity, achieving and maintaining a healthy body weight, and dietary modification consistent with that advocated for the prevention and treatment of cardiovascular disease.

8.5.5 Hypertension

The incidence of hypertension increases with age.[57] This increase is associated with changes in the vasculature and kidneys, and is exacerbated by excess weight gain. A number of clinical trials have demonstrated clear benefits of dietary modification to treat hypertension in older adults. The DASH (Dietary Approaches to Stop Hypertension) dietary pattern, rich in vegetables, fruits, and fat-free and low-fat dairy products, reduces blood pressure in individuals with a wide range of characteristics. Further coupling this dietary pattern with sodium restriction has been shown to further reduce blood pressure.[43]

8.5.6 Immune Function

The most commonly associated age-related change in the immune response is cell-mediated function.[69,70] Limited data suggest vitamin E supplementation may be beneficial in decreasing the incidence of respiratory infections in older adults living in residential settings.[71]

8.5.7 Cancer

The incidence of cancer shows tremendous variability on the basis of worldwide distribution, type, and site in the body. The incidence of all types of cancer increases with age. Support for a diet/cancer incidence link comes from data suggesting associations between markedly divergent food consumption patterns and incidence rates of cancer among different population groups.[72] Some data have been reported for associations involving the following dietary components: alcohol intake (laryngeal), calcium and vitamin D intake (stomach, colon, breast), fat intake (breast, colon, prostate), fiber intake (breast), and antioxidant vitamin and/or orange and dark green vegetable intake—vitamin A and beta-carotene, vitamin C, vitamin E, and trace elements (wide range of sites).[72–76] Results from randomized controlled supplementation trials are limited and not encouraging.[77] At this time, the general dietary guidance to reduce cancer risk is consistent with the dietary guidance to prevent the onset of chronic diseases of concern in the twenty-first century.

8.6 CONCLUSIONS

The aim of dietary guidance specifically targeted for older adults is to maintain optimal health and forestall the onset of chronic disorders. The actual dietary recommendations, for the most part, are consistent throughout the adult life cycle.

Evidence suggests that there is a direct relationship between the nutrient quality of the diet and survival rates. Due to decreased levels of physical activity, decreased metabolic rates, and increased proportions of fat to lean muscle mass, energy requirements decline with advancing years, yet nutrient requirements remain unchanged or increase. This situation requires a greater emphasis on choosing nutrient-dense foods within each food category. Special attention needs to be given to adapting living environments with advancing years to retain the ability to acquire and prepare food. Changes in social situations that could impact on food intake should be monitored on a regular basis. Evidence suggests that diet and lifestyle interventions can forestall the onset of cardiovascular disease, osteoporosis, diabetes, hypertension, immune function, and possibly some types of cancer. There are no data to suggest a person is too old to benefit from improvements in diet quality. The definitions for old age and expectations for the period of time individuals can remain active, productive, and live independently are expanding. Efforts toward improving diet quality and levels of physical activity with advancing years should keep up with this trend.

CLINICAL APPLICATIONS

- The major goal of dietary guidance specifically targeted for older adults is to maintain optimal health and forestall the onset of chronic disorders.
- Diet quality is directly related to physical and cognitive functioning in later years. The adoption of healthy lifestyle practices should be encouraged.
- Nutrient requirements either stay the same or increase with advancing years, whereas energy requirements decrease. Attention needs to be given to ensuring adequate nutrient intake and avoiding excess energy intake.
- Advancing years are often accompanied by declines in sensory perception such as taste, smell, vision and dexterity, and mobility. Such alterations may necessitate added attention to dietary behaviors in older adults.
- Special attention should be given to adapting living environments with advancing years to retain the ability to acquire and prepare food.

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9 Effects of an Active Lifestyle on Water Balance and Water Requirements

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KEY POINTS

- Water is essential to life, with body water content normally tightly regulated and remaining relatively constant from day to day.
- The main factors influencing total body water content are body mass and body fatness (lean tissue has a much higher water content than adipose tissue).
- Large excursions from euhydration are associated with loss of functional capacity and if sufficiently large, are potentially fatal.
- Water losses are increased by increasing ambient temperature and humidity and by increasing levels of physical activity.
- A variety of foods and beverages normally contribute to total daily water intake.

9.1 INTRODUCTION

The ability to regulate body water content and the osmolality of tissues within a relatively narrow range is one of the defining characteristics of all animal life. Small excursions in these parameters are normal, but large changes are incompatible with survival. This close regulation must be achieved in the face of a continuous, but variable, loss of water and salts from the body. Humans can survive for several weeks without food, but deprivation of water for even a few days can be fatal, with survival time dictated largely by the rate of water loss. Water comprises about 50–70% of body mass, making it the most abundant component in the human body, except in the very obese. This gives about 40–42 L of water in the average 70-kg male: because of their generally higher relative body fat content, females normally have a lower body water content than males of the same mass. A change—whether an increase or decrease—of more than about 10% of this value carries a number of risks, but regulatory and behavioral mechanisms normally intervene long before this point is reached. Approximately two-thirds of this water is found in intracellular compartments, with the remaining third in extracellular compartments. Euhydration is defined as body water levels being within about 0.2% of normal in temperate conditions and within about 0.5% when in the heat or during exercise.[1] Individuals are considered to be hypohydrated (reduced body water) or hyperhydrated (increased body water) outwith these limits. Both of these conditions, if sufficiently severe, can impair all aspects of physiological function and may prove fatal in extreme cases.

Physical activity poses a number of challenges to water and salt homeostasis, including increased rates of water and salt (particularly sodium and chloride) loss. These effects are amplified as the activity level, ambient temperature, and environmental humidity increase. Hard exercise, even if the duration is too short to induce substantial sweat losses, also causes a redistribution of water between body water compartments because of the large changes in osmolality within the active muscles.

Those who are physically active—whether on a recreational or an occupational basis—should be aware of their body's need for water and salt, and should not either ignore or consciously over-ride the physiological signals.

9.2 WATER BALANCE

Water balance occurs when water intake matches water losses, but water intake is episodic, whereas water losses are continuous, so water balance fluctuates throughout the course of a day. Over a 24-hour period, water balance is generally maintained without conscious attention to intake. Avenues of water intake include fluid consumed as drink, in the water content of ingested food, and a small amount generated by oxidative metabolism (Table 9.1). For sedentary individuals in temperate environments, daily water turnover is typically about 2–3 L, with the main avenue of loss via urine, with additional losses via respiration, transcutaneous loss, sweating, and fecal loss. Some individuals exercising in hot conditions may lose this amount in an hour, as sweating is induced to limit the rise of core temperature that occurs in these situations, particularly in hot/humid conditions.

Urine production is regulated by a number of hormones in response to changes in intravascular volume and osmolality: these include arginine vasopressin (AVP), aldosterone, and atrial natriuretic peptide (ANP). Secretion of AVP from the posterior pituitary is induced by an increase in plasma osmolality and a decrease in blood volume, increasing water reabsorption in the renal collecting ducts and the production of a smaller volume of more concentrated urine. A 1-mosm/kg increase in plasma osmolality results in a 0.41-pmol/L increase in plasma AVP concentration,[2]

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TABLE 9.1
Estimates of Water Intake and Loss by Various Routes in an Average Sedentary Male Living in a Temperate Climate

Water Intake (mL)	Water Output (mL)
Metabolism (400)	Urine (1400)
Drinking (1500)	Respiration (320)
Food Ingestion (1000)	Skin Loss (530)
	Sweat Loss (650)
	Water Loss in Feces (100)
Total (3000)	Total (3000)

Data are collated from a variety of sources and can vary greatly from day to day within the same individual as well as between individuals.

and a 3-mosm/kg increase in plasma osmolality results in a 250-mosm/kg increase in urine osmolality.[3] A change in blood volume of 7–10% is required for similar magnitudes of change in urine osmolality, making plasma osmolality the main determinant of AVP release.[2]. The renin-angiotensin aldosterone system is activated in response to decreases in blood volume, with aldosterone acting on the collecting ducts of the kidney to increase sodium reabsorption, which in turn, leads to water reabsorption and the production of a smaller volume of more concentrated urine. ANP is secreted from the right atrium in response to increases in blood pressure and leads to an increase in urine volume.

Thirst and habit are major drivers of fluid intake. Thirst is triggered by a complex interaction between physiological, psychological, and behavioral factors.[4] Changes in plasma osmolality and blood volume are thought to play important roles in the thirst response; thus, the same factors that regulate water loss are also involved in water intake. Animal models have suggested that substances such as angiotensin 2, bradykinin, and serotonin may also be involved in thirst response. Genetic factors may also account for some individual variation in thirst response, although the picture is not entirely clear.[5,6] Generally, thirst is considered to be a poor indicator of short-term deviations in body water, given observations that unlimited access to drinks after periods of fluid restriction tends not to fully restore water losses[7] and rapid fluid ingestion in these circumstances appears to alleviate the perception of thirst.[8] The thirst response is considered, however, to be sufficient to restore body water levels over longer time periods.

The European Food Safety Authority (EFSA) reports that total (i.e. water from food and fluid) adequate daily water intake is 2.0 liters for an average adult female and 2.5 liters for an average adult male.[9] Different adequate total water intakes are reported by the Institute of Medicine in the United States, with values reported as 2.7 liters and 3.7 liters for adult females and males, respectively.[10] The values reported by these bodies are an average (or median) volume consumed by healthy adults and are, therefore, classed as adequate intakes rather than recommended intakes. Considerable variation in the volumes of water consumed by healthy adults is observed. For physically active individuals who will lose greater volumes of water via sweating, which is exacerbated in hot environments, achieving the adequate intakes reported is not a guarantee that water intake is sufficient for that individual. For example, many sports/physical activities typically produce a sweat rate of 0.5–1.5 L/hour, but in some well-trained or very large athletes, sweat rates may reach and even exceed 3–4 L/hour. Therefore, there are settings where athletes or physically active individuals may lose more water in sweat than is recommended in these daily adequate intake values for water, meaning that more must be consumed to meet daily requirements in some athletes. It is likely, however, that water intake throughout the day will match water losses due to a combination of habitual fluid intake and the individual's thirst response driving further fluid intake.

9.3 SWEATING, WATER BALANCE, AND WATER TURNOVER

Metabolic heat production at rest is approximately 60 watts, but metabolic demand increases in a linear fashion and can reach 1 kilowatt during moderately hard exercise such as marathon running. This metabolic heat must be dissipated to avoid large increases in core temperature, and this is achieved largely by an increase in sweat rate.

There are many published reports of hydration status, sweat rates, and fluid intake in physically active individuals. Most of these studies have focused on elite athletes undertaking training sessions and/or matches in different environmental conditions. Maughan et al.[11] studied elite football players during a training session in warm conditions and observed a median pre-exercise urine osmolality of 666 mosm/kg (range of 103 to 1254 mosm/kg). During the 90-min training session, median fluid intake was 971 mL with a range of 265 to 1661 mL, and percentage body mass loss was 1.4% with a range of 0.5–2.6%. In a similar study performed in a cold environment, Maughan et al.[12] observed that pre-exercise urine osmolality was 872 mosm/kg (range: 481–1228 mosm/kg), fluid intake was 420 mL (range: 44–950 mL), and percentage body mass loss was 1.6% (range: 0.9–2.5%). Similar results have been observed during competitive football matches[13] and throughout a competitive handball tournament.[14] These studies demonstrate that some individuals are likely to begin exercise in a hypohydrated state (indicated by the high urine osmolality values of these athletes), that there are large inter-individual differences in sweat rate and fluid intake during exercise, and that some individuals are likely to become significantly dehydrated by undertaking relatively short but intense periods of physical activity. A few individuals drink more than they sweat: often, these are those who began exercise in a hypohydrated state.

Sweat consists of water, minerals, and organic components. Consequently, when sweat rate increases during

exercise, it is not just water that is lost. The main electrolytes that are lost via sweat are sodium and chloride at concentrations of approximately 15–80 mmol/L. There is large inter-individual variation in the composition of sweat, leading to large variations in electrolyte loss between individuals.[11,12] This, in addition to the large variation in sweat loss, means that no single hydration strategy is suitable for all physically active individuals, and hydration advice should be tailored to the individual in question.

Body water turnover, or the replacement of water lost over a given period, is approximately 5–10% of total body water content per day for a sedentary individual living in a temperate environment but can increase to 20–40% if prolonged exercise is undertaken in a hot environment. Water turnover is higher in children up to 15 years of age than in adults and higher in physically active individuals than in age-matched sedentary individuals.[15] Leiper et al.[16] reported that average median water turnover in a cool environment for a group of regular cyclists was higher (47 mL/kg/d) than in age-matched sedentary controls (36 mL/kg/d), with the difference in water turnover due primarily to non-renal water losses. When similar measurements[17] were made in recreational runners, water turnover rates were higher (4673 mL/d) than in sedentary age-matched controls (3256 mL/d), but the difference was due to a renal loss, suggesting that voluntary intake was increased beyond the needs dictated by sweat loss.

9.4 HYDRATION STATUS AND PERFORMANCE

Small changes in body water content occur throughout the day and have no measurable effect on physiological function, but large changes clearly have an impact. Despite the substantial volume of research in this area, however, there is no agreement regarding the point at which a reduction in body water is likely to affect physiological function. This is probably due to a variety of factors related to methodological issues in experimental design as well as inter-individual variability, as the factors that limit exercise capacity will also differ.

Case studies demonstrate that prolonged physical activity, especially but not exclusively in hot environments, without fluid ingestion can lead to impaired physiological function, hypernatremia, and collapse.[18] Other case studies demonstrate that extreme over-ingestion of fluid during exercise can also lead to impaired physiological function and hyponatremia, which can prove to be fatal.[19] At some level of dehydration, an effect must become apparent, but this will depend on the exercise model, the environmental conditions, and the individual susceptibility.

A review by Cheuvront and Kenefick[20] concluded that the majority of studies in this area have suggested that a reduction in body mass of 2% or more is likely to reduce endurance exercise performance, particularly when that exercise is performed in a hot environment. This agrees with the 2007 Position Stand on Exercise and Fluid Replacement published by the American College of Sports Medicine.[21]

A number of physiological and psychological mechanisms may contribute to the effect of hypohydration on exercise performance. Gonzalez-Alonso et al.[22] reported that stroke volume was reduced and heart rate increased when dehydrated participants undertook exercise in a hyperthermic environment. In addition to the impact of hypohydration on stroke volume and heart rate, Gonzalez-Alonso et al.[23] also reported a reduction in skin blood flow during exercise in the hypohydrated state. This reduction in skin blood flow will reduce the extent of heat loss at the skin and lead to increases in core temperature. An individual's perception of effort (rating of perceived exertion [RPE]) at a given exercise intensity has been shown to increase when exercising in a hypohydrated state compared with a euhydrated state,[24–26] which is likely to be another mechanism by which a reduction in body water negatively influences exercise performance. Interestingly, Fleming and James[27] demonstrated that habituation to exercise in a hypohydrated state reduced the detrimental effects of a reduction in body water on endurance exercise performance. This effect was not mediated by changes in cardiovascular system function but rather, by habituation reducing RPE.

It has been suggested that a reduction in body water of 3–4% is required to induce detrimental effects on muscle function,[28] although some studies that isolate the effects of hydration report impairments at much smaller degrees of hypohydration.[29] A meta-analysis of 28 published studies[30] concluded that hypohydration results in meaningful reductions in non-body weight–dependent muscle performance and that the method of inducing a reduction in body water was an important consideration. In particular, hypohydration induced by passive means resulted in less of an effect on muscular performance than those that involved an active component. This meta-analysis also concluded that body weight–dependent muscular performance may be improved by a reduction in body water of 3% or more.

Relatively mild levels of hypohydration have been shown to negatively affect cognition. Ganio et al.[31] observed that mild hypohydration of approximately 1.5% body mass resulted in reduced cognitive aspects, such as visual vigilance and visual working memory, when compared with the euhydrated state. Lindseth et al.[32] reported that flight performance and spatial cognition tests were reduced in pilots who were hypohydrated due to low levels of fluid ingestion compared with those who were euhydrated with adequate levels of fluid ingestion. Watson et al.[33] induced hypohydration in their volunteers by a period of fluid restriction that resulted in a reduction in body mass of 1.1%. During a two-hour simulated driving task, more minor driving errors were recorded when participants were hypohydrated than when they performed the task having followed current drinking guidelines. These studies suggest that even mild levels of hypohydration appear to have a negative impact on cognition.

One important consideration and caveat related to hydration and human performance, as well as one of the main criticisms of studies in this area,[34] is that the vast majority (all but a handful of recent studies) have been unblinded. That is, the athletes/participants undertaking the study are aware of which trial is the hypohydrated trial and which is the euhydrated trial (as they either drink or do not). This means the results of these studies may be influenced by placebo or expectation effects, which is particularly important, as many athletes perceive hypohydration to negatively impact their performance.[35] Therefore, the fact that they know which trial they are hypohydrated in could, at least partially, explain the impairment in performance in previous studies.

Recently, this potential methodological limitation in the hydration literature has been examined. James et al.[36] used gastric feeding tubes to give or not to give water to male recreationally active volunteers while they cycled in the heat, without their knowledge. This meant that it was possible to effectively blind the exercisers to the hydration manipulation while also mimicking the physiological and subjective responses typically observed with hypohydration. Interestingly, and counter to the researchers' hypothesis, they reported that endurance performance was impaired by ~8% in the hypohydrated trial with hypohydration equivalent to ~2.4% of body mass. This study demonstrated that hypohydration impairs performance but gave little insight into any expectation effects around hydration. In a follow-up study, also in the heat, the same research group[37] recruited two groups of trained male cyclists and had one group repeat the blinded study design used previously, while the other did everything as would normally be done in a hypohydration study (drink or not drink water during exercise in an unblinded manner), allowing expectation effects to be examined. Interestingly, hypohydration (equivalent to ~3% of body mass) impaired performance in both groups by ~10% and was not different between groups. This provides strong evidence that hypohydration does impair endurance performance and that the effects reported in the literature (at least when hypohydration is equivalent to ~3%) are unlikely to be due to expectation/placebo effects: at least for endurance exercise in the heat, in males.

9.5 HYDRATION FOR RECREATIONAL ACTIVITY (RPE, ENERGY BALANCE)

Physical activity is known to induce numerous health benefits, and lack of cardiorespiratory fitness is considered an independent risk factor for a number of disease states. Physical activity is therefore often prescribed to improve health. While physical activity alone does not appear to induce large degrees of weight loss, it does have beneficial effects on body composition, and the incorporation of physical activity into a weight loss strategy that also includes restriction of energy intake is likely to produce the greatest degree of body mass loss.[38] In addition, the extent of weight regain after a period of weight loss is likely to be lower if physical activity is incorporated into the initial weight loss strategy.[39] Adherence rates to exercise programs are generally poor, however.[40] An individual's RPE during physical activity is a key regulator of self-selected exercise intensity and will likely determine whether that individual continues or terminates an exercise session. Consequently, factors that alter an individual's RPE during exercise might be of importance to ensure compliance with exercise strategies used to promote health.

An individual's perception of effort during exercise is a complex phenomenon involving numerous physiological, psychological, and social factors[41] and is typically assessed using a Borg scale. Briefly, the perception of effort during exercise consists of physiological mediators such as ventilation, availability of energy substrate, and skin temperature activating neuromotor signals. This, combined with psychological factors (such as motivation, mood state, and experience), exertional symptoms (such as heavy breathing and sweat rate), and in the case of elite athletes, performance considerations, is processed by the sensory cortex. This results in a perceptual response that will affect the perceived effort of exercise.[42] The strongest physiological mediators of RPE are respiratory rate, sensation of strain in muscles and joints, perception of body temperature, and limb movement speed. Changes in heart rate, blood lactate concentrations, and oxygen uptake do not correlate as well with changes in RPE.[42] Given the close relationship between core body temperature, sweat rate, skin temperature, and hydration status, it is no surprise that there is interest in determining whether an individual's hydration status influences their perception of effort during exercise.

An important methodological consideration is that few, if any, studies have been carried out to study the effect of dehydration on RPE during exercise. Instead, RPE has been measured as a secondary outcome measure in studies examining the effect of dehydration on other markers of physiological function. A further important methodological consideration is whether an individual begins exercise in a dehydrated state or whether dehydration is accrued throughout exercise.

Cheuvront et al.[43] induced dehydration via heat (three hours of heat exposure that resulted in a 3% reduction in body mass) prior to undertaking a 30-minute exercise trial at 50% VO_{2max} and a 30-minute time trial. No differences in RPE were observed between the euhydrated and dehydrated states. Similarly, Kenefick et al.[44] reduced body water by 1.7–1.8 L via 75 minutes of exercise in hot conditions before a 75-minute heat tolerance test involving running exercise. During this heat tolerance test, there was little difference in RPE when participants were euhydrated compared with when they were dehydrated. Alternatively, Riebe et al.[45] induced a level of 4% dehydration via exercise in the heat before a period of rehydration or no fluid ingestion. During a subsequent exercise test, RPE was significantly higher in the dehydrated state compared with the euhydrated condition. Similar findings of an increase in RPE when previously dehydrated compared with a euhydrated condition

have been observed by Fleming and James[27] and Gonzalez-Alonso et al.[46] On balance, it would seem that beginning exercise in a dehydrated state is likely to lead to a small but meaningful increase in RPE.

Watson et al.[47] reported a significant increase in RPE when participants undertook an intermittent exercise trial at 55% VO_{2max} in hot conditions without fluid ingestion compared with when plain water was ingested to match sweat losses, i.e., dehydration was allowed to accrue. Similarly, Baker et al.[26] observed that three hours of treadmill walking without fluid replacement led to an increase in RPE in comparison to when fluid replacement was allowed. Ishijima et al.[48] reported that 90 minutes of cycle exercise at 55% VO_{2max} without fluid ingestion led to greater RPE than when exercise was undertaken with fluid ingestion. These observations would suggest that dehydration accrued while exercising for longer than about 30 minutes may also lead to a small but meaningful increase in RPE.

The mechanisms underlying the effects of hypohydration on RPE may include both physiological and psychological factors. As discussed previously, hypohydration leads to a reduction in stroke volume and an increase in heart rate[22] as well as a reduction in skin blood flow.[23] Blood-brain-barrier permeability may be altered[47] and cerebral perfusion reduced[49] in response to hypohydration, resulting in direct effects on the central nervous system. Hypohydration also leads to dryness of the mouth, thirst, and headaches, which could ultimately affect mood state and psychological factors that alter the perception of effort.

A substantial body of evidence exists to suggest that starting exercise in a hypohydrated state or allowing hypohydration to occur during exercise results in an increased perception of effort. The effect of hypohydration on RPE is an important consideration for situations of occupational activity as well as the prescription of physical activity for health and wellbeing. Consequently, in these situations, individuals should be provided with the opportunity and education to ensure they are adequately hydrated prior to beginning work or an exercise session to minimize the effect of impaired hydration status on RPE.

9.6 IMPLICATIONS FOR DRINKING STRATEGIES

Much attention has been given to strategies during exercise that may optimize exercise performance. As previously discussed, small acute reductions in body water (as assessed by changes in body mass) are unlikely to cause any negative effects on performance, and therefore, a drinking strategy that restores all body water lost during exercise is unnecessary. Similarly, generic advice to all physically active individuals is not appropriate due to the large inter-individual differences in sweat losses that occur during exercise.

Two main drinking strategies have been promoted in recent years. The first suggests that water and electrolyte losses can be assessed during training in response to different environmental conditions and a pre-exercise strategy implemented in order for an individual to avoid reductions in body water that may negatively influence exercise performance.[27] Alternatively, individuals can drink only when thirsty[50] or *ad libitum* (i.e., as and when they want). While these last two strategies are similar, they differ in that drinking to thirst relies solely on the thirst response to drive fluid intake, whereas drinking *ad libitum* involves other external cues in addition to thirst. Armstrong et al.[51] compared a drinking to thirst strategy with an *ad libitum* strategy in trained cyclists completing a 164-km road cycle at an ambient temperature of 36 °C. Although the percentage body mass lost and fluid intake were the same, the authors concluded that an *ad libitum* strategy may be easier to implement. Also, in situations where sweat rates are very high and/or drink breaks/stations are infrequent, drinking to thirst might be difficult, as ingesting a sufficient volume of fluid to satisfy thirst might not be possible.

It seems clear that a single hydration strategy is not appropriate for all individuals, and numerous confounding factors must be considered. These include the individual's pre-activity hydration status, the extent of water loss incurred, individual preference of taste and familiarity with drinks, the ambient temperature, and the temperature and composition of the drinks. An additional consideration is individual differences in gastrointestinal disturbance that may occur as a result of fluid ingestion during exercise. Relatively high intensity exercise (>70% VO_{2max}) reduces the rate at which fluid is emptied from the stomach,[52] as does ingestion of solutions with relatively high carbohydrate concentration.[53] Consequently, ingestion of large volumes of water and/or solutions containing carbohydrate during exercise may lead to gastric discomfort in some individuals. While there is some evidence that it is possible to train the gastrointestinal system to the ingestion of these volumes,[54] it is still an important consideration when planning hydration strategies during physical activity.

As hypohydration is a common occurrence after exercise, a large body of research on post-exercise rehydration exists. If a single exercise session is completed during the day, there is no need for an aggressive rehydration strategy to be implemented, as normal regulatory processes governing fluid intake will ensure that water balance is maintained over a 24-hour period. If a second exercise session is to be performed on the same day, a post-exercise rehydration strategy may be needed to ensure that this session is not started while hypohydrated. The most important factor to consider is the volume of fluid that is consumed. Shirreffs et al.[55] observed that a volume greater than that lost during exercise is required to account for obligatory urine losses. This is typically translated as 1.5 L of drink for every 1.0 L of net fluid deficit at the end of exercise. It also seems as though the rate at which fluid is ingested is an important consideration, with high rates of fluid ingestion less effective at maintaining fluid balance over a recovery period than low rates of ingestion of the same volume.[56] The composition of a rehydration solution is likely to alter the effectiveness of that solution to maintain fluid balance over a

recovery period. The most important constituent of a rehydration solution is the sodium concentration, as this is the most abundant ion in the extracellular fluid and therefore, has a significant impact on plasma osmolality. The addition of sodium to a rehydration solution has been shown to improve its effectiveness at maintaining fluid balance during a recovery period.[57] The addition of carbohydrate and protein to a solution may also be of benefit, as the addition of these nutrients reduces the rate of gastric emptying and overall water absorption, ensuring that water loss is minimized due to the avoidance of large changes in concentration and volume of the blood/plasma.[58,59] An additional consideration is whether food is ingested alongside a solution. Water is not considered to be an adequate rehydration solution when ingested on its own, as it is rapidly absorbed into the blood and causes a relatively large reduction in plasma volume and a diuresis,[60] but when ingested alongside a meal containing adequate electrolytes, water may be a suitable rehydration solution.[61]

9.7 HYDRATION AS PART OF A HEALTHY LIFESTYLE

As outlined previously, moderate reductions in body water are common as a result of physically active lifestyles, and these reductions may lead to changes in cardiovascular function as well as impairments of cognitive processes and mood. These observations are important for physical performance in elite athletes, for physically active members of the general public, and for those with occupations that involve manual work. What is less clear, perhaps, is the effect of acute and chronic reductions in body water on health. The majority of work in this area has focused on elderly populations, although an increasing amount of research is being undertaken in this space.

Chronic hypohydration is unlikely to result in severe physiological or cognitive health effects, as large deviations in body water will be, at least partially, corrected by mechanisms that regulate body water balance. Consequently, the effects of chronic hypohydration are likely to be relatively mild in most cases. Conversely, large acute reductions in body water could be relatively severe. Few studies have adequately examined the effects of hydration status on chronic disease, but there are some suggestions that low fluid intake (and therefore, hypohydration) may be linked to urinary stones (urolithiasis), constipation, bladder and colon cancer, hypertension, and diabetic ketoacidosis.[62] These observations should be treated with caution, however, due to the lack of studies demonstrating causality. Some recent studies have started to examine the effect of hydration/water intake on disease risk, but many of these studies are epidemiological in design, precluding the elucidation of cause and effect relationships. More work is needed in this area, but recent studies have suggested that drinking additional water might benefit kidney health[63] and those at risk of urinary tract infection.[64] For example, in a 12-month study of women who habitually drank less than 1.5 liters of fluid/day and who had a history of urinary tract infections, it was reported that those who were randomized to consume an additional 1.5 liters water/day had a reduction in urinary tract infections compared with those who did not consume additional water.[64]

The aging process results in a reduction in fat free mass, a reduction in bone mass, and a reduction in total body water, as well as a blunted thirst response, leading to an increased risk of hypohydration in these individuals. Additionally, aging results in a reduction in renal function and a reduced ability to concentrate urine, meaning more water is lost to excrete the same daily osmotic load. Hydration status is known to be a factor in disease progression for a number of medical disorders. Hypohydration is thought to lead to infection, which in elderly populations, can be fatal in up to 50% of cases if not diagnosed early.[65] In an analysis of UK death certificates between 2005 and 2009, it was observed that 667 deaths were due to dehydration compared with 157 as a result of malnutrition: it is, however, difficult to determine whether dehydration was the causative factor in these deaths.[66]

Leiper et al.[67] observed that water turnover, as assessed via a deuterium oxide tracer, was significantly slower in elderly individuals living in a residential care home than in those who lived at home. Similarly, Wolff et al.[68] reported that 12% of elderly patients admitted to hospital from a residential care home were hypernatremic (raised blood sodium levels, indicative of dehydration) upon admission compared with 1.3% of elderly patients who lived at home. The extent of hypernatremia upon admission is related to likelihood of in-hospital mortality, and consequently, patients from residential care homes had a greater likelihood of in-hospital death than those who lived at home. Similar results were reported by El-Sharkawy et al.[69] These observations indicate that elderly individuals, particularly those in care homes, should be targeted by care workers to ensure adequate water ingestion and avoidance of hypohydration.

Quality of life is of primary importance in elderly individuals and is often assessed as a profile of physical, psychological, independence, social relationships, environmental, and spiritual domains. In a study of 82 residents of Australian care homes, Courtney et al.[70] reported that quality of life was positively correlated with clinical care indicators. The three main indicators that affected quality of life were poor hydration status, number of fall incidents, and depression. These areas may be targeted to improve quality of life in residential care, and improvements in hydration may be one of the easiest and most cost-effective ways to achieve this.

It seems clear from this evidence that certain populations, such as the elderly, are more susceptible to the impact that reductions in body water can have on health. Further evidence of this can be seen when examining the effects of changes in environmental temperature on morbidity and mortality. Sardon[71] reports that temperatures throughout Europe were several degrees higher between June and September 2003 compared with other years. In an analysis

of heatwave days in 2003 compared with the same dates in other years from 1990 to 2004, D'Ippoliti et al.[72] observed that there were 7.6% more deaths in Munich, 10.4% more deaths in London, 26.8% more deaths in Rome, and 33.6% more deaths in Milan. In Mediterranean cities, where the heatwave had the largest impact on temperature, the percentage increase in all-cause mortality compared with other years was greatest in those aged 85+ years and was higher in females than males.

Similar observations have been made in Australia. Nitschke et al.[73] analyzed daily ambulance transports, hospital admissions, and mortality over a 13-year period from 1993 and compared heatwaves with non-heatwave periods. Total mortality was unaffected during heatwaves, but ambulance transports and hospital admissions increased by 4% and 7%, respectively. Total mental health and renal health hospital admissions were increased by 7% and 13%, respectively. Similarly, Khalaj et al.[74] surveyed 1,497,655 emergency admissions to hospital in sites across New South Wales. It was observed that on days of extreme heat, hospital admissions for heat illness, dehydration, and electrolyte disturbance were increased, whereas hospital admissions from other causes were not. Individuals with underlying medical conditions affecting the nervous, circulatory, respiratory, and/or renal systems were particularly affected by the high environmental temperatures.

It seems clear that certain populations, particularly the elderly and those with underlying medical conditions, are most at risk of high environmental temperatures and that this is likely to be at least partly due to the effect on hydration status. Warren et al.[75] examined the economic impact of hospital admissions due to hypohydration in US elderly adults. Almost 7% of hospitalizations in 1991 had dehydration listed as a diagnosis, with 1.4% listing it as the primary diagnosis. This resulted in $446 million in Medicare claims, suggesting that hypohydration-related hospital admissions have a significant economic impact. From these observations, it seems that the avoidance of hypohydration in these situations is a relatively straightforward but potentially effective intervention in certain populations for improving public health. It is important to consider how easily changes in hydration can be made, given the easy, low cost (almost free) access to water in most countries. This makes improvements in hydration status a potential quick, easy, and cheap win for health care costs in many parts of the world.

Much attention has been given to the acute and chronic effects of hypohydration, but large acute increases in body water, though less common than hypohydration, can also be hazardous. Over-hydration can occur as a result of the ingestion of water in excess of the amount needed to maintain euhydration, an electrolyte deficit, and/or an inability of the renal system to compensate for these changes by appropriate adjustments of renal function. As with chronic hypohydration, chronic over-hydration is unlikely to lead to serious health consequences in healthy individuals, but occasionally, it can be fatal. If the concentration of sodium in the extracellular space falls, water moves from the interstitial space into the cellular compartment, leading to swelling of cells. In most tissues, this is of little consequence, though it may have implications for a number of cellular functions.[76] If sufficiently severe, however, an increase in intra-cranial pressure will result, and symptoms associated with "water intoxication," including headache, nausea, confusion, and changes in behavior, may appear. If intra-cranial pressure continues to increase, this can lead to central nervous system dysfunction, coma, and death. Exercise associated hyponatremia, brought about by ingesting a greater volume of water than is lost via sweat, has been associated with several deaths and was reported in 13% of finishers of the Boston marathon in 2002 despite these individuals showing no clinical symptoms.[77] A number of non-exercise cases of "water intoxication," brought on due to excessive fluid ingestion, have also been described. These include cases from fraternity initiation practices, co-ingestion of large volumes of fluid with recreational drugs such as MDMA, water ingestion during weight loss plans, and social competitions involving large volumes of fluid intake.[78]

9.8 CONCLUSION

Despite the abundance of water in the human body, it is important to maintain levels within narrow limits. This is achieved by matching water intake and water output. An imbalance between water intake and output leads to either hypohydration or over-hydration. Chronic water imbalances are usually relatively mild, and homeostasis will be restored by normal regulatory processes. Acute imbalances can, if sufficiently severe, lead to changes in physiological function that can affect performance of physical activity and in extreme cases, lead to serious health consequences. Some elite athletes, exercisers, and manual workers have been shown to begin activities in a hypohydrated state even when there is a high risk of potentially harmful hypohydration. Sweat rates and fluid intake during physical activity both vary greatly between individuals. Undertaking physical activity in a hypohydrated state leads to an increase in subjective effort, which may have an impact on exercise performance and self-selected exercise intensity. Some populations, such as the elderly, are more likely to become hypohydrated, and they, and those who care for them, may need specific hydration advice in order to avoid potential adverse health consequences.

CLINICAL APPLICATIONS

High levels of physical activity, especially in warm environments, lead to increased sweat production and therefore, increased losses of water and salt from the body. Hypohydration and hypernatremia are the normal responses to prolonged exercise in the heat, but losses vary greatly between individuals even under the same exercise and environmental conditions and are normally self-limiting. Ingestion of water—especially with the addition of

carbohydrate and salt—can help maintain physiological function and performance capacity. If sweat losses exceed about 2–3% of body mass, performance is usually impaired. Ingestion of plain water or other low-sodium drinks in excess of sweat loss can lead to hyperhydration and the development of hyponatremia. Mild hyponatremia is generally asymptomatic and harmless, but if severe and treated inappropriately, can, on rare occasions, be fatal. Medical support personnel at endurance events must recognize that some of those requiring medical attention may be severely hypohydrated, while others finishing (or failing to finish) alongside them may be hyperhydrated and hyponatremic.

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10 Culinary Medicine

Uma Naidoo, MD

KEY POINTS

- Nutrition is a key driver of poor physical health and metabolic disease in the USA and worldwide.
- Culinary medicine is an easy solution to include food as medicine in a clinical discussion.
- Culinary medicine can help teach health professionals and patients to use nutrition to improve physical health, longevity, and quality of life.

10.1 BACKGROUND

Hippocrates of Kos, the Greek physician (460 BC–370 BC) considered to be the father of modern allopathic medicine, is known for his sage-like words about the power of food as medicine, but a lesser-known quote of his aptly captures culinary medicine:

> Just as food causes chronic disease, it can also be the most powerful cure.

Culinary medicine is a new evidence-based field in medicine that blends the art of food and cooking with the science of medicine. Culinary medicine is aimed at helping people reach good personal medical decisions about accessing and eating high-quality meals that help prevent and treat disease and restore well-being.[1]

Over the past approximately four decades, there has been an emerging and fast-growing movement around food, cooking, and ingredients in relation to physical health. Many people who may not know how to cook will frequently be found mesmerized by watching food shows on television. The formation of the Food Network in the early 1990s changed the face of modern television by introducing an entire food focused television network. Seen as a gamble[2] at the time, it is now a household name.

Food as medicine, however, is rooted in a significant deficit: medical doctors are not taught sufficient nutrition information during medical school. A study published in 2015 surveyed all 133 US medical schools with a four-year curriculum about the extent and type of required nutrition education during the 2012/13 academic year. They had a 91% response rate (121 medical schools responded). The study concluded that "many US medical schools still fail to prepare future physicians for everyday nutrition challenges in clinical practice."[3]

The result of this education gap is that medical doctors cannot be expected to adequately or effectively address obesity, diabetes, metabolic syndrome, malnutrition, or even heart disease if they are not taught how to identify and then treat any underlying nutritional causes of these and other diseases.

When reviewing these factors, the developing field of culinary medicine shows promise to support filling that gap in clinical care and potentially improving treatment of patients. With cardiovascular disease remaining the number one killer in the United States, it begs the question: how can we offer more solutions to improve cardiac healthcare along with cancer, chronic pulmonary diseases, diabetes, obesity, and cognitive impairment? After all, these are among the leading causes of death and disability throughout the world in both developed and developing countries.[4] Poor nutrition is the number one cause of illness in the United States and is responsible for more than half a million deaths per year.[5] With such devastating health data, it brings forth the concept that we need more tools in our tool kit, and one of them is nutrition.

10.2 THE HISTORY OF CULINARY MEDICINE

Dr. John LaPuma is credited with writing the first nonfiction trade book about culinary medicine in 2009, called *ChefMD's Big Book of Culinary Medicine: A Food Lover's Road Map to: Losing Weight, Preventing Disease, Getting Really Healthy.*

From this book, "culinary medicine" is described as the art of cooking blended with the science of medicine. As a trained professional chef, Dr LaPuma also shared many recipes that could be used easily by the reader to start to incorporate home cooking again, with the ultimate purpose of improving our health as well. In an academic paper from 2016, the following description emerged, describing what culinary medicine is not:

> Culinary medicine is not nutrition, dietetics, or preventive, integrative, or internal medicine, nor is it the culinary arts or food science. It does not have a single dietary philosophy; it does not reject prescription medication; it is not simply about good cooking, flavors or aromas; nor is it solely about the food matrices in which micronutrients, phytonutrients, and macronutrients are found.[6]

10.3 HEALTH DATA

While the reasons behind the rising rates of obesity and other chronic diseases are multifactorial, one concept could be the difference in time spent cooking over the decades.

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The Multinational Time Use Study[7] published in 2003 showed that Italian and French adults spend about 19 more minutes per day cooking than Americans. The Centers for Disease Control and Prevention reported that 36.6% of adult Americans eat at fast food restaurants on a daily basis.[8]

Other research has shown that cooking at home is associated with better nutrient intake as well as fewer overall calories.[9] Analysis of the Nurses' Health Study[10] data found that people who ate 11 to 14 home-cooked lunches and dinners per week had a 14% lower risk of developing type 2 diabetes than those who ate only 6 or fewer home-cooked lunches and dinners per week, and that this association was partly attributed to less weight gain linked with this dining behavior. When you summarize this information, you may conclude that preparing meals at home, spending more time in the kitchen than eating out at restaurants, and eating meals at home will contribute to overall improved physical health. Since most fast food restaurants use cost saving processed vegetable oils, which are pro-inflammatory, this also impacts mental health by causing inflammation. A study by University of São Paulo Medical School presented at the 2022 Alzheimer's Association International Conference (San Diego, CA) suggests that if 20% or more of your daily diet is made up of processed and ultra-processed food, cognitive function could also be impacted.[11] They asked 10,000 Brazilians, with an average age of 51, to record their eating habits for up to a decade. Researchers then looked at the results of cognitive tests—including immediate and delayed word recall, word recognition, and verbal fluency—in relation to the participants' daily diet. The study found that men and women who ate the most ultra-processed foods saw their global cognitive function decline 28% faster than those who ate a diet of non-processed food. The same group had a 25% faster rate of executive function decline compared with people who avoided processed foods in their diet.

Poor diet is the leading cause of death and disability (700,000 deaths/year).[12] Suboptimal diet is associated with many chronic diseases, such as obesity, diabetes, cardiovascular diseases, and cancer. Nearly 50% of deaths related to cardiovascular disease, stroke, and diabetes are also related to poor diet. Suboptimal diet is the number one risk factor for premature death from chronic disease, specifically cardiovascular disease, the number one killer of Americans. The World Health Organization reports that 1.9 billion adults were overweight in 2016, and 650 million were considered obese.[13] The prevalence of obesity in the United States was 30.5% in 1999, and this increased to 42.4% by 2017, according to the Centers for Disease Control.[14] While many factors have contributed to this epidemic, the Western diet, also called the Standard American Diet (SAD), is considered to be a major contributor to the growing rate of obesity in the United States.

Yet despite this data, most Americans continue to eat the SAD, even with compelling data that our current eating patterns predispose us to greater morbidity and mortality for COVID. A study from New York City found that patients with a body mass index (BMI) of 30–34 were 1.8 times more likely to be admitted to an intensive care unit (ICU), and those with a BMI greater than 35 were 3.6 times more likely to be admitted to an ICU.[15]

Culinary medicine can play a key role in helping to rethink what we are eating, looking at healthier but still delicious meal swaps, and integrating the knowledge that we are what we eat.

Since the field has emerged, there have been several advances alongside it, such as the Healthy Kitchens, Healthy Lives (HKHL) Conference, which began in 2006 under the leadership of Dr. David Eisenberg, Director of Culinary Nutrition and Adjunct Associate Professor, Department of Nutrition, Harvard T.H. Chan School of Public Health. This is now an annual conference co-hosted by the Harvard T.H. Chan School of Public Health and the Culinary Institute of America.[16] The intention of this conference is to bring together medical, public health, and culinary experts in a collaborative effort to educate health professionals about food and cooking, and to educate culinary experts about nutrition science and its implications in designing and providing healthier menu options.[17] The participants are tutored by demonstrators from the Culinary Institute of America, who offer practical demonstrations on how to prepare healthy meals and how to use specific foods for a healthy diet.[18]

From the very start, Dr. David Eisenberg envisioned a time when health professionals would build "teaching kitchens" to be used as learning laboratories in hospitals, medical and allied health schools, schools, and allied venues. What occurred was that many alumni, after completing the HKHL conferences over time, were inspired to create their own prototype "teaching kitchens." By 2016, more than 30% of the participants at the conferences confirmed that their host organizations had built or soon would build a teaching kitchen, and for this reason, the "Teaching Kitchen Collaborative" (TKC) was established by the Culinary Institute of America and the Harvard T H Chan School of Public Health in 2016. These initiatives, both the HKHL conferences and the TKC project, have certainly broadened the impact of education of healthcare practitioners to enable them to include culinary medicine principles into clinical practice.

Given that a prior study showed that only 38% of physicians discuss diet during routine office visits, all efforts to move this conversation forward are key.[19]

Dr. Michelle Hauser[20] is the Obesity Medicine Director of the Medical Weight Loss Program in the Stanford Lifestyle and Weight Management Center. Beyond delivering patient care and medical education, Dr. Hauser is a prevention researcher and trained chef. She combines her skills to help patients move away from lifestyles that lead to chronic disease and toward those that promote health and well-being.

Dr. Hauser wrote the first comprehensive Culinary Medicine Curriculum for healthcare professional training programs, now in use in more than 100 countries.[21]

It has been downloaded at least 2379 times in 83 countries by a wide variety of healthcare professionals interested in teaching culinary medicine. This educational resource serves to further spread the message of culinary medicine and allow further education and subsequent use of these healthy eating principles and recipes.

Positive use of the media sharing new frontiers in medicine can be very useful for both consumers and clinicians alike. An example is a feature in the *New York Times* in 2018 titled "The Doctor is Cooking," and in 2019, Time Health Website featured: "Why food could be the best medicine of all."[22,23]

Another positive outcome of raising the awareness of culinary medicine education has been its implementation in medical school electives and/or into medical education. Park (2019)[24] listed the "Necessary Ingredients for a Culinary Medicine Program," which included:

- Culinary medicine faculty (physician or clinician lead trained in culinary medicine, a chef, registered dietitian)
- Operational support for planning and logistics
- Curriculum and recipes (original or licensed)
- A teaching kitchen or other suitable space
- Partners (internal and community partners)

One of the difficulties many hospitals or medical schools face is a shortage of suitable space to host such a curriculum. And as noted earlier, those centers that were able to raise sufficient funds created a Teaching Kitchen Collaborative to host their programs.[17]

Certainly, some medical schools have taken up the challenge to educate their students with hands-on cooking programs. The Goldring Center for Culinary Medicine (GCCM) at Tulane University's School of Medicine is the first dedicated teaching kitchen to be implemented at a medical school.[25] The program was founded in 2012 and taught medical student and community cooking classes at kitchens around the city. By working in locations like churches and community centers, the center strengthened its connection to the New Orleans community. In 2014, the Goldring Center found a permanent home for its teaching kitchen. The center also provides hands-on training for medical students and residents at Tulane through culinary medicine classes, including electives and interdisciplinary seminars. Interns at Tulane University's School of Public Health who are studying nutrition and dietetics also complete rotations and attend a series of classes throughout their internship year. The GCCM also teaches continuing medical education classes for licensed medical professionals, including physicians, physician assistants, nurses, nurse practitioners, dietitians, and pharmacists. They serve the community with free classes where anyone from the public and local community can learn about nutrition and culinary medicine through hands-on cooking classes. The GCCM curriculum is also licensed by medical schools across the United States to increase nutrition education in programs.[26]

Beyond adults, some educational programs have included educating children. The researchers note that programs that include children in hands-on nutrition education appear to promote changes that positively impact the entire family. From this, they designed a dedicated pediatric cooking and nutrition class alongside a community-based culinary medicine class for adults.[27]

Another program based its objectives consistently with the US Presidential Executive Order of July 2019 with the goal to reduce the annual incidence of kidney failure by 25% or more by 2030.[28,29]

In summary, the Culinary Medicine movement is growing and developing in all directions, supporting both clinicians and consumers, as well as children.

Nutritional psychiatry in the United States is in its infancy when compared with culinary medicine but is really the missing clinical component that addresses our brain health and mental well-being.

The first nonfiction trade book on the subject of nutritional psychiatry was published in 2020, called *This Is Your Brain on Food: An Indispensable Guide to the Surprising Foods that Fight Depression, Anxiety, PTSD, OCD, ADHD, and More*.[30] It became a national and international best-seller, and while this is a newer field of psychiatry, the message appeared to resonate with individuals wanting to find a solution to feeling emotionally better using a different tool besides medications or therapy. It has been published in 22 countries and 18 languages thus far. The academic textbook on the same topic is being written, with an expected publication date of 2023. The first time that nutritional psychiatry was included in a chapter of *The American Psychiatric Association Textbook of Psychiatry* was in 2019.

The World Health Organization (WHO) identified that depression and other mental health conditions are on the rise globally and remain a threat to public health. Of these conditions, depression and anxiety disorders are increasing the most.[31]

A study from 2020 showed that diet can be important for the emergence and treatment of mental illness. Adherence to dietary recommendations, anti-inflammatory diet, fish consumption, exclusion of processed foods, and adequate intake of folic acid, magnesium, and different fatty acids were associated with a reduced risk of mental illness.[32]

The research around the gut microbiome and the gut brain ecosystem has also helped unfold the food mood connection. For example, in a large cross-sectional study, the intake of the B vitamins folate (B9) and vitamin B12 was inversely correlated with severity of depression.[33]

In a meta-analysis covering 16 studies, 15 of which were in non–clinically depressed populations, dietary intervention led to a significant improvement in mood but not in anxiety.[34]

The SMILES trial, despite a small cohort of 67, offered a 12-week dietary intervention using a modified Mediterranean diet to target MDD in adults, and showed that diet can help MDD symptoms.[35]

In a scoping review of anxiety conducted by my colleagues and myself, we identified a total of 55,914 unique

results, and 1541 articles met criteria for inclusion. An analysis revealed an association between less anxiety and more fruits and vegetables, omega-3 fatty acids, "healthy" dietary patterns, caloric restriction, breakfast consumption, ketogenic diet, broad-spectrum micronutrient supplementation, zinc, magnesium, and selenium, probiotics, and a range of phytochemicals. The analysis also revealed an association between higher levels of anxiety and high-fat diet, inadequate tryptophan and dietary protein, high intake of sugar and refined carbohydrates, and "unhealthy" dietary patterns. And while results are limited by a large percentage of animal and observational studies, the associations made are useful clinically.[36]

In a review of nutrition as a metabolic treatment for anxiety, it was found that nutrition regulates anxiety disorders by influencing the microbiome and inflammation, and the gut microbiome and inflammation are interrelated and influence anxiety. By acting on the gut microbial ecosystem, regulating inflammation, as well as through other pathways, particular nutritional strategies have been suggested to either harm or help disorders of anxiety. Sugar, processed vegetable oils rich in inflammatory omega-6 fatty acids, artificial sweeteners, and gluten were found to have a negative effect on anxiety, whereas omega-3 fatty acids, turmeric (curcumin), vitamin D, and ketogenic diets were thought to have a therapeutic effect.[37]

The mechanisms associated with the development of mental health symptoms are thought to be related to underlying inflammation and neuroinflammation.[38]

Of note, though, more than a century ago, the treatment of melancholia by Lactic Acid Bacillus was proposed![39]

Interestingly, as far back as 1893, the *British Medical Journal* published a call for medical students to attend four sick care and convalescent cookery courses to "gain practical information on matters of such vital importance to their future patients."[40] Yet despite this gap being identified 129 years ago, it is only in the past 2 decades that such changes, like the introduction of nutrition education and culinary medicine, have begun.

In reflecting on the newer and emerging field of culinary medicine, it is important to realize that unless a person has an allergy, a food intolerance, or a disease that requires restricting a certain food, cooking and making healthier choices are easy and can have significantly positive health and mental health benefits.

This book is the fourth edition of the *Lifestyle Medicine* book and the first time a chapter on culinary medicine has been included. The *American Journal of Lifestyle Medicine* began its culinary medicine column in 2019. These represent forward thinking areas of the food as medicine movement.

CLINICAL APPLICATIONS

1. Culinary medicine principles can be utilized by medical students and clinicians to change the narrative in clinical visits, e.g.,
   a. a cooking demo as part of an OP group visit
   b. a nutrition discussion: simple tips on how to navigate the supermarket aisles.
2. Since nutrition education is lacking in many US medical schools, physicians may need to bridge this gap by engaging in post graduate education in culinary medicine, nutritional psychiatry, and lifestyle medicine.
3. The more that physicians embrace the food as medicine movement, the greater the impact will be on day-to-day clinical care of patients.

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11 Nutrition, Lifestyle, and Environment

T. Colin Campbell, PhD

KEY POINTS

- Although the word "nutrition" is widely spoken, it remains exceedingly confusing and contentious because of its focus on discrete parts.
- Nutrition is the metabolic expression of food, upon consumption, centered on a symphony of nutrient effects within and among cells, within and among organs.
- Nutrition metabolism is comprised of countless nutrients and nutrient-like substances acting in a manner whereby its whole effect is greater than the sum of its parts, as Aristotle said.
- The nutrition protocol for health is essentially the same for all ages, for both genders, and for health promotion as well as for disease prevention and disease reversal.
- Nutrition dysfunction is best corrected not by single nutrients but by whole foods.
- Nutrition is best characterized as a wholist philosophy, unlike the reductionist philosophy of contemporary medical practice.
- Lifestyle medicine would be more appropriately described as lifestyle health; "medicine" places too much emphasis on the use of pharmaceuticals.
- The most easily applied and scientifically justified dietary recommendation is to consume a diet of plant foods in their whole food form, however prepared.
- The science of nutrition, as told here, is not taught in medical schools.
- Reimbursement for nutrition care by primary care physicians, dietitians, nurses, and physician assistants must enjoy more equivalence with disease treatment care.
- The U.S. National Institutes of Health (NIH), the leading biomedical research agency composed of 27 institutes, has no dedicated Institute for Nutrition.

Understanding nutrition has long been confusing and contentious, even though it has been widely discussed. For a more formal definition, nutrition is the biological expression of food upon its consumption, digestion, absorption, and metabolism, with an ultimate purpose of maintaining and restoring health and preventing disease. In many cases, the same dietary protocol can reverse or treat most chronic degenerative diseases, which account for most deaths in economically affluent societies. Unfortunately, our present understanding of nutrition, which can be traced back to the middle 1800s and early1900s, is largely responsible for the production and consumption of foods that seriously compromise human health while simultaneously degrading environmental, even , health. It is urgent that the society at large, both professionally and publicly, develop a reliable, easily understood definition of nutrition.

Even though there is abundant evidence showing what good nutrition can do, reality suggests that authoritative institutions pay little or no attention. Medical schools offer only about 20 contact hours during an entire medical school training program,[1] or by comparison, <1% of total contact hours for an undergraduate nutrition major. Among the 27 institutes of the U.S. National Institutes of Health, a leading health research funding agency in the world, none is dedicated to nutrition. Primary care physicians receive little or no compensation for nutrition-responsive consults. Dieticians are trained and accredited within a system controlled by the Academy of Nutrition and Dietetics, which boldly advertises support from the food and drug corporate sectors. Dietary guidelines, marginally revised every five years since 1980, are created by a government agency headed by a politically appointed Secretary beholden to the livestock industry. I challenge the reader to name a biomedical discipline offering more benefit for human health than nutrition yet being treated as if it had nothing to offer.

After more than six decades in research, education, and policy making on the topic of food and health and becoming more aware of the origin of nutrition confusion, it is not surprising that during the coronavirus pandemic, there has been no mention of nutrition, when it has so much to offer. Indeed, dismissing nutrition exposes a violation of the concept of science itself. Rather than employing scientific principles to investigate hypotheses wherever they may lead, we hear about "science" serving an intended purpose, a process more aptly described as technology. For example, during this pandemic, the public is told to "follow the science," meaning the tracking of disease trends and discovering a pharmacologic solution to treat disease, as if this were all there is. The possibility that nutrition might be important in controlling this viral disease[2–5] has been totally ignored. It is difficult to comprehend such irresponsible behavior for a disease having such profound social, economic, and political implications.

Yet, rather strangely, many people want to believe that nutrition is important, however it is defined. As much as 85% of the U.S. national health care budget is dedicated

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to the management of "diet-related" chronic diseases.[6] In parallel, 86% of people over 65 years have been diagnosed with one or more of these chronic diseases.[7] Another way to recognize the importance of nutrition is to reflect on its absence and how we offset that missing link. Here's a hint. Worldwide, the United States ranks #1 in per capita spending[8] for prescription drugs. "Nearly 9 in 10 (89%) adults 65 and older report that they are taking any prescription medicine," according to the Kaiser Family Foundation.[9] Relying on prescription drugs, however, does not mean superior health. Arguably, it's the contrary. Sixty to seventy percent of people in the United States take at least one prescription drug per day with adverse effects,[10] making the use of these products the third leading cause of death.[11–13]

Extensive literature now suggests that two main types of food have questionable nutritional value: a) foods derived from animals and b) "foods" fabricated and composed of plant food fragments enriched in refined carbohydrates and oils. Each of these food groups correlates with high rates of chronic degenerative disease that are associated, in the United States, with "by far the lowest life expectancy" among economically developed countries, according to the Commonwealth Fund.[14]

As previously stated, nutrition is the biological expression of whole food upon its consumption, digestion, absorption, and metabolism of its many nutrients working together throughout the body to optimize health. Unfortunately, we focus on individual nutrients as if they acted independently, a wellspring for confusion. A scientifically reliable, simply applied message that honors this complexity might be to address two perspectives on nutrition,[1] *the relative inability of individual nutrients to optimize health* and[2] the *type and form of foods to consume that relies on the comprehensive nutrient effects to optimize health*.

A focus on individual nutrients serves as the basis for recommending daily allowances (RDAs), assessing food quality, establishing guidelines for food labeling, and ultimately, developing highly influential dietary guidelines. This focus is called reductionism, which offers an endless supply of detailed information, a source for endless confusion.

Recognizing this confusion first arose (for me) in the 1980s[15,16] when it was reported that nutrients consumed in isolation, as in supplements, do not necessarily function in the body in the same way as when consumed in whole foods. They may even have opposite effects.[15,17] Healthy, whole foods contain countless nutrients and nutrient-like chemicals, which upon their consumption, act from within highly integrated networks of interdependent enzyme catalyzed reactions and events within cells, between cells, and within and between organs. These activities are exceptionally dynamic. They are coordinated and optimized within nanoseconds of time throughout the body by complex neurologic and hormonal systems, which instantly signal distant body parts. Focusing on one nutrient, one functional target, and one outcome cannot represent the whole health effect. If we continue to insist that nutrition be interpreted in this reductionist manner, then the far-reaching benefits of nutrition for human health will forever be ignored.

This questionable focus on individual items arose, for me, from a so-called "local theory of disease" discussion during the 1700s–1800s to explain cancer.[18] Surgeons believed that cancer could simply be resolved by surgical removal. Subsequently, this belief in localized effects morphed into further assumptions of simplicity, as if this represented the best of science. Specific chemicals (carcinogens) cause specific cancers acting on specific mechanisms that might be targeted by specific drugs. Target drug treatment became a hallmark of the War on Cancer initiated in 1971. After three decades, this protocol proved to be disappointing, because evidence was accumulated to show that cytotoxic chemotherapy increases five-year survival by only 2.1%.[19] And further, simplifying biology in this arbitrary and reductionist manner became the primary basis for the entire pharmaceutical industry, which refuses to acknowledge a nutrition-based hypothesis unless single nutrient activities are assumed.

This single nutrient idea, however, also is questionable. For example, consumption of beta-carotene rich foods (whole plants) was shown to be inversely associated in a dose-dependent manner with lung cancer mortality among heavy smokers,[20] but in a subsequent report, isolated beta-carotene in supplement form significantly *increased* lung cancer within only five years.[15,21] Statins, which are targeted to a specific enzyme in the cholesterol synthesis pathway, decrease blood cholesterol and cardiovascular disease events by upwards of 20%, but with adverse side effects[22] In contrast, whole food, plant-based (WFPB) nutrition quickly and safely decreases blood cholesterol within days with few or no adverse side effects, thus being consistent with a 90% lifetime reduction in coronary heart disease for diets nearly void of animal protein.[23–25]

In contrast to the nineteenth-century "local theory" hypothesis for cancer and its evolution into reductionism, a counter theory called "the constitutional nature of disease"[26] offered a perspective that forecast whole food nutrition. Ample evidence now supports this hypothesis, which reverses/treats a broad range of degenerative diseases. I call this *wholism* ("w" intended), which relies on the *in vivo* process of homeostasis, and which acts like a default mechanism to optimize health. In contrast to the huge infrastructure costs of prolonged disease care and medication costs associated with side effects, wholist nutrition provides superior health at far less cost than a reductionist-dependent reliance on pills and procedures. A wholist nutrition protocol, further described later, addresses a broad spectrum of disease conditions and in many instances, both prevents and reverses disease with the same protocol. Relying on reductionist theory in the present medical care paradigm is why medical schools do not teach nutrition, why primary health caretakers (physicians, nurses) are not adequately compensated for nutrition advice, and why there is no dedicated institute of nutrition at the premier medical research funding agency, NIH. Nutrition as a health science

is negated. The sinister implications of this perspective cannot be overstated.

Wholist nutrition favors the consumption of *whole foods*, meaning that all nutrients in food are generally consumed together, however these foods are prepared. This practice contrasts with the consumption of "convenience" foods, which are re-formulations of isolated parts of whole foods, especially using added fats/oil, refined sugars, and salt. These components are parts of healthy, whole foods, but they often do not retain these properties when used independently. They add flavors with addictive-like behavior, good for commerce but not for human health.[27]

When choosing foods *to* eat, one nutrient has influenced food choice more than any other, for well over a century. It is the protein of animal-based foods, long understood to be "high quality" compared with the protein of plant-based foods. Very simply, high quality means a higher proportion of consumed protein being retained for body growth,[28] helpful for livestock growth and production but not for humans. Nonetheless, the assumption of high-quality protein is a long-standing, powerful marketing message, while few, if any, know its origin. It generally remains buried in our subconscious mind. Retaining more animal protein also increases serum cholesterol[29,30] and heart disease,[29] increases growth hormone and cancer,[31] increases activation of chemical carcinogens and mutations,[32,33] increases serum estrogen,[34,35] resulting in earlier menarche and more breast cancer,[36] decreases natural killer cells[37] that suppress viral diseases and cancer, and decreases physical endurance,[38,39] among other health outcomes. Not surprisingly, these effects are never voiced in the public narrative, for they would question the highly revered concept of high-quality animal-based protein.

It seems to me that this reverence mainly started when protein was isolated from meat experimentally fed to a dog in 1839.[40] It was deemed essential for the dog's life. It was named after the Greek word *proteios*, meaning "first" or "prime importance,"[41] indicating an even more profound reverence for eating animals going back to biblical times in the Judeo-Christian world.[42] Thereafter, influential scientists called protein (i.e., from animals) "life itself" and the "stuff of civilization."[40,41] Since then, many families have planned their meals primarily around their choice of protein (animal-based), if they could afford it. From my youth on our family dairy farm, we certainly did, and I had no reason to question this view when I did a doctoral dissertation with an objective to promote animal protein consumption.[43]

During my subsequent research career, experimental animal studies (rats, mice) conducted over three decades were especially instructive. Animal protein (as casein) but not plant protein markedly promoted[44] experimental cancer development, which could be turned on and off, respectively, simply by increasing or decreasing consumption of animal protein or by replacing it with plant protein. Because this finding was so provocative, it was important to identify the key mechanism for this effect, both to establish biological plausibility and to identify a mechanism that might be amenable to inhibition, perhaps pharmaceutically.

In a long series of experiments over a dozen years, at least ten candidate mechanisms were identified, as mentioned earlier.[45] Interestingly, animal protein increased activities of eight mechanisms that normally promote cancer development but decreased two "fail-safe" mechanisms that help us to avoid cancer. Each mechanism is known to have a specific function, identity, and cellular location. All ten mechanisms, some increasing and some decreasing in response to increased dietary animal protein, acted in unison to cause the same result, a truly remarkable response. It demonstrated a central theme of wholism, which presented a critical challenge to our conventional method for understanding nutritional biochemistry and function.

I suggest that a multi-mechanistic, intricately woven network of interdependent "mechanisms" is a generalizable algorithm having broad application. It stands to reason that it should apply across species, among nutrients,[45] at varied intervention times from disease prevention to disease reversal,[46–49] and in a broad spectrum of health and disease events, like heart disease, diabetes, obesity, chronic kidney disease, and certain autoimmune diseases. This breadth of effect documents Aristotle's suggestion over two millennia ago that the whole is greater than the sum of its parts. I suggest that it is a fundamental principle of biology and a core theme of lifestyle medicine, provided that we re-imagine the meaning of "lifestyle medicine." In popular conversation, "medicine" generally refers to pharmaceuticals, and its emphasis is on parts, which is the antithesis of nutrition and its emphasis on whole. While advocating for a new perspective on healthcare, with its greater emphasis on natural health practices, I suggest that it be described in this way, so that nutrition retain its true meaning of whole food instead of nutrient parts.

Consistent with this perspective is the evidence obtained in human epidemiological studies. Mortality rates for multiple degenerative diseases show linear correlations with the consumption of animal protein or its co-variates. These include heart disease and cholesterol intake,[50] breast cancer and saturated (mostly animal) fat intake,[51,52] breast cancer and meat intake,[53] prostate cancer and non-fat milk intake,[25] renal cancer and animal protein intake,[54] and colon cancer and meat intake.[54] Each of these linear correlations intercepts very near the x/y origin, which suggests zero disease risk with zero animal protein intake. These correlations, however, do not rely on disease occurrence caused by animal protein alone, a reductionist interpretation. There is more. Because total food intake is limited by calorie intake, increased consumption of animal foods customarily associates with decreased consumption of plant foods with their own disease-preventative nutrients, all of which strengthen and expand the wholist effect.[45] Then, when combining this evidence with the evidence on biological plausibility, the inference drawn in favor of wholist nutrition is unusually impressive.

While the evidence discussed here concerns prevention and treatment of disease, it also applies to health maintenance, such as physical fitness. A Yale University study 125

years ago showed an impressive increase in 15 strength and endurance tests among young men when they switched to a low protein, mostly plant-based diet.[38] The same benefit also occurred for already fit athletes.

In the late 1970s, interest was emerging in the cancer research community on a possible role for nutrition, especially nutrition provided by foods of plant origin. As the only nutrition researcher on a review committee of cancer researchers of the U.S. National Cancer Institute (of NIH), I was asked to comment on how this interest in a nutritional effect on cancer might be interpreted. Because this evidence inferred cancer prevention by plant foods, I chose the words "plant-based" to emphasize its empirical basis and to distinguish it from the animal rights motivation of vegetarianism. Shortly thereafter, when testifying in Federal Trade Commission hearings over a three-year period on health claims being made by the rapidly emerging nutrient supplement industry, I added the word "whole," thus giving the description "whole food, plant-based."

These nutrition benefits are not limited by geography or ethnicity; thus, the pleasurable flavors and foods associated with ethnic cuisines may be retained without compromising the nutritional effect. Very simply, individuals merely need to consume a variety of foods of plant origin, as much as possible in the whole food form. This advice is best considered as a goal, not as a mandate. Although sources of carbohydrates, as main sources of energy, vary among societies (rice, wheat, corn, white potatoes, sweet potatoes, or camote beets), these complex, natural carbohydrates generally provide very similar health benefits, notwithstanding allergy-related responses for certain individuals. Leafy (bok choy, sea vegetables, spinach, cabbage, broccoli, kale) and fruiting plant foods (fleshy fruits, seeds, nuts, etc.), virtually unlimited in variety, also possess the same health effects. Without confusing what is vegetable or fruit and what is grain or seed, it is far more important not to lose sight of the commonality of a variety of plant-derived foods, regardless of geography or ethnicity. This concept of nutrition is international in scope.

This proposal for a new concept of nutrition mostly concerns the association of nutrition with chronic degenerative diseases. I would be remiss, however, if I failed to consider a similar effect of nutrition on viral diseases, especially the COVID-19 pandemic. A recent report of ours[2] summarized correlations of nutrient risk factors with hepatitis B virus (HBV)-induced primary liver cancer, based on an observation of 8990 adults in rural China collected in 1989. When limiting the interpretation only to the highly significant cause–effect correlations ($p < 0.001$), consumption of more plant source foods associated with a higher HBV antibody prevalence, lower antigen prevalence, and lower disease mortality. In contrast, consumption of animal-based foods (average animal protein as a percentage of total diet calories was only about 10% of Western experience) associated with higher prevalence of HBV antigen (active virus), lower prevalence of HBV antibody, and higher liver cancer mortality. This effect of a cluster of highly significant associations all pointing in the same direction is unusually convincing.

In a separate HBV-transgenic mouse study, animal protein markedly increased hepatocellular carcinoma while decreasing circulating natural killer cells (T cells).[37] These findings, obtained more than three decades ago, suggest that even a relatively small quantity of animal-based foods is able to repress antibody prevalence (human study) and natural killer cell (T-cell) activity (animal study), while promoting liver cancer (animal and human studies). I suggested that this evidence, published in early 2021, might apply to COVID-19. A few months later, other researchers[3,4] showed a substantial decrease in COVID-19 disease severity for individuals using plant-rich diets. Over 90% of the COVID deaths occur in individuals over 65 years who are diagnosed with diseases readily prevented, even reversed, by this same plant-oriented diet. Cancer, cardiovascular diseases, chronic kidney disease, chronic lung diseases, diabetes mellitus, hypertension, immunosuppression, and obesity are the main co-morbid diseases.[55,56]

Although there are reports on nutrition in viral disease etiology and treatment, almost all concern individual nutrients, not the whole food nutrition presented here. An impressive commentary on immune system complexities was reported just prior to the COVID-19 pandemic, although it, too, chiefly focused on single nutrient effects.[5] Specific benefits may occur with nutrient supplements or nutrient-fortified foods, but it is likely that these effects will be short-lived, null, or even the reverse of that which occurs with whole foods.

Choosing the right food is critical for us to bring under control two colossal societal problems, personal health and its costs[6] and environmental and planetary destruction.[57] And in choosing the right food, we must collectively understand nutrition, for it is the scientific rationale for global warming, climate change, and environmental degradation. An increasing number of publications on the association of climate change with livestock production are now appearing, especially since the seminal 2009 report of Goodland and Anhang[58] at the World Bank, who estimated 51% or more of global warming as being caused by livestock production. Since then, others have affirmed that same estimate, even concluding that it may be as high as 87%.[59]

I recommend two sources of information impressively connecting the consumption of food with environmental problems. Dana Hunnes at University of California, Los Angeles[60] discusses a baffling array of several serious environmental problems. The public narrative usually accompanying information of this type is to assume specific causes of specific problems and in doing so, not to see the possibility of there being a common cause. Hunnes emphasizes livestock agriculture as being that common cause. Compared with plant-based agriculture, seven to ten times more land is required to produce an equivalent amount of food calories from animal-based agriculture[59] primarily to meet the widespread public demand, consciously or unconsciously, for consuming high-quality animal protein.

Rationalizing the consumption of animal food for its protein is a myth from at least two perspectives. First, animal protein is not high quality, and second, rationalizing consumption of animal food for its protein causes less consumption of disease-preventative whole plant-based foods, which further compromises our health and shortens our life expectancy.

My second recommendation is that of Jim Hicks, who succinctly and boldly emphasizes the association of environmental degradation with livestock agriculture in a series of so-called "SOS memos," now standing at 159. Hicks urgently describes in these memos[61] and in his books[62,63] the climate change disaster, especially emphasizing the distressing difficulty for authoritative individuals and institutions to take this matter seriously. Hicks's weekly SOS memos are a powerful and constant reminder of the urgency of this impending disaster.

In conclusion, I suggest that the concept of "lifestyle medicine" embrace a larger dimension than its sole reference to "medicine," which may give too much emphasis to pharmaceuticals. I suggest that improving our lifestyle should consider the effects of our eating habits not only on our personal health and its costs but also on our environmental surroundings. For many people, this is a growing concern, which can be a motivation for changing our lifestyle.

CLINICAL APPLICATIONS

- Consume a variety of plant-derived foods, available in all ethnic cuisines.
- Consume these foods in the whole food form, so that our body (Nature) can choose which nutrients to use.
- Permanently adopting this diet occurs only when sufficient time is allowed for taste adaptation, perhaps one to three months.
- As a first priority, consider using this diet to reverse (treat) many chronic degenerative diseases.
- Consider using this diet for physical performance as well as mental health.
- Limit use of added oil, refined sugar, and salt.
- Flavors and spices are acceptable.

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Part III

Physical Activity



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12 The Health Benefits of Regular Physical Activity

James M. Rippe, MD

KEY POINTS

1. Regular physical activity is one of the most important things that individuals can participate in to improve their short- and long-term health and quality of life.
2. Increased physical activity lowers the risk of various chronic diseases and can also serve as an adjunct to treatment.
3. Increased physical activity plays crucial roles for individuals at all stages of their lives.
4. The Physical Activity Guidelines 2018 Scientific Report (PAGA 2018) provides an exhaustive and important summary for the benefits of physical activity for individuals at all stages of their lives and in various physical conditions. All clinicians should be familiar with this seminal document.
5. Physicians play a critically important role in urging their patients to make positive decisions in their lives concerning physical activity.
6. The central recommendation from the PAGA 2018 states that individuals should be encouraged to participate in 150 minutes of moderate to vigorous physical activity or more each week and strength training sessions twice a week with at least one day separating the two sessions.
7. Only 25% of individuals engage in regular physical activity necessary to meet the guidelines from the Centers for Disease Control (CDC), the American College of Sports Medicine (ACSM), and PAGA 2018.

12.1 INTRODUCTION

What individuals do in their daily lives profoundly impacts on short- and long-term health and quality of life. This is the essence and cornerstone of lifestyle medicine. These habits include regular physical activity, proper nutrition, weight management, avoiding tobacco products, stress reduction, adequate sleep, and many other practices. All of which we have put together in the discipline of "lifestyle medicine."[1]

Among the various important practices that individuals can perform in their daily lives, there is no single lifestyle habit or practice more powerfully associated with improved short- and long-term health and quality of life than regular physical activity. An enormous and compelling literature generated over the past few decades demonstrates that moderate to vigorous physical activity profoundly impacts the likelihood of developing chronic disease. Regular physical activity also exerts a uniquely powerful impact on quality of life.[2] In addition, regular physical activity has been found in multiple studies to play a role not only in the reduction and risk of chronic disease, but also as an adjunct and component of treatment.

For all of these reasons, physical activity is a cornerstone for the prevention and treatment of virtually every chronic metabolic disease. This is acknowledged in the guidelines of multiple professional organizations, including the American Heart Association (AHA),[3] American Academy of Pediatrics (AAP), American Diabetes Association (ADA),[4] PAGA 2018, and many others.[5–15] Regular physical activity is the cornerstone to the recommendations for Healthy People 2020[7] and also the Healthy People 2030 Guidelines.[8] The PAGA 2018 Scientific Report provides an enormous and compelling body of evidence for the multiple benefits of regular physical activity. These benefits extend throughout the lifespan and for multiple chronic diseases as well as issues related to quality of life. The American College of Sport Medicine (ACSM) has been a leader for many decades in this area.[9] The American College of Lifestyle Medicine (ACLM)[10] and the AHA[11] have also played significant roles in advocating more physical activity and have recommended physical activity as a key component of preserving health and improving quality of life.

Despite the enormous body of evidence now available concerning the positive relationship between physical activity and health, the medical community has been slow to embrace this concept as an important component of regular healthcare and counseling. It has been estimated that fewer than 40% of physicians regularly counsel their patients on the importance of regular physical activity.[12] This is a wasted opportunity, since over 70% of individuals see their primary care physician at least once a year.

The American public has also been slow to embrace the habit of regular physical activity. It has been estimated that fewer than 25% of adults in the United States meet the recommended levels of physical activity, which include 30 minutes of moderate to vigorous physical activity on most, if not all, days (accumulating at least 150 minutes of moderate intensity physical activity per week) and fitness based

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in two sessions of musculoskeletal strength training each week.[13] These guidelines are recommended by virtually every major professional organization in the area of physical activity.

12.2 THE RELATIONSHIP BETWEEN MODERATE AND VIGOROUS PHYSICAL ACTIVITY AND THE RISK OF DEVELOPING CHRONIC DISEASE

Enormous data are available spanning a wide spectrum of chronic diseases showing that individuals who are physically active decrease their risk of these conditions compared with inactive individuals.[12] The PAGA 2018 provides a wealth of evidence related to chronic conditions showing the benefits of regular physical activity to both lower the risk of chronic disease and assist in its treatment. Some of these benefits occur after a single acute bout of physical activity. Others require a consistent increase of physical activity throughout the lifespan. Among the conditions where regular physical activity can benefit are cardiovascular disease (CVD), some cancers, diabetes (T2DM), dementia, brain health, and risk of falling and other injuries, particularly in older individuals.[2]

Importantly, the benefits of physical activity occur in children as young as 3 years old, continue all the way up through adolescence, and are prominent in adults, even individuals over the age of 65. A summary of the physical activity–related health benefits that are enumerated in the PAGA 2018 Scientific Report is found in Table 12.1.

There is also a strong relationship between increased physical activity and multiple aspects of improved quality of life. Individuals who are physically active have less anxiety, depression, and stress, in general, and feel better and sleep better.[2] All of these improvements result in higher quality of life for individuals who participate in regular physical activity.

The benefits of physical activity are so profound in lives that some investigators have likened physical activity to a "polypill" that contributes to virtually every aspect of health. These individuals have argued that if exercise were actually a pharmaceutical treatment, it would be impossible for the pharmaceutical industry to keep it in supply!

12.3 PHYSICAL ACTIVITY AND CHRONIC DISEASES

12.3.1 Cardiovascular Disease

Regular physical activity significantly reduces the risk of CVD and all-cause mortality.[14] As recommended by PAGA 2018 and various documents from the ACSM, AHA, and ACLM, the recommendation of 150 minutes of moderate intensity physical activity per week as well as two strength training sessions per week will substantially lower the risk of CVD and all-cause mortality, as depicted in Figure 12.1.

Further reductions in mortality are also available for individuals who engage in physical activity above 150 minutes per week, which is also indicated in Figure 12.1. It is important to point out, however, that even small amounts of physical activity can result in lowering both CVD and all-cause mortality. Also indicated in Figure 12.1, there is no lower threshold to the benefits of increased physical activity with regard to reduction of risk of all-cause mortality. Even individuals who engage in moderate or vigorous physical activity for as little as 30 minutes per week achieve a 20% reduction in cardiovascular disease.

Unfortunately, only 25% of adults meet the minimum recommendations from PAGA 2018 and CDC for over 150 minutes of moderate intensity physical activity per week. Young people are even less likely to follow the recommended standards. Fewer than 20% of adolescents perform the 60 minutes or more of daily physical activity recommended by the PAGA 2018.[13]

On the other end of the spectrum, individuals who participate in more than 150 minutes of physical activity per week can continue to achieve more reductions in the risk of CVD. However, the return on this additional investment of time is much less than for the first 150 minutes.

If individuals who are physically active are compared for risk of CVD with sedentary individuals, the sedentary individuals are at 150–240% higher risk. In addition, it should be noted that regular physical activity lowers the risk of adult weight gain and helps control high blood pressure, thus reducing the rate of hypertension.[2,16] Increasing amounts of physical activity also lower the risk of stroke and heart failure in a dose-dependent relationship.

Despite these known benefits, physicians have typically not emphasized the role of regular physical activity in reducing the risk of heart disease. In one survey of 175 primary care physicians, only 12% were aware of the recommendations from ACSM or PAGA 2018.[17] The relationship between physical activity and reduction of risk of heart disease is described in more detail in Chapter 21.

12.3.2 Physical Activity and Diabetes, Prediabetes, and the Metabolic Syndrome

Lifestyle modalities such as physical activity are the cornerstones of diabetes care. Recommendations for people with diabetes from PAGA 2018 are similar to those for reducing the risk of CVD.[3] The ADA also recommends that physical activity sessions should be at least 10 minutes with the goal of 30 minutes per day, or more, on most days of the week. These are somewhat more vigorous recommendations than those of PAGA 2018. Individuals with diabetes should also be encouraged to reduce time spent in sedentary activities such as working at a computer, watching T.V., or other activities while sitting or lying down (except sleep). There are good data on the association of sedentary activity with increased risk of diabetes.

According to the ADA Consensus Report on Physical Activity and Diabetes, prior to starting an exercise program,

TABLE 12.1

Physical Activity–Related Health Benefits for the General Population and Selected Populations Documented by the 2018 Physical Activity Guidelines Advisory Committee

Children	
3 to <6 years of age	**Improved bone health and weight status**
6 to 17 years of age	**Improved cognitive function (ages 6 to 13 years)**
	Improved cardiorespiratory and muscular fitness
	Improved bone health
	Improved cardiovascular risk factor status
	Improved weight status or adiposity
	Fewer symptoms of depression
Adults, all ages	
All-cause mortality	Lower risk
Cardiometabolic conditions	Lower cardiovascular incidence and mortality (including heart disease and stroke)
	Lower incidence of hypertension
	Lower incidence of type 2 diabetes
Cancer	Lower incidence of **bladder**, breast, colon, **endometrium**, **esophagus**, **kidney**, **stomach**, and **lung cancers**
Brain health	**Reduced risk of dementia**
	Improved cognitive function
	Improved cognitive function following bouts of aerobic activity
	Improved quality of life
	Improved sleep
	Reduced feelings of anxiety and depression in healthy people and in people with existing clinical syndromes
	Reduced incidences of depression
Weight status	**Reduced risk of excessive weight gain**
	Weight loss and the prevention of weight regain following initial weight loss when a sufficient dose of moderate to vigorous physical activity is attained
	An additive effect on weight loss when combined with moderate dietary restriction
Older adults	
Falls	Reduced incidence of falls
	Reduced incidence of fall-related injuries
Physical function	**Improved physical function in older adults with and without frailty**
Women who are pregnant or postpartum	
During pregnancy	**Reduced risk of excessive weight gain**
	Reduced risk of gestational diabetes
	No risk to fetus from moderate intensity physical activity
During postpartum	**Reduced risk of postpartum depression**
Individuals with pre-existing medical conditions	
Breast cancer	**Reduced risk of all-cause and breast cancer mortality**
Colorectal cancer	**Reduced risk of all-cause and colorectal cancer mortality**
Prostate cancer	**Reduced risk of prostate cancer mortality**
Osteoarthritis	**Decreased pain**
	Improved function and quality of life
Hypertension	**Reduced risk of progression of cardiovascular disease**
	Reduced risk of increased blood pressure over time
Type 2 diabetes	**Reduced risk of cardiovascular mortality**
	Reduced progression of disease indicators: hemoglobin A1c, blood pressure, blood lipids, and body mass index
Multiple sclerosis	**Improved walking**
	Improved physical fitness
Dementia	**Improved cognition**
Some conditions with impaired executive function (attention deficit hyperactivity disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke)	**Improved cognition**

Benefits in **bold** font are those added in 2018; benefits in normal font are those noted in the 2008 Scientific Report. Only outcomes with strong or moderate evidence of effect are included in the table.

From the 2018 Physical Activity Guidelines Advisory Committee Submits Scientific Report Office of Disease Prevention and Health Promotion, Washington, DC. 2018

Source: 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC. Part D: Integrating the Evidence. D5-6.

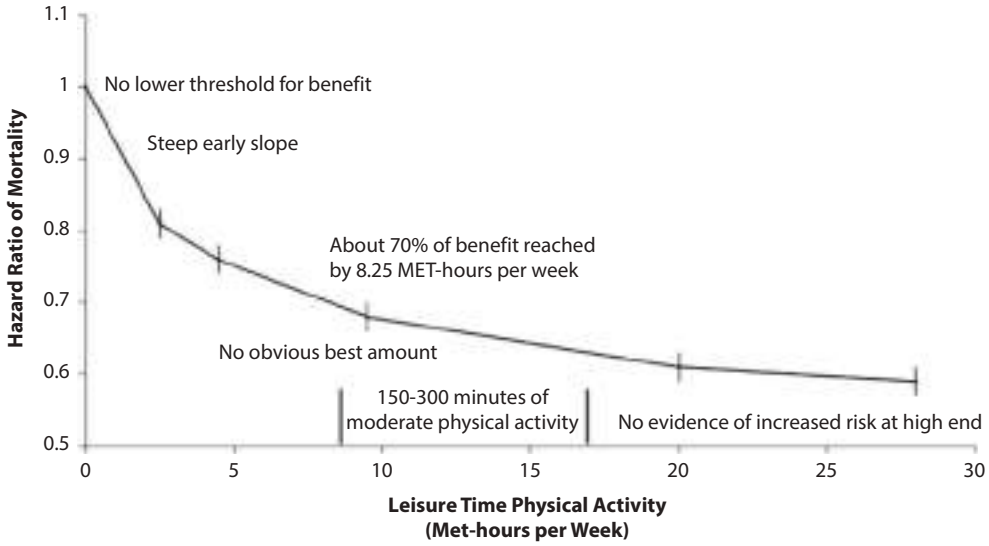


FIGURE 12.1 Relationship of moderate to vigorous physical activity to all-cause mortality with highlighted characteristics common to studies of this type. Source: All-cause Mortality, Cardiovascular Mortality, and Incident Cardiovascular Disease. Part F. Chapter 6. In 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services, 2018.

medical providers should perform a history of cardiovascular risk factors in order to customize physical activity regimens for individual needs.[18] Both the ADA and PAGA 2018 provide detailed recommendations for physical activity in individuals with diabetes.

In addition, regular physical activity plays an important role in preventing pre-diabetes from turning into diabetes. The Diabetes Prevention Program (DPP)[19] as well as the Da Qing Study[20] and the Finnish Diabetes Prevention Study[21] all showed significant reductions in pre-diabetes turning into diabetes for individuals who are engaged in regular physical activity. In the DPP, individuals who were engaged in 150 minutes per week of physical activity and in addition, lost 7% of body weight lowered their risk of pre-diabetes advancing to diabetes by 58%. It should also be noted that in some studies, up to 80% of individuals over the age of 70 have pre-diabetes. Several studies have now suggested that only 9% of these individuals will proceed to develop diabetes over a seven-year period. These recent studies may influence the ADA in favor of even stronger recommendations of physical activity and some moderation in how pre-diabetes is treated.

The metabolic syndrome also benefits from increased physical activity. The metabolic syndrome is a cluster of metabolic abnormalities that significantly increases the risk of CVD.[22] Core interventions for the metabolic syndrome include regular physical activity at the same levels recommended for CVD and diabetes. In addition, following proper nutrition such as Dietary Approaches to Stop Hypertension (DASH) or Mediterranean or comparable diets is also recommended by the ADA. A detailed summary of physical activity and other lifestyle modalities for diabetes, pre-diabetes, and metabolic syndrome can be found in Chapter 20.

12.3.3 Physical Activity, Weight Gain, and Obesity

It is currently estimated that 73% of adults in the United States are either overweight (body mass index [BMI] ≥25 kg/m^2 to ≤30kg/m^2), obese (BMI ≥32 kg/m^2), or severely obese (BMI ≥35 kg/m^2).[23] Regular physical activity has been shown in numerous studies to reduce the likelihood of weight gain and is also vitally important for long-term maintenance of weight loss.[24,25] More detail on physical activity, weight gain, and obesity can be found in Chapter 20.

12.3.4 Physical Activity and Cancer

Numerous cancers have been linked to inactive lifestyle. Physical activity has been shown to play an important and positive role in lowering the risk of many cancers in the first place and helping in their treatment.[26] The PAGA 2018 Scientific Report has greatly expanded the literature for a number of cancers where there is strong evidence that increased physical activity can play multiple positive roles. Every clinician should discuss and prescribe physical activity to cancer patients in terms of the entire spectrum of their treatment. Physicians should also include counseling relative to reducing the risk of developing many cancers and discuss the benefits of physical activity with all patients.

Physicians may understand the role of physical activity in metabolic diseases such as CVD, diabetes, and T2DM. However, many physicians are not aware that regular physical activity can significantly reduce the likelihood of developing cancer. Other known lifestyle related preventable causes of cancer include tobacco use, alcohol intake, diet,

obesity, and behaviors that increase exposure to oncogenic viruses. The issue of various lifestyle modalities and their role in reduction of risk of cancer is discussed in detail in Chapters 21 through 23.

12.4 PHYSICAL ACTIVITY AND WOMEN'S HEALTH INCLUDING PREGNANCY

Physical activity is a vitally important lifestyle behavior for women throughout their lifespan. Guidelines from AHA, ASCM, PAGA 2018, and the American College of Obstetrics and Gynecology (ACOG) all recommend 30 minutes of moderate intensity physical activity on most days of the week[27] with the goal of accumulating 150 minutes of moderate intensity physical activity per week. Numerous studies have shown that women who engage in regular physical activity lower their risk of a variety of chronic diseases, including heart disease. For example, women who engage in exercise for 1.5 hours or more per week reduce their risk of heart disease by 30%. Multiple other studies have shown that similar reduction in the risk of heart disease and other chronic diseases occurs in women who are physically active.[28–30] More details about the relationship between regular physical activity and women's health may be found in Chapters 20 and 21.

12.5 PHYSICAL ACTIVITY AND ITS RELATIONSHIP TO BRAIN HEALTH AND COGNITION

As the population in the United States and other industrialized countries continues to grow older, finding cost effective ways of improving brain health and cognition assumes ever increasing importance. A significant relationship exists between physical activity and various aspects of cognition and brain health.[31] This relationship is often underestimated or ignored by physicians and patients.

Regular physical activity has been demonstrated to improve cognition and lower the risk of various forms of dementia, including Alzheimer's disease.[31] PAGA 2018, as well as the Presidential Advisory from AHA and the American Stroke Association (ASA), recommends increased physical activity as a key modality in improving brain health.

Regular physical activity improves sleep and has been demonstrated to reduce feelings of anxiety and depression in healthy people and also in those with significant affective symptoms. Both PAGA 2018 and the Presidential Advisory from AHA and ASA recommend physical activity as a modality for improving brain health. In fact, the AHA/ASA Presidential Advisory entitled "Optimizing Brain Health" includes physical activity as a key recommendation.[31] The relationship between physical activity and brain health has been demonstrated across a lifespan and is particularly important in a population over the age of 65, where there is an increasing prevalence of cognitive decline and dementia. Additional information in this area may be found in Chapter 20.

One theory for why physical activity is beneficial for brain health is that it helps establish cognitive reserve. This is discussed in more detail in Chapter 21. Researchers in the area of Alzheimer's disease have emphasized that regular physical activity should start well before the older years to reduce the likelihood of Alzheimer's disease. Increasingly, Alzheimer's disease is being regarded as at least somewhat a function of inflammation. This is one theory for why physical activity reduces the risk of Alzheimer's disease.

12.6 PHYSICAL ACTIVITY IN YOUTH

Physical activity results in multiple benefits for children. The 2008 Physical Activity Guidelines for Americans recommended 60 minutes of moderate intensity physical activity per day for children between the ages of 6 and 17.[32] This recommendation was expanded in PAGA 2018, since additional data were available to indicate that there are also benefits for children aged three to six.[2] In addition to lowering risk of heart disease and weight gain in children, physical activity has been demonstrated to improve bone health and weight. In addition, muscular fitness, cognitive function, and respiratory fitness are also improved in individuals aged 6–17 through regular physical activity. These issues are dealt with in more detail in Chapter 22.

12.7 PHYSICAL ACTIVITY IN OLDER ADULTS

Multiple benefits for older adults are derived from increased physical activity. Individuals in this age group are particularly susceptible to cognitive decline and dementia, both of which have been shown to be reduced in individuals who participate in regular physical activity.[33] Regular physical activity has also been demonstrated to result in decreased likelihood of falls and fall-related injuries. Aerobic physical activity and musculoskeletal strength are important as well as balance and flexibility exercises.[34,35] Recommendations from PAGA 2018 for obtaining 150 minutes of moderate intensity physical activity and two sessions of strength training per week also apply to individuals over the age of 65, although it may be necessary to modify these levels slightly depending on the current level of fitness of these individuals.

12.8 PHYSICAL ACTIVITY IN INDIVIDUALS WITH CHRONIC CONDITIONS

Regular physical activity has been associated with reduced risk of a variety of chronic conditions, including some cancers (e.g., breast cancer, colorectal cancer, prostate cancer), as well as improved quality of life and function in individuals with osteoarthritis.[26] The roles of regular physical activity in individuals with chronic conditions are discussed in multiple chapters throughout this book.

12.9 OVERCOMING SEDENTARY BEHAVIOR

Over the past decade, there has been increased scientific interest in data related to the increased risk of chronic disease from sedentary behavior. It is currently estimated that children and adults spend approximately 7.7 hours per day (55% of waking time) in sedentary pursuits. Sedentary behavior is also associated with increased risk of CVD, T2DM, obesity, and the metabolic syndrome. Of note, the highest risk of CVD occurs in individuals who are in the least active group and also get the least amount of physical activity. Individuals who participate in higher levels of physical activity can largely ameliorate the health risks of sedentary behavior.

12.10 THE ROLE OF PHYSICIANS IN PROMOTING INCREASED PHYSICAL ACTIVITY

Physicians are a trusted source of information. Physician counseling has been shown in a number of studies to play an important role in multiple, positive lifestyle behaviors, including physical activity, weight management, proper diet, and avoidance of tobacco. It is incumbent upon physicians to include these issues in every counseling visit with every patient.[36] Physicians should also take a leadership role in their communities, state, and nation in developing public policy that is friendly to these lifestyle endeavors. A more detailed discussion on ways to promote physical activity is found in Chapter 20.

12.11 EVALUATING PATIENTS FOR INCREASED PHYSICAL ACTIVITY AND PRESCRIBING INCREASED PHYSICAL ACTIVITY FOR HEALTHY INDIVIDUALS AND SPECIAL POPULATIONS

A variety of resources are available from multiple organizations, including the Exercise in Medicine Movement (EIM)[37] and ACSM, to assist physicians in evaluating individuals prior to recommending increased physical activity and providing exercise prescriptions both for the healthy population and for those with chronic disease. These tools are spelled out in considerable detail in Chapters 20 and 21. It should be noted that for normal intensity physical activity, a formal evaluation is often not necessary. PAGA 2018 emphasizes that it is important to remove barriers to getting people started on physical activity. However, this document also provides instances where evaluation from a physician who is knowledgeable about physical activity will be helpful for both the safety and the benefit of patients. This would be particularly true for older or very sedentary individuals and also with those who have either diabetes or a history of CVD.

My research team at Rippe Lifestyle Institute (RLI) has been routinely prescribing physical activity to our patients and research subjects for over 25 years. In this chapter, we will provide some background to the processes that we use.

12.12 PRE-PARTICIPATION SCREENING

Both the PAGA 2008 and 2018 make the important statement that in the area of physical activity, "some is better than none." Both of these guidelines and the ACSM recommend that clinicians have a discussion on physical activity with every patient and make it as easy as possible for individuals to become physically active. A good way to start this discussion is to utilize a Two-Question Questionnaire that is supported by the U.S. National Physical Activity Plan and the EIM initiative. Tools to inaugurate this discussion were developed at Stanford University and involve asking the following two questions:

- On average, how many days per week do you engage in moderate or strenuous physical activity (like a brisk walk)?
- On average, how many minutes do you engage in exercise at this level?

Answers to these two questions will give a clinician a good place to start to help individuals gradually increase their physical activity and ultimately achieve guidelines from the PAGA 2018 Scientific Report and the CDC as well as the AHA. More detailed tests are available for people who need more extensive pre-evaluation testing. These are discussed in multiple chapters throughout the book, including Chapters 20 and 21.

12.13 PRINCIPLES OF EXERCISE PRESCRIPTION

The framework that ACSM has developed for exercise prescription goes by the acronym "FITT":[38]

- Frequency
- Intensity
- Time
- Type

It should be emphasized, however, that this framework would be more relevant for individuals who have previously been sedentary and simply want to obtain more physical activity in their lives. A counseling session during the regular clinical visit with a physician should suffice for these individuals. Clinical judgement will determine if more precise exercise prescription is necessary. There are also professionals who can help in this, such as exercise physiologists.

12.14 AEROBIC PHYSICAL ACTIVITY/ EXERCISE PRESCRIPTION

Aerobic physical activity is defined as those activities that require oxygen to provide energy. These activities typically

involve large muscle groups, which are used in repeated rhythmic fashion. While there are many forms of physical activity that can certainly be included in this area of "aerobic activity," the most common form is walking. Recent advances in technology have given us the ability to prescribe this type of physical activity with more precision than we had in the past. Even though the PAGA 2018 Scientific Report recommends individuals to participate in 150 minutes of aerobic physical activity per week, individuals who have been sedentary and who want to start at a lower level and work up slowly should be encouraged. Remember to emphasize the mantra "some is better than none."

As already indicated, walking is the most popular form of aerobic physical activity. When physicians are asked about what kind of physical activity they would recommend for their patients, over 90% say walking. My laboratory at RLI has been a leading source of walking research for the past 25 years. In fact, we coined the term "Fitness Walking" with the publication of our first book by that name in the early 1980s.[39] My team and I at RLI have published extensively in the walking literature and have written five books on walking, which are available through my Amazon book page. Of course, there are many other forms of aerobic activities, such as stationary cycling or swimming. PAGA 2018 recommends activities that are low impact and less likely to cause injuries than, for example, contact sports.

12.15 MUSCULAR FITNESS

Muscular fitness is also an important component of physical activity for a variety of reasons. Improving muscle fitness can reduce the risk of injuries during activities of daily living as well as helping to maintain balance and the ability to safely perform all types of physical activity. To improve muscle fitness, a good place to start is to recommend patients seek professional guidance, which may be available from a certified fitness trainer or health club or YMCA. The highest levels of fitness trainers also carry a fitness training certification from the ACSM. When working on muscular fitness, it is important to include exercises involving all the major muscle groups. A trained fitness professional can take their patients through the way to perform these exercises safely. PAGA 2018 recommends two sessions of musculoskeletal strength training per week separated by at least one day. Unfortunately, only about 10% of adults engage in regular muscular training.

12.16 FLEXIBILITY

Flexibility is the ability of a joint to move through a whole range of motion. This is an important part of an overall, comprehensive program for physical activity. It is particularly important for the aging population, since lack of use and the aging process itself can lower this parameter. We at RLI typically recommend flexibility programs for all individuals whom we see in our clinic or research facility.

Flexibility is also highlighted in multiple ways in multiple publications and the PAGA 2018 Scientific Report. We typically recommend to individuals that they utilize their stretching program both before and after exercise in order to also focus on mind/body issues.

12.17 BALANCE

Balance is a very important part of an overall plan for physical activity, and balance exercises should be a component of the exercise prescription. This is particularly important for older individuals. Improved balance can be built either by utilizing specific balance exercises or by increasing physical activity and muscular fitness. A wide variety of balance exercises is also available through various ACSM publications.

12.18 MIND/BODY APPROACHES

There has been an increasing emphasis in exercise prescriptions on recognizing the interactions between mind and body. This is a powerful way of helping people understand that there are both multiple health and fitness benefits as well as psychological benefits from increased physical activity. This topic is so important that we have devoted an entire chapter to mind/body strategies. (See Chapter 30.)

12.19 DURATION OF WORKOUT

For many years, it was thought that the duration of physical activity needed to be at least 30 minutes per session to achieve maximum benefits. This was reduced to 10 minutes per session in the 1980s in a Position Statement from the ACSM and by the American Medical Association in 1995.[40] However, the publication of PAGA 2018 reports that any duration of physical activity can yield important benefits. It is important to emphasize to patients who have been sedentary that such strategies as taking the stairs at work or walking across the parking lot when shopping can all add up to increased levels of physical activity. Many people have utilized fitness tracking devices to determine the number of steps that they take each day with the goal of achieving 10,000 steps.

12.20 SPECIAL POPULATIONS

Some modifications for physical activity programs may be necessary for special populations. The general guidance from PAGA 2018, however, remains for individuals to attempt to accumulate 150 minutes of moderate intensity physical activity per week. Special population groups include pregnant individuals, cancer survivors, older individuals, overweight individuals, and many other populations. Recommendations for each of these are handled in separate chapters in this book.

12.21 EXERCISE ADHERENCE

Some benefits of physical activity occur immediately following each session. Most of the long-term benefits, particularly with regard to reduction of risk of chronic diseases, accrue to individuals who stay with an exercise program for a lifetime. We have developed a strategy for helping people stick with their exercise programs. The last section of this chapter details the tips we have developed.

12.22 TIPS FOR STARTING AND STAYING WITH A PROGRAM OF REGULAR PHYSICAL ACTIVITY

Over the years, we at RLI have developed a list of tips to help people stay with their exercise program. The key is to find forms of exercise that are low in injury, involve socialization, and are enjoyable. Here is a brief list that we often give to individuals who are either just starting or having trouble staying with an exercise program:

- Exercise with others
- Establish a specific time and place
- Find an activity you enjoy
- Keep a journal
- Enlist the support of family and friends
- Set realistic goals
- Purchase appropriate equipment
- Vary your exercise routines
- Chose forms of exercise that are low in injury potential
- Upgrade your fitness program as you progress
- Reward yourself

12.23 PUBLIC HEALTH CONSIDERATIONS

Regular physical activity is, of course, very important for every individual. However, there are often issues that involve public health considerations, which can be beneficial to people who are trying to increase their exercise program and either facilitate or discourage people from physical activity. Many health clubs and YMCAs offer specific exercise programs for either older adults, youths, healthy adults, or individuals with specific medical needs. The community can be involved in the built environment and facilitating types of facilities, such as parks and trails, that will encourage people to become involved in increased physical activity. New technologies, such as wearable activity trackers and web based internet, can also enhance the likelihood of increased physical activity. These factors are all discussed in more detail in Chapter 20. Physician leadership in all of these areas will facilitate more community involvement and is an important part of the patient healthcare provider role.

12.24 STEPS IN PROMOTING REGULAR PHYSICAL ACTIVITY

A number of factors that involve not only the individual but also the community and the environment impact on the likelihood of people starting and staying with an exercise and physical activity program. These factors are discussed in more detail in Chapter 20.

12.25 CONCLUSIONS

Physical activity plays a critically important role in enhancing the health of individuals and communities in the United States and other countries. The multiple benefits of physical activity are applicable to the entire age range and involve healthy individuals as well as individuals with chronic conditions. Increased physical activity is one of the most powerful mechanisms that all physicians can recommend to their patients to improve their health. Multiple chapters throughout this book will discuss specific aspects of physical activity and how to prescribe it for both healthy individuals and special populations.

CLINICAL APPLICATIONS

Physician recommendation is a powerful motivator to help people improve their lifestyle in multiple areas, including physical activity.

Physicians should recommend increased physical activity to all patients.

Physical activity not only plays an important role in decreasing the risk of chronic diseases, but also serves as an adjunct to their treatment.

Physical activity plays an important role in improving quality of life for individuals.

Counseling on physical activity and its benefits should be a routine part of every physician encounter with patients.

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13 Implementation of the Exercise Prescription

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KEY POINTS

- Physician-directed implementation of the exercise prescription is effective in helping patients make long-term lifestyle changes.
- Exercise and physical activity referral networks are not currently being utilized effectively, but successful strategies and programs have been identified and can be used as models for the future.
- Healthcare professionals can learn effective exercise and physical activity referral practices and implement them in clinical practice.
- Personal trainers, exercise physiologists, physical therapists, and health coaches can be important members of a physician's referral network.

13.1 INTRODUCTION

Substantial evidence supports the efficacy of clinician-initiated physical activity counseling, prescription, and referral, which has led to the recommendation of exercise being considered a standard component of clinical care in healthcare settings.[1,2] Physical activity assessment in clinical settings is feasible and valid,[3] and for the first time, the scientific report of the Physical Activity Guidelines for Americans 2018 concluded that "the primary care setting may be an appealing venue for offering physical activity counseling or referral and represents a scalable opportunity to influence population-level physical activity if effective approaches can be implemented."[4] Research strongly shows that exercise prescription and referral to exercise professionals is effective in helping patients make long-term lifestyle changes.[5–7] To that end, physical activity counseling has a United States Preventive Services Task Force (USPSTF) Level of Evidence B recommendation,[8] and physical activity and nutrition counseling must be included in new health plans under the Affordable Care Act's Prevention and Health Promotion activities for populations at increased risk of cardiovascular disease.

The Physical Activity and Health Innovation Collaborative (PA IC) of the National Academies of Sciences, Engineering and Medicine has specifically called upon healthcare settings to expand the use of the physical activity vital sign (PAVS)[9] within the scope of electronic health records.[10] The best current evidence suggests that the three-question PAVS and the two-question Exercise Vital Sign can ascertain compliance with the PA Guidelines and take less than one minute to administer.[3,11] Importantly, these assessment tools are scientifically sound and often lead to clinician-directed PA counseling and/or referral, which results in improvements in patients' physical activity.[12]

While all healthcare providers should be educated on implementing counseling, prescription, and referral practices,[13], physicians specifically, are beginning to answer the call and are successfully including exercise counseling in their practices.[1, 14] However, there are still inconsistencies in exercise counseling and referral practices in the healthcare setting.[15] This is due, in part, to a research-to-practice gap in scalable practices to guide the integration between the healthcare and fitness sectors.[15,16] This chapter will identify challenges to implementing exercise referral systems as well as successful real-world models of the exercise prescription. It will further outline the range of trained exercise professionals who serve as the providers ready to implement the exercise prescription.

13.1.1 Challenges to Implementing the Exercise Prescription

Clinicians and healthcare providers agree that exercise is powerful medicine and that exercise prescriptions can be an effective strategy to increase physical activity in the clinical population. While a robust referral network should connect clinicians and trained exercise professionals,[17] scalable systems bridging the gap between these professionals remains elusive, and several perceived barriers to integration exist. Roughly 50% of physicians believe[18] that they play an important role in promoting exercise to their patients, yet also reported that only 20% of patients or fewer were provided with an exercise prescription. Approximately one-quarter of physicians did not refer patients to exercise professionals because they were not adequately informed about the local exercise facilities available,[18] and fewer than 20% of physicians collaborated with exercise professionals. This is despite the fact that nearly 75% of physicians expressed interest in such a partnership if it were available to them.[18] Moreover, although physicians reported being familiar with health clubs and generally believed health clubs to be an appropriate venue for their patients,[19] fewer

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than half of the physicians recommended health clubs to their patients.[16] Lastly, clinicians believed that access to and cost of health clubs and personal trainers present an important barrier to their patients.[16]

While barriers perceived by individual physicians, exercise professionals, and patients present challenges to implementation, there are also institutional barriers to consider. In a recent review of over 50 research articles examining implementation barriers to integrating exercise into real-world cancer care, 243 barriers were identified across all levels of the healthcare system,[20] with nearly 40% of barriers existing at the organizational level. Lack of structures to support exercise integration and absence of staff/resources to facilitate delivery were among the most common issues reported.

Given that several obstacles make implementation of the exercise prescription and referral process difficult, it is important to take a closer look at current successful systems in place for effective referral. Specifically, it is critical that the roles of exercise professionals as well as successful community programs are examined, and that systems are understood and best practices followed. Indeed, clinical counseling, prescription, and referral to an exercise specialist can result in increased physical activity for patients who are insufficiently active.[17,21] It is important to note, however, that these systems are only just emerging and leave much room for expansion and improvement.

13.1.2 Exercise Professionals Ready to Implement Exercise Prescriptions

13.1.2.1 Personal Trainer

A certified personal trainer (CPT) is a fitness professional who works with mostly healthy individuals to achieve their exercise goals.[22] The job entails conducting fitness evaluations and creating performance programs for clients. Various assessments can and should be done in order to design a proper fitness plan, including, but not limited to, a preparticipation screening, submaximal aerobic exercise test, and muscular, flexibility, and body composition tests. Using such information will help the personal trainer develop appropriate cardiorespiratory, strength and conditioning, and stretching programs. These professionals also promote positive health behavior and motivate their clients.

According to the Institute for Credentialing Excellence, there are 12 personal trainer certifying organizations accredited by the National Commission of Certifying Agencies (NCCA) (Institute for Credentialing).[23] Among the organizations offering a CPT certification are the American College of Sports Medicine (ACSM), the National Academy of Sports Medicine (NASM), the National Strength and Conditioning Association (NSCA), and the American Council on Exercise (ACE). Within these organizations, additional certifications may be offered for specific areas of expertise. For example, in addition to the CPT certification, NSCA offers a Certified Strength and Conditioning Specialist (CSCS) certification, and ACSM offers an Exercise Is Medicine® (EIM) credential.

CPTs generally work at gyms, in fitness and community centers, and in corporate wellness programs. In addition to CPTs, Group Exercise Instructors (GEI) play an integral role in fitness facilities.

Currently, there is no standardized process for physicians to refer patients to a CPT. However, ACSM created an exercise referral model through the EIM® initiative (see later).[24] In an effort to help connect primary care practitioners (PCPs) with CPTs and to deliver physical activity prescriptions, EIM® also created an exercise professional credential. Anyone who holds an NCCA accredited fitness professional credential is eligible to obtain the EIM® credential.[25] In addition, the ACE offers an NCAA-accredited Certified Medical Exercise Specialist credential,[26] which was created to help train CPTs to create programs for clients with a range of medical conditions. ACE Certified Medical Exercise Specialists must hold a bachelor's degree in exercise science or a related field and have completed 500 hours of work experience designing and implementing exercise programs for apparently healthy individuals and/or high-risk individuals.

13.1.2.2 Exercise Physiologist

An exercise physiologist is a health professional who helps diagnose and treat a number of diseases through exercise. They work with clients and/or patients to provide exercise prescriptions based on health history and physical assessment.[22] Common areas of focus include cardiovascular, pulmonary, and metabolic diseases. Exercise physiologists can work in a number of settings—both clinical and nonclinical. Weight management and obesity are other traditional areas where exercise physiologists may be employed, while cancer care is a growing specialty for exercise physiologists.[27] In addition to hospitals and clinics, exercise physiologists can work in fitness and wellness centers as well as corporate, government, and university settings.[28]

In the United States, there are currently two certifications for exercise physiologists, each of which requires a minimum of a bachelor's degree. The ACSM offers exams for the certified exercise physiologist (ACSM-EP) and the certified clinical exercise physiologist (ACSM-CEP).[28] While it is not necessarily required for exercise physiologists to obtain a certification, many employers do require it.

One of the most popular areas of the exercise physiology profession is cardiac rehabilitation. According to the Clinical Exercise Physiology Association (CEPA), approximately 45% of exercise physiologists work in cardiac rehabilitation.[29] Even though cardiac rehabilitation is one of the largest venues for exercise physiologists, there is evidence that it is not being used enough. According to the American Heart Association, "[D]espite being recommended by guidelines, rates of referral to cardiac rehabilitation are historically suboptimal."[30] Referral rates depend highly on procedure type and where the procedure was performed, as some institutions and/or departments vary.

13.1.2.3 Physical Therapist

According to the American Physical Therapy Association (APTA), the role of a physical therapist (PT) is to "examine each individual and develop a plan using treatment techniques to promote the ability to move, reduce pain, restore function, and prevent disability."[31] The PT profession also involves working with patients in a preventive manner, as this can help prevent the loss of mobility before it occurs through the development of an exercise program. Much like an exercise physiologist, a PT's job begins with a patient assessment or evaluation. This includes taking a medical history and performing tests and measures to identify problems, both existing and potential. After a general review is conducted, PTs use the gathered information to design and implement a plan of care.

In the United States, the education requirement for PTs is a Doctorate of Physical Therapy (DPT).[31] In addition to obtaining a degree, PTs must pass a state licensure exam. PTs work in a variety of settings, including, but not limited to, outpatient clinics and offices, inpatient rehabilitation facilities, home care, research institutes, hospices, fitness centers, and sports training facilities. The American Board of Physical Therapy Specialties (ABPTS) offers several certifications for PTs. The following are areas of specialization: cardiovascular and pulmonary, clinical electrophysiology, geriatrics, neurology, oncology, orthopedics, pediatrics, sports physical therapy, and women's health. Though a certification is not required to work in any particular field, the goal of ABPTS is to promote high-quality physical therapy through acknowledging the knowledge and skill of specialty areas.[32] A referral to PT is typically required under most insurance companies.

While physical therapy is often seen as a rehabilitation profession, the job function of a PT includes preventive aspects. PTs are not only an excellent resource for prevention of injury but are also in a good position to promote a physically active lifestyle. As reported by the APTA, PTs are knowledgeable and skilled professionals who can provide non-treatment physical activity advice.[33] As they are easily accessible to a number of populations, they could have a more predominant role in public health.

13.1.2.4 Health Coach

A health coach is a certified professional trained in patient-/client-centered behavior change who can work in concert with the exercise professional to implement the exercise prescription. Typically, health coaches work with individuals to facilitate healthy lifestyle changes like achieving adequate physical activity, improved nutrition, smoking cessation, and stress reduction. While health coaches do not diagnose conditions, prescribe treatments like exercise, or provide psychological interventions, they are able to work with individuals to provide guidance and personalized motivation to create behavior change strategies and goal setting. Specifically, health coaches "assist clients to use their insight, personal strengths and resources, goal setting, action steps and accountability toward healthy lifestyle change."[34] Often, health coaches will hold multiple certifications or even content-relevant degrees (e.g., Exercise Science or Nutrition) that aid in their practice. In 2017, the National Board of Health and Wellness Coaches (NBHWC) was formed, in partnership with the National Medical Examining Board, to develop an accredited certification, the National Board Certified Health & Wellness Coach (NBC-HWC).[34] Coaches are often self-employed but can also work at gyms, in fitness and community centers, and in corporate wellness programs, and are also becoming part of integrated care teams in some healthcare settings. Currently, there is no standardized process for physicians to refer patients to a health coach, although there are programs approved by the American Medical Association (AMA) for direct referral and reimbursement being implemented for NBH-HWCs in the Department of Veteran's Affairs.[35]

13.1.3 Successful Programs

Programs for the successful implementation of the exercise prescription can be brief or highly comprehensive. This section will examine evidence-based strategies to engage patients, from utilizing systems as simple as referral guides to cultivating an entire hospital-wide referral scheme.

13.1.3.1 Referral Guides

A straightforward and effective strategy to use limited clinical time for exercise referral may simply be to refer patients to a list of regionally offered community programs. Indeed, many community departments and health agencies have collected local information to develop resource collections, with the goal of increasing provider awareness of the scope and array of existing community resources. These resource collections can be utilized as referral guides to provide contact information to patients in electronic or paper form. Some clinicians have demonstrated concerns over the simplicity and usefulness of referral guides[36] and emphasize that the guides (1) do not eliminate the need for individualized counseling, (2) must be updated frequently, and (3) may provide information about programs unfamiliar to the practitioners. However, when utilized in practice, referral guides have actually been shown to be effective and can be helpful because "providing patients with specific activity suggestions was more effective than providing general advice in facilitating behavior change."[36] Moreover, as technology advances, there is the opportunity to utilize smartphone applications in conjunction with, or in addition to, referral guides in order to provide up-to-date and personalized recommendations.

13.1.3.2 Physical Activity Vital Sign (PAVS)

The PAVS can be used individually by providers in healthcare settings and has begun to be added to electronic health records.[10] PAVS was created by investigators at the Department of Family and Preventive Medicine at the University of Utah, Salt Lake City, Utah, to implement

in family medicine clinics in the Utah Health Research Network, and can be administered in <30 seconds.[11] The best current evidence suggests that the three-question PAVS can ascertain compliance with the Physical Activity Guidelines for Americans.[3] Importantly, these assessment tools are scientifically sound and often lead to clinician-directed PA counseling and/or referral, which results in improvements in patients' physical activity.[12]

The PAVS consists of two specific questions:[9,11]

1. On average, how many days per week do you engage in moderate to vigorous physical activity (like a brisk walk)? ____days
2. On average, how many minutes do you engage in physical activity at this level? ____minutes
   Total minutes per week of physical activity (multiply #1 by #2) ____minutes per week
   A third question can be added, and ACSM EIM® suggests:[24]
3. How many days a week do you perform muscle strengthening exercises, such as bodyweight exercises or resistance training? ____days

13.1.3.3 Diabetes Prevention Program for Patients with Prediabetes

Proven to be successful in preventing the onset of type 2 diabetes, the Diabetes Prevention Program (DPP) is an evidence-based program available nationwide that physicians can easily refer patients to. It is generally a 12-month program in which participants attend 16 weekly core sessions and are subsequently followed month to month through regular maintenance sessions. The goal of the DPP is to help individuals with prediabetes prevent the onset of type 2 diabetes by making better food choices, increasing their level of physical activity, and losing excess weight. DPP programs have been shown to be twice as effective as approaches that are less structured.[37,38]

According to the AMA[39] website, the AMA and the Centers for Disease Control (CDC) recommend that physicians take measures to prevent diabetes in their patients by screening them for prediabetes and referring them to the DPP if positive. The CDC website provides a list of available DPP programs across the nation, which physicians can access at any time. To address the barrier of insufficient finances, many DPPs are now covered through Medicare and other health insurance providers, thus making the referral process easier and providing even more incentive to patients.

The YMCA DPP[40] is one example of a program that physicians can easily refer patients to. There are more than 200 YMCA sites throughout the country that run the DPP, and there is a large body of evidence supporting the program's effectiveness.[37] For instance, an existing partnership between the YMCA, UnitedHealth Group, and the CDC brought the DPP to nearly 30,000 participants in more than 1,000 locations across the country.[37]

13.1.3.4 SilverSneakers and Enhance Fitness for Older Adults

SilverSneakers is a no-cost gym membership for eligible seniors to which physicians can refer patients.[41] Targeted toward older adults, ages 65 and up, this is a fitness program covered by many Medicare Advantage plans. Participants receive access to more than 15,000 gyms and fitness centers in the network in addition to online and streaming classes, and membership includes fitness classes by SilverSneakers trained instructors.

Enhance Fitness (EF) is a nationally disseminated program for older adults that offers group-based exercise classes in community settings.[42] Each class lasts 1 hour and follows a set format, including exercises targeting cardiovascular endurance (20–25 min), strength (20 min), and balance and flexibility (10 min), all of which are adaptable to individual ability level. While EF is not covered by Medicare, it is often subsidized by and integrated into healthcare systems.

Programs like SilverSneakers and EF have demonstrated positive benefits on overall physical function as well as fall prevention in older adults.[43] In addition to increased fitness and fall prevention, these programs have also been shown to be significant healthcare cost–saving programs.[44, 45]

13.1.3.5 American College of Sports Medicine's Exercise Is Medicine® Model

In 2015, the ACSM developed a multi-component conceptual model, called Exercise Is Medicine® (EIM),[24] for healthcare settings to integrate PA assessment and prescription as a part of their clinical workflow, and refer patients to evidence-based PA programs.[1,24] The EIM® model is designed to improve the reach of evidence-based PA interventions by identifying and engaging patients who would benefit from increased PA. The individual components of the EIM® model include: 1) assessing PA levels of patients, 2) providing brief PA counseling and/or a PA prescription, and 3) referring patients to PA resources for further guidance. Individual components of the EIM® model have been deployed in U.S. and international health settings, demonstrating moderate-to-strong evidence bases for PA assessment,[9,46–50] prescription,[51–53] and referral.[54–56]

To date, the largest implementer of the EIM® model is Exercise Is Medicine Greenville® (EIMG®; www.EIMGreenville.org).[57] In 2016, the University of South Carolina School of Medicine Greenville, Prisma Health System, and the YMCA of Greenville, educated by the EIM® conceptual model, designed and implemented a clinic-to-community program to comprehensively integrate PA across multiple primary care practices, connecting patients to evidence-informed PA programs delivered in community settings. With 8 inpatient hospitals and more than 100 outpatient facilities and affiliated doctor offices,[58] Prisma Health is the first and largest health system in the United States committed to a multi-level process of implementation of PA by integrating all EIM® model components

into their clinical workflow and connecting patients with chronic diseases to community-based PA programs.[57] EIMG® is the first full-scale example of an initiative bringing together medical practitioners, clinical staff, health system administrators, health behavior researchers, public health and exercise professionals, and patients from diverse backgrounds around PA promotion.

Prisma Health clinics receive standardized onboard training to: 1) assess PA levels at the clinic visit and identify EIMG®-eligible patients, 2) provide patient education on the benefits of PA using the ACSM's Prescription for Health Series, and 3) initiate an electronic referral process through the health system's EPIC electronic health records to the EIMG® referral team, who subsequently connect Prisma Health patients to participating YMCAs to implement the exercise prescription. Patients are eligible for engagement in EIMG® at participating Prisma Health clinics if they are between the ages of 18 and 80, are physically inactive (<150 minutes per week of moderate intensity aerobic activity) or have a chronic condition (i.e., overweight/obese, hypertension, type 2 diabetes, stable heart disease) that is positively impacted by PA. Referred patients are guided by EIMG®-qualified and credentialed exercise professionals through a 12-week evidence-informed PA program. Through EIMG®, patients with lifestyle-related chronic disease learn how to reduce their risks and improve their overall health by adopting healthy behaviors that include exercise and movement. In order to ensure long-term success, upon completion of the 12-week program, participants are encouraged to continue in EIM® in the maintenance program. There is an individual cost for the program ($249 for the 12-week program, which includes membership to the PA facility) that currently is not covered by Medicaid.

The YMCAs of Greenville understand that EIMG® will only succeed as a population health strategy if it is affordable and delivered equitably. Therefore, the YMCA of Greenville provides substantive in-kind support for operations of the program, as well as securing a percentage of their annual giving campaign to EIMG® so that no patient is turned away due to their inability to pay. To date, >$300,000 has been set aside for patient scholarships, a model that can be replicated by other YMCAs and communities outside of Greenville, SC. Between 2017 and 2019, 70%, 57%, and 73% of patients each year received scholarships covering 5–100% of the costs to participate in the 12-week PA program.[59]

Preliminary results published from EIMG® demonstrated that from 2016 to 2019, 210 patients completed the program (>60% graduation rate). Also, patients diagnosed with hypertension receiving usual care who were referred by their HCP and graduated from the program decreased body weight ($p = 0.001$) and systolic and diastolic BP ($p < 0.001$), and were highly satisfied (>4 on a 5-point Likert scale) with the program and personnel.[59]

13.2 SUMMARY

Physicians generally view exercise as an important component of a healthy lifestyle and have begun to use physical activity vital signs and exercise prescriptions in their practices. Still, data indicate that only 20–30% of physicians are actively prescribing physical activity, signaling room for improvement. Barriers to implementation of the exercise prescription do exist, including time, knowledge of programming, and professionals. However, these barriers can be overcome with simple clinical strategies and a robust referral network. Physical activity and exercise professionals such as personal trainers, exercise physiologists, physical therapists, and health coaches are trained to work with patients to implement physical activity and exercise prescriptions, as noted in Table 13.1. Moreover, there are several clinic-based strategies, such as referral guides and referral to community-based programming, that can be utilized to educate and encourage patients to implement, or "fill," their own exercise prescriptions. While writing the physical activity or exercise prescription falls in the

TABLE 13.1
Physical Activity and Exercise Professionals

Physical activity professional	Target population	Reason for referral
Personal trainer	Non-specific	Works with individuals to achieve their exercise goals. Conducts fitness evaluations and creates performance programs for clients. Uses various assessments to design an appropriate fitness plan. Promotes positive health behavior and motivates clients.
Exercise physiologist	Non-specific	Helps diagnose and treat a number of diseases through exercise in either a clinical or a nonclinical setting. Works with individuals to provide exercise prescription based on health history and physical assessment.
Physical therapist	Non-specific	Examines individuals and develops a plan using treatment techniques to improve the ability to move, reduce pain, restore function, and prevent disability. Works with patients in a preventive manner in order to prevent the loss of mobility before it occurs. Based on various assessments and tests, PTs use the gathered information to design a plan of care.
Health coach	Non-specific	Works with individuals to facilitate healthy lifestyle changes like achieving adequate physical activity, improved nutrition, smoking cessation, and stress reduction. Provides guidance and personalized motivation to create behavior change strategies and goal setting.

purview of the physician, practical execution relies on a robust network of systems and professionals designed to support patient engagement and behavior change. Creating these networks is critical for the successful implementation and future of the use of physician-directed exercise prescriptions.

CLINICAL APPLICATIONS

- Physicians generally view exercise as an important component of a healthy lifestyle and have begun to use physical activity vital signs and exercise prescription in their practices.
- Barriers to prescribing exercise exist, including time, knowledge of programming, and professionals.
- Barriers can be overcome with simple clinical strategies and a robust referral network.
- Clinic-based strategies of implementation can include referral guides and referral to community-based programming that can be utilized to educate and encourage patients to "fill" exercise prescriptions.

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14 The Role of Physicians in Promoting and Prescribing Increases in Physical Activity

James M. Rippe, MD

KEY POINTS

1. Physician counseling has been repeatedly demonstrated to be one of the most powerful motivators for encouraging patients to make positive lifestyle decisions.
2. Unfortunately, fewer than 40% of physicians counsel their patients about physical activity.
3. Since >70% of individuals see their primary care physician at least once a year, there is a great opportunity to increase the likelihood of patients engaging in physical activity levels.
4. Currently, less than 25% of the adult population meets the recommended levels of physical activity in the Physical Activity Guidelines for Americans 2018 Scientific Report.
5. Physician recommendation for physical activity should include aerobic exercise, strength training, balance, and flexibility.
6. Increased physical activity levels among physicians themselves can yield a variety of personal health benefits and also increase the likelihood that they will counsel their patients about physical activity.

14.1 INTRODUCTION

There is no longer any serious question that regular physical activity yields multiple benefits for both short- and long-term health and quality of life.[1] Regular physical activity significantly reduces risk factors for many chronic diseases, including cardiovascular disease (CVD), type 2 diabetes (T2DM), some cancers, metabolic syndrome, and many other conditions.[1,2] Regular physical activity also serves as an important component of the treatment of many chronic diseases. Virtually every professional organization includes physical activity as a key, evidence based guideline for both prevention and treatment of chronic diseases.[3]

As a cardiologist and lifelong exerciser, I am both professionally and personally committed to regular physical activity. In addition, my research organization, Rippe Lifestyle Institute (RLI), has included regular physical activity as a key component of virtually every study that we have performed over the last 25 years and every patient we have seen in our clinic. Regular physical activity is also a key component that we have combined with other lifestyle factors in our various lifestyle medicine publications. For these reasons, I feel very strongly that there are both academic and personal reasons why every physician should include promotion and prescription of regular physical activity in every office visit.

Even though there are well-documented benefits for physical activity, unfortunately, the medical community has not been as active as it should have been in the promotion and prescription of regular physical activity. In fact, a number of studies have shown that 40% or fewer of physicians include discussion of physical activity in office visits with patients.[4]

It has been a struggle to get people to engage in meaningful amounts of physical activity. It has been estimated that 75% of adults in the United States do not meet current physical activity guidelines promulgated by the Physical Activity Guidelines for Americans (PAGA) 2018 (Figure 14.1).

Adolescents also are not obtaining enough physical activity. In addition to the known benefits of regular physical activity, increasing evidence exists now that an inactive lifestyle contributes to multiple, long-term, adverse health consequences. The World Health Organization (WHO) ranked physical inactivity as the fourth leading cause of death worldwide.[5]

Physician recommendation is a powerful motivator to encourage people to make behavioral changes. In fact, a number of studies have shown that physician recommendation is the most powerful source to help people make changes in their habits and practices. For this reason, there is a clear mandate for physicians to become involved in recommending physical activity to every patient that they see.[6]

The purpose of this chapter is to provide both a framework and overall guidance to help physicians and other healthcare workers engage in counseling and recommendations to increase physical activity for every patient that they see and in their own lives.

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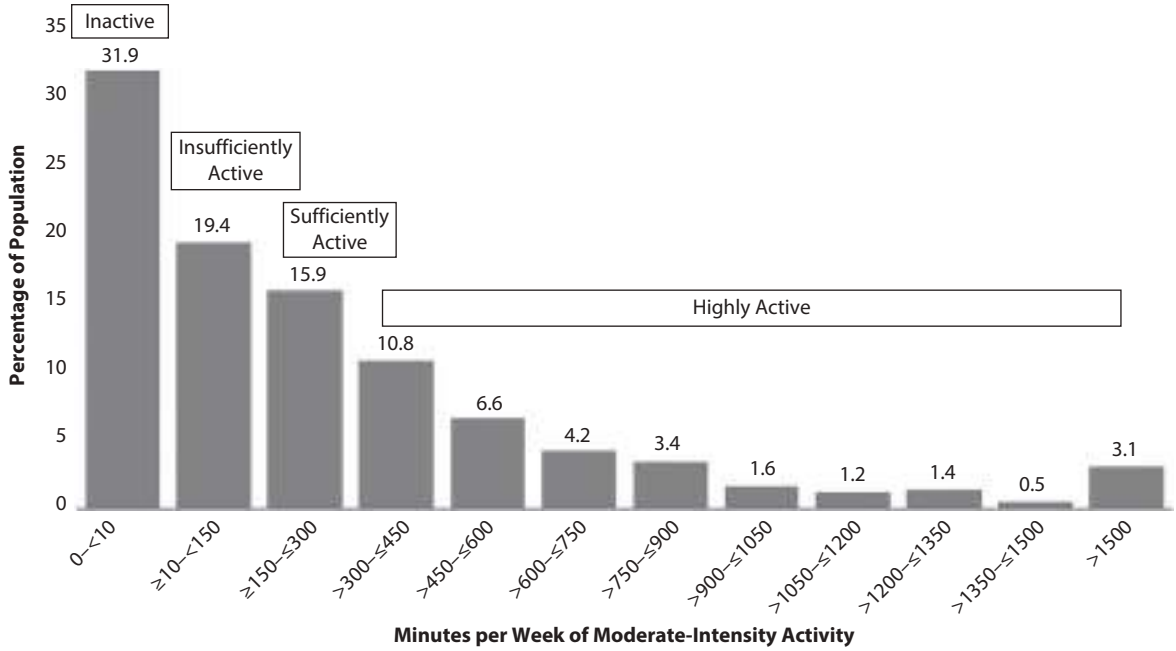


FIGURE 14.1 Distribution of self-reported volume of moderate-to-vigorous physical activity, 150 minutes per week increments, U.S. adults, 2015. (Adapted from data found in the National Health Interview Survey, 2015.)

14.2 THE ROLE OF PHYSICAL ACTIVITY IN LIFESTYLE MEDICINE

Lifestyle medicine is the discipline that explores how daily habits and actions impact on short- and long-term health and quality of life. While there are many factors in these daily habits and actions that powerfully impact on health and quality of life, physical activity is arguably the most important of all of these factors. In fact, in the area of cardiovascular medicine, an inactive lifestyle is a more powerful predictor of CVD than any other risk factor, including hypertension, dyslipidemia, and obesity.[7]

The field of lifestyle medicine has grown dramatically over the past two decades. In the first major textbook of lifestyle medicine, which I edited, I was pleased to have named this field in 1999.[8] Subsequently, a number of organizations have adopted the framework of lifestyle medicine to describe the importance of lifestyle choices in maintaining good health and provide background and education for physicians and other healthcare workers who wish to become involved in this field.[9] The most prominent organization in this area is the American College of Lifestyle Medicine (ACLM) which has grown over 1,200% in its membership between 2003 and 2020. This makes lifestyle medicine the most rapidly growing specialty within the area of medicine.

14.3 PHYSICAL ACTIVITY PROMOTION AND INVOLVEMENT OF PHYSICIANS AND OTHER HEALTHCARE PROFESSIONALS

The world is in the midst of what has been described as an epidemic of non-communicable diseases. This is in contrast to previous epidemiologic eras. For example, in the 1900s, communicable diseases, such as infectious diseases, resulted in the top three causes of death in the United States and accounted for 30% of all deaths.[10] By 2014, seven out of the ten top causes of death were attributable to chronic non-communicable diseases.[11] For example, CVD and cancer represent 46% of all deaths each year in the United States and also represent the majority of healthcare expenditures in the United States.[12] While the link between lifestyle and CVD is well recognized, many people do not recognize that lifestyle habits and actions such as cigarette smoking, an inactive lifestyle, and also conditions such as obesity result in the majority of cancer deaths. It has been estimated by the WHO that lifestyle habits and actions contribute to 75–80% of chronic disease.[13] There is no longer any doubt that lifestyle issues, in general, and physical activity, in particular, represent critically important targets for medical intervention.

14.4 CALLS FOR MORE PHYSICIAN AND OTHER HEALTHCARE PROFESSIONAL INVOLVEMENT FOR RECOMMENDING PHYSICAL ACTIVITY

The emphasis on lifestyle factors may be traced back to the clarion call issued by U.S. Surgeon General, Julius Richmond, in 1979 in his report "Healthy People, a Surgeon General's Report on Health Promotion and Disease Prevention."[14] Recommending increased physical activity was a major theme of this report, as well as the recommendation that the healthcare sector should lead in the promotion of this activity.

Healthy People Reports have subsequently been issued and updated every decade. A number of changes in emphasis

have occurred, but the importance of physical activity has remained an essential focus. For example, the Healthy People 2020 contained multiple recommendations concerning the importance of regular physical activity, including the central recommendation of increasing the proportion of physician office visits in both children and adults where recommendations for increased physical activity occur.[15]

The initial framework for the Healthy People 2030 also includes the recommendation to improve built environments such as sidewalks, bike lanes, trails, and parks to increase the likelihood of physical activity.[16] This framework also focuses on both schools and childcare settings and workplaces as important venues where increased physical activity can be achieved. In all of these settings, increased physician involvement is emphasized as a central component of improving levels of physical activity for the population.

Among the specific recommendations related to physical activity in Healthy People 2020 was encouraging the proportion of adults to engage in early physical activity of at least moderate intensity 150(+) minutes per week and increasing the proportion of adults who perform muscle strengthening activities on two or more days per week. Similar objectives were also listed for adolescents. The Healthy People 2020 document also recommended increasing the proportion of elementary schools that require daily physical education for all students and also increasing the number of adolescents who participate in daily school physical education. Many other recommendations for increased physical activity from Healthy People 2020 are consistent with other national guidelines and particularly, the Physical Activity Guidelines for Americans 2018 Scientific Report (PAGA 2018).[2]

14.5 PHYSICAL ACTIVITY RECOMMENDATIONS: THE NATIONAL PERSPECTIVE

The first U.S. National Activity Plan was released in 2010 and subsequently updated in 2016.[17] The healthcare section was identified as one of the nine major areas identified in both of these plans. These plans include a recommendation to prioritize efforts in healthcare to promote physical activity, as well as recognizing physical inactivity as preventable and treatable, since it carries both health and cost implications. The U.S. National Activity Plan also emphasized the importance of partnering across sectors and extending education in the area of physical activity in the training of all healthcare professionals.

14.6 THE ROLE OF PROFESSIONAL ORGANIZATIONS IN PROMOTING PHYSICAL ACTIVITY

A number of professional organizations have become involved in recommending and promoting increased levels of physical activity. The most prominent organization in this area has been the American College of Sports Medicine (ACSM).[18] The ACSM has been the professional home of exercise physiologists and other healthcare professionals with a particular interest in exercise for many decades.

Recently, the ACSM has joined forces with the American Medical Association (AMA) in the initiative entitled "Exercise Is Medicine" (EIM).[4] The goal of EIM is "for the healthcare community to make physical activity a standard part of the medical paradigm for the prevention and treatment of non-communicable diseases (NCDs) in healthcare systems." The EIM initiative was initially launched in the United States, but has now spread to more than 40 countries. This initiative started as an effort to increase awareness of the important health benefits of increased physical activity. The focus has now broadened, however, to include implementation of a standard model to help primary care physicians prescribe physical activity as well as recommend access to community resources. The EIM initiative has also provided multiple tools to help guide physicians through the steps to increase physical activity. One of these tools is the "Healthcare Providers Action Guide." This is a free source of information, which can be downloaded from the EIM website as well as other resources. More detailed information about the EIM program can be found in Chapter 19.

In addition to ACSM, the American Academy of Geriatrics, the American College of Preventive Medicine, the American Academy of Pediatrics, and the American Academy of Orthopedic Surgeons have all issued statements encouraging their members to recommend increased physical activity for all patients.[19]

The American Heart Association (AHA) has also been a leader in emphasizing the importance of physical activity and other lifestyle actions in the prevention of CVD. In fact, one of the Councils of the American Heart Association actually changed its name in 2013 from the "Council on Nutrition, Physical Activity and Metabolism" to the "Council on Lifestyle and Cardiometabolic Health."[20] Lifestyle has been emphasized for both the improvement of lipids and control of blood pressure in multiple scientific statements issued by the AHA. Among these statements, in 2013, the AHA and the American College of Cardiology (ACC) issued guidelines for lifestyle medicine to reduce cardiovascular risk. These guidelines included a major emphasis not only on diet but also on physical activity. Diet is particularly important in the area of lipid management and the combination of proper nutrition and weight management. Physical activity was recommended to play a very important role in blood pressure management and weight management in combination with proper nutrition.[21]

14.7 THE RATIONALE FOR MORE PHYSICIAN INVOLVEMENT

Numerous studies have demonstrated that physicians play a unique role in influencing patients' behavior. These studies have documented that physicians are the most trusted

source of physical activity information and that patients prefer to receive their initial advice concerning physical activity from their physician as opposed to other healthcare providers such as physical therapists or dietitians.[22–24] There is also evidence that a physician's advice may serve as a catalyst for change by making patients more aware of health information and programs and making this information more relevant.[25]

Since over 70% of adults see their primary care physician each year, physicians can play a powerful role and have a significant responsibility in recommending physical activity.[26–28] There seems to be some progress in this area, although a distinct minority of physicians recommend physical activity during counseling sessions with their patients. In 2010, only 32% of adults who saw a physician received advice about physical activity. More recent studies have suggested that up to 40% of patients who see physicians have received recommendations for increased physical activity.[29] Physicians need to recognize that patient visits represent a potent opportunity for recommending multiple lifestyle changes, including physical activity.

14.8 EDUCATIONAL RESOURCES

A number of educational resources are currently available to provide physicians and other healthcare workers with evidence based information concerning various aspects of physical activity. Formal medical education, unfortunately, still does not emphasize physical activity enough.[30] In 2012, a systematic review of behavior change counseling in medical schools showed that increased physical activity was the least addressed topic of all health behaviors reviewed, following smoking, nutrition, and alcohol/drug use.[31] In 2014, another systematic review showed that only 11 programs in medical schools existed that were focused on physical activity counseling, and that the content of these programs was inconsistent with regard to program duration and placement within the curriculum.[32] These results suggest that medical students and other physicians in training do not achieve adequate levels of training with respect to prescribing physical activity.[33]

A number of professional organizations and documents are currently available to provide education for physicians in the area of physical activity. Perhaps the most comprehensive of these documents for recommendations comes from the Physical Activity Guidelines for Americans 2018 Scientific Report (PAGA 2018).[2] This extensive, evidence based document provides comprehensive documentation of the benefits of regular physical activity for multiple population groups throughout the lifespan and summarizes scientific literature, while providing extensive background references.

ACSM also provides numerous tools for practicing physicians and their patients regarding physical activity. These may be obtained by visiting the ACSM website (acsm.org). The ACLM also provides education for various aspects of lifestyle medicine through the Lifestyle Medicine Education Collaborative (LMEd).[34] This program was created in 2013 and has been accepted by half of all medical schools. The LMEd program also has supplied a collection of peer reviewed materials through the MEDEd platform, which is maintained by the Association of American Medical Colleges.

CME opportunities also exist in the area of physical activity promotion. These will be listed at the end of this chapter.

14.9 PRE-PARTICIPATION SCREENING

Both the Physical Activity Guidelines for Americans 2008 and the PAGA 2018 Scientific Report embrace the concept that when it comes to physical activity, "some is better than none." With this in mind, both the ACSM and the PAGA 2018 recommend that clinicians have a discussion with every patient they see to discuss physical activity. This is particularly true of individuals who are very inactive.

To initiate this process, the first order is pre-participation screening. This is simply to inquire of individuals how much physical activity they currently do and then to begin to work with them to increase the amount of physical activity in order to ultimately reach the guidelines recommended by the PAGA 2018: to accumulate 150 minutes of moderate to vigorous physical activity on a weekly basis and participate in two strength training sessions per week. It should be emphasized, however, that for inactive individuals, even a physical activity level of 30 minutes per week is sufficient to yield significant reduction in risk for both all-cause mortality and specifically, mortality from CVD.[35] The rationale for this is depicted in Figure 14.2.

One good way of starting the conversation about physical activity is to use the recommendations incorporated by both the U.S. National Physical Activity Program and the Exercise Medicine Initiative, which utilize a tool consisting of two questions that was developed by Stanford University:

- On average how many days a week do you engage in moderate or strenuous physical activity (like a brisk walk)?
- On average how many minutes do you engage in exercise at this level?

Once these questions are answered, the clinician has a good place to start to help an individual to gradually increase their physical activity, with the goal of ultimately meeting the guidelines from the PAGA 2018 Scientific Report. The screening could involve a brief questionnaire called the "PARQ."[36] This stands for "Physical Activity Readiness Questionnaire" (Table 14.1).

14.10 PHYSICAL ACTIVITY AND EXERCISE PRESCRIPTION

It is important to emphasize again that the key for sedentary individuals is simply to obtain more activity in their lives. Thus, the typical exercise prescription, which is

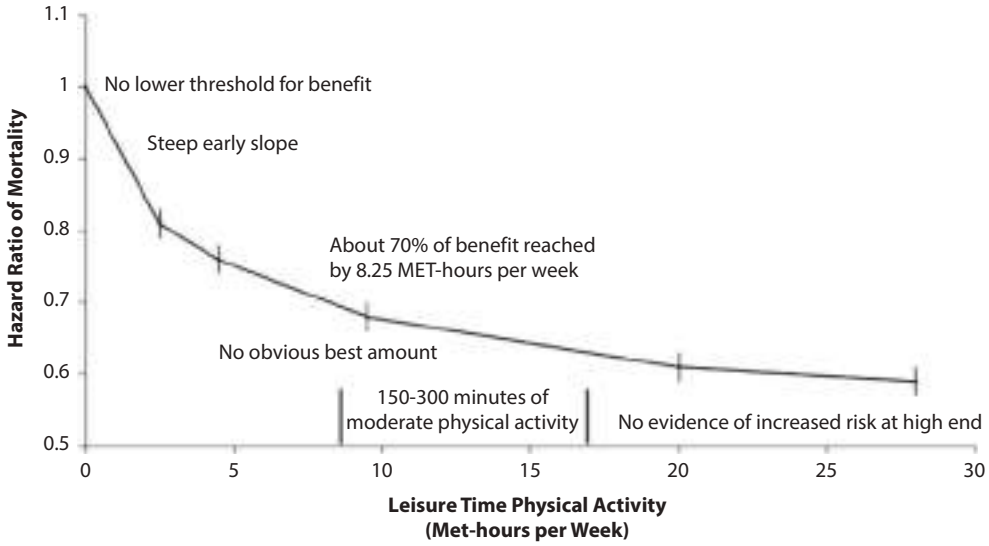


FIGURE 14.2 Relationships of moderate-to-vigorous physical activity to all-cause mortality, with highlighted characteristics common to studies of this type. (From the 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington DC: U.S. Department of Health and Human Services; 2018.)

prescribed by exercise physiologists according to the principles endorsed by organizations such as ACSM, may not be not necessary for individuals who have been sedentary and simply want to incorporate more physical activity into their lives.

If the clinician wants to be more precise in terms of exercise and the physical activity prescription, the framework developed by ACSM, which goes by the acronym FITT, can be utilized:

- Frequency
- Intensity
- Time
- Type

Typically, the frequency is three or more times a week of moderate physical activity, recommended at a level of 50–70% of VO_{2max} heart rate and at a perceived exertion considered to be "moderate." "Time" denotes the number of minutes that the individual is involved in physical activity. "Type" denotes the kind of physical activity performed.

Overall, the ACSM considers the following five points:[18]

1. All individuals should engage in at least 20–60 minutes of aerobic physical activity of at least a moderate intensity on at least 5 days per week.
2. Additional health and fitness benefits can be achieved by adding more time in moderate intensity activity or by substituting more vigorous activity.
3. Previously inactive men and women and people at risk for heart, metabolic (diabetes), and renal diseases should first consult a healthcare provider before initiating a program of vigorous physical activity to which they are unaccustomed.
4. Persons with symptomatic heart, diabetes, or renal disease who would like to increase their physical activity should be evaluated by a healthcare provider and provided with an exercise program appropriate for their clinical status.
5. Muscular strength–developing activities (resistance training) should be performed at a minimum of two times per week with at least one day between sessions. Flexibility and balance exercises should be included in a prudent overall program.

14.11 PHYSICAL ACTIVITY AND FITNESS EVALUATION

The vast majority of individuals who wish to increase the amount of physical activity in their lives may do so without a formal evaluation. This is a position supported by the PAGA 2018 Scientific Report and ACSM. This does not mean that physicians should not discuss the importance of physical activity safety and the benefits of physical activity with all patients.

There may be times when particular clinical circumstances may warrant a more formal evaluation. This may be particularly true for individuals who have a history of coronary heart disease or individuals who have been extremely inactive. In these settings, a variety of potential activity or fitness evaluations are appropriate. These evaluations may include a variety of different exercise tests, including a treadmill or bike test. For some patients, it may be appropriate to take a pencil and paper test rather than one of the physical activity tests. Background materials are also provided in numerous resources from ACSM.

TABLE 14.1

Physical Activity Readiness Questionnaire (PAR-Q)

Data Collection Sheet

NAME:_____ DATE:_____HEIGHT:_____in. WEIGHT:_____lbs.
AGE:_____PHYSICIANS NAME:_____ PHONE:_____

Questions Yes No

1. Has your doctor ever said that you have a heart condition and that you should only perform physical activity recommended by a doctor?
2. Do you feel pain in your chest when you perform physical activity?
3. In the past month, have you had chest pain when you were not performing any physical activity?
4. Do you lose your balance because of dizziness or do you ever lose consciousness?
5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
6. Is your doctor currently prescribing any medication for your blood pressure or for a heart condition?
7. Do you know of any other reason why you should not engage in physical activity?

If you have answered "Yes" to one or more of the above questions, consult your physician before engaging in physical activity. Tell your physician which questions you answered "Yes" to. After a medical evaluation, seek advice from your physician on what type of activity is suitable for your current condition.

GENERAL & MEDICAL QUESTIONNAIRE
Occupational Questions Yes No

1. What is your current occupation?
   _____
2. Does your occupation require extended periods of sitting?
3. Does your occupation require extended periods of repetitive movements? (If yes, please explain.)
   _____

4 Does your occupation require you to wear shoes with a heel (dress shoes)?

5 Does your occupation cause you anxiety (mental stress)?

Recreational Questions Yes No

6 Do you partake in any recreational activities (golf, tennis, skiing, etc.)? (If yes, please explain.)
_____
_____

7 Do you have any hobbies (reading, gardening, working on cars, exploring the Internet, etc.)? (If yes, please explain.)
_____
_____

Medical Questions Yes No

8 Have you ever had any pain or injuries (ankle, knee, hip, back, shoulder, etc.)?
(If yes, please explain.)
_____
_____

9 Have you ever had any surgeries? (If yes, please explain.)
_____
_____

10 Has a medical doctor ever diagnosed you with a chronic disease, such as coronary heart disease, coronary artery disease, hypertension (high blood pressure), high cholesterol or diabetes? (If yes, please explain.)
_____
_____

11 Are you currently taking any medication? (If yes, please list.)
_____
_____
_____

14.12 DURATION OF WORKOUT SESSIONS

For many years, it was thought that the duration of physical activity needed to be 30 minutes in order to yield important benefits. This was subsequently modified to 10-minute sessions and accumulating 30 minutes per day.[37] This latter approach was incorporated in the guidance from the ACSM and the 2008 Physical Activity Guidelines for Americans. In the decade between 2008 and 2018, however, abundant new information became available indicating that physical activity sessions of less than 10 minutes per session could also result in significant health and fitness benefits. For this reason, the PAGA 2018 Scientific Report recommended that any duration of physical activity could yield important benefits. This is particularly important to emphasize to patients who have been sedentary. Sedentary individuals should be advised that even small amounts of regular physical activity, such as taking the stairs at work or parking further away from stores or walking across the parking lot when shopping, if done on a regular basis can yield important health and fitness benefits. Thus, the barrier of physical activity sessions needing to take 10 minutes or more has now been essentially removed.

14.13 PHYSICAL ACTIVITY AND EXERCISE PRESCRIPTION FOR SPECIAL POPULATIONS

Some modifications in physical activity programs may be necessary for special populations. In general, the same recommendation of trying to achieve 150 minutes of moderate intensity aerobic physical activity and two-weekly sessions of muscular strength training per week should apply to most individuals.

Some modifications may be necessary in some populations or with populations with special needs. For example, the PAGA 2018 Scientific Report recommends that children try to accumulate 60 minutes of moderate intensity activity on most, if not all, days. Older adults (over the age of 65) can typically achieve 150 minutes of moderate intensity physical activity per week, but may also wish to supplement aerobic physical activity with balance exercises on 2–3 days per week to improve balance and decrease the risk of falling.

Physical activity for most women is the same as for men. During pregnancy and postpartum, however, there may be some slight modifications, although the physical activity guideline of 150 minutes of moderate intensity physical activity per week will be appropriate for most individuals. Issues related to physical activity for special populations are described in great detail in the Physical Activity Guidelines for Americans 2018 Scientific Report.

14.14 GETTING STARTED

As already indicated, individuals who recommend increased physical activity for patients can utilize the two question program developed at Stanford University as described previously in this section. The goal is to make it simple for physicians to open the discussion with all patients regarding the importance of increased physical activity.

14.15 UTILIZING EXPERTS

A variety of experts are available to help physicians in the goal of increasing physical activity for patients. Physicians may refer to professionals such as exercise physiologists at a health club or a local YMCA.[18] It is important to ensure that the physical activity referral is given to a professional with appropriate credentials. It may be useful to inquire if the individual has the ACSM Registered Clinical Exercise Physiologist (RCEP) certification.[38] This is the gold standard for individuals prescribing physical activity and exercise. This certification identifies people who have a minimum of a Master's Degree in Exercise Science and 600 documented hours of experience in a variety of areas. This background ensures that patients will be effectively prescribed safe and effective physical activity. Individuals with the ACSM RCEP must also have CPR certification and pass extensive testing of their knowledge and skill levels.

14.16 BE A ROLE MODEL

Physicians should aspire to serve as role models in the area of physical activity for their patients. Numerous studies have shown that there is a strong relationship between a physician's lifestyle and health habits and his/her related counseling practices. This is true in a variety of areas, including smoking cessation, vaccination, and screening practices and for physical activity counseling as well. In fact, in 1 review including 24 studies, there was an 80% correlation between physicians' personal physical activity habits and their behaviors with regard to counseling patients about physical activity.[38] Moreover, a patient's perception of a physician's physical activity behaviors also may play a role in whether or not the patient engages in physical activity.[39]

Finally, there are emerging data that a physician's physical activity helps reduce the likelihood of burnout.[40–42] Burnout has been described as a "symptom of emotional exhaustion, loss of meaningful work, feelings of ineffective interactions with other human beings." Unfortunately, over half of U.S. physicians have reported experiencing substantial symptoms of burnout. In one study of 80 internal medicine residents, it was demonstrated that those meeting U.S. guidelines for physical activity were significantly less likely to experience burnout than those who failed to achieve recommended levels of physical activity.[40]

14.17 RESOURCES

A wide variety of resources are currently available to assist physicians in gaining knowledge of physical activity and transferring this information to their patients. The following are highly recommended.

- Physical Activity Guidelines for Americans 2018 Advisory Committee Scientific Report. This is available at https://health.gov/sites/default/files/201909/PAG_Advisory_Committee_Report.pdf
- American College of Lifestyle Medicine Annual Conference online CMEs and Resources (see curriculum available at LifestyleMedicine.org)
- Lifestyle Medicine Education Collaborative Curricula Resources Webinars (available at LifestyleMedicineEducation.org)
- Multiple ACSM books and other educational resources
- Materials from the Exercise Is Medicine initiative (available at https://www.exerciseismedicine.org/)

14.18 CONCLUSIONS

There is no longer any serious doubt that regular physical activity substantially lowers the risk of various chronic diseases and improves short- and long-term health and quality of life. Given that there is a low level of physical activity currently found in the general population of the United States, it is critically important that members of the healthcare community, and physicians in particular, become involved in recommending physical activity to all patients. Unfortunately, at the current time, only 40% of physicians include counseling on physical activity to their patients. A wide variety of resources are available to help physicians who wish to get started or become knowledgeable in this area. Physical activity is an important part of comprehensive healthcare. In addition, regular physical activity can confer a wide variety of benefits upon physicians themselves and will increase the likelihood that they will counsel on this very important area to their patients.

CLINICAL APPLICATIONS

Physical activity recommendations should be included in every counseling encounter by physicians.

Physicians should emphasize current guidelines for physical activity, such as obtaining 30 minutes of moderate or vigorous physical activity on most, if not all, days, with the goal of accumulating 150 minutes per week as well as two sessions of musculoskeletal exercises per week.

A wide variety of resources are available to help physicians to make proper physical activity recommendations to their patients.

Simple steps, such as making physical activity a part of vital signs, may help clinicians initiate a conversation with their patients to speak about increased physical activity. Utilization of the two question Stanford developed test outlined in this chapter can also assist in this process.

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15 Physical Fitness Evaluation

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KEY POINTS

- Lifestyle strategies play a significant role in both the prevention and treatment of cardiovascular disease.
- Physical fitness and more specifically, cardiorespiratory fitness is inversely related to the incidence of numerous chronic disease and all-cause mortality.
- Body composition is associated with health outcomes.
- Accurate evaluation of physical activity and body composition status is essential in risk assessment of patients.
- Counseling for physical activity and weight management should be a part of every healthcare visit to improve health outcomes.

15.1 DEFINITION OF PHYSICAL FITNESS

The Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) define physical fitness as "a set of physical attributes that people have or achieve that relates to the ability to perform physical activity."[1,2] These attributes have important implications for overall health, including one's ability to perform recreational or occupational activities, the determination of disability, injury prevention, and skeletal muscle, bone, and cardiovascular health. Moreover, higher fitness is strongly associated with better long-term health outcomes.[3,4] Engaging in proper physical training leads to an improvement in these physical attributes and physical fitness. The degree of improvement is determined by several factors, including training, diet, rest, psychological factors, and genetics.

15.2 AEROBIC AND ANAEROBIC FITNESS

The energy necessary to sustain life and perform work is extracted by the cells in one of two ways: with the use of oxygen and without oxygen. Historically, the utilization of oxygen to extract energy has been referred to as aerobic metabolism, and extracting energy without utilizing oxygen has been referred to as anaerobic metabolism.

However, it is important to note that muscle cells are never entirely aerobic or anaerobic. Rather, their energy requirements are met through the harmonious interaction of the two systems, with the energy contribution of each system depending largely on the intensity of activity. In general, high-intensity activities derive their energy mainly independently of oxygen, while low-intensity activities utilize oxygen to meet their energy requirements. Therefore, aerobic fitness refers to the ability to provide the required energy for a specific task in which the body's cardiopulmonary system adequately supplies the needed oxygen to the working muscle cells. Conversely, anaerobic fitness refers to the body's ability to provide the required energy for a specific task independently of oxygen. Aerobic activities consist of repetitive, low resistance movements (e.g. walking or cycling) that last over a relatively extended period of time (generally five minutes or more). Anaerobic activities, on the other hand, are characterized by bursts of intense activity lasting a comparatively short period of time (sprinting, lifting a heavy weight, jumping, etc.). It is important to emphasize that these two energy systems (aerobic and anaerobic) are almost always working together in a harmonious way, sharing the responsibility for providing the energy requirements for the working muscles and the entire body. However, one is likely to be the predominant system to provide most of the energy for the particular activity at hand.[5]

15.3 DETERMINING EXERCISE CAPACITY: DIRECT METHOD-OPEN-CIRCUIT SPIROMETRY

The "true" maximum aerobic capacity is the maximum amount of oxygen (referred to as maximal oxygen uptake or VO_2 max) the body can utilize during work. This is assessed in laboratories by *open-circuit spirometry*. VO_2 max is usually determined by a graded exercise test (GXT). A brief description and rationale for this procedure is as follows.

The individual breathes room air via a mouthpiece (nose occluded) or a face mask connected to an automated system (often termed a metabolic cart) by plastic tubes. The mouthpiece or mask is designed in such a way that it allows the measurement of the volume of expired air, while a small sample of the expired air enters the metabolic cart and is analyzed for its oxygen and carbon dioxide (CO_2) content. Oxygen uptake is determined by the product of ventilation and the difference between the O_2 content of the ambient and expired air. After resting samples are taken, the individual is subjected to a standardized exercise protocol on a treadmill or stationary bike. The exercise begins at a very low workload and increases progressively until volitional fatigue or until a clinical indication for stopping is reached. The rate of increase in external work depends on the exercise protocol used, but it is typically recommended that the test be individualized to last between 8 and 12 minutes.

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Since the relationship between the increase in workload and oxygen consumption is linear, oxygen requirements also increase. At some point, the individual reaches a volitional fatigue endpoint, and the test is terminated. This level is referred to as the maximal aerobic capacity of the individual. The oxygen utilized by the body at the point of fatigue is referred to as the VO_2 max. The measurement of VO_2 max implies that an individual's physiological limit has been reached. True VO_2 max has historically been defined by a plateau in VO_2 between the final two exercise work rates and requires that maximal effort be achieved and sustained for a specified period. Because this determination is subjective, can be difficult to define, and is rarely observed when patients with cardiovascular or pulmonary disease are tested, the term *peak* VO_2 is more commonly used clinically to express exercise capacity. Conversely, the term VO_2 *max* is more often used to describe exercise capacity in apparently healthy individuals, in whom achievement of a maximal physiological response is more likely. VO_2 max is expressed in milliliters of oxygen per minute (ml/min) or ml of oxygen per kilogram (kg) of body weight per minute (ml/kg/min). The latter is usually the preferred expression, since it allows comparisons between subjects of different weights.

The direct measurement of VO_2 max is most often used for research purposes and has a number of important clinical applications for patients with cardiovascular or pulmonary disease. However, it is not often practical for someone who simply wishes to know the appropriate exercise intensity during his or her training. For this purpose, exercise intensity can be easily determined by the heart rate (HR) that corresponds to the appropriate percentage of oxygen consumption. Since HR and oxygen uptake are continuously recorded during the metabolic test, one can easily match the desired percentage of HR to the corresponding oxygen consumption. The advantage of the direct method is that it is highly accurate. It allows an accurate assessment of the exercise intensity of an individual based on directly measured rather than estimated aerobic capacity. However, it is an elaborate method that requires expensive equipment and trained personnel and is, therefore, cost prohibitive for large populations. It is mostly used in individuals with specific clinical needs and for research purposes.[5]

15.4 DETERMINING AEROBIC FITNESS BY STANDARDIZED TESTS USING INDIRECT METHODS

The need for more practical methods to assess aerobic capacity for large populations led to the development of standardized exercise tests and the common practice of estimating energy requirements from different workloads. An indirect method for estimating the fitness level of an individual is based on the same principle as that for the direct assessment of VO_2 max, with one exception; oxygen consumption is not directly measured. Rather, it is estimated based on treadmill speed and grade utilizing equations derived from the direct assessment of VO_2 max. The actual procedure is similar to that described for the assessment of VO_2 max, with the exception that the individual is not connected to a metabolic cart (no breathing apparatus). While an ECG is monitored, the individual undergoes a standardized exercise protocol on a treadmill or stationary cycle ergometer. The most commonly used exercise protocols in the United States are described in Table 15.1, and these are discussed further later in the chapter. Exercise begins at a very low workload and increases every one to three minutes depending on the exercise protocol. The workload is determined by the speed and elevation of the treadmill, or the resistance if a cycle ergometer is used. HR is continuously monitored and recorded during the entire test, and blood pressure is recorded every two to three minutes.[2,5]

The O_2 consumption for each exercise stage is estimated based on regression equations for walking and running speeds. These equations were based on directly measured energy requirements at submaximal steady states (defined as a constant VO_2) and subsequently used to estimate VO_2 at maximal, non-steady-state work rates during a progressive exercise test.[2] This estimated metabolic demand for a given work rate has conventionally been expressed in metabolic equivalents (METs). One MET represents the amount of oxygen used during resting conditions (approximately 3.5 ml of oxygen per kg of body weight per minute). Thus, any increase beyond the 1-MET level represents higher total body oxygen consumption, directly associated with a higher workload. Based on this rationale, several standardized exercise protocols have been developed to assess the MET level of individuals for clinical and other reasons. The MET level achieved upon termination of the test (the individual reaches volitional fatigue) represents an estimate of the peak aerobic capacity of the individual. Because each MET is equal to approximately 3.5 ml O_2/kg/minute, VO_2 max can be estimated by multiplying the MET level achieved by 3.5.[2,5]. It is important to note that exercise capacity assessed by such exercise tests is in part related to the physical activity status of the individual. However, the ability to perform aerobic work is also determined by age and gender, as well as an important genetic component.[6,7]

As indicated, the regression equations developed to estimate VO_2 at each workload were based on directly measured energy requirements (VO_2) at submaximal steady states (defined as a constant VO_2) and subsequently used to estimate VO_2 at maximal, non-steady-state work rates during a progressive exercise test.[2,8,9]

However, the steady state assumed by these equations is influenced significantly by several factors, including the individual's age, health and fitness status, and walking efficiency and handrail use.[9,10] Therefore, the accuracy of the equation is compromised when applied to compute non-steady-state work rates. In addition, the most often used equations for walking and running speeds, referred to as the ACSM equations, are based on <100 young (19–26 years old) participants, a specific protocol, and were developed

TABLE 15.1

Measured and Estimated Oxygen Consumption Based on the American College of Sports Medicine (ACSM) and the Fitness Registry and the Importance of Exercise National Database (FRIEND) Equations (Mean ± Standard Deviation)

PROTOCOL	N	Age	Measured Maximal Oxygen Uptake	FRIENDMaximal Oxygen Uptake	% ErrorFRIEND	ACSMEquations[a]	% ErrorACSM
BALKE	353	54 ± 14	24.8 ± 8.5	25.0 ± 5.6	5.3 ± 17.8	29.9 ± 9.3	23.0 ± 19.6
BRUCE	936	40 ± 13	40.2 ± 11.1	38.4 ± 7.7	−1.7 ± 15.4	45.9 ± 9.0	17.6 ± 20.3
BRUCE-RAMP	2,224	48 ± 13	31.3 ± 9.6	33.8 ± 6.4	12.8 ± 21.0	42.0 ± 8.3	39.8 ± 26.4
RAMP	230	54 ± 16	26.3 ± 11.7	26.0 ± 9.7	4.3 ± 24.4	26.7 ± 14.0	1.8 ± 32.3
MODIFIED BALKE	108	56 ± 9	16.2 ± 2.8	16.0 ± 2.3	−0.8 ± 4.6	11.1 ± 3.3	−32.0 ± 5.1
MODIFIED BRUCE	38	53 ± 14	28.3 ± 9.7	29.3 ± 8.6	6.7 ± 20.0	35.1 ± 10.8	27.3 ± 24.9
MOD-NAUGHTON	407	57 ± 9	23.6 ± 5.3	23.7 ± 2.5	3.8 ± 17.1	26.5 ± 5.6	14.0 ± 16.1
MANNUAL-I	3017	43 ± 11	37.9 ± 10.7	37.5 ± 9.0	1.2 ± 14.2	42.9 ± 11.5	14.4 ± 17.2
MANNUAL-II	670	56 ± 15	20.4 ± 8.5	21.6 ± 7.8	9.1 ± 18.6	23.5 ± 10.2	15.8 ± 20.1
ENTIRE COHORT	7,983	47 ± 14	32.9 ± 11.8	33.3 ± 9.7	5.1 ± 18.3	39.0 ± 12.6	21.4 ± 24.9

[a]Walking and running speed equations were used.

nearly four decades ago. These factors contributed to the well-documented overestimation of VO_2 max (MET levels) by these equations during a progressive exercise test, especially at higher workloads.[9,11]

The ACSM equations for walking and running speeds are presented here.[2,9,12]

ACSM Walking Equation (Speed 1.9–3.7 miles per hour)
*VO_2 max = [Treadmill Speed (m/min) * 0.1 ml/kg/min] + Speed (m/min) * Treadmill Grade (decimal) * 1.8 ml/min/m] + 3.5 ml/kg/min*

The accuracy of the walking equation is best for treadmill speeds between 1.9 and 3.7 miles per hour or 50–100 m/min (1 mile/h = 26.8 m/min). Walking economy changes above this speed range, and the accuracy of the equation declines.

ACSM Running Equation (Speed >5.0 mph)
*VO_2 max = [Treadmill Speed (m/min) * 0.2 ml/kg/min] + Speed (m/min) * Treadmill Grade (decimal) * 0.9 ml/min/m] + 3.5 ml/kg/min*

Generally, the accuracy of the running equation is best for treadmill speeds >5 mph or 134 m/min. However, the height of the individual influences the speed at which one changes from walking to running. Thus, some individuals may choose to run at speeds as low as 3.7 mph.[12].

We recently developed new equations to estimate VO_2 max in apparently healthy adults and in patients with heart failure (HF) using directly measured VO_2 max instead of steady-state.[13,14] The equation for healthy individuals, referred to as the FRIEND Equation,[13] is based on 7,983 men (n = 4,798) and women (n = 3,183) aged ≥20 years (mean age 47 ± 13 years), who participated in The Fitness Registry and the Importance of Exercise National Database (FRIEND).

FRIEND Equation for Exercise Protocols Using Treadmill
*VO_2 max in ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ = Speed (m/min) * (0.17 + Fractional Treadmill Grade * 0.79) + 3.5*

Comparisons between the predicted values based on the ACSM equations and the FRIEND equation revealed that the ACSM equations overestimated VO_2 max, as previously reported,[2,9,12] with a percent error for the entire cohort of 21.4% (21.4 ± 24.9) versus 5% (5.1 ± 18.3) for the FRIEND equation. When different protocols were considered, the percent error ranged from –32.0 ± 5.1% to 39.8 ± 26.4%. In contrast, the percent error for the FRIEND equation ranged from 1.7 ± 15.4 to 12.8 ± 21.0 (Table 15.1).

15.5 FRIEND EQUATION FOR HF PATIENTS

The FRIEND equation for HF patients[14] was based on 1,453 patients (955 men; mean age ± standard deviation [SD] 56.8 ± 14.6 years and 498 women; mean age 52.1 ± 15.6 years). Treadmill speed and the interaction of treadmill speed and grade were again the main determinates of VO_2 max, with age and gender having only a minor impact. Gender-specific formulas did not yield substantially different findings, and therefore, one formula for men and women was developed.

The HF-specific formula for treadmill testing was as follows.

FRIEND Equation for HF Patients Using Treadmill
*VO_2 max (ml/kg/min) = Speed * (0:17 + Fractional Treadmill Grade * 0:32) + 3:5*
Where speed is in m/min (1 mile/h = 26.8 m/min)

To assess the external validity of the FRIEND equations for HF patients, we applied it to the HF-ACTION cohort (n = 1,612; mean age ± SD 58.6 ± 12.7 years), an NIH-sponsored multicenter, randomized controlled trial to evaluate the effect of medically supervised and home-based exercise training on cardiovascular outcomes in stable outpatients with HF and reduced ejection fraction.[15] The superiority of the FRIEND compared with the ACSM equations in predicting measured VO_2 max was evident regardless of the cohort, especially when applied to the FRIEND HF cohort (percent error 0.04 ± 20.7) (Table 15.2).

We also developed the following correction formula that allows the conversion of estimated METs using the ACSM equations to METs derived using the FRIEND equations.

*FRIEND METS = ACSM-Derived METs – (1.01 * Fractional Grade – 0.07) * Speed (m/min)/3.5*

15.6 PROTOCOLS

The purpose of the test and the person tested are important considerations in selecting the protocol. Exercise testing may be performed for diagnostic purposes, for functional assessment, or for risk stratification. An often ignored but nevertheless, consistent recommendation in the recent exercise testing guidelines is that the protocol is individualized for the patient being tested.[8,9,16] For example, a maximal, symptom-limited test on a relatively demanding protocol would not be appropriate (or very informative) for a severely limited patient. Likewise, a very gradual protocol might not be useful for an apparently healthy, active person. Use of submaximal testing, gas exchange techniques, the presence of a physician, and the exercise mode and protocol should be determined by considering the person being tested and the goals of the test.

Commonly used exercise protocols, their stages, and the MET level for each stage are outlined in Table 15.3. The most suitable protocols for clinical testing should include a low-intensity warm-up phase followed by progressive, continuous exercise in which the demand is elevated to a patient's maximal level within a total duration of 8 to 12

TABLE 15.2

Measured and Estimated Oxygen Uptake in Heart Failure Patients Based on the Fitness Registry and the Importance of Exercise National Database (FRIEND) and the American College of Sports Medicine (ACSM)* Equations (Mean ± SD)

A. FRIEND Cohort- Heart Failure

Exercise Mode	n	Age	Measured VO_2 max (mL/kg/min)	FRIEND VO_2 max (mL/kg/min)	% Error FRIEND	ACSM VO_2 max (mL/kg/min)	% Error ACSM
Treadmill (All)	1,453	55.2 ± 15.1	21.3 ± 6.3	20.8 ± 6.0	0.04 ± 20.7	28.0 ± 11.6	29.6 ± 36.3
Men	955	56.8 ± 14.6	21.8 ± 6.3	21.1 ± 6.1	-1.0 ± 19.8	28.5 ± 11.5	29.0 ± 34.5
Women	498	52.1 ± 15.6	20.5 ± 6.2	20.4 ± 5.9	2.0 ± 22.2	27.2 ± 11.6	30.7 ± 39.4

B. HF-ACTION study cohort

	n	Age	Measured $V0_2$ max (mL/kg/min)	FRIEND VO_2 max (mL/kg/min)	% Error FRIEND	ACSM VO_2 max (mL/kg/min)	% Error ACSM
All (Treadmill)	1,612	58.6 ± 12.7	15.3 ± 4.6	16.4 ± 2.9	14.2 ± 29.0	24.1 ± 6.0	63.7 ± 35.1
Men	1,195	59.5 ± 12.5	15.7 ± 4.7	16.5 ± 3.0	12.2 ± 28.6	24.4 ± 6.0	61.4 ± 34.2
Women	417	56.2 ± 12.9	14.2 ± 4.0	16.0 ± 2.5	20.1 ± 29.5	23.3 ± 5.6	70.2 ± 36.8

minutes.[8,9,16–19]. In the absence of gas exchange techniques, it is important to report exercise capacity in METs rather than exercise time, so that exercise capacity can be compared uniformly between protocols. METs can be estimated from any protocol using standardized equations that have been put into the tabular form.[8,9,20]. In general, 1 MET represents an increment on the treadmill of approximately 1.0 mph or 2.5% grade. On a cycle ergometer, 1 MET represents an increment of approximately 20 W (120 kgm/min) for a 70-kg person. The assumptions necessary for predicting MET levels from treadmill or cycle ergometer work rates (including not holding the handrails, that oxygen uptake is constant [i.e. steady-state exercise is performed], that the subject is healthy, and that all people are similar in their walking efficiency) raise uncertainties as to the accuracy of estimating the work performed for an individual patient. For example, the steady-state requirement is rarely met for most patients on most exercise protocols; most clinical testing is performed among patients with varying degrees of cardiovascular or pulmonary disease, and people vary widely in their walking efficiency.[20] It has therefore been recommended that a patient be ascribed a MET level only for stages in which all or most of a given stage duration has been completed.[21]

15.7 CYCLE ERGOMETER PROTOCOLS

Although there are specific bicycle protocols named for early researchers in Europe, such as Astrand,[22] bicycle ergometer protocols tend to be more generalized than the treadmill. For example, 15- to 25-W increments per 2-minute stage are commonly used for patients with cardiovascular disease, whereas for apparently healthy adults or athletic individuals, appropriate work rate increments might typically be between 40 and 50 W/stage. Most modern, electronically braked cycle ergometers have controllers that permit ramp testing, in which the work rate increments can be individualized in a continuous fashion (see next section).

15.8 VO_2 MAX ESTIMATIONS USING CYCLE ERGOMETRY

O_2 consumption estimations with cycle (leg) ergometry require knowing the work rate.

Work rate during leg ergometer exercise is computed in kg * meters per minute (kg * m/min). Another way to express work rate is in watts, calculated as follows:

$$\text{Watts} = \frac{\text{Kg} * \text{m/min}}{6.12}$$

15.8.1 Estimating Work Rate

To calculate work rate, one needs to know the distance the flywheel travels with each pedal revolution. This is not constant across the different bike manufacturers. Here, we provide the most common cycles in use and the distances per pedal revolution:

Monarch: 6 m per pedal revolution
Tunturi: 3 m per pedal revolution

The ACSM equation is:

$$VO_2 = 1.8\ (\text{Work rate/Body weight in kg}) + 3.5 + 3.5$$

or

$$VO_2 = 1.8\ (\text{Work rate/Body weight in kg}) + 7.0$$

- The 1.8 value represents the resistance imposed by the flywheel which is approximately 1.8 ml/kg/min.
- The first 3.5 represents the O_2 demand cycling at approximately 50–60 revolutions per minute without any resistance.
- The additional 3.5 represents the O_2 demand at rest.

TABLE 15.3
Commonly Used Treadmill and Bicycle Exercise Protocols

Stage	Minutes	Speed (MPH)	% Grade	METS
Bruce Protocol				
1	3	1.7	10	4.6
2	3	2.5	12	7.0
3	3	3.4	14	10.2
4	3	4.2	16	13.5
5	3	5.0	18	17.2
6	3	5.5	20	20.4
7	3	6.0	22	23.8
Modified Bruce				
1	3	1.7	0	2.3
2	3	1.7	5	3.5
3	3	1.7	10	4.6
4	3	2.5	12	7.0
5	3	3.4	14	10.2
6	3	4.2	16	13.5
7	3	5.0	18	17.2
8	3	5.5	20	20.4
9	3	6.0	22	23.8
Balke-Ware				
1	3	3.3	1	4.0
2	3	3.3	2	4.4
3	3	3.3	3	4.9
4	3	3.3	4	5.3
5	3	3.3	5	5.8
6	3	3.3	6	6.3
7	3	3.3	7	6.7
8	3	3.3	8	7.2
9	3	3.3	9	7.6
10	3	3.3	10	8.1
11	3	3.3	11	8.5
12	3	3.3	12	9.0
13	3	3.3	13	9.4
14	3	3.3	14	9.9
15	3	3.3	15	10.3
16	3	3.3	16	10.8
17	3	3.3	17	11.3
18	3	3.3	18	11.7
19	3	3.3	19	12.2
20	3	3.3	20	12.6
21	3	3.3	21	13.1
22	3	3.3	22	13.5
23	3	3.3	23	14.0
24	3	3.3	24	14.4
25	3	3.3	25	14.9
26	3	3.3	26	15.4

(Continued)

TABLE 15.3 (CONTINUED)
Commonly Used Treadmill and Bicycle Exercise Protocols

Stage	Minutes	Speed (MPH)	% Grade	METS
Balke				
1	2	3.0	2.5	4.3
2	2	3.0	5	5.4
3	2	3.0	7.5	6.4
4	2	3.0	10	7.4
5	2	3.0	12.5	8.5
6	2	3.0	15	9.5
7	2	3.0	17.5	10.5
Naughton				
1	2	1	0	1.8
2	2	2	0	2.5
3	2	2	3.5	3.5
4	2	2	7.0	4.5
5	2	2	10.5	5.4
6	2	2	14.0	6.4
7	2	2	17.5	7.4
8	2	2	21.0	8.3
Standard Bicycle Protocol				
1	2 or 3	50	150	25
2	2 or 3	50	300	50
3	2 or 3	50	450	75
4	2 or 3	50	600	100
5	2 or 3	50	750	125
6	2 or 3	50	900	150

15.8.2 Limitations of the ACSM Equation

It is important to know that the ACSM equation is based on O_2 values measured directly at steady state. Thus, the accuracy of the equation deteriorates progressively at higher work rates. Relatively acceptable accuracy is maintained at work rates between 300 and 1200 kg * m/min or 50–200 watts.

15.9 THE FRIEND EQUATION

Recently, we developed a new equation for estimating VO_2 using cycle ergometry based on 5,100 (3,378 men; mean age 35.9 ± 12.1 years and 1,722 women; mean age 47.5 ± 14.0 years) of the Fitness Registry and the Importance of Exercise National Database. The ACSM equation overestimated VO_2 max for both men and women with an overall relative bias of 15.46% ± 0.13. In contrast, the FRIEND-ergometry equation predicted VO_2 max with an overall relative bias of 0.51% ± 0.11 (Table 15.4).[23]

The non-gender-specific equation is as follows:

FRIEND Equation for predicting VO_2 max using Cycle Ergometer
Men
*VO_2 max in ml O_2/kg/min = 1.76 * (watts * 6.12/body weight [kg]) + 3.5*
Women
*VO_2 max in ml O_2/kg/min = 1.65 * (watts * 6.12/body weight [kg]) + 3.5*
The non-gender-specific equation:
*VO_2 max in ml O_2/kg/min = 1.74 * (watts * 6.12/body weight [kg]) + 3.5*

TABLE 15.4
Measured and Estimated Oxygen Consumption

	Measured maximal oxygen uptake	FRIEND maximal oxygen uptake		Gender-specific FRIEND maximal oxygen uptake		ACSM formula maximal oxygen uptake	
	Mean (SD)	Mean (SD)	Relative bias, % (SD)	Mean (SD)	Relative bias, % (SD)	Mean (SD)	Relative bias, % (SD)
Entire cohort (n = 5100)							
Men (n = 3378)	42.43 (9.57)	41.94 (9.33)	–0.78 (0.09)	42.39 (9.44)	0.26 (0.09)	46.77 (9.65)	11.23 (0.10)
Women (n = 1722)	23.25 (10.01)	24.01 (10.81)	3.04 (0.13)	22.95 (10.25)	–1.37 (0.12)	28.22 (11.18)	23.77 (0.15)
All (n = 5I00)	35.95 (13.30)	35.89 (13.00)	0.51 (0.11)	35.82 (13.38)	–0.29 (0.10)	40.51 (13.45)	15.46 (0.13)
Validation using 30% of the cohort (n =1530)							
Men (n = 1133)	42.30 (9.81)	41.84 (9.58)	–0.77 (0.09)	42.28 (9.69)	0.27 (0.09)	46.66 (9.91)	11.34 (0.10)
Women (n = 625)	23.06 (9.91)	23.81 (10.7)	3.04 (0.13)	22.76 (10.15)	–1.37 (0.13)	28.01 (11.07)	23.83 (0.15)
All (n = 1758)	35.46 (13.48)	35.43 (13.2)	0.59 (0.11)	35.34 (13.58)	–0.31 (0.1)	40.03 (13.66)	15.78 (0.13)

Measured and estimated oxygen consumption based on the American College of Sports Medicine (ACSM)* and the Fitness Registry and the Importance of Exercise National Database (FRIEND) equations (mean ± standard deviation).

The overestimation of METs by the ACSM equation can be corrected by the following formula:

*ACSM-derived METs – 0.06 * (watts * 6.12/kg) – 3.5*

15.10 RAMP TESTING

An approach to exercise testing that has gained interest in recent years is the ramp protocol, in which work increases constantly and continuously. In 1981, Whipp and colleagues[24] first described cardiopulmonary responses to a ramp test on a cycle ergometer, and many of the gas exchange equipment manufacturers now include ramp software. Treadmills have also been adapted to conduct ramp tests.[19,25,26] The ramp protocol uses a constant and continuous increase in metabolic demand that replaces the "staging" used in conventional exercise tests. The uniform increase in work allows a steady increase in cardiopulmonary responses and permits more accurate estimation of oxygen uptake.[19] The recent call for "optimizing" exercise testing[8,14,16,19] would appear to be facilitated by the ramp approach, because large work increments are avoided, and increases in work are individualized, permitting test duration to be targeted. Because there are no stages per se, the errors associated with predicting exercise capacity alluded to previously are lessened.[8,9,19]

15.11 SUBMAXIMAL TESTING

In general, maximal, symptom-limited tests are not considered appropriate until one month after myocardial infarction (MI) or cardiac surgery. Thus, submaximal exercise testing has an important role clinically for pre-discharge, post-MI, or post-bypass surgery evaluations. Submaximal tests have been shown to be important in risk stratification,[26–29] for making appropriate activity recommendations, for recognizing the need for modification of the medical regimen, or for further interventions in patients who have sustained a cardiac event. A submaximal, pre-discharge test appears to be as predictive for future events as a symptom-limited test among patients less than one month after MI. Submaximal testing is also appropriate for patients with a high probability of serious arrhythmias. The testing endpoints for submaximal testing have traditionally been arbitrary but should always be based on clinical judgment. A heart rate limit of 140 beats per min and a MET level of 7 are often used for patients younger than age 40 years, and limits of 130 beats per min and a MET level of 5 are often used for patients older than 40 years. For those using beta-blockers, a Borg perceived exertion level in the range of 7 to 8 (1 to 10 scale) or 15 to 16 (6 to 20 scale) is a conservative endpoint. The initial onset of symptoms, including fatigue, shortness of breath, or angina, is also an indication to stop the test. A low-level protocol should be used, that is, one that uses no more than 1-MET increments per stage. The Naughton protocol[30] is commonly used for submaximal testing. Ramp testing is also ideal for this purpose, because the ramp rate (such as 5 METs achieved over a ten-minute duration) can be individualized depending on the patient tested.[19]

Submaximal testing can also be used to assess the capacity of apparently healthy individuals to exercise safely or to estimate VO_2 max by extrapolation. The premise of estimating VO_2 max from a submaximal test is based on the linear relationship between HR and oxygen consumption, provided that the work is aerobic in nature. In submaximal test protocols, the HR at each workload is plotted against the workload and extrapolated to VO_2 max at an age-predicted maximal heart rate (typically 220 – age). VO_2 max can be calculated using prediction equations[2] or estimated from values obtained by commonly used exercise protocols if the following assumptions are met: 1) the workload is reproducible; 2) a steady-state HR is obtained during each stage; and 3) a linear relationship exists between HR and oxygen consumption over a wide

range of values. Examples of submaximal tests used to estimate peak VO_2 include the YMCA test, the Astrand test, and others.[22,31,32]

15.12 WALK TESTS FOR CARDIORESPIRATORY FITNESS ASSESSMENT

A number of walking tests have also been developed for estimating cardiorespiratory fitness or assessing the functional status of patients with cardiovascular or pulmonary disease in clinical settings. Advantages of walk tests include the fact that they are easy to perform and are relatively inexpensive, and thus, can be applied to large populations. These include: 1) the 6-minute walk test; 2) the Cooper 12-minute test; 3) the 1.5-mile test; and the 4) Rockport One-mile Fitness Walking Test.[2]

The six-minute walk test is popular for assessing functional status in clinical settings and is mostly used among diseased populations, such as patients with HF, stroke, and peripheral vascular disease. The objective of the test is to cover the greatest possible distance by walking in six minutes. Its obvious advantages are that it requires practically no equipment (other than a stopwatch) and little time.

Although the association between six-minute walk performance and exercise capacity is only modest, peak VO_2 can be estimated from six-minute walk distance by the following multivariate equation along with other readily available information:

$$Peak\ VO_2 = (0.02 * distance\ [m]) - (0.191 * age\ [yr]) - (0.07 * weight\ [kg]) + (0.09 * height\ [cm]) + (0.26 * RPP\ [*10^{-3}])$$

m = meter; kg = kilogram; cm = centimeters; yr = years

RPP = rate pressure product (systolic blood pressure [mm Hg] * heart rate)

The Cooper 12-minute test is based on a similar concept (covering the greatest distance in 12 minutes), while the objective of the 1.5-mile test is to run the distance (1.5 miles) in the shortest period of time. Unlike the six-minute walk test, both of these tests are more suitable for healthy, younger individuals. They also require little or no additional equipment and can be administered to large populations.

The Rockport One-mile Fitness Walking Test involves covering a 1-mile distance in the shortest period of time. However, in addition to the time required to cover the 1-mile distance, the test utilizes peak HR achieved during the last minute of the walk, and an estimate of peak VO_2 is derived. If HR monitoring is not an option during the test, a 10-second HR obtained immediately after the completion of the test can be used as an alternative. However, this is likely to overestimate peak VO_2 compared with that calculated when HR is obtained during the last minute of the walk.

15.13 NON-EXERCISE-TEST ESTIMATES OF CARDIORESPIRATORY FITNESS

The recent call for the inclusion of fitness as a clinical vital sign[33] has placed a renewed focus on non-exercise-test methods to estimate cardiorespiratory fitness (CRF). This is because although CRF has been increasingly recognized as a critical factor in stratifying risk, objective measures of CRF are rarely available during a routine clinical encounter. Thus, the ability to estimate CRF without performing a formal exercise test is attractive, because it can be obtained quickly and inexpensively without exposing an individual to the risk and discomfort of an exercise test. Many non-exercise-test-based equations have been proposed using commonly available information during a typical clinic visit. Non-exercise-test regression equations have typically included age, gender, body mass index (BMI), and self-reported physical activity patterns, although many other health metrics have been employed. In addition to being quick and simple to obtain, these equations have a surprisingly robust correlation with objective fitness measures, typically in the range of 0.50 to 0.80, and they have also been reported to strongly predict outcomes.[34–44] However, limitations of these tools include the fact that they are subjective and that they lack the ability to assess symptoms, ECG, and hemodynamic responses that are available during a formal exercise test. In addition, they tend to underestimate and overestimate CRF at the upper and lower end of the distribution, respectively.

A systematic review of this issue was performed using 13 non-exercise-test equations developed using various combinations of age, gender, body weight (or BMI, percentage of body fat, or waist circumference), physical activity patterns (self-reported or measured), smoking, resting heart rate, or perceived functional ability as predictors of CRF.[37] The R^2 values (with measured or estimated peak VO_2 as the dependent variable) ranged from 0.50 to 0.86. Non-exercise CRF estimates have been shown to be similar in accuracy to submaximal exercise prediction models.[3738,43,44] Although most of these studies have focused on healthy asymptomatic populations, non-exercise-test approaches that include assessment of symptoms during daily activities are more applicable to clinically referred populations. The latter include the Veterans Specific Activity Questionnaire (VSAQ) and Duke Activity Status Index (DASI) and similarly correlate well with measured exercise capacity.[34,35]

Estimates of CRF using these tools have also been shown to provide valid estimates of long-term risk, including mortality.[37,38,43–46] The VSAQ combines a one-page assessment of symptoms during daily activities with age, and was shown to correlate strongly with exercise capacity determined on a treadmill test (multiple R = 0.82). McAuley et al.[40] performed a follow-up study in a group of veterans referred for exercise testing for clinical reasons, who were followed for a mean of 4.5 years. Expressed in tertiles, age-adjusted relative risks for all-cause mortality using the VSAQ were 1.0 (low CRF, referent), 0.54 (moderate CRF),

and 0.22 (low CRF) (p for trend <0.001). Each 1-MET increase in the VSAQ conferred a 10% survival benefit. Similarly, the DASI was developed in a cohort of consecutive subjects undergoing exercise testing for clinical reasons and consists of a 12-item scale related to a patient's ability to perform daily activities. The DASI has been shown to be strongly correlated with peak VO_2 (r = 0.80), and studies have reported it to be a good predictor of risk for adverse outcomes in a variety of populations.[35,48,49] Both the VSAQ and DASI have been widely used both to estimate exercise capacity and to estimate long-term risk in a wide range of clinical populations, and both have been translated into several languages.[34,36,47–52]

In a combined analysis using 8 British cohorts that included 32,319 individuals, a non-exercise-test estimate of CRF was performed using age, gender, BMI, resting heart rate, and self-reported physical activity level.[45] Cardiovascular disease (CVD) and all-cause mortality were determined over a mean of nine years, and 9.4% and 7.4% lower risks of all-cause and 15.6% and 16.9% lower risks of CVD death per 1-MET increase were observed in men and women, respectively. In the Norwegian HUNT study,[39] a similar algorithm was used to estimate CRF among 37,112 individuals who were followed for a mean duration of 24 years. After adjustment for potential confounders, each 1-MET higher CRF was associated with 21% lower CVD mortality for both men and women who were younger than 60 years at baseline; the corresponding lower risks for all-cause mortality were 15% for men and 8% for women. Thus, although these non-exercise-test estimates of CRF are likely population specific and should not be viewed as a replacement for an exercise test when it is clinically necessary, they provide the clinician with a platform for counseling a patient regarding the importance of physical activity. When an exercise test is unavailable or impractical, they also serve to identify individuals with low CRF who are at increased risk.

15.14 MUSCULAR FITNESS

The ACSM defines muscular fitness as the ability of the muscle to perform tasks that require muscular strength or muscular endurance. Strength is an important component of fitness assessment, since it has implications for an individual's functional capabilities, disability, bone health, and insulin resistance, and has been shown to have a strong association with long-term outcomes.[53]

15.14.1 Muscular Strength

Muscular strength is defined as the ability of the muscle or muscle groups to exert force during a voluntary contraction.[1] The maximal force a muscle or group of muscles can exert is traditionally assessed by tests that require maximum effort against the greatest resistance at which one can move through the full range of motion once. This is known as the 1-repetition maximum (1-RM). A percentage of the 1-RM is then used to determine the number of repetitions one should perform to enhance the strength for a specific muscle. Generally, 8–12 repetitions at 40% to 60% of 1-RM are sufficient to enhance muscular strength. An appropriate resistance training regimen involves performing these 8–12 repetitions 1–3 times, 2–3 times per week. While intensities as high as 80% and relatively low numbers of repetitions (such as three to five) have been shown to be quite effective for rapid strength gains, this approach is generally limited to athletes whose performance requires great amounts of force.

It is important to note that intensity for resistance exercise is not always easy to determine, and the 1-RM does not depict a true intensity. The number of repetitions and the percentage of resistance based on 1-RM differ significantly between individuals and muscle groups. Thus, the 1-RM should only be used as a general guideline.[2]

15.14.2 MUSCULAR ENDURANCE

Muscular endurance is defined as the ability of the muscle or muscle groups to perform repetitive contractions over a period of time against resistance, such as lifting a set amount of weight several times.[2] Muscular endurance is assessed by tests requiring more than 12 repetitions. A simple test of muscular endurance is the maximum number of push-ups or sit-ups one can execute without rest.[2]

15.14.3 Tests of Anaerobic Power

Because *anaerobic* power is an important determinant of athletic performance requiring high levels of exertion over short periods, tests have been developed to measure the capacity of the anaerobic energy systems. One of the more common tests of this type is the *Wingate* test, which involves 30 to 120 seconds of high-intensity effort on a cycle ergometer. The resistance is based on body mass (originally 0.075 kp per kg body mass, though this may vary) and is applied after initial inertia and unloaded resistance are overcome. *Peak power* is considered to represent the highest mechanical power generated during any three- to five-second period during the test; *average power* is the average of the total power generated during the test. An underlying assumption of the Wingate test is that peak power reflects the energy-generating capacity of the oxygen-independent high energy phosphates, whereas average power is a representation of one's glycolytic capacity.[54,55] In studies comparing the Wingate test results with athletic performance and laboratory findings, it has been demonstrated to be a good index of these energy systems, although studies are mixed in terms of its ability to predict success in events requiring high exercise intensity.[55]

15.15 BODY COMPOSITION

In the United States and most of the industrialized world, obesity has reached epidemic proportions.[56] Overweight

and obesity are not simply cosmetic problems, but serious health conditions. They are both considered to be leading risk factors for a number of chronic health conditions, including diabetes, hypertension, coronary heart disease, and premature mortality, in developed countries. Although the mechanisms and causes of obesity are poorly understood, experts agree that obesity is largely the result of a chronic imbalance between caloric intake and caloric expenditure. This imbalance is likely the outcome of a complex interaction between genetic and environmental factors.[57]

15.15.1 Definition, Assessment, and Classification of Overweight and Obesity

Body composition is comprised of three major structural components: muscle, bone, and fat. Obesity is defined as the accumulation of excess body fat, usually ≥25% of the total body weight for men and ≥33% for women.[58] Assessing body fat is not a simple task. Several methods have been developed with mixed success. The most commonly used methods and their strengths and weaknesses are presented in the following subsections.

15.15.2 Hydrodensiometry or Underwater Weighing

One of the historically common assessments of body composition is hydrodensiometry or underwater weighing. This method is based on Archimedes' principle, which states that the weight an object loses when immersed in water is equal to the weight of the displaced water resulting from that immersion. The method is still widely used, but is less common today given the advent of DEXA and the fact that it is highly dependent on proper technique.

Percent body fat is estimated from body density, knowing that lean mass (bone and muscle) is denser than body fat. The density of fat is estimated to be 0.90 g/cm^{-3} and 1.10 g/cm^{-3} for fat free tissue.[59,60]

The following two most commonly used equations for estimating body composition from underwater weighing were developed in the late 1950s and early 1960s[59, 60] and are still in use:

$$\% \text{ Body fat} = (495/\text{Body density}) - 450^{57} \text{ (Siri)}$$

$$\text{Body fat} = (457/\text{Body density}) - 414.2^{58} \text{ (Brozek)}$$

For example, if a person weighs 100 kg on land and 5 kg submerged in water, the body density of this person is computed as mass divided by volume:

$$\text{Body density} = 100{,}000 \text{ g}/95{,}000 \text{ cm}^3 = 1.0526$$

Percent body fat is then calculated by the two formulas as follows:

$$\text{Percent body fat} = (495/1.0526) - 450$$
$$= 470.26 - 450 = 20.26$$
$$\text{Percent body fat} = (457/1.0526) - 414.2$$
$$= 434.16 - 414.2 = 19.96$$

Lean body mass (LBM) is then calculated by subtracting body fat from total body weight. Thus, the LBM of this individual weighing 100 kg is approximately 80 kg.

Please note that body density is inversely related to the water temperature. Body density at 4 degrees C or 39.2 degrees F is 1.0 and declines as water temperature increases. For practical reasons, warmer temperatures are generally used to perform underwater weighing, and the appropriate density value for that water temperature is applied.

It is also important to emphasize that the generalized density values of 1.10 for fat free (1.10 g/cm^{-3}) and fat (0.90 g/cm^{-3}) are based on young and middle-aged white men. The density of LBM is higher for blacks (1.113) than whites. This leads to an overestimation of LBM and underestimation of body fat for blacks. Thus, the following modification of the Siri formula has been proposed for blacks:

$$\text{Percent body fat} = (437.4/\text{Body density}) - 392.8^{56}$$

15.15.3 Other Methods

Direct assessment of body fat by densitometry is one of the most accurate methods, but it is generally not practical for large populations. Thus, several indirect techniques have been developed over the years to assess body composition. The most commonly used methods for estimating or assessing body composition and their advantages and disadvantages are described in Table 15.5.[5]

Because direct body fat assessment is impractical for large populations, the American Heart Association (AHA) and other health organizations have adopted BMI as a practical clinical indicator of adiposity.[57] BMI, calculated as weight (kg) divided by height (m) squared (kg/m^2), correlates well with total body fat and is related to cardiovascular and all-cause mortality.[61–63] The estimated BMI for different weights and heights is presented in Table 15.6.

A set of cut-points at five BMI intervals to classify overweight and obesity have been adapted by the National Heart, Lung, and Blood Institute and the World Health Organization.[58] Based on this classification, men and women with a BMI ≥30 kg/m^2 are considered obese (Table 15.7). However, it is important to keep in mind that BMI may not accurately reflect true adiposity for some populations. For example, a relatively muscular male weighing 100 kg, 1.80 m in height and with approximately 20% actual body fat, has a BMI of 30.86 (BMI = 100/1.80^2). Conversely, a male 1.80 m tall, weighing 80 kg, with 30% actual body fat, has a BMI of 24.7. According to the classification system commonly used (Table 15.7), these individuals will be misclassified as obese and normal weight, respectively.[5]

TABLE 15.5
Various Methods of Assessing Body Composition

Method/Techniques	Method of Assessment	Advantages	Disadvantages
Densitometry from Underwater Weighing	Subject fully exhales all air. Then, he/she is submersed in water for only a few seconds. Weight is assessed under water.	It is based on Archimedes' Principle. This method computes percentage body fat from body density (body mass/ body volume).	Expensive and time consuming. Requires a laboratory equipped with a water tank and trained personnel. It also requires that individuals exhale forcefully to reduce all possible air from lungs. Then, they are submersed in water for several trials, each lasting several seconds. This may not be tolerated well by some subjects, who will either not undergo the procedure or make it difficult to obtain an accurate reading.
Dual-Energy X-Ray Absorptiometry (DXA)	Uses two low energy distinct X-ray beams that penetrate bone and soft tissue areas to the depth of 30 cm. Computer software reconstructs the attenuated beams and produces an image of the tissues that can be used to quantify muscle and fat mass.	Quick, takes approximately 12 minutes to complete, and correlates very highly with densitometry. Total body mass or regional tissue mass can be assessed.	Expensive, requires trained personnel.
Bod-Pod	Relatively new procedure that uses an elliptical-shaped box that the subject sits in. It is based on air displacement plethysmography.	Quick, takes approximately three to five minutes, and has high reproducibility. Does not require any special skills by technician.	Expensive. Claustrophobia may be an issue with some participants.
Magnetic Resonance Imaging (MRI)		Can distinguish between changes in muscle mass and fat. Good for studies designed to assess changes in muscle mass (i.e., resistance [weight] training).	Very expensive, requires highly trained technicians. Cost prohibitive for large cohort studies.
Bioelectrical Impedance	A light current is introduced to the individual. Body fat is estimated by opposition to current flow.	Quick, relatively inexpensive.	Tends to overpredict body fat. Requires trained personnel and standardized conditions (hydration, environmental temperature) that may not be possible in all situations.
Skinfolds	Requires a caliper that measures body fat at standardized anatomical body sites.	Relatively easy and inexpensive to perform (requires a caliper). No special laboratory required other than a room for some privacy. Time requirements are only a few minutes per subject, thus allowing large numbers of individuals to be processed.	Skilled and experienced personnel are required.
BMI	Weight and height are needed.	The simplest and least expensive method, requiring only the weight (kg) and height (m) of the individual.	It is only an index of body dimensions. It does not measure body fat, but only assumes that higher BMI translates to higher body fat content. This may or may not be true and can vary greatly for different populations.
Waist circumference and waist-hip ratio	Measurements of waist and hip circumference.	Simple, inexpensive and relatively quick to perform.	Both waist circumference and the waist-to-hip ratio are indices of body composition. They do not measure body fat. However, they both provide an index of fat distribution.

TABLE 15.6
Body Mass Index (BMI) Based on Weight and Height

	Body Weight (lbs)													
Height (inches)	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**	**250**
58	25	27	29	31	33	36	38	40	42	44	46	48	50	52
59	24	26	28	30	32	34	36	38	40	42	44	46	48	50
60	23	25	27	29	31	33	35	37	39	41	43	45	47	49
61	23	25	26	28	30	32	34	36	38	40	42	43	45	47
62	22	24	26	27	29	31	33	35	37	38	40	42	44	46
63	21	23	25	27	28	30	32	34	35	37	39	41	43	44
64	21	22	24	26	27	29	31	33	34	36	38	39	41	43
65	20	22	23	25	27	28	30	32	33	35	37	38	40	42
66	19	21	23	24	26	27	29	31	32	34	36	37	39	40
67	19	20	22	23	25	27	28	30	31	33	34	36	38	39
68	18	20	21	23	24	26	27	29	30	32	33	35	36	38
69	18	19	21	22	24	25	27	28	30	31	32	34	35	37
70		19	20	22	23	24	26	27	29	30	32	33	34	36
71		18	20	21	22	24	25	26	28	29	31	32	33	35
72		18	19	20	22	23	24	26	27	28	30	31	33	34
73			18	20	21	22	24	25	26	28	29	30	32	33
74			18	19	21	22	23	24	26	27	28	30	31	32
75				19	20	21	22	24	25	26	27	29	30	31
76				18	19	21	22	23	24	26	27	28	29	30
77				18	19	20	21	23	24	25	26	27	28	30

TABLE 15.7
Classification of Body Weight and Obesity Based on BMI and Waist Circumference

	Obesity Class	BMI (kg/m²)	Waist Circumference (cm)	Associated Health Risk
Underweight		<18.5		
Normal		18.5–24.9		Average
Overweight		25.0–29.9	Men: ≥94Women: ≥80	Increased
Obesity	I	30.0—34.9	Men: ≥102Women: ≥102	Moderate
Moderate Obesity	II	35.0–39.9		High
Severe Obesity	III	≥40		Very High

BMI <18 is not recommended, and therefore, these values are not represented in this table.
Source: Jakicic, J.M. et al. *Med. Sci. Sports Exerc.*, 33(12), 2145–2156, 2001.

15.15.4 Waist Circumference

Evidence supports the concept that excess accumulation of adipose tissue in the abdomen, characteristic of male type fat distribution (android, abdominal, or central obesity), is associated with a higher risk for mortality than peripheral distribution of body fat.[65] This is because fat that surrounds the internal organs, known as *visceral fat*, is most closely associated with metabolic disorders that increase cardiovascular risk, including insulin resistance, lipid abnormalities, and heightened markers of inflammation. Since BMI also fails to take body fat distribution into account, waist circumference provides a practical method for assessing mortality risk associated with central distribution of fat if a direct body fat assessment is not available. Waist circumference correlates more strongly with abdominal fat than BMI. Waist circumferences >102 cm for men and >88 cm for women are associated with increased cardiovascular risk.[66,67]

15.15.5 Skinfold Assessment

Body composition estimated by skinfold measurements is based on the premise that approximately one-third of the total body fat is subcutaneous fat and the remaining is visceral fat. Thus, skinfold thickness parallels total body fat and is another method often used to estimate body

composition. Because proportionally more fat is deposited viscerally with advancing age, age-adjusted equations should be used in older men and women. Assuming that the appropriate technique is used and factors that contribute to measurement error are controlled, the technique correlates fairly well with hydrodensiometry (r = 0.70 to 0.90). Accuracy is also compromised with extremely obese or extremely lean individuals.

Over the years, several sites and techniques have been identified and used to assess body composition via skinfolds. A thorough review of anthropometric assessments related to skinfolds is recommended for those interested in a more detailed description of this methodology.[68] These techniques are also reviewed in the ACSM Guidelines for Exercise Testing and Prescription.[2]

CLINICAL APPLICATIONS

The main objective of this chapter is to provide an overview of the procedures and techniques applied to assess physical fitness, which includes cardiorespiratory fitness, muscular strength, muscular endurance, and body composition.

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16 Exercise Prescription for Apparently Healthy Individuals and for Special Populations

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KEY POINTS

- Those who regularly practice physical activity carry a lower risk of premature mortality and of contracting several of the most prevalent chronic diseases, including cardiovascular disease, type 2 diabetes, and several cancers. Functional abilities are also likely to be preserved to an older age.
- It is recommended that adults participate in 150–300 minutes of moderate-intensity physical activity, or 75–150 minutes of vigorous-intensity physical activity, per week. Muscle-strengthening exercise should also be practiced on two to three days per week. Balance exercise should also be included for those who may be at risk of falling.
- These guidelines can be met though varying combinations of frequency, intensity, and duration. Enjoyable modes of physical activity should be chosen in order to enhance adherence.
- Everyone should be physically active. If these guidelines cannot be met due to disease or frailty, they should be attained to the best of a person's ability.
- It is considered safe for persons not possessing and without signs and symptoms of cardiovascular, metabolic, or renal disease to participate in moderate-intensity physical activity and if desired, to gradually progress to vigorous-intensity physical activity without prior medical clearance.

16.1 INTRODUCTION

The proper practice of physical activity has become increasingly recognized as an important means of optimizing one's health. Tables 16.1 and 16.2 list the currently documented health benefits of physical activity.[1] *Physical activity* is defined as "any bodily movement that is produced by the contraction of skeletal muscle and that increases energy expenditure above a basal level."[2] *Exercise*, on the other hand, is a more strictly defined subset of physical activity that is "planned, structured, repetitive, and performed with the goal of improving health or fitness" (e.g., cardiorespiratory endurance, muscular strength).[2] Increases in both exercise and overall physical activity can maintain and improve health. Accordingly, this chapter will 1) review the current recommendations for physical activity, 2) discuss prescription of both fitness-oriented exercise and overall physical activity, and 3) discuss prudent alterations to the normal exercise prescription in some of the more prevalent clinical populations.

16.2 PHYSICAL ACTIVITY RECOMMENDATIONS

In 2018, the U.S. Department of Health and Human Services (DHHS) released the second edition of its *Physical Activity Guidelines for Americans*.[2] Using mostly the same evidence base, the World Health Organization (WHO) released its *Guidelines on Physical Activity and Sedentary Behaviour* in 2020.[3] Both these documents provide minor adjustments to their respective recommendations published in 2008 and 2010 and discuss the growth of the evidence base of physical activity's health-based contributions. For adults aged 18 to 64, 150 weekly minutes of moderate-intensity aerobic activity are advocated, with recognition that increasing benefits are likely to accrue through at least 300 minutes per week. Alternatively, 75 to 150 minutes of vigorous-intensity aerobic activity can be performed to amass similar benefits (*moderate-* and *vigorous-intensity* aerobic activity are defined and discussed later). A combination of moderate- and vigorous-intensity activity may also be employed. In addition, resistance training involving all major muscle groups is recommended at least twice weekly. Additional recommendations for children, the elderly, and other special populations are discussed later in this chapter.

As mentioned, both sets of *Guidelines* provide minor adjustments to their earlier reports. Regarding the *accumulation* of moderate-to-vigorous intensity physical activity, there is no longer a premise that only activity bouts of 10 minutes or longer are recognized as being beneficial to health. Newer evidence indicates that moderate-to-vigorous bouts of any time length that are included in one's weekly total lead to health benefits. In addition, there is no *threshold* amount of physical activity needed to produce health benefits. Although not optimal,

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TABLE 16.1
Documented Health Benefits of Physical Activity – General Population

Children	
3 to <6 years of age	Improved bone health and weight status
6 to 11 years of age	Improved cognitive function (ages 6 to 13 years)
	Improved cardiorespiratory and muscular fitness
	Improved bone health
	Improved cardiovascular risk factor status
	Improved weight status or adiposity
	Fewer symptoms of depression
Adults, All Ages	
All-cause mortality	Lower risk
Cardiometabolic conditions	Lower cardiovascular incidence and mortality (including heart disease and stroke)
	Lower incidence of hypertension
	Lower incidence of type 2 diabetes
Cancer	Lower incidence of bladder, breast, colon, endometrium, esophagus, kidney, stomach, and lung cancers
Brain health	Reduced risk of dementia
	Improved cognitive function
	Improved cognitive function following bouts of aerobic activity
	Improved quality of life
	Improved sleep
	Reduced feelings of anxiety and depression in healthy people and in people with existing clinical syndromes
	Reduced incidence of depression
Weight status	Reduced risk of excessive weight gain
	Weight loss and the prevention of weight regain following initial weight loss when a sufficient dose of moderate-to-vigorous physical activity is attained
	An additive effect on weight loss when combined with moderate dietary restriction
Older Adults	
Falls	Reduced incidence of falls
	Reduced incidence of fall-related injuries
Physical function	Improved function in older adults with and without frailty

Source: 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services, 2018. Available at: https://health.gov/paguidelines/second-edition/report/pdf/PAG_Advisory_Committee_Report.pdf

increasing a low level of physical activity to a volume that is still below that recommended in the *Guidelines* will still yield some benefit. In addition, although no threshold has been identified, there is increased emphasis on reducing sedentary behavior. It is now recognized that even in people meeting the physical activity recommendations, habitual prolonged sitting can still lead to health detriments, and additional physical activity may be necessary to counteract them.[1–3]

16.3 EXERCISE PRESCRIPTION

16.3.1 Physical Fitness Parameters

Physical fitness is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies."[2] Elements of physical fitness have traditionally been categorized as either health-related (cardiorespiratory endurance, muscular endurance, muscular strength, body composition, flexibility) or skill/performance-related (agility, balance, coordination, speed, power, reaction time). Definitions of the various physical fitness elements are listed in Table 16.3. The health-related fitness components are certainly important in chronic disease prevention and rehabilitation. However, particularly among the elderly and those with certain musculoskeletal diseases, maintenance of a certain level of skill-related fitness is also critical to independent function and quality of life. For example, the ability to drive a car or cross a busy street safely depends as much on *skill*-related as *health*-related fitness. Conversely, all of the health-related fitness parameters are key elements of various athletic and recreational activities. Therefore, while categorization of these elements may be helpful in developing fitness goals and an exercise plan, one should realize that training toward elements of *both* health-related and skill-related fitness may be prudent with many clients. The most recent version of the *Physical Activity Guidelines for Americans* recognizes this by including cardiorespiratory endurance, muscular strength, and flexibility in both categories and now considers balance more as an element of health.[2]

TABLE 16.2
Documented Health Benefits of Physical Activity—Individuals with Pre-Existing Medical Conditions

Breast cancer	Reduced risk of all-cause and breast cancer mortality
Colorectal cancer	Reduced risk of all-cause and colorectal cancer mortality
Prostate cancer	Reduced risk of prostate cancer mortality
Osteoarthritis	Decreased pain Improved function and quality of life
Hypertension	Reduced risk of progression of cardiovascular disease Reduced risk of increased blood pressure over time
Type 2 diabetes	Reduced risk of cardiovascular mortality Reduced progression of disease indicators: hemoglobin A1c, blood pressure, blood lipids, and body mass index
Multiple sclerosis	Improved walking Improved physical fitness
Dementia	Improved cognition
Some conditions with impaired executive function (attention deficit disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke)	Improved cognition

Source: 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services, 2018. Available at: https://health.gov/paguidelines/second-edition/report/pdf/PAG_Advisory_Committee_Report.pdf

TABLE 16.3
Health-Related and Performance-Related Physical Fitness Parameters

Health-Related	Performance-Related
Balance—the maintenance of equilibrium while stationary or moving	**Agility**—the ability to rapidly change the position of the entire body in space with speed and accuracy
Body composition—the relative amounts of muscle, fat, bone, and other vital parts of the body	**Balance**
Cardiorespiratory endurance—the ability of the circulatory and respiratory systems to supply fuel during sustained physical activity and to eliminate fatigue products after supplying fuel	**Cardiorespiratory endurance**
Flexibility—the range of motion available at a joint	**Coordination**—the ability to use the senses, such as sight and hearing, together with body parts in performing motor tasks smoothly and accurately
Muscular endurance—the ability of muscle groups to exert external force for many repetitions or successive exertions	**Flexibility**
Muscular strength—the amount of external force that a muscle can exert	**Muscular strength**
	Power—the rate at which one can perform work
	Reaction time—the time elapsed between stimulation and the beginning of the reaction to it
	Speed—the ability to perform a movement within a short period of time

Although physical fitness is dichotomized into health- and performance-related categories, overlap exists between the two (see text).
Definitions from Corbin CB, Lindsey R. *Concepts in Physical Education with Laboratories* (8th edition). Dubuque, IA: Times Mirror Higher Education Group, 1994.

16.3.2 Exercise Training Principles

Although goals and responses to physical activity and exercise training can vary considerably from person to person, three general principles should be considered when developing an exercise plan: *progressive overload*, *specificity*, and *reversibility*.

16.3.2.1 Progressive Overload

Adaptations only occur in physiological systems when the systems are stressed at levels to which they are unaccustomed. In other words, for any physical fitness parameter, a *threshold* of physical activity exists that a person must exceed in order to experience improvement. This minimal amount of training needed depends upon both the baseline level of the variable to be changed and a person's genetic capacity to experience positive changes in the targeted physiological system(s).

Given a steady overload, physiological improvement will level off or plateau after a given period of time. The term *progressive* overload indicates that the training stimulus

must continue to increase in order for further improvement to be recognized. The overall training stimulus can usually be augmented by increasing the *intensity*, *duration*, and/or *frequency* of physical activity.

16.3.2.2 Specificity

Overload will only result in an adaptation to the muscle groups and physiological systems that are stressed in training. Specificity of training applies to the motor units involved (e.g., muscles used, joint angle), speed of contraction, and the energy systems and primary substrates used (e.g., aerobic versus anaerobic metabolism, fat versus carbohydrate). Unless a person is severely untrained (e.g., frail elderly), strength training will do little to improve cardiorespiratory endurance, and vice versa. Furthermore, although distance cycling and running are both aerobic activities using the legs, the carryover from training in one mode to performance improvement in the other is limited. Similarly, while squat training mainly improves quadriceps strength, this improvement may not be recognized when testing with another exercise (e.g., leg extension) that uses different motor unit recruitment and accessory muscles. Therefore, in addition to training specifically toward a person's goals, assessment of improvement should involve testing that is congruent with the training that has been employed. The more specific a person's training goals (e.g., athletic performance), the more important these issues become.

16.3.2.3 Reversibility

Just as the body adapts positively to increases in physical activity, it adapts negatively to inactivity. The rate of deconditioning varies depending on the previous training level and how much it is curtailed. For example casting or extended bed rest can result in sharp, rapid declines in strength and endurance performance. In a more practical sense, fitness levels tend to decline significantly after about two weeks of exercise cessation. Endurance training of two to three days per week and resistance training of at least once per week are generally necessary to maintain previously attained fitness levels.

16.3.3 Cardiorespiratory Endurance Training

Maximal oxygen consumption (VO_{2max}) is the most accurate measure of cardiorespiratory fitness. Although some health benefits can be recognized with the practice of moderate-intensity physical activity that is less likely to improve VO_{2max},[4] strong inverse relationships exist between VO_{2max} and overall mortality and most major chronic diseases.[5] As such, the American College of Sports Medicine has traditionally recommended the following frequency, intensity, time, and type (***FITT***) of exercise for the improvement of cardiorespiratory fitness.[6]

16.3.3.1 Type (Mode) of Exercise

Activities that overload the cardiorespiratory system are repetitive (rhythmic) in nature and involve larger muscle groups. Examples include brisk walking, running, cycling, rowing, and exercising on an elliptical machine. Sports that constantly require intermittent bouts of vigorous body movement, such as basketball, soccer, and tennis, can also contribute to improved cardiorespiratory fitness. Unless medical conditions dictate otherwise, the majority of exercise should be weight-bearing in order to help prevent osteoporosis.

While specificity of training is very important for athletes, persons training more for overall health and fitness purposes will likely benefit from practicing a variety of exercise modes. Such practice will likely lead to fewer overuse injuries and will also add variety to the training regimen, possibly leading to better program compliance. For beginning exercisers, walking is generally a very good activity to include, since it requires little skill and results in fewer overuse injuries than most other modalities.

16.3.3.2 Intensity of Exercise

Improvement in VO_{2max} can usually be attained by exercising regularly at 50–85% of $VO_{2reserve}$ ($VO_{2reserve} = VO_{2max} - VO_{2rest}$). Obviously, this range is wide; the most effective intensity will depend in part upon the duration and frequency of exercise. Nevertheless, larger improvements in VO_{2max} typically occur with higher intensities. However, higher volumes of exercise (to include intensity, duration, and frequency) are more likely to result in overtraining symptoms (e.g., fatigue, injury, decreased performance, suppressed immune function). Exercise training at 60–80% $VO_{2reserve}$ generally results in improved VO_{2max}. However, the intensity threshold for improved VO_{2max} also depends upon baseline fitness level; low-fit, untrained individuals often experience improvement in the light-to-moderate-intensity range, while highly trained and fit individuals might need to spend a considerable amount of their training time above 80% $VO_{2reserve}$ to continue to improve their cardiorespiratory fitness.[6]

As stated in this chapter's introduction, the *Physical Activity Guidelines for Americans* give health-oriented recommendations for both moderate- and vigorous-intensity physical activity. In relative terms, *moderate-intensity* physical activity is defined as activity requiring 40–60% of $VO_{2reserve}$, while *vigorous-intensity* physical activity is anything that requires above 60% $VO_{2reserve}$. While moderate-intensity physical activity may result in some fitness improvement for those starting at a low fitness level, the progressive overload necessary to elicit and maintain improvement lies in the vigorous-intensity range for many people, especially those who are younger and/or more fit.

If a person's VO_{2max} has been measured or estimated through exercise testing,[6] exercise intensity may be prescribed as a given percentage of $VO_{2reserve}$. $VO_{2reserve}$ is calculated by subtracting the estimated value for VO_{2rest} (1 MET = 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) from VO_{2max}. $VO_{2reserve}$ is then multiplied by the target percentage, and VO_{2rest} is then added back to the product to yield the target VO_2 (Table 16.4).

Knowing the MET ("metabolic equivalent of task") levels of various activities can be useful in prescribing

TABLE 16.4
Calculation of Target Oxygen Consumption ($VO_{2target}$) and Target Heart Rate (HR_{target}) by Reserve Method

$VO_{2target}$[a]

Step 1: Calculate $VO_{2reserve}$

$VO_{2reserve} = VO_{2max} - VO_{2rest}$

Step 2: Multiply $VO_{2reserve}$ by the desired percentage

$VO_{2fraction} = VO_{2reserve} \times$ Target Percentage

Step 3: Calculate $VO_{2target}$ by adding VO_{2rest} to $VO_{2fraction}$

$VO_{2target} = VO_{2fraction} + VO_{2rest}$

***Example*:** You want a person with a VO_{2max} of 35 $mL \cdot kg^{-1} \cdot min^{-1}$ to exercise at 65% $VO_{2reserve}$:

Step 1: Calculate $VO_{2reserve}$

$VO_{2reserve} = 35.0 - 3.5 = 31.5\ mL \cdot kg^{-1} \cdot min^{-1}$

Step 2: Multiply $VO_{2reserve}$ by the desired percentage

$VO_{2fraction} = 31.5 \times 0.65 = 20.5\ mL \cdot kg^{-1} \cdot min^{-1}$

Step 3: Calculate $VO_{2target}$ by adding VO_{2rest} to $VO_{2fraction}$

$VO_{2target} = 20.5 + 3.5 = 24.0\ mL \cdot kg^{-1} \cdot min^{-1}$

HR_{target}

Step 1: Estimate HR_{max}[b]

$HR_{max} = 220 - age$[c]

Step 2: Calculate $HR_{reserve}$

$HR_{reserve} = HR_{max} - HR_{rest}$

Step 3: Multiply $HR_{reserve}$ by the desired percentage

$HR_{fraction} = HR_{reserve} \times$ Target Percentage

Step 4: Calculate HR_{target} by adding HR_{rest} to $HR_{fraction}$

$HR_{target} = HR_{fraction} + HR_{rest}$

***Example*:** You want a 50-year-old person with a HR_{rest} of 70 bpm to exercise at 65% $HR_{reserve}$:

Step 1: Estimate HR_{max}[b]

$HR_{max} = 220 - 50 = 170$ bpm[c]

Step 2: Calculate $HR_{reserve}$

$HR_{reserve} = 170 - 70 = 100$ bpm

Step 3: Multiply $HR_{reserve}$ by the desired percentage

$HR_{fraction} = 100$ x $0.65 = 65$ bpm

Step 4: Calculate HR_{target} by adding HR_{rest} to $HR_{fraction}$

$HR_{target} = 65 + 70 = 135$ bpm

[a]MET values may be substituted for VO_2 ($1\ MET = 3.5\ mL \cdot kg^{-1} \cdot min^{-1}$).
[b]When possible, use HR_{max} from maximal graded exercise test instead of estimation.
[c]Alternatively, the formula "$HR_{max} = 207 - (0.7 \times age)$" may be used.

physical activity after a target VO_2 range has been determined. One MET is an estimation of a person's energy expenditure when seated at rest ($3.5\ mL \cdot kg^{-1} \cdot min^{-1}$). As an example, if a person performs an activity that requires six times the energy requirement of sitting at rest, that activity would carry a MET level of six, requiring a VO_2 of approximately 21 $mL \cdot kg^{-1} \cdot min^{-1}$ ($6 \times 3.5 = 21$). The *Compendium of Physical Activities* (https://sites.google.com/site/compendiumofphysicalactivities/) has been published to provide the MET requirements of more than 800 leisure-time and occupational activities.[7] Table 16.5 includes examples of MET levels for some more common activities. If a target MET range has been determined ($MET_{target} = VO_{2target} \div 3.5$), the *Compendium* can be used to identify activities of appropriate intensity.

Many professionals find it more practical to prescribe exercise intensity by heart rate rather than VO_2. Since heart rate and VO_2 have a linear relationship during graded exercise, a given percentage of heart rate reserve ($HR_{reserve}$) parallels the same percentage of $VO_{2reserve}$ and therefore, may be used in its place. When available, it is preferable to use the maximal heart rate (HR_{max}) attained from a maximal graded exercise test. If a true HR_{max} is not available, an age-predicted value may be used. Just as with the $VO_{2reserve}$ method, HR_{rest} is subtracted from HR_{max} to obtain $HR_{reserve}$. The target heart rate is then derived by multiplying $HR_{reserve}$ by the desired percentage and adding HR_{rest} to the product (Table 16.4).

The most common formula for estimating HR_{max} in adults is "$HR_{max} = 220 - age$." It is most accurate around the age of 40 years and over- and underestimates HR_{max} in younger and older people, respectively. A more accurate formula, "$HR_{max} = 207 - (0.7$ x age)," has been reported.[8] While this formula is slightly more complicated, it may result in a more appropriate intensity prescription, particularly among the elderly. Regardless of the formula used, it is important to realize that HR_{max} has a standard deviation of 10–12 beats per minute (bpm) across the adult age span. This can obviously limit the value of using age-predicted HR_{max} in determining a target heart rate. As such, many professionals prescribe HR_{target} as a range of 10% $HR_{reserve}$ or so. A person's subjective feeling of effort should also be considered during exercise. On a scale of 0 to 10, where sitting is 0 and maximal effort is 10, moderate-intensity activity should yield a rating of 5 or 6 and vigorous-intensity activity of 7 or 8.[2] Such ratings are particularly useful for people who have clinical conditions or take medications that affect the heart rate response to exercise.

As an alternative to the $HR_{reserve}$ method, exercise intensity may be prescribed using a straight percentage of HR_{max} (65–90% HR_{max} is approximately equivalent to 50–85%

TABLE 16.5
Sample Metabolic Equivalent (MET) Levels of Common Physical Activities

Activity	METs	Activity	METs
Walking, 2 miles per hour	2.8	Aerobic dancing	5.0–9.5
Walking, 3 miles per hour	3.5	Golf, using power cart	3.5
Walking, 4 miles per hour	5.0	Golf, walking, pulling/carrying clubs	4.3–5.3
Running, 6 miles per hour	9.8	Tennis	4.5–8.0
Running, 7.5 miles per hour	11.5	Soccer	7.0–10.0
Running, 9 miles per hour	12.8	Washing and waxing car	2.0
Bicycling, 5.5 miles per hour	3.5	Most housecleaning activities	2.5–3.5
Bicycling, 9.4 miles per hour	5.8	Gardening	2.3–5.8
Bicycling, 15 miles per hour	10.0	Mowing lawn, riding mower	2.5
Swimming, sidestroke	7.0	Mowing lawn, walk, power mower	4.5–5.0
Swimming, crawl, ~50 yards per min	8.3	Mowing lawn, walk, hand mower	6.0
Swimming, crawl, ~75 yards per min	10.0	Shoveling dirt or snow	5.3–7.8

Source: Ainsworth BE, Haskell WL, Hermann SD, et al. *The Compendium of Physical Activities Tracking Guide*. Healthy Lifestyles Research Center, College of Nursing and Health Innovation, Arizona State University. https://sites.google.com/site/compendiumofphysicalactivities/

$HR_{reserve}$). However, many professionals prefer the $HR_{reserve}$ method, as it is more individualized by taking HR_{rest} into account.

16.3.3.3 Time (Duration) of Exercise

For improvement in cardiorespiratory fitness, 20–60 minutes per session is recommended, with duration and intensity interacting with one another. For example, 20–30 minutes of exercise at a higher intensity can yield similar benefits to 50–60 minutes of exercise at a lower intensity. Similar fitness benefits are recognized regardless of whether exercise is performed continuously or intermittently throughout the day.

16.3.3.4 Frequency of Exercise

Three to five days of exercise have traditionally been recommended for the improvement of cardiorespiratory fitness. While six or seven days per week may be practiced to accumulate the moderate-intensity guidelines of 150–300 minutes per week, such a frequency of vigorous-intensity exercise will likely increase one's chance of injury while yielding few additional health or fitness benefits. Therefore, as with other exercise prescription parameters, exercise frequency should vary with goals. For example, daily or near-daily physical activity is advocated for weight loss or maintenance, while "recovery days" of rest or lighter activity are usually necessary between more intense workouts.

16.3.3.5 Overall Exercise Volume

While vigorous exercise intensity may carry limited advantages for some health parameters, it is the overall volume of physical activity that matters most in improving and maintaining good health; i.e., longer bouts of moderate-intensity and shorter bouts of vigorous-intensity physical activity produce similar benefits. In recognition of a dose–response relationship between physical activity and health, both DHHS and WHO advocate a range of 150–300 weekly minutes of moderate-intensity physical activity, 75–150 weekly minutes of vigorous physical activity, or an appropriate combination of the two.[2,3] While fitness improvement might be minimal, increased physical activity that falls below the lower ends of these ranges is still likely to result in some health benefit ("some activity is better than none"). On the other end, although a higher risk of musculoskeletal injury exists, exceeding the recommended physical activity ranges will likely lead to even greater health benefits. Also, as stated earlier, people spending larger parts of their days in sedentary activities may need to exceed these recommended physical activity ranges in order to counteract the effects of prolonged periods of inactivity.

16.3.3.6 Rate of Progression

Training volume can be increased though alteration of exercise frequency, intensity, and/or duration. Many professionals first choose to implement small changes in exercise duration (5–10 minutes per session), as they are usually well tolerated and may be less likely to negatively affect exercise adherence. Depending upon a person's beginning exercise volume and their goals, frequency and/or intensity may then be increased. Although somewhat anecdotal, the "ten percent rule" is a good rule of thumb; exercise volume (usually quantified by distance or time) should not be increased by more than 10% per week. Overtraining symptoms (e.g., upper respiratory infection, muscle/joint pain) should be recognized, and a reduction of training volume and/or a change of exercise modality should be implemented. Additionally, periodization (changing intensity, duration, and/or overall training volume within and across weeks) can enhance fitness improvement and reduce overtraining symptoms.

16.3.4 Resistance Training

The *Physical Activity Guidelines for Americans* and the *Guidelines on Physical Activity and Behaviour* both

recommend that muscle-strengthening (resistance) activities that involve all major muscle groups be performed on two or more days per week.[2,3] Benefits of resistance training include maintenance or increases in bone mass, insulin sensitivity, and skeletal muscle mass, the latter two being important for those attempting to reduce body fat. Maintenance or gain in strength can also be important in preserving physical function in the elderly and persons with certain disabilities.

16.3.4.1 Type of Resistance

Dynamic resistance exercises alternately overcome (*concentric* contractions) and accommodate (*eccentric* contractions) a given force. This force is often in the form of weights (either "free" weights or stacked weights on various machines) but can also exist in other forms, such as elastic bands or one's own body weight. The type of resistance to be used in training depends largely upon the goals of the participant, and a combination of resistance modes is often employed. More "controlled" modes (e.g., weight machines, resistance bands) are generally safer and less likely to require a spotter, while less controlled modes (e.g., free weights) require more balance and tend to mimic real-life movement more. In addition, lifting in a more stable position (e.g., from a bench) allows more weight to be lifted, resulting in greater strength gain. Lifting from less stable surfaces (e.g., stability balls) requires lowering of the training resistance and will likely result in lower specific strength gain, but causes adaptation over a wider range of motor units, resulting in a more functional training effect. As such, the greatest performance gains may result from employing a combination of resistance modes. Regarding exercise adherence, preference of exercise type should also be considered.

For the purposes of safety and effectiveness (i.e., specificity), proper technique (e.g., keeping back straight, controlling eccentric portion of exercise) should be stressed with any type of exercise. In addition, unless the development of isometric (static) strength is a specific training goal, resistance exercises should be dynamic, generally taking the involved joints through the fullest range of motion possible. This allows a greater number of motor units to be trained, creating more functional benefits.

Regardless of the mode(s) of resistance used, all major muscle groups should be exercised. At least eight to ten different exercises are generally required to target all of the major muscle groups. Accordingly, to encompass the entire body and lessen the chances of strength imbalances, opposing (antagonistic) muscles groups should be exercised. For example, if the abdominal muscles are focused upon in one exercise, another exercise should target the lower back muscles; both the biceps and triceps should be targeted in separate exercises, etc. For practical purposes, multi-joint exercises (e.g., bench press, squat) that simultaneously train more than one muscle group are preferred over single-joint exercises (e.g., triceps extension, leg extension) because they are more time-efficient and tend to represent real-life movements more. However, single-joint exercises can still serve as useful adjuncts, particularly if they mimic a particular movement in a sport or other activity for which a person is training.

16.3.4.2 Amount of Resistance; Repetitions and Sets

To achieve improvements in both muscular endurance and strength, completion of 8 to 12 repetitions of each exercise to a point of *fatigue* (not necessarily *failure*) is recommended. Lifting to fatigue infers that an additional repetition would be difficult to perform without help.[2] Performing 8–12 repetitions to fatigue generally requires a resistance of about 60% of a person's 1-repetition maximum (1RM; the maximum amount of weight that can be lifted in a single effort in that same exercise).[6] Performing fewer than 8–12 repetitions to fatigue (which would employ a greater resistance) will result in more strength gain than gain in endurance, while performing more than 8–12 repetitions (requiring less resistance) will result in more improvement in muscular endurance.

The compilation of repetitions of an exercise performed at one time (e.g., 8–12) is termed a *set*. Multiple sets of an exercise may be performed, with one to three minutes' rest in between being recommended; shorter rest periods are more time-efficient, while longer rest periods allow greater amounts of work to be performed. For beginners, performing a single set of an exercise for 8–12 repetitions to fatigue on a regular basis will almost always result in strength gains. In time, additional sets will likely be necessary for further improvement.[2] For continued improvement, ACSM suggests that four or more sets per week should be performed with each muscle group. More than one exercise may be employed for a given muscle group. For example, both the bench press and dips involve the pectoralis and triceps muscles, but require different movement patterns. Therefore, completing two sets of both of these exercises over the week would satisfy the recommendation of four sets per week for these muscle groups.[6] In short, the number of sets to be performed depends upon the goals of the participant. Health and functional benefits can be recognized with a minimum number of sets, but a dose–response relationship exists between training volume and strength gain.

16.3.4.3 Frequency of Training

For the novice, resistance training sessions should be spaced at least 48 hours apart from one another to allow sufficient recovery.[6] Therefore, two to three sessions per week of resistance training are recommended. With more experienced participants, lifting frequency has little effect on strength gain when training volume (e.g., number of sets) is held constant.[6] If time constraints do not permit all exercises to be performed in a given day, then the same muscle groups should not be exercised on consecutive days (e.g., train the upper body one day and the lower body the next).

16.3.4.4 Rate of Progression

As mentioned earlier, resistance training sets should be performed to fatigue in order for muscular fitness gains to

be achieved. A person should increase the resistance of an exercise when they can perform one or two extra repetitions with good form. To remain in the desired repetition range (e.g., 8–12), increases of 2.5 to 5 pounds are generally appropriate for smaller muscle groups and increases of 5 to 10 pounds are generally appropriate for larger ones.

Even when these criteria are followed, people training for larger gains in muscle size and strength often *plateau*, or fail to experience continued improvement after many months. In this case, *periodization*, the frequent alteration of training intensity, repetitions, sets, and/or resistance mode, can be useful. While beyond the scope of this chapter, ACSM has published a position stand addressing this topic.[9]

16.3.5 Flexibility Training

Maintenance of flexibility, the range of motion around a joint, can be important for the prevention of low back pain and for the maintenance of activities of daily living. While stretching might help prevent injury in activities where one's range of motion is taken to its limits (e.g., gymnastics), there is no conclusive evidence that stretching prevents injury in activities requiring less range of motion (e.g., jogging) or that it prevents muscle soreness.[10,11]

Nevertheless, since flexibility decreases with aging, stretching is an important component of a well-rounded fitness program. Both static stretching, where a person holds a stretch for an extended period, and dynamic stretching, which involves controlled movements (e.g., swinging of arms, high knee stepping) with a gradually increasing range of motion, are effective in increasing flexibility. Static stretching is more effective, and possibly safer, after a person has gone through a warm-up period. In fact, unless a person is getting ready to perform activities that challenge their range of motion, static stretching is usually most effective at the end of an exercise session rather than at the beginning. Prior to activities that challenge one's range of motion, dynamic stretching is effective and also helps warm up the muscles. ACSM recommends that stretching exercises be performed for 10–30 seconds each on at least 2 or 3 days weekly.[6]

16.3.6 Warm-Up and Cool-Down

Both before (*warm-up*) and after (*cool-down*) the conditioning phase of an exercise session, at least five to ten minutes of low-intensity physical activity should be performed. The increased blood flow and body temperature resulting from the warm-up period allow the muscle and connective tissue to become more pliable, reducing the chance of injury during vigorous activities. It also allows a more gradual cardiovascular adaptation to the stress of exercise, which is particularly important for people who are more likely to experience cardiac events. Similarly, a proper cool-down period helps prevent venous pooling in the lower extremities, thereby facilitating venous return to the heart and brain. Muscular endurance activities, such as abdominal exercises, and stretching may also be better performed during the cool-down phase.

16.3.7 Physical Activity Adherence

Specific strategies for enhancing physical activity participation are detailed in Chapter 21. In general terms, the clinician should recognize that a good bit of flexibility exists in how a person can choose to meet physical activity guidelines (i.e., wide ranges exist in the components of FITT) and that physical activity may be practiced in a variety of settings (at home, outside, in a fitness facility, etc.). In addition, leisure-time physical activity may be practiced alone, with a partner, or in a group setting. Everyone should be encouraged to experiment with a variety of exercise regimens and to continue to practice the one(s) they enjoy the most.

Approximately one-quarter of adults worldwide[3] and one-half of U.S. adults[12] fail to meet current guidelines for aerobic physical activity, while approximately three-quarters of U.S. adults fail to meet the combined aerobic and muscle-strengthening activity guidelines.[12]. As patients are more likely to be physically active when such behavior is endorsed by their physicians, *Healthy People 2020* and *Healthy People 2030* both included initiatives for patients with cardiometabolic conditions to receive physical activity counseling during healthcare visits.[15] However, most physicians have received little education on physical activity counseling as part of their medical training. Appropriately, in order to facilitate delivery of prudent physical activity information by healthcare providers, ACSM and the American Medical Association provide an educational website, *Exercise Is Medicine* (http://exerciseismedicine.org).[15] This and other clinician resources are discussed in Chapter 11.

16.4 EXERCISE PRESCRIPTION FOR SPECIAL POPULATIONS

With rare exceptions, everyone should be physically active. However, physical limitations and safety issues sometimes necessitate that the "normal" exercise prescription described previously be altered. As such, this next section discusses recommendations for children and older adults and people with some of the more prevalent chronic diseases. This discussion is only introductory in nature; other sources dedicated to the subject of clinical exercise physiology are available and cover a wider variety of chronic conditions in greater detail.[16,17] Exercise prescription for pregnant women (Chapter 54) and individuals with cardiovascular disease (CVD) (Chapter 67) and obesity (Chapter 37) are detailed elsewhere in this book.

16.4.1 Children and Adolescents

Proper physical activity can help develop and maintain a healthy body weight and cardiometabolic risk profile, can

reduce symptoms of anxiety and depression, and can instill positive habits that may carry over into adulthood. Current *Guidelines* recommend that youth accumulate at least 60 minutes of moderate- and vigorous-intensity physical activity daily.[2,3] These 60 minutes should include a combination of aerobic activities (e.g., bicycling, dancing) and short bursts of activity (e.g., playing tag, soccer) as well as activities that promote muscular fitness (e.g., climbing trees or playground equipment) and bone health (impact activities such as running or jumping rope). The *Guidelines* can be met through structured sports, games, and exercise classes and/or unstructured play. While specific time guidelines are not currently provided, it is also recommended that preschool-aged children (ages three to five years) be physically active throughout the day.[2]

Adults can facilitate physical activity among youth by providing ample opportunity for participation. Two examples of how to do this are by limiting screen time (television, video games, and computers) and increasing the amount of time dedicated to physical activity during the school day. Academic performance is not sacrificed when students are provided with opportunities for daily physical activity in school, such as daily recess, physical education classes, or implementation of physically active learning opportunities in other classes.[18] Many youth will choose to be active when given ample opportunity. However, some cohorts that tend to be less active (adolescent girls, the obese) may benefit from structured exercise programs that include like peers and focus on a variety of activities that are popular within a given gender and age group (e.g., dance for adolescent girls).

Compared with adults, a couple of physiological differences in children are worth noting. First of all, children sweat less than adults and do not acclimatize to heat exposure as quickly. They also possess a delayed thirst response. Therefore, it is important to gradually expose children to exercise in warmer environments and to emphasize frequent fluid intake (every 15–20 minutes). Second, while precise exercise prescription is generally not necessary, adult formulas for maximal heart rate do not apply to children and adolescents, who typically have maximal heart rates of approximately 200–205 bpm. RPE and a noticeable increase in breathing are generally sufficient monitoring tools for health-related physical activity.[2]

16.4.2 Older Adults

Among older adults, proper physical activity can increase and maintain physical function, improve and maintain body composition, promote psychological and cognitive well-being, and assist in primary and secondary prevention of chronic diseases. Keeping in mind that exercise intensity is relative (e.g., a given walking speed may be considered light for one person and vigorous for another), the physical activity guidelines are essentially the same for adults over the age of 65 as they are for middle-aged and younger adults.[2,3] Frail persons, who may have difficulty meeting the guidelines, should practice as much physical activity as they can tolerate with the goal of safely advancing their physical activity into the range recommended for the general population.

In addition to the same endurance and resistance exercise advocated for the general population, older adults at risk for falling should add exercises on two to three days per week that focus on balance. While a wide variety of such activities exist, the ones performed should focus on a person's particular needs. Examples include walking sideways and backward, repetitively standing and sitting, standing with eyes closed, tai chi, etc. Functional resistance exercises can also be useful in this regard. Previously inactive seniors, in particular, may benefit from the services of a properly credentialed personal trainer or exercise class in the beginning stages of an exercise program.

16.4.4 Diabetes Mellitus

Both type 1 and type 2 diabetes mellitus are characterized by abnormally high blood glucose levels. Since physical activity facilitates glucose uptake by skeletal muscle, it can serve as an important mechanism of managing glucose concentration in either disease. In addition, through its effect on weight management, an adequate amount of physical activity (combined with a prudent diet) may assist in partial or more rarely, full reversal of type 2 diabetes. Proper physical activity can also improve one's CVD risk profile. Exercise can also be an effective means of preventing diabetes onset in people with impaired glucose tolerance.[20]

It is generally safe for persons with diabetes to participate in light-to-moderate physical activity as long as they are asymptomatic and are at low risk (ten-year Framingham risk of <10%) for CVD.[6,21] However, a physical examination is recommended before engaging in vigorous-intensity exercise. Although many people with type 1 and 2 diabetes participate independently in exercise and sports, it is recommended that novices begin training with a qualified exercise physiologist, particularly when resistance training is involved, in order to avoid injury and blood glucose abnormalities that are more likely to occur in persons with diabetes.[21]

Chronic hyperglycemia can lead to neural, retinal, and circulatory damage, which can present special problems during and as a result of exercise in persons with more advanced diabetes. Silent ischemia may be present in persons with underlying CVD. In addition to having proper screening for CVD, such patients need to be aware of other warning signs of CVD (e.g., dizziness, unusual shortness of breath). In addition, advanced neuropathy may cause a diabetic patient to be oblivious to foot ulcerations, which are more common due to microcirculatory damage. Therefore, diabetic patients should always exercise with clean, dry socks and proper fitting footwear. In addition, they should check their feet daily for blisters and ulcerations. Non-weight-bearing exercises should be practiced in persons with foot injuries or open sores.[22] Thermoregulation can

also be impaired in persons with advanced diabetes, so particular precaution (e.g., keeping extremities warm, proper hydration) should be practiced in cold and hot weather.

Due to the risk of intraocular hemorrhage, diabetic patients with retinopathies should be carefully screened before participating in exercise. High-impact activities (including running) and high-intensity activities are not recommended. In addition, although it may be beneficial in helping manage blood glucose, higher-intensity resistance training that causes straining on the participant's part is contraindicated due to high increases in blood pressure.[22]

Maintenance of a proper blood glucose concentration is important during and following exercise. As long as they are feeling well, type 2 diabetics may exercise with elevated glucose levels (>300 mg·dL^{-1}), but intense exercise should be avoided until glucose falls below 250 mg·dL^{-1}.[22] However, type 1 diabetics should not exercise in this condition (or with glucose >250 mg·dL^{-1} and presence of ketone bodies), as this represents insulin deficiency, and exercise will likely exacerbate the hyperglycemia.

Hypoglycemia is a more common incident during and following exercise. As such, proper balance and timing of exercise, diet, and medication is important. Due to increased glucose uptake during exercise, insulin or insulin secretagogue doses may need to be decreased in both type 1 and 2 diabetes patients, particularly in the hours preceding exercise. Exercise should not be practiced during times of peak insulin uptake, and insulin injections during the hours before exercise should not be in the vicinity of the exercising muscles. To avoid nocturnal hypoglycemia, it is best not to exercise within a few hours before bedtime. However, if this must be done, a carbohydrate snack should be ingested before going to sleep. In addition, carbohydrates should be consumed following intense or prolonged exercise. While it may vary among individuals, the ideal pre-exercise range for blood glucose is 90–250 mg·dL^{-1}. In its position statement on physical activity/exercise and diabetes, the American Diabetes Association provides guidelines for carbohydrate intake, ketone testing, and potential refrainment from exercise with various baseline glucose concentrations.[22] Considerations for various medication dose adjustments when beginning an exercise program are also discussed. Regardless of medication type, all diabetic patients should be aware of hypoglycemic symptoms (weakness, nervousness, etc.).

With some important alterations, the exercise prescription for persons with diabetes should be very similar to that for healthy adults. The overall volume of physical activity should be 150 minutes per week or greater, recognizing the importance of a dose–response relationship, especially as far as weight management is concerned. Although previously inactive persons should begin exercise at a moderate intensity, progression to mostly vigorous-intensity exercise may lead to a greater improvement in blood glucose concentration.[23] Since exercise-induced alterations in insulin sensitivity can begin to reverse within a few days of inactivity, it is recommended that no more than two days of inactivity be allowed between exercise bouts.[6,22] In fact, daily, or near-daily, physical activity of similar intensity and duration can be useful in maintaining a balance among the glycemic effects of physical activity, diet, and medications. Due to beneficial effects on insulin sensitivity, resistance training is recommended on at least two, and preferably three, days per week in patients without retinopathies.[6,22] With both aerobic and resistance training, increases in exercise volume should occur gradually to avoid disruptions in glycemic control.

Finally, although cardiac reactivity to physical activity should be normal in most diabetics, autonomic neuropathy may result in a blunted heart rate response in some patients. Unless a maximal heart rate has been obtained through graded exercise testing, calculation of a target heart rate using an age-predicted maximum is inappropriate in patients with known or suspected neuropathy. Use of subjective feelings of exertion should be employed instead.

16.4.5 Cancer

Whether currently undergoing treatment or in remission, regular physical activity can yield both physiological and psychological benefits for most cancer patients. Physical activity can help reduce the decline of functional capacity during treatment. Even during palliative care, properly practiced physical activity may prolong independent function and can reduce depressive symptoms and generate a greater sense of control. During recovery, in addition to contributing to a faster and more complete restoration of physical function, proper physical activity can reduce the chances of the reoccurrence of certain cancers, particularly those of the breast and colon. Additionally, since some cancer treatments increase the likelihood of future CVD and diabetes, the practice of physical activity is important in the management of cardiometabolic risk.

Exercise prescription should vary based on the type and severity of cancer. Since the side-effects of cancer treatments can in some cases be nearly as severe as the disease itself, the type and time-course of treatment should be taken into account as well. Similarly, during recovery, a person's capacity to exercise will be affected by any tissue damage they encountered due to the cancer and treatments and how far they are into remission. Potential contraindications to exercise include fever, ataxia, severe fatigue, significant anemia, profound weakness, and any other worsening conditions and should be brought to the attention of one's medical provider.[6,24]

Due to the wide variety of cancers and treatments, there are numerous potential precautions to take when prescribing exercise. In general terms, exercise prescription and progression need to be highly individualized and should vary day-to-day as the patient deals with the side-effects of their treatments and the disease itself. Fatigue will commonly persist for days, and often for weeks or more, following chemotherapy and radiation. Although exercise is generally good for bone health, the bone of cancer patients

may be more susceptible to fracture due to radiation therapy and/or cancer metastases. As such, higher-impact activities should be avoided during cancer treatment and if desired, should be introduced very gradually during recovery. Due to the risk of contamination, bone-transplant patients and patients with low white blood cell counts should take care to exercise in a clean environment. Post-mastectomy patients experiencing lymphedema should attain physician consent before performing upper-body exercise, should wear compression sleeves, and should begin with light-to-no resistance and progress slowly. Also, although water exercise can be very beneficial to some patients, it should be avoided in those with indwelling catheters or central lines and feeding tubes and for those receiving radiation. In addition, patients undergoing radiation therapy may develop severe skin irritations. Therefore, comfortable clothing should be worn, and the skin should be kept dry and clean during and after exercise.[6] In the majority of cases, cancer patients will benefit from beginning their exercise program in a medically supervised setting with an exercise physiologist possessing specialized training. Communication among patients, medical providers, and exercise professionals is key for the individualization of exercise prescriptions, especially during active treatment and for patients with metastatic cancers. Vigorous-intensity (and possibly moderate-intensity) exercise should generally be avoided on the day of intravenous chemotherapy and within 24 hours after treatment.

In general, ACSM recommends that cancer patients perform aerobic physical activity on 3–5 days, accumulating at least 30 minutes per day, realizing that a patient's condition may necessitate periodic adaptation. Although a moderate intensity of 40–60% $VO_{2reserve}$ or $HR_{reserve}$ is recommended, some patients will find this difficult and should adjust their intensity accordingly. For resistance training, the lower end of the Physical Activity Guidelines is generally recommended; eight to ten exercises of major muscle groups, on two to three days per week, at least one set of at least eight repetitions with at least one minute of rest in between. Flexibility training, which can be particularly beneficial following some surgeries, is recommended on two to seven days per week. Static stretches of 10–30 seconds are suggested.[6] With the exception of high-impact activities, a wide range of exercise types can be used to meet a patient's goals. In addition, some exercise modalities, such as tai chi, offer the opportunity to complete moderate-intensity exercise in a supportive group atmosphere.

16.4.6 Arthritis

Both osteoarthritis and rheumatoid arthritis result in pain with movement. This often sets up a vicious cycle in which a person moves less due to pain. In turn, stamina and neuromuscular conditioning decline, which can eventually result in a decreased ability to perform activities of daily living. As functional tolerance deteriorates and arthritic pain increases, physical activity levels will most likely decline further, making the individual less functionally tolerant and more susceptible to hypokinetic diseases. As such, a major objective of exercise in individuals with arthritis is to increase and preserve physical function. Although physical activity may acutely cause pain, chronically practiced physical activity can actually reduce joint pain and stiffness, resulting in a higher quality of life. Also, as arthritis is common in overweight and obese individuals, physical activity can also serve as a means of weight control and cardiometabolic disease risk factor management.

Exercise levels recommended for the general population also increase physical fitness and produce health benefits in persons with arthritis.[6] However, certain adaptations may make physical activity more tolerable and increase compliance. While adequate warm-up is important in all cases, it is particularly important with arthritis, as the increased blood flow warms the joints and makes movement easier and less painful. Since many arthritic patients experience more stiffness and pain in the morning, exercise later in the day is often wise, especially after morning medications have had time to reach their peak effects. In addition, many patients find warm water (83–88 ζF, 28–31 ζC) exercise to be more comfortable than other environments. Out of the water, proper fitting shoes with adequate stability and cushioning may help prevent excessive knee, hip, and/or back pain. Custom-made orthotics may be beneficial for persons with biomechanical abnormalities.

To increase and maintain functional ranges of motion, flexibility exercises are particularly important for patients with arthritis. Although resistance training can increase strength and stability around affected joints, maximal isometric contractions, practiced at a few angles per joint, may be preferable to dynamic contractions in persons who experience higher levels of joint pain. As this becomes less painful, patients can then advance to dynamic exercise with lighter resistance, increasing the resistance as tolerated. With aerobic training, people with more pain and/or less functional tolerance may need to exercise intermittently in the beginning, but should be able to progress to more continuous activity.

Some pain during exercise is to be expected with arthritis. However, if joint pain persists for more than two hours following exercise, the volume of training should be reduced.[6] Pain makes physical activity less enjoyable and is likely to negatively affect exercise compliance. Therefore, patients should not be pushed to a point where they are less likely to continue to stay active.

16.4.7 Disabilities

Depending on the type and extent of disability, proper physical activity may improve physical fitness and functional abilities and may reduce a person's risk for cardiometabolic diseases. The range of disabilities (cerebral palsy, spinal cord injury, stroke, etc.) is too wide to permit a thorough discussion of exercise prescription for each in this chapter. However, a few points are important to remember across many conditions. For example, disabilities resulting in

autonomic impairment will yield abnormal cardiovascular responses to exercise and impaired thermoregulation. Therefore, perceived exertion may be a better gauge of exercise intensity, and special precaution should be taken to prevent hyper- or hypothermia. In addition, adaptations in equipment or clothing may be needed to help persons with particular disabilities perform common exercises. For example, persons with impaired gripping ability may benefit from Velcro gloves when performing resistance exercises or arm ergometry. Shorter bouts of physical activity spread throughout the day may be necessary for persons with very low physical tolerance.

When possible, persons with disabilities should perform the same physical activity recommended for more able-bodied adults.[2,3] When this is not possible, they should perform as much physical activity as they are able to accomplish without undue fatigue. Aerobic, resistance, and flexibility exercise should all be practiced. Even when exercise tolerance is very low, physical inactivity should be avoided to maintain as much functional independence as possible and to avoid hypokinetic diseases.

16.5 SUMMARY

Current physical activity guidelines advocate a well-balanced exercise program to include aerobic, resistance, and flexibility training. To allow for individual preferences and abilities, these guidelines allow a good bit of flexibility among the frequency, intensity, and duration of physical activity, as long as a critical overall volume is met. Health and fitness–related benefits can also be obtained with a variety of exercise modalities. The chosen modalities should be safe for a given individual and should be enjoyable to enhance program adherence.

In addition, disease or disability should not inhibit anyone from being physically active. Individuals who are not able to meet the physical activity levels recommended for the general public should still strive to be as active as possible within the confines of any disease or disability. *Everyone* can benefit from physical activity.

CLINICAL APPLICATIONS

- About one-half of Americans do not meet current recommendations for aerobic physical activity, and approximately two-thirds do not meet the combined recommendations for aerobic and muscle-strengthening activity. This makes physical activity one of the most prevalent risk factors for a number of prevalent chronic diseases and conditions.
- A strong recommendation from a healthcare provider can be a key factor in convincing a patient to make lifestyle changes. Although exercise prescription might need to be quite precise to attain high levels of specific fitness parameters, the healthcare provider need not be intimidated about providing health-related physical activity recommendations, as wide ranges of exercise intensity and duration allow one to improve one's health and fitness. A key factor for adherence is for the patient to participate in activities that they enjoy in an unintimidating environment. Including physical activity as part of their daily schedule is also important.
- The U.S. Centers for Disease Control and Prevention offers useful resources for patients wishing to begin a physical activity program (www.cdc.gov/physicalactivity/basics/index.htm). In addition, the American College of Sports Medicine sponsors Exercise Is Medicine, which offers resources for healthcare providers wishing to promote physical activity to their patients (www.exerciseismedicine.org/).

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17 Physical Activity and Health: Key Findings from the Physical Activity Guidelines for Americans 2018

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KEY POINTS

- Regular physical activity is a powerful modality for lowering the risk of various chronic diseases.
- Recommendations from the Physical Activity Guidelines for Americans 2018 Scientific Report state that adults should try to accumulate 150 minutes per week of moderate intensity physical activity or 75 minutes of strenuous activity and two sessions of resistance strength training.
- The PAGA 2018 Scientific Report is an important document for all individuals practicing lifestyle medicine and should be in every clinician's toolbox.

17.1 INTRODUCTION

Physical activity (PA) plays a significant role in multiple health parameters.[1–9] It is one of the pillars of lifestyle medicine. In some studies, it has been shown that physical activity is more correlated with cardiovascular disease (CVD) than any other parameter.[9]

While the benefits of physical activity are generally known, the relationship between physical activity and multiple health considerations, such as reduction in risk for chronic disease, improved health for both children and adults over the age of 65, as well as the important role in quality of life, sleep, energy, and the ability to live a full life, is often underappreciated. Recently, the scientific basis for regular physical activity was substantially enhanced by the release of the Physical Activity Guidelines for Americans 2018 (PAGA 2018).[7] This seminal document provides robust data in virtually every area of health where physical activity interacts with a variety of parameters. This extensive, evidence based document should be in the toolbox of every lifestyle medicine practitioner. The PAGA 2018 document itself is quite extensive, but the Executive Summary should be familiar to all practitioners of lifestyle medicine and indeed, all physicians and other healthcare professionals. The purpose of this chapter is to provide a brief summary of the key findings from the PAGA 2018.

17.2 LIFESTYLE MEDICINE, PHYSICAL ACTIVITY, AND HEALTH

Increased physical activity plays a significant and beneficial role for individuals at all stages of their lives. In addition to lowering the risk of various chronic diseases, physical activity can also play an important role in their treatment. The recommendations from the PAGA 2018 to incorporate 150 minutes of moderate to vigorous physical activity, or more, each week and strength training twice a week are recommendations shared by the American College of Sports Medicine (ACSM),[10] American Heart Association (AHA),[4,6] and other important scientific organizations. Unfortunately, according to Centers for Disease Control (CDC) criteria, only 25% of individuals engage in regular levels of physical activity necessary to meet these widely accepted guidelines for physical activity and health. Physicians play a very important role in helping people to make the positive decision in their lives to incorporate the recommended levels of physical activity. A summary of the guidelines recommended by the PAGA 2018 is found in Table 17.1. The PAGA Scientific Guidelines Advisory Committee summarized the broad range of these guidelines by saying that when it comes to health, physical activity is a "best buy."

PA confers a wide variety of benefits on physically active individuals. These benefits may occur after a single bout of physical activity, but others require consistent increased physical activity throughout the lifespan. As already indicated, physical activity plays an important role in the quality of life. People who are physically active feel better and sleep better, and are able to accomplish more in their daily lives. In addition, regular physical activity lowers the risk of anxiety, stress, and depression.

17.3 PHYSICAL ACTIVITY AND CARDIOVASCULAR DISEASE (CVD)

Regular physical activity reduces the risk of all-cause mortality and CVD. Even small amounts of physical activity can significantly lower the risk of CVD. As shown in Figure 17.1, the recommended amount of physical activity from the PAGA 2018, 150 minutes of moderate intensity physical

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TABLE 17.1

Physical Activity-Related Health Benefits for the General Population and Selected Populations Documented by the 2018 Physical Activity Guidelines Advisory Committee

Children	
3 to <6 years of age	**Improved bone health and weight status**
6 to 17 years of age	**Improved cognitive function (ages 6 to 13 years)**Improved cardiorespiratory and muscular fitnessImproved bone healthImproved cardiovascular risk factor statusImproved weight status or adiposityFewer symptoms of depression
Adults, all ages	
All-cause mortality	Lower risk
Cardiometabolic conditions	Lower cardiovascular incidence and mortality (including heart disease and stroke)Lower incidence of hypertensionLower incidence of type 2 diabetes
Cancer	Lower incidence of **bladder**, breast, colon, **endometrium**, **esophagus**, **kidney**, **stomach**, and **lung cancers**
Brain health	**Reduced risk of dementia**Improved cognitive function**Improved cognitive function following bouts of aerobic activity****Improved quality of life****Improved sleep****Reduced feelings of anxiety and depression in healthy people and in people with existing clinical syndromes**Reduced incidences of depression
Weight status	**Reduced risk of excessive weight gain**Weight loss and the prevention of weight regain following initial weight loss when a sufficient dose of moderate to vigorous physical activity is attained**An additive effect on weight loss when combined with moderate dietary restriction**
Older adults	
Falls	Reduced incidence of falls**Reduced incidence of fall-related injuries**
Physical function	**Improved physical function in older adults with and without frailty**
Women who are pregnant or postpartum	
During pregnancy	**Reduced risk of excessive weight gain****Reduced risk of gestational diabetes**No risk to fetus from moderate intensity physical activity
During postpartum	**Reduced risk of postpartum depression**
Individuals with pre-existing medical conditions	
Breast cancer	**Reduced risk of all-cause and breast cancer mortality**
Colorectal cancer	**Reduced risk of all-cause and colorectal cancer mortality**
Prostate cancer	**Reduced risk of prostate cancer mortality**
Osteoarthritis	**Decreased pain****Improved function and quality of life**
Hypertension	**Reduced risk of progression of cardiovascular disease****Reduced risk of increased blood pressure over time**
Type 2 diabetes	**Reduced risk of cardiovascular mortality****Reduced progression of disease indicators: hemoglobin A1c, blood pressure, blood lipids, and body mass index**
Multiple sclerosis	**Improved walking****Improved physical fitness**
Dementia	**Improved cognition**
Some conditions with impaired executive function (attention deficit hyperactivity disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke)	**Improved cognition**

Benefits in **bold** font are those added in 2018; benefits in normal font are those noted in the 2008 Scientific Report. Only outcomes with strong or moderate evidence of effect are included in the table.

Source: 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC. Part D: Integrating the Evidence. D5-6.

activity, substantially lowers the risk of CVD. While there is additional lowering of the risk of CVD for amounts greater than 300 minutes, the incremental benefit is very small. An important part of the relationship between physical activity and CVD illustrated in Figure 17.1 is that even 30 minutes of moderate intensity physical activity lowers the risk of CVD by 20%.

As illustrated in the figure, there is no lower threshold for benefit, and there is a steep, early slope. Regular physical activity has been repeatedly shown to lower the risk of a variety of forms of CVD, including coronary heart disease (CHD), hypertension, heart failure (HF), diabetes, and obesity. Despite the overwhelming evidence that regular physical activity is a powerful tool for lowering the risk of CVD, unfortunately, only 25% of adults achieve levels of PA to meet minimum standards from the CDC.

It should be emphasized that CVD is the leading cause of morbidity and mortality in the United States, with over 37% of mortality coming annually from CVD.[11,12] The amount of benefit from regular physical activity is substantial. When

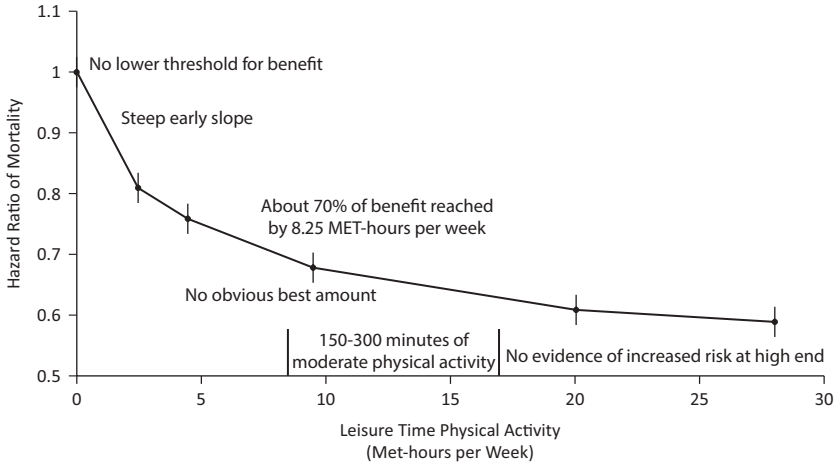


FIGURE 17.1 Relationships of moderate to vigorous physical activity to all-cause mortality, with highlighted characteristics common to studies of this type.

physically active people are compared with sedentary individuals, the risk of CHD is 150–240% higher in sedentary individuals.[9] The recommendations for the amount of physical activity for adults and also older adults (over the age of 65) are very similar. The PAGA 2018 Scientific Report states that adults should optimally strive for at least 150 minutes a week of moderate intensity physical activity or 75 minutes of vigorous intensity physical activity or a combination of the two, and muscle strengthening performed two or more days per week, which will result in additional risk reduction. Individuals who achieve these levels of physical activity achieve approximately 70% reduction in the risk of CVD.

The recommendations are slightly different for children and adolescents. The PAGA 2018 Scientific Report recommends that children and adolescents should perform 60 minutes of moderate intensity physical activity daily. In addition, the PAGA 2018 recommends that vigorous physical activity should be performed at least three days a week. Unfortunately, fewer than 20% of children and adolescents in the United States achieve these levels.[7]

17.4 PHYSICAL ACTIVITY AND THE PREVENTION AND TREATMENT OF CANCER

Physical activity plays a significant role in the prevention and treatment of various cancers.[13–16] Furthermore, numerous cancers are linked to an inactive lifestyle. In the Physical Activity Guidelines for Americans 2008, both breast and colon cancer were cited as cancers where physical activity particularly lowered the risk.[17–21] In the PAGA 2018, this list was greatly expanded to include bladder cancer, colon cancer, endometrial cancer, gastric cancer, renal cancer, and thyroid cancer.[7]

Cancer is very prevalent in the United States and around the world. Nearly one in six deaths worldwide are attributable to cancer, which equates to 8.8 million deaths annually.[14] Global cancer is expected to rise over the next 20 years by 70%. In 2016, over 15.5 million living Americans (approximately 4.8% of the population) have been diagnosed with cancer at some point in their lives. On average, 38% of American women and 48% of American men will be diagnosed with invasive cancer at some point in their lives.[22]

Physical activity or lack thereof plays an important role in the likelihood of developing cancer.[23,24] Other known lifestyle and preventable causes of cancer include tobacco use, alcohol intake, poor diet, and obesity. Clearly, lifestyle habits and practices are vitally important in lowering the risk of cancer.

Unfortunately, most people in the general public regard cancer as a "act of God" and do not understand the powerful role that daily habits and actions play. Physicians should counsel patients on this aspect of lifestyle and cancers in every clinical encounter.

17.5 PHYSICAL ACTIVITY, DIABETES, PRE-DIABETES, AND THE METABOLIC SYNDROME (METS)

Regular physical activity is a cornerstone in both the treatment and prevention of diabetes, pre-diabetes, and the metabolic syndrome.[25–27] For this reason, routine physical activity should be recommended for individuals in all of these categories. The level of aerobic activity that should be recommended is the same as for non-diabetic individuals, namely, 150 minutes of moderate intensity physical activity per week.

In addition to lowering the risk of diabetes, regular physical activity can play a significant role in the management of diabetes for individuals who already have this condition. This fact is recognized by the Physicians' Statement on Physical Activity from the American Diabetes Association[25]

as well as the Lifestyle Management Standards for Medical Care and Diabetes 2018 from the American Diabetes Association.[28]

The Diabetes Prevention Program (DPP) showed that individuals who have pre-diabetes (fasting glucose between 100 and 125 mg/dL) could reduce their risk of progressing to diabetes by 58% by performing regular, moderate physical activity and losing five to seven pounds.[29] Recommendations for physical activity and the metabolic syndrome are similar to those for diabetes and pre-diabetes and recognized by multiple organizations, including the AHA.

It has been estimated that 36–38% of individuals in the United States have metabolic syndrome by National Cholesterol Education Program III and IV (NCEP III and IV) criteria.[30,31] The clustering of risk factors in metabolic syndrome, including elevated fasting glucose, reduced high-density lipoprotein cholesterol (HDLC), elevated triglycerides, increased waist circumference, and elevated blood pressure, makes this a particularly dangerous condition with regard to risk of CVD. In fact, NCEP III recommends that people who have metabolic syndrome be treated as though they already have CVD. The association of regular physical activity represents a proven strategy for lowering the risk of developing MetS as well as assisting in its treatment.[32]

17.6 PHYSICAL ACTIVITY AND WOMEN'S HEALTH

The PAGA 2018 Scientific Report concluded that regular physical activity can play multiple important roles in women's health.[33,34] These benefits include reducing the likelihood of dying from multiple chronic diseases, including CHD, obesity, diabetes, and certain cancers. Regular physical activity also plays important roles in pregnancy and post-partum, including reducing the risk of excessive weight gain and improved fitness and emotional wellbeing.[33–35] (See Chapters 21 and 22 for more details.)

17.7 PHYSICAL ACTIVITY AND YOUTH

The PAGA 2018 Scientific Report lists multiple benefits from physical activity for children between the ages of 3 and 17.[7] In 2008, not enough information was available for children below the age of five, but the PAGA 2018 document reported that numerous studies in the preceding ten years had allowed the recommendations to extend down to the age of three.

The recommendation made by the PAGA 2018 was 60 minutes of moderate to vigorous physical activity (MVPA) on a daily basis and three sessions of musculo-skeletal training weekly for children between the ages of 3 and 17. Unfortunately, only 20% of children achieve these levels.[36,37] It is particularly unfortunate that the levels of physical activity are so small in children. We now know that the roots of many chronic diseases that become manifest in adults have their roots in childhood. For all of these reasons, it is important that physicians counsel both children and families on the importance of the multiple benefits of physical activity for all children over the age of three.

17.8 PHYSICAL ACTIVITY IN OLDER ADULTS

The same recommendations for regular moderate or vigorous intensity physical activity that apply to younger adults also apply to adults over the age of 65, according to the PAGA 2018 Scientific Advisory Report. In 2016, individuals over the age of 65 comprised approximately 13% of the U.S. population and are projected to reach 72.1 million individuals (19%) of the total population by Year 2030.[38] This age group is the most rapidly growing of all population segments in the United States.

Physical activity conveys multiple benefits for people over the age of 65, including decreased risk of chronic disease or as an adjunct to its treatment, increased physical function, and decreased risk of falls.[39] Increased physical activity may be particularly valuable for individuals who are frail or have lower levels of current physical activity. Unfortunately, only 27% of individuals over the age of 65 meet current recommendations for levels of physical activity.[40] For all of these reasons, clinicians should emphasize to individuals over the age of 65 the multiple and important health benefits from continuing to maintain an active lifestyle.

17.9 PHYSICAL ACTIVITY IN INDIVIDUALS WITH CHRONIC CONDITIONS

The PAGA 2018 Scientific Advisory Committee Report recommends that individuals who have chronic conditions try to maintain the same levels of physical activity that are recommended for individuals without chronic conditions. However, individuals with chronic conditions need to be conscious of any limitations that they may have and discuss their current situation and potential modifications of the Physical Activity Guidelines with their personal physicians.

Chronic conditions are very common in the U.S. population. Over half of the American population (51.7%) have at least one chronic condition, and approximately one-third (31.5%) have multiple chronic conditions.[41] About 80% of individuals over the age of 65 have multiple chronic conditions.

The list of the most common chronic conditions in the United States in adults and children is found in Figure 17.2. Physical activity is particularly important in the areas of osteoarthritis[42] and hypertension[43,44] as well as either management or prevention of type 2 diabetes (T2DM).[45] Individuals who have multiple sclerosis,[46] spinal cord injuries,[47,48] or intellectual disabilities[49] may need to make modifications of the physical activity plan in order to meet with the realities of their current condition. However, increased physical activity is important even for these individuals.

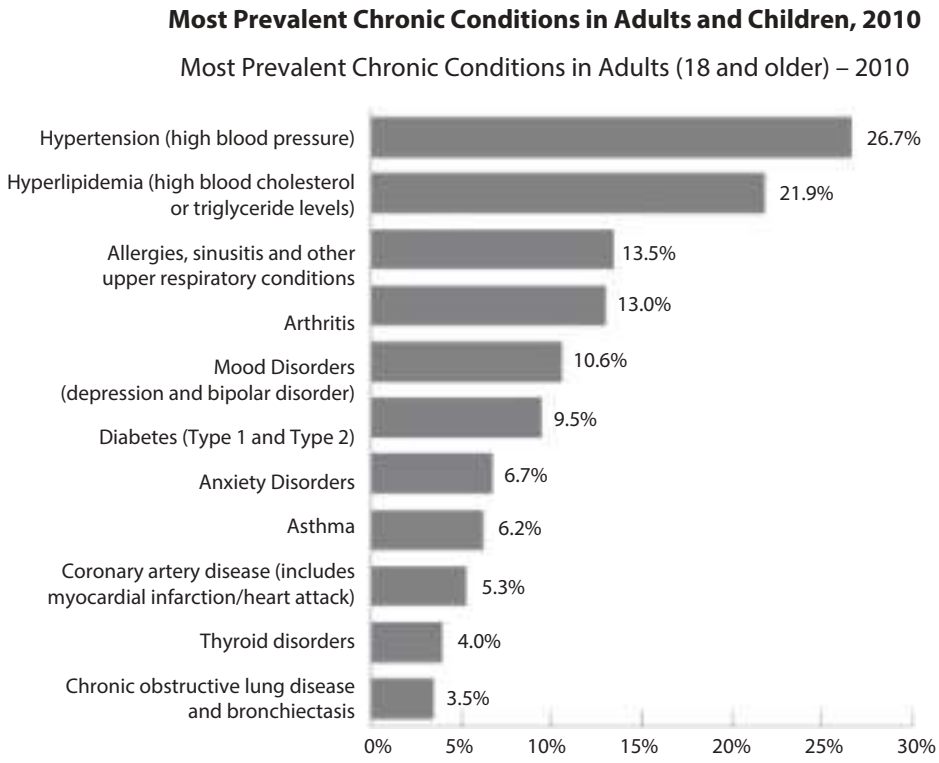


FIGURE 17.2 Most prevalent chronic conditions in adults and children, 2010.

17.10 PHYSICAL ACTIVITY, WEIGHT GAIN, AND OBESITY

The PAGA 2018 states that regular physical activity lowers the risk of weight gain and obesity. In the United States, unfortunately, over 70% of the adult population is either overweight or obese. While physical activity alone is not a powerful modality for acute weight loss, it is critically important to the long term maintenance of weight loss.[50,51] Moreover, physical activity lowers the risk of weight gain, which is also a significant risk factor for a variety of diseases, such as CVD, T2DM, and MetS.[52] Moreover, physical activity in combination with caloric restriction has been demonstrated in multiple trials to increase the likelihood of short-term weight loss.[50–53]

For all of these reasons, it is important for all clinicians to discuss weight, weight gain, and obesity in every clinical encounter. More information concerning obesity and its treatment and relationship to other chronic diseases is found in Chapters 20 and 21.

17.11 PHYSICAL ACTIVITY, COGNITION, AND BRAIN HEALTH

Many clinicians are surprised to learn that physical activity plays a critically important role in brain health.[54,55] This was underscored in the PAGA 2018 as well as a Presidential Advisory issued by the AHA and the American Stroke Association (ASA) on "Optimizing Brain Health."[56] The risk factors for diminished brain health are similar to those for CVD. For this reason the AHA and ASA have recommended that people follow what is called the "Life's Essential 8,"[6] which are the lifestyle related guidelines for reducing the risk of CVD. There is now also accumulating evidence that regular physical activity lowers the risk of dementia and Alzheimer's disease[57,58] (see also Chapter 21). There is a suggestion that inflammation plays a role in the development of dementia and Alzheimer's disease. The recommendation is to begin positive lifestyle measures as early in life as possible and maintain them throughout the lifespan.

17.12 THE ROLE OF PHYSICIANS IN PROMOTING AND PRESCRIBING INCREASED PHYSICAL ACTIVITY

Numerous studies have shown that physician recommendation is a powerful motivational tool for changing behavior. This is particularly true in the area of physical activity. As already indicated, only 25% of the adult population in the United States is active at the level recommended by the

PAGA 2018 and the AHA. Unfortunately, fewer than 40% of physicians routinely counsel people in the area of physical activity.[59–61] This is particularly unfortunate, since over 70% of individuals see their primary care physician at least on an annual basis. Thus, it is important for physicians to recognize the power of physical activity to lower the risk of multiple chronic diseases and counsel every patient on this. The recommendation of 150 minutes of moderate intensity physical activity per week is highly appropriate for virtually every patient and should be referred to by clinicians.

17.13 PRACTICAL APPLICATIONS

Both the American College of Sports Medicine (ACSM) and the PAGA 2018 Guidelines have stated that for the vast majority of individuals, physician evaluation is not necessary before starting a moderate level of physical activity program.[62] Individuals who have been extremely sedentary, however, might benefit from additional workup by their physician.

For the vast majority of people, the goal is to remove any impediment that might occur that prevents individuals from exercising. Thus, following the mantra of "starting low and going slow" is appropriate for virtually every individual. Patients who are either overweight or obese or have been very inactive could benefit from further evaluation from their physician. Also, individuals who have a history of CHD might benefit from procedures such as an exercise tolerance test prior to starting an exercise program.

Most individuals, however (even those with a history of CHD), can simply start and use common sense to be their guidance if they begin at a low level and proceed slowly, working their way up over a period of weeks or months to the 150 minutes of moderate intensity physical activity per week. It should be noted that in 2008, part of the guidance for people deriving multiple benefits from physical activity involved bouts of at least 10 minutes in duration with a total accumulated daily duration of at least 30 minutes. In the PAGA 2018, this recommendation was revised because evidence existed that even much shorter bouts of physical activity could accumulate to generate important health benefits.

17.14 OVERCOMING SEDENTARY BEHAVIOR

The PAGA 2018 Guidelines emphasize for the first time accumulating data that sedentary behavior increases the risk of CVD. Individuals who are sedentary for more than seven hours per day sitting or lying down during waking hours are at particularly high risk for all-cause mortality and mortality from CVD and T2DM and perhaps some cancers.[63,64]

The good news is that individuals who have relatively sedentary occupations can virtually eliminate the increased risk by being active at the level recommended by PAGA 2018. The people who are at the greatest risk of CVD and T2DM are those who are sedentary and also do not engage in any meaningful amount of physical activity. Unfortunately, the average adolescent and adult in the United States spends approximately 7.7 hours a day (55% of monitored time) in sedentary activities.[65,66] Reversing this sedentary behavior trend when advising people who have sedentary occupations involves discussing the danger of this sedentary behavior and the means to ameliorate it by engaging in the recommended levels of physical activity. The relationship between sedentary behavior and levels of physical activity is found in Figure 17.3. This figure depicts that individuals who are sedentary and also have little physical activity in

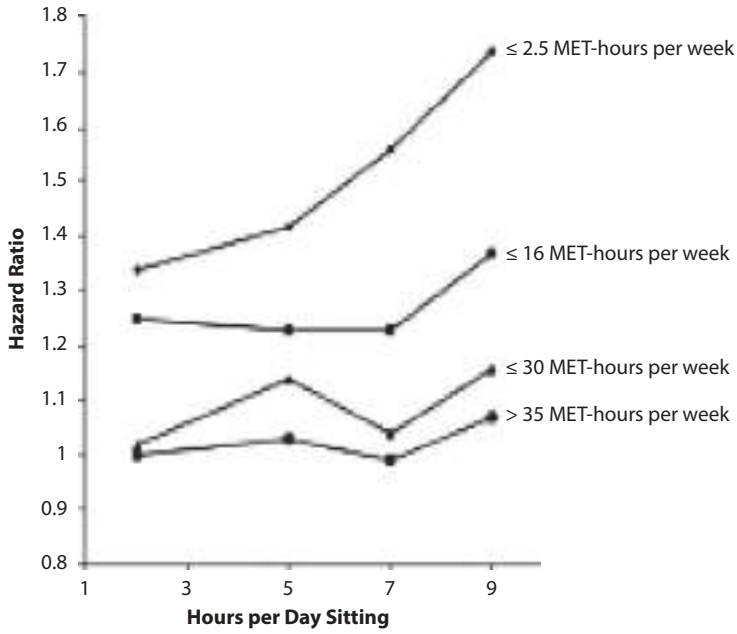


FIGURE 17.3 Relationship between sitting and all-cause mortality, stratified by amount of moderate to vigorous physical activity.

their daily lives are at the greatest risk for CVD and other chronic diseases.

17.15 PUBLIC HEALTH CONSIDERATIONS

The PAGA 2018 Scientific Report focuses attention on activity that can be done from a public health perspective to increase the likelihood of individuals becoming more physically active.[65–71] This involves endeavors such as creating more parks and green space, utilizing school facilities, and mounting campaigns concerning the benefits of physical activity.[72–75] It is clear that lack of physical activity in the United States is both an individual problem and a significant public health problem. In the world, overall, inactive lifestyle is a major component of the World Health Organization's campaign to ameliorate non-communicable diseases (NCDs). The good news is that there is an emerging literature showing that well-designed public health programs that are structured and follow a sound theoretical basis can make a difference in many individuals' lives in terms of their level of physical activity.

17.16 SUMMARY/CONCLUSIONS

There is no longer any serious doubt that regular physical activity yields multiple benefits. Conversely, an inactive lifestyle is hazardous to individuals' health. There is an accumulating literature about the multiple benefits of increasing physical activity. Perhaps most important in this area is the enormous compendium of background information contained in the Physical Activity Guidelines for Americans 2018 Scientific Advisory Report. This is a report that should be in the toolbox of every lifestyle medicine clinician.

Certainly, physical activity is one of the most important of the lifestyle medicine pillars. It is incumbent upon physicians to counsel patients about the importance of regular physical activity on every clinical encounter. Moreover, it has been demonstrated that physicians who are physically active themselves are more likely to counsel patients in this area. For all these reasons, the relationship between lifestyle medicine and physical activity is very important, as summarized and expanded upon in the PAGA 2018 Scientific Report.

CLINICAL APPLICATIONS

- The Physical Activity Guidelines for Americans 2018 contains a vast compendium of scientific literature on the multiple benefits of physical activity.
- The PAGA 2018 Report (at least the Executive Summary) should be in the toolbox of every lifestyle medicine physician.
- Regular physical activity is one of the best strategies that most people can use in their lives to lower their risk of various chronic diseases and improve their daily quality of life, sleep, energy level, and happiness.
- All of these points are made clear with substantial evidence in the PAGA 2018 Scientific Report.

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18 Overcoming Sedentary Behavior

James M. Rippe, MD

KEY POINTS

1. Sedentary behavior, particularly at levels higher than seven hours of sitting or lying down during waking or throughout the day, is associated with increased risk of all-cause mortality, mortality from cardiovascular disease, type 2 diabetes, as well as some cancers.
2. Regular, moderate to vigorous physical activity has been shown to offset many of the increased risks associated with sedentary behavior.
3. The benefits of moderate to vigorous physical activity are particularly strong for individuals with high levels of sedentary behavior who are also currently inactive. This information suggests that individuals who spend a considerable amount of time each day in front of computer screens or in other sedentary activities should be particularly counseled about the important need for regular physical activity to offset some of the consequences of sedentary behavior.

18.1 INTRODUCTION

A great deal of research has emerged over the past decade linking sedentary behavior to a variety of adverse health concerns.[1] Good data are now available to suggest that sedentary behavior increases the risk of a variety of conditions, including coronary heart disease (CHD), type 2 diabetes (T2DM), and some cancers. Sedentary behavior has been defined in this research as "any behavior which is characterized by energy expenditure of 1.5 METs or less while in a sitting, reclining or lying position."[2] In addition to the negative association with health outcomes, unfortunately, sedentary behavior is highly prevalent in the United States. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) indicate that children and adults in the United States spend on average approximately 7.7 hours per day (55% of monitored time) being sedentary.[3] Thus, reversing the sedentary behavior trend in the United States can generate significant health improvement. The current chapter examines sedentary behavior and its relationship to various health issues utilizing the framework established by the Physical Activity Guidelines for Americans 2018 (PAGA 2018) Advisory Committee Scientific Report.

18.2 SEDENTARY BEHAVIOR AND ALL-CAUSE MORTALITY

The PAGA 2018 Scientific Report rated the evidence for a relationship between the greater amount of time in sedentary behavior and all-cause mortality as "strong." Based on a total of 9 systematic reviews and meta analyses that consisted of 20 original studies, a significant relationship between sedentary behavior and all-cause mortality was revealed.[4–11] Some of these studies also showed that T.V. viewing or screen time was also related to all-cause mortality.[12,13] Importantly, there appears to be a dose–response relationship between sedentary behavior and all-cause mortality.[7,9] Studies that have reviewed this relationship have revealed that for every one-hour increase in sitting time, or for more than seven hours a day sitting, there were dose–response relationships between increased sedentary behavior and all-cause mortality.[7] A similar response was revealed between T.V. viewing and all-cause mortality, where a dose–response relationship was also found.[9]

An inverse relationship exists between moderate to vigorous physical activity and sedentary behavior when it comes to all-cause mortality.[10,11] The adverse effects of sedentary behavior on all-cause mortality are strongest among people who have low amounts of physical activity. This relationship is illustrated in Figure 18.1.

Individuals who had greater than seven hours of sedentary behavior combined with low levels of moderate or vigorous physical activity substantially increased their risk for all-cause mortality. Conversely, individuals who accumulated between 15 and 30 MET hours per week of moderate intensity physical activity substantially lowered their risk of all-cause mortality, even if they were sedentary for more than seven hours a day.[11] The relationship between MET hours per week exercising and risk based on the number of hours per day sitting showed that individuals who exercise at the recommended level of accumulating 150 minutes per week of moderate intensity physical activity will substantially lower the increased risks caused by sedentary behavior. Thus, it is particularly important for individuals who have sedentary occupations to engage in regular physical activity at levels recommended by PAGA 2018.

To put this in perspective, the PAGA 2018 Scientific Report recommends 10–15 MET hours per week of physical activity. There are additional benefits for individuals who choose greater than 30 MET hours per week (roughly 150

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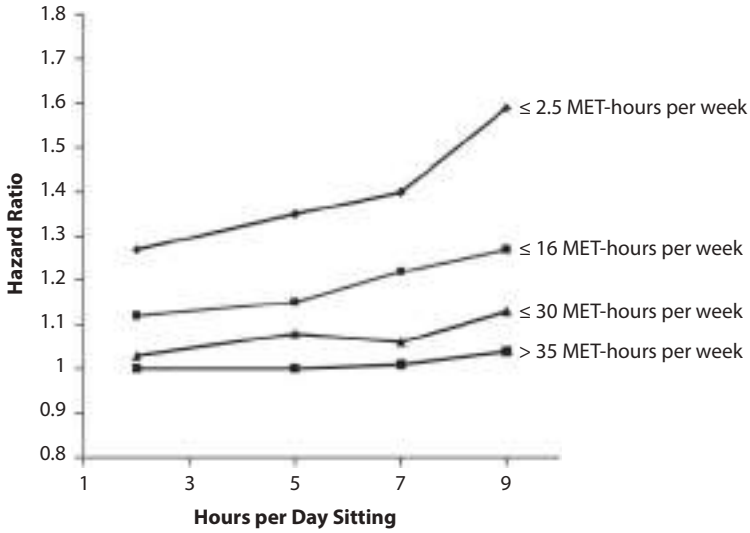


FIGURE 18.1 Relationship between sitting and all-cause mortality, stratified by amount of moderate-to-vigorous physical activity. (Source: Adapted from data found in Ekelund et al, 2016.)

minutes per week of moderate intensity physical activity), although the incremental benefit is small compared with the benefit of achieving the recommended dosage of moderate to vigorous physical activity outlined in the PAGA 2018 document. The important take home point is that individuals who have sedentary occupations (such as office work) will particularly benefit from following the guidelines for moderate to vigorous physical activity on a weekly basis.

In addition, there has been some suggestion that taking breaks in sedentary behavior may reduce the adverse health consequences related to all-cause mortality. Although there is some research in this area, further research is required to determine whether or not periodic breaks to sedentary behavior will ameliorate some of the adverse health effects of this behavior.

The relationship between sedentary time and moderate to vigorous physical activity is depicted graphically in Figure 18.2.

As this figure illustrates, the more sedentary time an individual participates in, the greater the risk of all-cause mortality, unless they are physically active. Physical activity at levels recommended by the PAGA 2018, as shown in this figure, can largely ameliorate the increased risks of sedentary behavior.

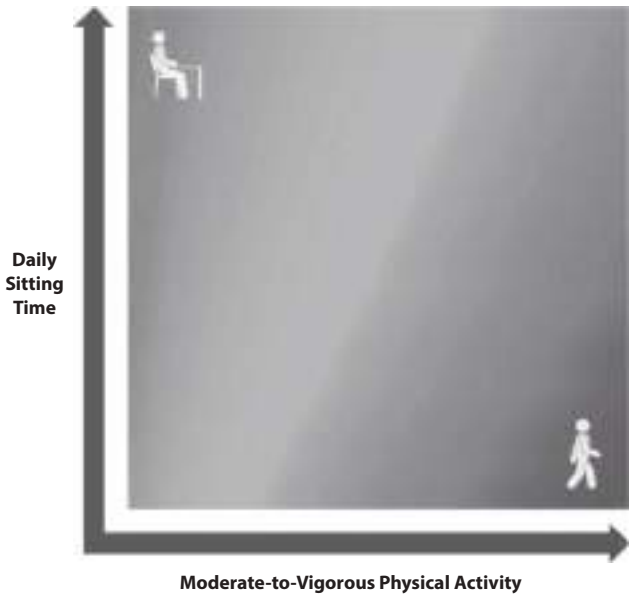


FIGURE 18.2 Relationship among moderate-to-vigorous physical activity, sitting time, and risk of all-cause mortality. (Source: Adapted from data found in Ekelund et al, 2016.)

18.3 SEDENTARY BEHAVIOR AND CARDIOVASCULAR DISEASE (CVD) MORTALITY

The risk of mortality from cardiovascular disease (CVD) and its relationship to sedentary behavior are very similar to the relationship between sedentary behavior and all-cause mortality.[6,10] The PAGA 2018 Scientific Report documented that increased physical activity ameliorated increases in sedentary behavior and also demonstrated that there is strong evidence of a dose–response relationship. Thus, the more physical activity an individual participates in, the more the increased risk of sedentary behavior is reduced. As depicted in Figure 18.3, sedentary behavior of greater than five hours a day starts to significantly increase the risk of cardiovascular disease and is further increased if sedentary behavior is greater than seven hours a day.

18.4 SEDENTARY BEHAVIOR AND CANCER MORTALITY

The PAGA 2018 Scientific Report judged that the evidence of a direct relationship between the amount of time spent

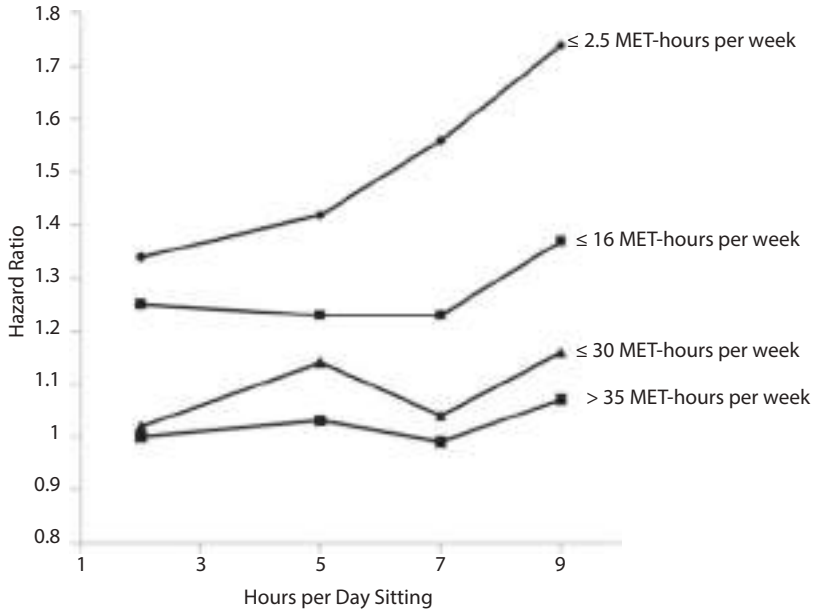


FIGURE 18.3 Relationship between sitting and cardiovascular disease mortality, stratified by amount of moderate-to-vigorous physical activity. (Source: Adapted from data found in Ekelund et al, 2016.)

in sedentary behavior and higher mortality rates from cancer is limited.[10] A number of studies have reported a significant association between sedentary activity and cancer, but the results are inconsistent. Furthermore, cancer is a heterogeneous disease, and many of the risk factors for cancer mortality are clearly affected by such issues as cancer screening, treatment availability, and efficacy. The PAGA 2018 Scientific Report also concluded that there was insufficient evidence available to determine whether or not the relationship between sedentary behavior and cancer mortality was modified by physical activity. Evidence among specific types of cancer judged by the PAGA 2018 was determined to be "moderate."[14] For example, moderate physical activity in sedentary individuals decreased the added risk of sedentary behavior for breast cancer, ovarian cancer, prostate cancer, and lung cancer.

18.5 SEDENTARY BEHAVIOR AND TYPE 2 DIABETES (T2DM)

A strong and significant relationship exists between the amount of time spent in sedentary behavior and the risk of type 2 diabetes (T2DM).[4–6,10,13] The issue of whether or not this is a dose–response relationship is supported by only limited evidence. The issue of T2DM appears to be different between individuals who are active and inactive. Active individuals did not experience elevated risk of T2DM, whereas inactive participants who reported high T.V. viewing were at increased risk of T2DM. The relationship between physical activity and T2DM is outlined in more detail in Chapter 20.

18.6 SEDENTARY BEHAVIOR AND WEIGHT STATUS

There is a limited amount of evidence to support the relationship between sedentary behavior and weight status.[4,5] Studies that are available in this area show a great deal of variation among results with regard to adiposity. Once again, studies are heterogeneous, which allows only limited support for the concepts and their behavior associated with adiposity.

18.7 SEDENTARY BEHAVIOR AND MODERATE TO VIGOROUS PHYSICAL ACTIVITY

Some evidence suggests that moderate to vigorous physical activity lowers the risk of sedentary behavior.[11] It is important to note, however, that the relative reductions in risk are significant only for those who are the most sedentary. In general, the same relationship holds for CVD mortality as for all-cause mortality, with the significant interaction between levels of physical activity and sedentary behavior for both. The most significant benefits come to those who are the most sedentary. When the data concerning sedentary behavior are stratified by levels of sitting while T.V. viewing, the relationships are still quite similar to the amount of sedentary behavior. Thus, sitting or T.V. viewing significantly increases the risk of all-cause mortality, while the level of moderate to vigorous physical activity lowers the added risk in a dose dependent manner.

18.8 PUBLIC HEALTH IMPACT

High levels of sedentary behavior are associated with increase in all-cause mortality and also mortality from

CVD and T2DM. The high levels of sedentary behavior are also associated with moderate increases in certain cancers, such as breast, ovary, prostate, and lung cancer.

There is good evidence that moderate or vigorous physical activity can lower the increased risk of sedentary behavior. This is particularly true for individuals who have the highest level of sedentary behavior. For all of these reasons, it is important for physicians to assess the level of sedentary behavior in every patient and if needed, recommend increased levels of moderate to vigorous physical activity. The public health impact of these changes could be very significant.[1]

18.9 CONCLUSIONS

Both children and adults in the United States have become increasingly sedentary. The average child or adult in the United States spends 7.7 hours per day being sedentary. This includes screen time, watching T.V., and other tasks sitting or lying down. These levels of sedentary behavior have now been clearly associated with an increase in the risks associated with all-cause mortality and mortality from CVD, T2DM, and some cancers. On the other hand, levels of moderate to vigorous physical activity can offset the increase in sedentary behavior. This is particularly true for individuals who have the highest levels of sedentary behavior and are also inactive. For all of these reasons, physicians should assess the level of sedentary behavior in every patient and recommend increased levels of moderate to vigorous physical activity if individuals are quite sedentary to lower the risk that this behavior carries.

CLINICAL APPLICATIONS

- Physicians should assess the level of sedentary behavior in every patient and recommend increased levels of moderate to vigorous physical activity, if needed.
- Sedentary behavior levels of greater than seven hours per day are associated with the increased risk of all-cause mortality.
- Sedentary behavior is also associated with increased risk of mortality from CVD and T2DM as well as some cancers.
- Moderate to vigorous physical activity may offset the adverse consequences of sedentary behavior. This is particularly true for individuals with a high level of sedentary behavior who are also currently inactive.

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19 Promoting Regular Physical Activity

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KEY POINTS

1. Physicians are credible voices in the area of multiple lifestyle decisions and in particular, promoting physical activity.
2. Physicians should take the lead in not only recommending physical activity to their own patients, but also promoting community involvement to increase physical activity and even national strategies for physical activity.
3. Physical activity yields multiple benefits.
4. Currently, a distinct minority of individuals in the United States are physically active at levels that yield health benefits.
5. Multiple factors impact on the likelihood of maintaining a physically active lifestyle. These include individual factors, community, the communication environment (information technology), physical environment, and public policy.
6. These domains provide important mechanisms for exploring what is known about effective ways of promoting physical activity.

19.1 INTRODUCTION

An enormous literature exists demonstrating the positive relationship between regular physical activity and multiple health benefits. This literature underscores and corroborates two key concepts. First, physical activity can play numerous positive roles in lowering the risk of chronic disease and improving daily lives in individuals throughout their lifespan. Second, despite the known benefits of physical activity, the majority of Americans do not participate in enough of it. This chapter will focus attention on ways that physicians can play an important role in promoting physical activity not only for their own patients, but also for the community and for the nation.

As already indicated in previous chapters of this book, physical activity levels for Americans are typically not enough to obtain the full benefit of an active lifestyle, In fact, in 2015, fewer than half of American adults reported levels of aerobic physical activity consistent with federal guidelines as articulated in the Physical Activity Guidelines for Americans 2018 (PAGA 2018),[1] and 30% of adults reported high levels of inactivity during leisure time.[2] Unfortunately, these data also apply to high school students. Only 27% of U.S. high school students report levels of physical activity that are consistent with guidelines recommended by the PAGA 2018 of 60 minutes or more of physical activity a day.[3] For these reasons, and because the input of physicians is critically important to promote physical activity, it is important to explore ways that physicians can be successful to encourage people to exercise and which carry the most promise to elevate the level of physical activity in the future. In addition, since concern has been raised about sedentary behavior, this chapter will also briefly explore ways of reducing this type of behavior. (More detail about reducing a sedentary lifestyle will be found in Chapter 14.)

19.2 CONCEPTUAL FRAMEWORK FOR FACTORS INFLUENCING PHYSICAL ACTIVITY

There are numerous conceptual frameworks that can be utilized to illustrate the factors that impact on physical activity in the United States. The PAGA 2018 uses the conceptual figure found in Figure 19.1.

As indicated in this figure, multiple influences interact in ways that impact on physical activity. This starts at the individual but extends to the community, communication, and environment as well as public policy.[4] This type of framework has also been used in other areas of behavior, such as nutrition, where a similar socio-ecological model was employed in the Dietary Guidelines for Americans (DAGA) 2020–2025 to address factors that need to be addressed when considering more healthful eating in the United States.

19.3 INDIVIDUAL LEVEL

The most robust data that are currently available relating to effective ways of promoting physical activity come from initiatives that are designed to increase physical activity in individuals.[5] This is not only true for the general population[6–8] but also specifically relates to older adults as well as postmenopausal women and youth.

The types of strategies used to promote physical activity typically involve either one on one sessions or group delivered programs involving structured exercise. Educational approaches have also been used to teach individuals how to employ various strategies to increase regular physical activity. Individual interventions for adults typically are the most flexible way of tailoring advice and support to help individuals to meet their physical activity needs and

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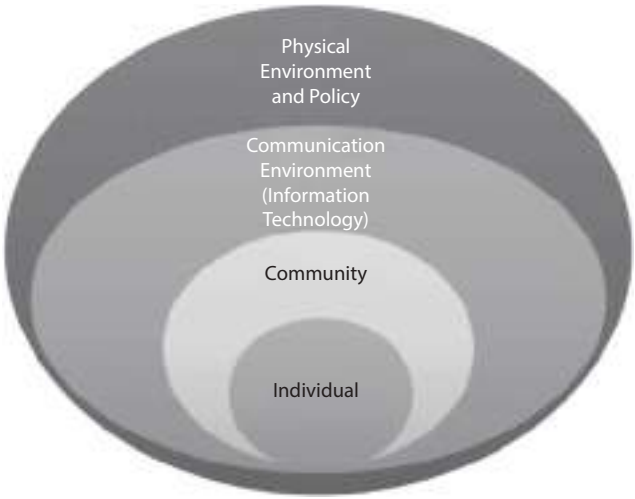


FIGURE 19.1 Conceptual framework for factors that impact on physical activity in the Unites States. (*2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC: U.S. Department of Health and Human Services, 2018).

preferences. Unfortunately, the downside of such programs is that they require a high level of staff involvement and can result in significant costs in the long run. Examples of this kind of initiative are personal training and various types of structured exercise classes that have also been employed to target older individuals. These interventions generally demonstrated a small, but positive, effect on physical activity when compared with controls.

The PAGA 2018 rated the evidence for individual approaches to promote physical activity as "strong." These initiatives often focus on not only physical activity but also other health promoting lifestyle measures such as improved diet (more fruits, vegetables, and whole grains) as well as weight loss and other behaviors.

A variety of interventions have also been utilized in postnatal individuals. This is a group of individuals for whom adequate physical activity may be difficult to increase or maintain.[9] The PAGA 2018 viewed evidence in this area as "limited" because there were heterogeneous results from these programs. The most promising of these efforts involved behavior change strategies including goal setting and behavioral self-monitoring. Particularly promising results have occurred in generally healthy, but inactive, women in the postnatal period.

A variety of efforts have also been employed to promote increased physical activity in healthy youth and have been shown to have considerable promise.[10,11] For this reason, PAGA 2018 rated evidence in this area as "strong." The benefits of these approaches were most apparent when incorporating families or delivered in school settings. It is particularly important to focus on lifetime physical activity such as leisure time pursuits in non-competitive sports in youth. Schools have the additional benefit of utilizing facilities that may be available after school hours. Several studies have emphasized improving sidewalk and street design to promote active commuting to and from school.

19.4 THEORY BASED INTERVENTIONS TO INCREASE PHYSICAL ACTIVITY

Most of the interventions involved in various aspects of lifestyle medicine are based on changing behavior. This, of course, is true of efforts to increase physical activity. Many different theory based interventions have been demonstrated to carry some efficacy in helping people make behavior changes in their lives.[12] Education concerning utilizing these theories for behavior change is becoming more common in medical school studies. This area is so important that we have devoted an entire section to behavior change in this textbook as well as the third edition of this book.[13] The behavior change models that are briefly discussed in this chapter are examined in much more detail in Chapters 20, 25, and 29.

19.4.2 Health Belief Model (HBM)[14–16]

This model was initially developed to explain why many individuals back in the 1950s were not participating in preventive health services. The model posits that the likelihood that individuals will participate in a given health behavior largely depends on their perception of the following three issues:

- Severity of illness(es)
- Benefits from engaging in behavior
- Barriers to engaging in behavior

This model suggests that individuals are more prone to adopt a healthy behavior if they believe it is likely to lower their risk of potential illness and that engaging in these actions carries some benefits. Multiple different factors may prompt actions in this area, such as media campaigns, physician reminders, and the experience of friends and colleagues.

The concept of self-efficacy was subsequently added to the Health Belief Model to increase its ability to actively predict health behaviors. This model has been applied to a variety of long-term health behaviors, including physical activity. Some investigators have criticized HBM because of constructs such as "cues to action," which are empirically difficult to test. In addition, some other models have subsequently been demonstrated to exhibit stronger predictive ability to predict health behavior changes. Nonetheless, HBM may be useful in the hands of physicians, particularly if they are counseling patients to initiate programs of increased physical activity.

19.4.3 Theory of Reasoned Action, Planned Behavior, and Integrated Behavior Model

The Theory of Reasoned Action (TRA) starts from premises found in both cognitive and social psychology.[17,18] This

model proposes that an individual's likelihood of engaging in a particular health behavior, such as increased physical activity, can be predicted by the strength of their intention to engage in the behavior. These intentions are a combination of individual's attitudes about the behavior and "social norms." The TRA model is extended to what is called the Theory of Planned Behavior (TPB), which added perceived facilitators and barriers to behavior. The Integrated Behavior Model (IBM) further extended TRA and TPB models by adding the importance of evaluating the intention to engage in behavior.[19] These models have all been demonstrated to be efficacious in various behaviors, including increased physical activity.

19.4.4 Transtheoretical Model

The Transtheoretical Model (TTM)[20,21] is a model developed from many different psychological theories. Prochaska and colleagues first described this model by noting that people vary in terms of motivational readiness to make behavior change. It was initially applied to cessation of smoking. The model is based on people progressing to a series of changes called "stages of change." The model outlines moving from pre-contemplation to contemplation, followed by action, and subsequently followed by maintenance. The TTM model has been widely adopted throughout behavior medicine and is very useful in the area of physical activity.

19.4.5 Social Cognitive Theory[22, 23]

The Social Cognitive Theory (SCT) is a model based on social learning theory. It focuses on individuals' responses to watching others' behavior (this is referred to as "modeling"). Self-efficacy is the main psychological construction for SCT and can be increased through mass experiences, social modeling, improved physical and emotional states, and verbal recommendations.

19.4.6 Positive Psychology[24]

The science of positive psychology has emerged as an area of interest in behavior change. Positive psychology is defined as the scientific study of "conditions and practices that contribute to the flourishing or optimal function of people, groups and institutions." This model is based on the belief that the best way to address behavioral changes is by leveraging psychological strengths. This model has been utilized in a variety of chronic diseases. The typical framework for applying positive psychology includes recommendations to express gratitude to others, recognizing a person's individual strengths, and engaging in acts of kindness as well as mindful meditation.

19.4.7 Overcoming the Intention/Behavior Gap[25]

Recent attention has focused on how to overcome the gap between what individuals intend to do and what they actually accomplish in terms of making behavioral change. Intention alone typically has not been found to be reliable behavior for physical activity changes. To employ this model to increase individuals' likelihood of actually changing their behaviors, physicians should consider such strategies as helping the patient plan specific goals and enhance self-efficacy and positive emotional response.

19.5 COMMUNITY BASED INTERVENTIONS TO INCREASE PHYSICAL ACTIVITY

Physicians can play an important role in leading or supporting community based interventions to increase physical activity.[26] A variety of community-wide efforts have been undertaken to attempt to increase levels of physical activity. These have been divided into a variety of domains, including informational, behavioral/social, and policy/environmental approaches.

These approaches are based on the concept that many adults report barriers to increasing regular physical activity that can be traced to community issues. For example, the most commonly cited factor is lack of access to facilities or safe places to engage in physical activity. Healthcare practitioners can encourage physical activity behavior, but unless individuals have a place in which to be active, they are often unable to follow such recommendations. The goal of community approaches is to make the community more "physically active friendly" and includes both general initiatives and specific recommendations for places. Included in these initiatives and places are the following:

- *Schools*[27–29]—Many physical education and health education curricula are available to provide a framework for promoting physical activity and have been shown to be effective. Unfortunately, there is a paradox in the United States. School buildings and grounds, which are the most widely available public resources and could be used for physical activity, are often underutilized. Studies show that students' engagement in physical activity during leisure time at school suggests that few students use this time to be physically active. Factors associated with increased physical activity at schools include the presence of dedicated spaces for physical activity (e.g., sports fields, gyms, access to sports equipment, interesting and newer playgrounds, and sufficient space for physical activity). Supervision also has been shown to increase participation in physical activity. Unfortunately, many schools have policies to restrict access to school grounds by students and community members outside of school hours. This is a particular problem in low income communities, which often lack other safe spaces for physical activity.
  In addition, active transport by walking or cycling to and from school can yield substantial physical

activity benefit for children and youth. This has been shown by recent evaluation by the Safe Routes to School Program.[30] Some states, such as California, have now dedicated funding to begin to address this issue.

- *Worksites*[31,32]—Many employees spend at least half of their waking hours at work, so worksites are a natural place to try to increase physical activity. Furthermore, physically active jobs have decreased and sedentary jobs have increased in the past few decades. A variety of initiatives have shown some promise in increasing physical activity in the workplace. These include flexible work hours and removing potential barriers to physical activity, such as establishing facilities and a safe place to park bicycles, and providing showers for employees to encourage them to be physically active. One interesting initiative in this area was performed by Dishman et al. in their "Move to Improve" in a multi-site, randomized controlled trial. This study involved putting together specific plans to remove perceived barriers and improve management support for physical activity. At the end of a 12-week intervention, only 2.5% of individuals at control sites engaged in 150 minutes of moderate to vigorous physical activity on a weekly basis, while 51% of the intervention sites met these criteria.[33] This suggests that well-structured worksite programs can make a substantial difference.
- *Community organizations*—Numerous community organizations are available to provide facilities and programs with the goal and potential to increase physical activity. These include health clubs, dance studios, swimming pools, sports leagues, etc. Non-profit organizations such as the YMCA, YWCA, and Boys' and Girls' Clubs can also provide spaces for increased physical activity. In addition, many new housing developments are now including recreational and fitness facilities. This area remains one of active study.
- *Public recreation facilities and built environments*—Public parks and recreational facilities are widely used, with about 80% of the population making some use of municipal facilities. A substantial portion of individuals also utilize parks' programs and services.[34] In fact, in one survey of 114 parks in major U.S. cities, walking and fitness facilities were particularly well utilized. Not surprisingly, parks in low income neighborhoods are utilized less than those in more affluent communities. It should also be noted that parks are eager to have the public use their facilities as venues for increased physical activity. A survey of 144 recreation center directors in San Diego showed that 75% were interested in partnering with health professionals and trained staff on physical activity leadership.[35]

  The Community Preventative Sources Task Force now includes recommendations for making built environments more "activity friendly" along with increasing physical activity.[36] The built environment strategy combines improved pedestrian lanes and environmental design to improve pedestrian bicycling activity, which can facilitate increasing the level of physical activity.

19.6 PROMOTING USE OF PLACE FOR PHYSICAL ACTIVITY

A number of health departments have become involved in analyzing ways of attracting more people to utilize such facilities as part of the initiative to increase physical activity. This initiative includes publicity campaigns and fun walks with refreshments and tee shirts donated by local businesses. These initiatives have often resulted in recommendations from the public to increase the number of trails available for walking.

It should also be recognized that often, environmental policy interventions designed to increase physical activity need to be justified for cost effectiveness. A program such as the CATCH (Coordinated Approach to Child Healthcare) program showed a large economic benefit with regard to quality of life as well as years of life saved (2 ALY).[37] This suggests that an important body of literature may demonstrate that increased physical activity can generate a high rate of return on investment. A number of programs have been developed utilizing the Guide for Preventative Community Services, which rates the effectiveness of various programs.

- *Primary care settings*—A number of different primary care interventions to increase physical activity have been attempted, including counseling sessions with primary care providers of short duration (2–10 minutes) or long duration (e.g., 40 minutes).[38,39] Some of these programs provide physician contact only, while others provide a combination of counseling and printed materials.
  Evidence cited in the PAGA 2018 report showed that primary care initiatives to promote physical activity were effective when compared with "usual care conditions." The primary care setting is particularly appealing, since over 70% of adults see their primary care physician at least once a year. Counseling with written prescriptions has been demonstrated to be more effective than simply a limited amount of counseling.[40]
- *Nurse delivered programs*—A number of studies have also demonstrated some benefit from nurse delivered programs to increase physical activity.[41,42] These programs are particularly attractive, since nurse outreach can be useful given the convenience for some populations, such as frail adults

and those with chronic conditions. Nurses also can provide personal contact and program customization, which may be particularly useful for behavior change in these populations. The ability of nurses to see patients in their home environment can also involve family members and can further facilitate physical activity participation. Continuity of care can be an additional benefit from nurse delivered programs.

19.7 COMMUNICATION/ ENVIRONMENTAL LEVEL

A variety of new Information and Communication Technologies (ICTs) have provided additional modalities with considerable potential for increasing the level of physical activity for a wide variety of individuals. Importantly, these ICTs reach out across to individuals at every stage of lifespan. Approaches to studying ICTs have been divided into domains such as wearable activity monitors, cellphone assisted interventions, web based or internet developed interventions, computer tailored print, multiple, and phone programs, and interactive video games, which are designed to promote activity through player exercise.

- *Wearable activity monitors*—The PAGA 2018 report rated the evidence for wearable activity monitors such as pedometers, accelerometers, etc. used in conjunction with behavior strategies to potentially increase levels of physical activity in the general population of adults as well as those with type 2 diabetes as "strong."[43–45] These monitors, used in conjunction with behavioral strategies, expand and enhance the possibilities for motivation to increase physical activity. Newer activity monitors have been shown to have good reliability and fluidity, which makes them promising intervention tools for population-wide physical activity promotion.
- *Telephone assisted intervention*—A number of interventions have been taken over the last few decades involving telephone reminders.[46,47] These interventions have been shown to generate strong evidence for increased physical activity in the general adult population. Since phone ownership is highly prevalent in the United States, these interventions show great promise for increasing physical activity, because they allow broad dissemination of advice and counseling for adult populations.
- *Web based or internet delivered interventions*[48]—A number of new web based and internet delivered interventions are now available. The PAGA 2018 rated the effects of these interventions as "strong" for increasing physical activity in the general population. PAGA 2018 Guidelines also rated web based or internet delivered programs for individuals with T2DM as "limited" due to the heterogeneity of studies and results. These interventions are particularly attractive because they have such broad dissemination and can allow even small increases in physical activity to generate significant public health impact.
- *Computer tailored print interventions*—These are interventions that collect information through mailed surveys and then are utilized to generate computer tailored mailings containing advice about personal physical activity and support.[49] There are some data to suggest the benefit of these types of interventions when compared with treatment controls. These interventions are particularly useful in populations that have lower computer technology literacy or who live in remote areas.
- *Mobile phone programs*—Programs that utilize text messages appear to have a small to moderate positive effect on physical activity in the general adult population.[50–52] Smartphone applications may be particularly appropriate for children and adolescents. Smartphone applications are particularly appropriate for text-savvy children. Their use with children and adolescents appears to result in a stronger association with increasing physical activity in these populations.
- *Social media*—Physical activity monitors that utilize social media are rapidly developing.[53–55] There is a paucity of long -term trials for these interventions. However, the use of social media with complementary communication channels may improve the likelihood of physical activity messages being beneficial. This is true for population groups that are particularly strong users of social media.
- *Interactive video games promoting active player exercise*—Some evidence exists that this type of intervention can increase levels of physical activity.[56–58] This is particularly true for youths who are actively utilizing video games. This approach may be particularly useful during school times and classroom settings. There is very little research, however, on the efficacy of these programs.
- *Point of decision prompts*—There is good evidence that point of decision prompts such as signage to encourage use of stairs rather than elevators can have a positive impact on levels of physical activity.[59,60] Another advantage of this type of intervention is the ubiquitous presence of stairways in most public accommodations.
- *Access to indoor/outdoor facilities*—Having access to either indoor facilities (e.g., gyms, other recreational facilities, health clubs, swimming pools) or outdoor recreational facilities (e.g., parks, trails, and green space) is associated with

increased levels of physical activity in both children and adults compared with environments that do not have these features.[61–63] A useful summary of these types of interventions can be found at the National Physical Activity Plan (U.S. Report Card on Walking and Walkable Communities 2017).[64]

19.8 INTERVENTIONS TO REDUCE SEDENTARY BEHAVIOR

An accumulating body of information and evidence has emerged that sedentary behavior can have a significant adverse impact on health consequences. This issue is so important that an entire chapter (Chapter 18) has been devoted to this aspect. Strategies to promote physical activity should also address ways of reducing sedentary behavior.

Sedentary behavior in youth can be addressed by such strategies as lowering the amount of television viewing and other screen time. These interventions have been shown to have small, but consistent, results in reducing sedentary behavior.[65–67] This evidence may also be applied to home based interventions, although research in this area is in its infancy. With regard to adult interventions, some data suggest that the educational and behavioral approaches to reduce sedentary behavior may be effective.[68,69] Research in this area has demonstrated small, but consistent, impacts on increasing levels of physical activity.

Work site interventions, such as those that target workers who perform duties primarily while seated, may also have significant short-term impact on reducing sedentary behavior.[70,71] These interventions are appealing because they can be implemented during times when physical activity is generally not feasible.

19.9 CONCLUSIONS

Physicians can and should play a significant role in promoting increased levels of physical activity not only for their own patients but also for the community at large. As already indicated in multiple chapters in this book, lack of physical activity is a significant and pervasive health risk in the United States and other industrialized countries. To solve this problem will require a multifaceted approach.

It has been estimated that less than 25% of the adult population is active enough to attain benefits outlined by the Centers for Disease Control (CDC), the American College of Sports Medicine, and the PAGA 2018. The various modalities discussed in this chapter may help improve this very low participation rate. Since physicians are a trusted source of information, it is incumbent upon physicians to play a role in multiple aspects and initiatives to promote increased physical activity. The good news is that there are multiple opportunities available to help people become more physically active. These opportunities should be discussed by physicians in every office visit.

CLINICAL APPLICATIONS

Physicians are a credible and respected source of information about various health issues. Physical activity should certainly be one of these.

Physicians should routinely recommend increased physical activity not only in their clinical encounters but also in the various venues in the community where options exist to encourage more increased physical activity.

The model proposed by the Physical Activity Guidelines for Americans 2018 Scientific Report 2018 emphasizes that multiple domains, such as individual, community, communication environment, physical environment, and policy domains, exist where physicians can play a significant role.

Behavioral models exist that can contribute to increasing physical activity. Physicians should be aware of and utilize these theoretical constructs, which have been proven to be effective and are outlined in this chapter.

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Part IV

Behavioral Medicine



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20 Behavior Change

Elizabeth Pegg Frates and James E. Eubanks

KEY POINTS

1. Behavior change is the foundational activity through which Lifestyle Medicine works.
2. Healthcare providers need to be versed in behavior change techniques that foster self-efficacy and cultivate a therapeutic relationship to empower the change process.
3. Four key theories outlining behavior change are the Health Belief Model, the Transtheoretical Model of Change, the Social Cognitive Theory, and the Social Ecological Model of Change.
4. The overall approach to any behavior change includes goal setting, follow-up, self-monitoring, action planning, problem solving, and social support.

"Knowledge is power," said Sir Francis Bacon. However, knowledge alone is not powerful enough to instill lasting change. Patients need more than lectures from healthcare providers to adopt healthy habits. The field of behavior change has been an active one for decades, dominated by psychologists, psychiatrists, social workers, nurses, and others at the front line of counseling patients. The entire field is blossoming as more and more attention is being given to the impact of lifestyle on health. Research in this area is on the rise, and the groundwork has been laid by academics and clinicians dedicated to helping people quit unhealthy behaviors and adopt healthy ones: people like Dr. James Prochaska, who created the Transtheoretical Model of Change, and Drs. Miller and Rollnick, who described and continue to teach the process of motivational interviewing. This Behavioral Medicine section of the textbook is an essential one for all lifestyle medicine practitioners. Patients might know the right amount of exercise they need to improve their health. Also, they might know that they need to eat more vegetables or quit smoking. But, they might not do it without the aid of a healthcare provider who is versed in behavior change techniques that foster self-efficacy, who can tap into intrinsic motivation, and who can cultivate a therapeutic partnership that can serve to empower and fuel the change process.

As physicians and clinicians, we are trained in the expert approach. In the expert approach, we spend a significant amount of time lecturing, informing, and convincing the patient to follow the doctor's orders and advice. This is, at times, a necessary approach, especially when managing acute medical conditions like myocardial infarctions, strokes, sepsis, bacterial pneumonia, and meningitis. However, with lifestyle changes, the best approach is a different approach, the coach approach. With the coach approach, the emphasis is on listening to the patient rather than informing the patient, motivating the patient rather than convincing the patient, and collaborating with the patient rather than directing the patient. It takes some time to adopt the coach approach after years of practicing the expert approach, but it is worth it. In order to adopt this approach, the practitioner needs to be familiar with and understand the process of behavior change. This entire section of the textbook is devoted to this important topic.

There are many behavior change theories and techniques. There is also a plethora of research examining their use. By reviewing the state of the current literature, lifestyle medicine practitioners will be able to better understand which techniques are most powerful and in which situations they are most effective. Learning about the different theories is essential, and practicing the different techniques with patients will enable the practitioner to become proficient with them. The more familiar the practitioners are with the concepts and the research, the more likely they are to adopt these behavior change strategies. Many lifestyle medicine specialists are going through their own process of change in the way they practice medicine and prevention.

Most medical schools did not teach behavior change in the past. Although the research on behavior change is more mainstream, teaching behavior change theories and techniques is not yet a routine part of medical training. The Medical College Admission Test (MCAT) changed a few years ago and added a section on psychology, which includes information on behavior change. When standardized tests like medical school entrance exams and board exams change, the courses and curriculum in pre-med courses, medical school courses, and residencies will have to change as well. There is movement in this direction, and it is gaining momentum.

The National Institutes of Health have been interested in behavior change for years. Karen Glanz, PhD, MPH, from the University of Pennsylvania, has spent her career studying behavior change. Dr. Glanz is Director of the UPenn Prevention Research Center at the University of Pennsylvania and Senior Editor of the textbook *Health Behavior and Health Education: Theory, Research, and Practice*.[1] She has been designated a highly cited author, in the top 0.5% of authors in the field, over a 20-year period.

Four theories that Dr. Glanz highlights in her electronic resource on behavior change include the Health Belief

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Model, the Transtheoretical Model of Change, the Social Cognitive Theory, and the Social Ecological Model of Change.[2] These are four theories that every lifestyle medicine practitioner needs to understand. In the Health Belief Model, the theory states that people's beliefs about the risks and benefits of changing behavior influence their readiness to change. If a patient believes that quitting smoking will actually help them to prevent lung cancer, then they are more likely to be interested in quitting. If they believe that since no smokers in their family were diagnosed with lung cancer, they are somehow protected from cancer, that person is less likely to consider quitting. Using the Health Belief Model in practice requires that healthcare practitioners hold conversations with their patients in which they ask open-ended questions that invite patients to talk and share their beliefs. Understanding the beliefs of the patient is key to successful behavior change counseling.

The Transtheoretical Model of Change (reviewed in detail in Chapter 23 by Dr. James Prochaska) describes Five Stages of Change that a patient can transition through for a particular behavior. A patient can be in different stages of change for different behaviors. The stages are:

- Pre-Contemplation
- Contemplation
- Preparation
- Action
- Maintenance

In pre-contemplation, the patient is not even thinking of change, whereas in contemplation, as the name suggests, the patient is contemplating change. They are ambivalent about it. Some people stay in contemplation for years, called Chronic Contemplation. Those in preparation want to change and have an intention to change. They are not ambivalent anymore, but they have yet to take action. Action is the next phase. When the patient makes strides to adopt the new behavior and starts practicing the behavior, they are in action. After action comes maintenance. If the patient has been practicing the new healthy behavior for over six months, they are in maintenance. With each stage comes a set of specific strategies for the healthcare practitioner to use to help the patient move along through the stages. These are outlined in Chapter 23. Patients do not necessarily move through the stages in a stepwise fashion. This is not a straightforward staircase but more of a spiral staircase, where the patient might slip while in action and wind up in contemplation or slip during maintenance and land in preparation. Asking the patient about their readiness to change is key in behavior change counseling.

The Social Cognitive Theory is another behavior change theory that lifestyle medicine practitioners need to know. Albert Bandura, PhD, created this theory, and it explains human behavior using a three-way dynamic, which includes 1) personal factors,2) behaviors, and 3) environmental influences. Dr. Bandura's theory highlights the importance of reciprocity among these three factors. Each one influences the others. When lifestyle medicine practitioners are counseling a patient, they need to account for personal factors, including personality, preferences, beliefs, strengths, and weaknesses. Behaviors that are being reinforced currently and triggers for those behaviors need to be addressed with patients. The environmental influences surrounding the patient are critical and play a role in the behavior change process as well.

Examining the patient's social environments is one of the main points in the Social Ecological Model of Change. In this model, the patient is at the center. Surrounding him is the interpersonal circle, which includes his social network at work, school, home, or on the internet. Around that is the organizational level of influence, including the ethos of his home, work, neighborhood, city, state, and country. Beyond that level is the community influence, which factors in cultural values and norms for the patient. The last level or sphere of influence, the most far-reaching, is the public policy level, where laws impact behavior and require strict guidelines to be followed. This model of change helps practitioners work to set the patient up for success in their daily lives by exploring the world in which the patient lives. It is important to know about the patient, and it is equally important to know about the patient's environment and the external influences on that patient. Taking all these factors into consideration is critical for lasting behavior change.

Looking at the research in the medical literature helps practitioners to share findings from a wide variety of sources about other practitioners helping patients to adopt healthy habits. Specific studies use different patient populations and different behavior change techniques. Review studies collect a number of research articles and examine them for similarities and differences.

In terms of nutrition and diet counseling, a study in the *Journal of the American Dietetic Association* reported that effective counseling techniques were cognitive behavioral therapy (CBT), motivational interviewing, self-monitoring, meal replacement and/or structured meal plans, goal setting, problem solving, and social support. Working with the patient in these areas with these strategies helped them to adopt healthy eating habits. In terms of ineffective strategies, the authors state, "Compelling evidence exists to demonstrate that financial reward strategies are not effective." These extrinsic rewards, like money or gift certificates, might motivate patients, but that motivation rarely lasts after receiving the reward, and it is not compatible with sustainable change.[3]

In a review article that included 22 studies, researchers specifically looked at patients of retirement age to identify the most effective techniques to help this population increase fruit and vegetable consumption. According to the review article, the most useful strategies include barrier identification, problem solving, social support, goal setting, use of follow-up prompts, and providing feedback on performance.[4] There are some consistent messages that are found in different populations and for different behaviors.

Continuing to examine the research will result in highlighting those strategies that are effective across populations and which are best for targeting healthy habits.

Patients with diabetes have been the focus of attention nationally in the public media and in academic institutions with various research studies. In one review article that included research studies from 1975 to 2015, 14 randomized controlled studies were included that examined patients with diabetes and their physical activity levels as well as their dietary patterns. This review identified four behavior change techniques that were repeatedly utilized successfully. They included instruction on how to perform the behavior, behavior rehearsal, demonstration of the behavior, and action planning. Strategies that helped patients to adopt and sustain these two healthy behaviors included supervised physical activity, group sessions, contact with an exercise physiologist, and contact with a dietician. In addition, this review pointed out that the more sessions and the greater the frequency of sessions, the better the results of the trials.[5]

Another diagnosis that has received much attention, from the media as well as from academic researchers, is obesity. In a review article specifically looking at patients with obesity and how to increase their levels of physical activity, the results were split into two areas: 1) how to increase self-efficacy and 2) how to increase the behavior. In order to increase self-efficacy (a belief held by the patient that they could perform the physical activity successfully), the strategies that were most effective included action planning, time management, prompt self-monitoring of behavioral outcome, and planned social support. For increasing the behavior of physical activity, prompt self-monitoring of the behavioral outcome, planned social support, teaching to use prompts, prompt practice, and prompt rewards contingent on effort, not on progress toward behavior, were found to be the most effective.[6]

In another review article that included overweight and obese individuals, there were similar results. Effective behavior change techniques in the short term included goal setting and self-monitoring of behavior. Effective behavior change techniques in the long term included goal setting, self-monitoring, feedback on outcome of behavior, implementing graded tasks, and adding objects to the environment, like a step counter. Using the Social Cognitive Theory and the Social Ecological Model of Change concepts that the individual is influenced by their environment is key for sustaining behavior change. In addition, autonomy-supportive, person-centered counseling, including motivational interviewing, was found to be the most effective counseling strategy to help maintain behavior change over time in this population of patients.[7]

In a review of 35 studies, which included adult patients and focused on weight change as well as physical activity behavior, the results revealed that higher autonomous motivation, higher self-efficacy, and higher self-regulation skills like self-monitoring were the best predictors of beneficial weight and physical activity outcomes. Specifically for weight control, a positive body image and flexible eating restraint were identified as important factors.[8]

Looking at the pediatric population reveals important information for providers. In one review that included 17 studies examining childhood obesity with regard to changing physical activity and eating, the researchers identified several effective techniques and only a few ineffective techniques. The effective techniques included providing information about the consequences of the behavior to that specific individual (personalized information), providing environmental restructuring, giving prompt practice, identifying a role model or position advocate, working on stress management and emotional control training, and focusing on communication training. Ineffective techniques included providing information on the consequences of the behavior in general, providing rewards contingent on successful behavior, and facilitating social comparisons.[9]

Putting this all together, the focus for sensible behavioral change in healthcare must be balanced by a sound scientific base and practical solutions that will reach the intended audience. Behavior change techniques must be effective, and counseling strategies must support specific goals. The general approach to behavior change includes elements of goal setting, follow-up, self-monitoring, action planning, problem solving, and social support. Each of these process components has a vital role in facilitating the development of goal behaviors.

Empathy is an important factor among clinicians, not only for the mutual understanding and respect it engenders among patients but also for the determination of clinical outcomes. Hojat and colleagues found that high empathy scores among physicians supporting patients with diabetes also led to better control of hemoglobin A1c (HbA1c) and low-density lipoprotein cholesterol (LDL-c) in their patients.[10] When physicians take time to connect with their patients and learn more about them on a personal level, patients are also more likely to endorse their medical care as "excellent."[11] Key aspects of empathy include the development of a trusting, caring relationship, self-reflection, listening, and being respectful, supportive, and non-judgmental.

While motivation is a required component for any behavioral change effort, it is the alignment between motivation and goals that allows goals to be achieved. Once initial motivation for a behavior change is identified, motivational interviewing can be employed to support patients as they identify additional reasons for seeking and sustaining change efforts. Central to the skilled use of motivational interviewing is the ability to use open-ended questions that help patients appreciate their priorities in life. Using motivational interviewing in the clinical setting has been shown to improve patient mood and even reduce mortality among stroke patients.[12]

Confidence building empowers behavior change by providing sequentially stronger foundations from which new actions can be carried out. It includes asking about strengths so that patients reflect on moments in their personal lives when they achieved a goal. Relating to a time

when they could carry out the tasks necessary to achieve a goal allows them to appreciate the potential for applying similar behaviors in the present moment.

SMART goals are specific, measurable, action-oriented, realistic, and time-sensitive. This general strategy ensures that behavior change efforts are achievable through each step along the pathway by breaking actions down. Each smaller step in the change pathway should contain an element of accountability, which allows for the follow-through needed to complete the behavior change process. Once an immediate step along the process of change is achieved, the conditions are maintained to proceed to the next. Since behavior change involves incremental changes over time, setting up an accountability structure that includes a positive and motivating support system increases the chance of success and reinforces the confidence needed to continue moving forward. In addition to the strong social support system, it is important for the practitioner to check in with patients and to encourage self-monitoring as well as the use of tracking systems as appropriate to help patients enjoy continued, long-term success with their healthy habits.

As created by one of the authors and first described in 2011 in the *Archives of Physical Medicine and Rehabilitation*,[13] the 5 Step Cycle for Behavior Change uses the key elements of behavior change to enable practitioners to experience success with lifestyle counseling. It is shown here in Figure 20.1. Physicians and clinicians can work through the five-step process with their patients by following these steps: 1) be empathetic, 2) align motivation, 3) build confidence, 4) set SMART goals—those that are specific, measurable, action-oriented, realistic, and time-sensitive—and finally, 5) set accountability. Step 1 is critical. This is a cycle that starts and ends with empathy. With behavior change work, it is important to know the details and idiosyncrasies of the person who has the condition. This will only happen if the person feels they are in an environment that is free of shame, blame, and guilt, also called a judgment free zone. By expressing empathy, the healthcare provider sets the tone for the encounter to be one that is safe and one in which the patient feels comfortable sharing their full experience and their true selves. Without honesty, it is difficult to make progress. Step 2 helps connect the patient to their "why" by aligning motivation. Why change? Motivational interviewing discussed in Chapter 22 will explore this topic in great detail. Step 3 is to build confidence, and this step cannot be skipped. People need to feel that they are capable of change. Everyone has strengths and talents. The healthcare provider can empower patients to embrace these skills, gifts, and strengths that the patient embodies by asking, "What are your strengths?" and then stating, "Tell me about a time when you were at your best." When a patient feels confidence and pride, which is a powerful positive emotion, they are ready for creativity and brainstorming and the next step, Step 4. Step 4 is setting SMART goals. A lofty, vague goal can be inspirational, but it is not practical. Behavior change needs to be practical. SMART goals are just that. They are specific, measurable, action-oriented, realistic, and time-sensitive. Many patients need guidance in setting SMART goals. Guidance is different than telling someone what to do. The healthcare provider is not meant to set the SMART goal, but rather, to collaborate and help the patient to set a SMART goal that aligns with their priorities and their sense of purpose. Lastly, there is Step 5. This is the crucial step of setting accountability. Healthcare providers set accountability so that benchmarks are available to measure success or the need for adjustments in strategies and planning to ensure the goal is achievable. Patients are often motivated by the check-ins and the tracking that comes with accountability. It can be simple logging, data from a wearable device, journaling, or monitoring step counts or number of vegetables consumed. Sharing progress helps keep patients motivated. This 5 Step Cycle has helped healthcare providers by providing a roadmap to behavior change counseling sessions.



FIGURE 20.1 5 Step Collaboration Cycle. (Reprinted with permission from Healthy Learning, publisher of ***Lifestyle Medicine Handbook*** 2nd edition, Chapter 2.)

Central to the process of counseling patients on behavior change is mindfulness. The healthcare provider and the patient both need mindfulness for this process to be successful. The impact of mindfulness on behavior change has been the focus of recent research.[14] Data from an eight-week pilot study on Mindfulness Based Stress Reduction groups tailored to patients with high blood pressure demonstrated significant changes in lifestyle behaviors like physical activity, diet, and alcohol intake for those nonadherent to American Heart Association (AHA) guidelines at baseline, with the changes sustained even after a year.[15] There is some magic to mindfulness that has not yet been fully elucidated, but with the surge in research studies on the topic, it might become clearer soon.

Recent trends in behavior change counseling around nutrition have brought mindfulness about language to the forefront. For example, in an article about reconceptualizing how we speak about eating, the authors, Olstad and

Kirkpatrick, recommend using the terms *eating practices* and *patterns* rather than *behaviors*.[16] They recommend that the focus be shifted away from just will power and individual choices and decisions to including the complex nature of what people eat, which involves their local environment, culture, food industry products, socioecological conditions, and the influence of community on eating patterns. Another important point is to adapt the language of behavior change interventions to suit the literacy level of the patients, using clear language and images that are labeled, and consider color coding for clarity in some cases (green for good and red for bad).[17] Food insecurity has become more and more of an issue with COVID 19 and the Ukraine War. Working on the social determinants of health (SDOH) as part of behavior change counseling around healthy lifestyles is critical. According to the Healthy People 2030, "Social determinants of health (SDOH) are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks."[18] Figure 20.2 demonstrates the social determinants of health, including economic stability, education access and quality, healthcare access and quality, neighborhood and built environment, and social and community context. When healthcare providers counsel patients on behavior change, the socioecological model of change needs to be front and center so that providers can meet people where they are and empower them to make strides to a healthier lifestyle.



FIGURE 20.2 Social Determinants of Health from Healthy People 2030. The $ indicates economic stability, the blue graduation cap indicates education access and quality, the red cross indicates healthcare access and quality, the blue house and building represents neighborhood and built environment, and the yellow people represent social and community context. (From https://health.gov/healthypeople/priority-areas/social-determinants-health)

Behavior change counseling takes time. It is usually not accomplished in one visit of 10 or 15 minutes. It takes follow-up and repeated visits. If the practitioners are too busy and do not have the time to do the behavior change counseling themselves, then they can hire a nurse, social worker, health coach, therapist, or behavior change expert to work with the patient. It is important that someone in the office focuses on this behavior change if healthy habits are going to stick. On average, it takes about 60 days or 2 months for a new behavior to become habit. If the patient is in the maintenance stage of change according to the Transtheoretical Model of Change, then the clinician can continue to encourage the healthy habit by asking about it and pointing out all the positive outcomes that are a result of the habit. Keeping on track with healthy habits is the key for patients, and lifestyle medicine practitioners can empower patients to do this by following evidence-based behavior change strategies.

CLINICAL APPLICATIONS

- Use the 5 Step Cycle[13] in your clinical encounters, focusing on making a connection and fostering collaboration.
- Catch yourself using the expert approach when working on behavior change and redirect your efforts to using a more collaborative style of counseling that is consistent with the coach approach.
- Work on making SMART goals with patients that are specific, measurable, action-oriented, realistic, and time-sensitive.
- Make sure there is built-in accountability for the patient; have them check in with you at the next visit, or have them buddy up with a family member or friend.
- If you do not have the interest or time to counsel patients on behavior change, consider hiring someone with this expertise, or consider having someone in your practice trained in motivational interviewing and behavior change so that they can spend the time needed to empower people to change.

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21 Applying Psychological Theories to Promote Healthy Lifestyles

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KEY POINTS

- Theories vary based on their focus on the primary force(s) influencing behavior change.
- The primary force(s) influencing behavior change are: individual, interpersonal, and ecological.
- The Socioecological Model is based on the concept that behavior has multiple levels of influences, including intrapersonal, interpersonal, organizational, community, environmental, and policy.
- Health behavior change interventions are most effective when they target the key constructs of behavior change.

21.1 INTRODUCTION

The application of psychological theories and models to health behavior change research, program development, and policy has soared in popularity over the past few decades. Desired outcomes are most likely achieved within the context of health behavior change programs that are based on an objective understanding of the target health behaviors and the variables that influence them; theories and models enable researchers and other program developers to organize these variables to achieve these outcomes.[1]

In this chapter, we focus on select theories and models that have consistently received attention to guide health behavior research: Health Belief Model (HBM), Theory of Reasoned Action (TRA)/Planned Behavior (TBP), Integrated Behavior Model (IBM), Social Cognitive Theory (SCT), Transtheoretical Model (TTM), and Socioecological Model (SEM). Later in this chapter, we discuss theory-based lifestyle interventions that have been broadly used in both research and practice, either by implementing a full model or by using a subset of the most effective constructs.

Many of these theories share some similar or even identical constructs, including the widely adopted concept of self-efficacy, which was coined by the famous psychologist Albert Bandura.[4,5] This construct refers to confidence in one's abilities to successfully perform a particular behavior (i.e., walk 1 mile) despite barriers such as bad weather or a busy schedule. Most incorporate static individual differences (e.g., demographic variables), dynamic individual differences (e.g., mood/affect), and interpersonal factors (e.g., social support), but the degree to which each of these variables is highlighted varies widely from one theory or model to another. Although similarities among the models and theories are clearly apparent, their differences set them apart from one another and make them more or less useful as frameworks through which to understand and/or modify different types of health behaviors. For example, some are more applicable to one-time or short-term health behaviors (e.g., HBM), while others are better suited for longer-term ones (e.g., TTM). An overarching characteristic that differentiates models and theories is their relative focus on the primary force(s) influencing behavior change. Thus, we organize the selected models and theories into three broader levels: individual, interpersonal, and ecological.

21.2 INDIVIDUAL LEVEL

21.2.1 Health Belief Model

The HBM,[6–8] depicted in Figure 21.1, was initially developed in the 1950s in attempt to understand and explain why many individuals were not participating in preventive health services, even when they were offered at no cost. The HBM proposes that the likelihood that individuals will engage in any given health behavior largely depends on their *perceptions* of the following variables: severity of the illness(es) it helps prevent, their susceptibility to the illness(es), benefits of engaging in the behavior, and barriers to engaging in the behavior. According to the HBM, individuals are more likely to adopt the target health behavior if they believe the potential illness is serious, that they are highly susceptible to it, and that the benefits of engaging in the behavior outweigh the associated barriers. The construct "cues to action," which are factors that prompt action (e.g., media campaigns, physician reminders), was later added to the model to increase its explanatory power. Other factors, such as demographic characteristics (e.g., age, race, ethnicity, gender) and psychosocial variables (e.g., peer influence, mood/affect), also exert considerable influence over individuals' decisions to engage in a specific health behavior according to the HBM. Self-efficacy, described as behavior-specific self-confidence,[4,5,9] was also later added to the HBM in attempt to increase its ability to accurately predict health behavior.[9] Self-efficacy was not initially included as

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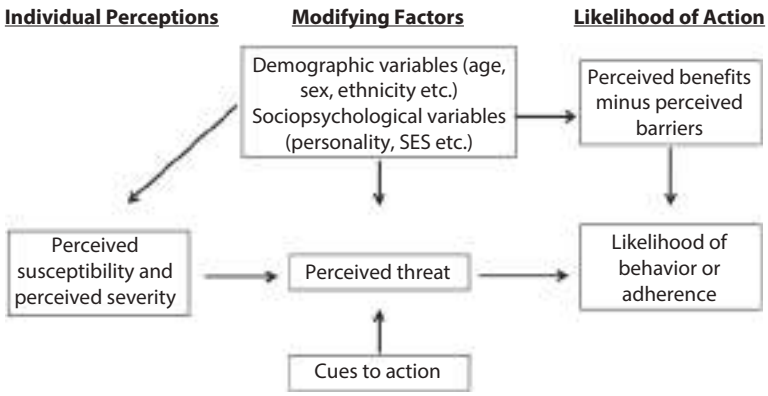


FIGURE 21.1 Health Belief Model.

an HBM construct because the model was primarily used to predict one-time or short-term health behaviors, such as getting a vaccination or health screening, for which self-efficacy is not particularly relevant. Nevertheless, these modified or extended versions of the HBM have been utilized in relatively recent research examining the model's ability to predict short-term behaviors such as breast self-examination among women with a family history of breast cancer[10] and human papillomavirus (HPV) vaccination initiation among adolescent girls in high risk communities.[11]

The HBM has since been applied to longer-term health behaviors and habits, such as exercise, smoking cessation, and dieting, with some success, but it has received significant criticism and has not held up to rigorous scientific examination in these contexts. Indeed, a recent meta-analysis of studies using HBM constructs to longitudinally predict health behavior concluded that utilizing the direct effects model may not be useful, because the two primary constructs (perceived severity and perceived susceptibility) only weakly predicted behavior.[12]

Although the HBM has been one of the most utilized models in health behavior research,[13] many concerns about the model remain. For example, the relationships among the model's constructs are not clearly delineated; measurements of some HBM constructs are not standardized; and some of its constructs (especially "cues to action") are difficult to empirically test.[12,14] Furthermore, other models have exhibited stronger predictive ability of health behavior than the HBM.[15] Thus, although some HBM constructs may be helpful to consider in the prediction of health behavior, the model as a whole may not be particularly useful except in the context of single or short-term behaviors.[12]

21.3 THEORY OF REASONED ACTION, THEORY OF PLANNED BEHAVIOR, INTEGRATED BEHAVIOR MODEL

The TRA, developed by Ajzen and Fishbein,[16,17] stems from premises of cognitive and social psychology. The TRA posits that individuals' likelihood of engaging in a particular health behavior can be predicted by the strength of their *intentions* to engage in that behavior. Intentions represent a combination of their own attitudes toward the behavior and their "social norms." According to the TRA, attitudes are formed by individuals' beliefs about the consequences of the health behavior and the weight they place on those consequences. Likewise, social norms are products of individuals' beliefs about others' expectations of them regarding the behavior and their motivation to comply with those expectations.

Research examining the TRA has demonstrated that it is most useful at predicting behaviors under volitional control. Therefore, Ajzen[18] proposed an extension of the TRA called the TPB in attempt to better predict health behaviors. The TPB incorporates TRA constructs and adds a construct called perceived behavioral control, which is defined as individuals' perceptions of their ability to perform a given behavior.[18] The TPB's perceived behavioral control construct is similar to the concept of self-efficacy[4,5] and is defined in terms of control beliefs (the presence or absence of perceived facilitators and barriers associated with a given behavior) and perceived power (the impact of these facilitators and barriers).

Unlike the HBM, the TRA and TPB models clearly delineate the relationships between their individual constructs. As a result, research examining the predictive abilities of these models has generally supported each of them as a whole.[15] However, a major concern about the models is that they do not incorporate any constructs that allow for affective/emotional or psychosocial variability,[19] which has also been a noted concern with the HBM.[20] Furthermore, the models do not take into account the fact that some behaviors are so habitual that they are not subject to planning or reasoning; in these cases, even the strongest of intentions are not likely powerful enough to overcome the automatic nature of well-established habits.[19]

Although the TRA and TPB have received less attention in health behavior research than some of the newer models in recent years, they consistently rank among the most utilized theories in the field and demonstrate considerable predictive value.[21] The TRA and/or TPB have been used as guiding frameworks for assessing, understanding, and

influencing behavior change in diverse populations with a variety of health behaviors, such as smoking behavior,[126,127] female condom use among Chinese sex workers,[22] safer sex intentions and protected sex among heterosexual, HIV-negative methamphetamine users,[23] family meal frequency among adolescents,[24] healthy nutrition,[25,128] and physical activity,[26,129] among others.

The IBM, developed by Fishbein and colleagues,[27,28] is an extension of the TRA and TPB and similarly posits that the most important determinant of a given behavior is the intention to engage in the behavior. In addition to TRA and TPB, the IBM incorporates variables from other notable theories including HBM[8,29] and SCT.[4,5,30] According to the model (Figure 21.2), a behavior is likely to occur if (1) one has a strong intention to engage in the behavior, (2) one has the required skills and abilities to perform it, (3) the behavior is salient and has occurred before, and (4) there are no environmental constraints to impede behavioral engagement.[31] If, however, intentions to engage in the behavior have not been formed, the model suggests that emphasis may need to be placed on three primary determinants of intention: attitude toward the behavior, perceived norms, and personal agency. The first construct, *attitude toward the behavior*, is further divided into two dimensions in the IBM. Experiential attitude or affect[32] is the emotional response to the idea of engaging in the suggested behavior. Individuals are unlikely to engage in the behavior when strong negative emotional responses are elicited, while individuals with a strong positive response are more likely to engage in it. Instrumental attitude refers to beliefs about the consequences of engaging in the behavior, as is found in the TRA and TPB.

The second construct, *perceived norms*, is a reflection of the social pressure to either engage in or not engage in a certain behavior. Fishbein[32] describes normative influence as being composed of both subjective and descriptive norms. Subjective norms (formerly social norms in TRA/TBA) are one's beliefs about what others think about them engaging in the behavior and their motivation to comply with others' expectations, whereas descriptive norms are one's perceptions of what others in their social network are doing.

The final construct, *personal agency*, has been previously described by Albert Bandura[33] as exerting personal influence to impact one's own functioning and environmental conditions. In the IBM, two constructs make up personal agency—self-efficacy and perceived control. Self-efficacy refers to confidence in one's ability to perform a specific behavior in a given situation. Meanwhile, perceived control (as previously described in TRA/TPB) is one's perceived amount of control over one's ability to engage in a behavior, which is determined by one's perceived degree of difficulty in engaging in the behavior due to various environmental factors.

The IBM indicates that the aforementioned constructs composing attitudes, perceived norms, and self-agency are all functions of underlying beliefs. For instance, experiential attitudes are a function of one's feelings regarding the idea of engaging in a specific behavior. The more positively one feels about the behavior, the more likely a favorable emotional response will be elicited when thinking about engaging in it.

Previous successful applications of the IBM include understanding behavioral intention and behavior for

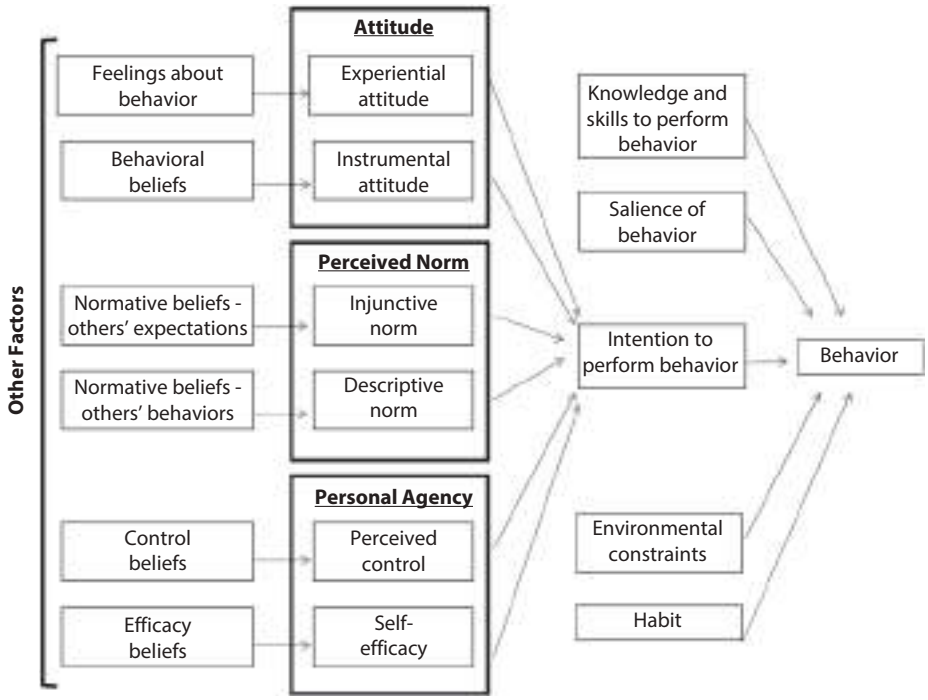


FIGURE 21.2 Integrative Behavior Model.

drinking behavior among university students,[130] condom use among injecting drug users and other HIV risk groups,[34,35] HIV/STD prevention in Zimbabwe,[36,37] adolescent sexual behavior,[38] and road user behaviors in Vietnam.[39] Moreover, IBM has been used as a theoretical framework for Project Respect, a large multisite randomized controlled trial testing HIV/STD risk reduction strategies among participants visiting public health clinics for STDs.[40,41]

21.4 TRANSTHEORETICAL MODEL

The TTM is extensively described in Part IV, Chapter 4, of this book.

Although the TTM originated in the addictions research field, it has since been applied to numerous health behaviors (e.g., fruit and vegetable consumption,[48,131] weight control,[49,132,133] contraceptive use,[50] sun protection,[52,134] medical compliance,[53,135] cervical cancer and mammography screening,[54,55] stress management,[56] intimate partner violence,[57,58] and exercise[59,60]), in diverse populations (e.g., college students,[61] adolescents,[48,136,137] and patients with severe mental illness,[62] tuberculosis,[63] HIV,[64] and multiple sclerosis[53]), and in many countries (e.g., Taiwan,[54] Nepal,[64] Malaysia[63]).

However, several criticisms of this model have been raised.[65,66] For example, the complexity of health behaviors is an issue when considering stage-based behavior change theories. Staging algorithms typically ask about physical activity or diet in general, but motivational readiness for change may vary for subcategories not fully captured by these algorithms (e.g., interested in walking and vegetable consumption but not strength training or reducing fat intake). The TTM also focuses on stage progression as a significant outcome, but this is not always associated with actual behavior change.[67,68] Nevertheless, the TTM has been a highly influential theoretical framework comprised of a number of useful organizing constructs that have been shown to be meaningfully related in empirical data and psychometric studies.

21.5 INTERPERSONAL LEVEL

21.5.1 Social Cognitive Theory

SCT is one of the most robust health behavior change theories.[3,69] It evolved from Social Learning Theory[3,42] and originally focused on observational learning, or learning by watching others' behavior (also called modeling), and the reinforcements (both positive and negative, internal and external) that help determine whether or not one will repeat the behavior. Updated by Bandura and colleagues, SCT posits that behavior change is influenced by internal individual factors (e.g., cognitive, affective, biological) as well as the social and physical environment. The model is reciprocal in that each of these factors affects the others in a continuous, dynamic feedback loop (Figure 21.3).[3]

Self-efficacy is the main construct of SCT[4] and as mentioned previously in this chapter, a powerful predictor of behavior change that has been incorporated into numerous social and behavior science theories.[3,69] Self-efficacy beliefs have been strongly associated with actual performance of a diverse range of health behaviors.[70,71] According to Bandura, self-efficacy can be increased through mastery experiences, social modeling, improving physical and emotional states, and verbal persuasion.[69] Mastery experience is gained through succeeding in attainable, yet increasingly challenging, health behavior change goals and is considered to have the strongest influence on self-efficacy beliefs.[3,69,72] Modeling, as previously discussed, can be accomplished by watching others perform the desired behavior; it is especially effective when relatable peer(s) perform the behavior. Finally, maintaining an optimal level of physiological intensity (i.e., excited but not too anxious) for performing the behavior, which can be accomplished by using relaxation techniques and positive self-talk as well as receiving encouragement from others, can increase self-efficacy.[3,69,72]

Self-regulation strategies are also used to enhance confidence for behavior change and typically begin with self-monitoring, or systematically observing, one's current health behaviors.[69] Overlapping to a degree with the concept of mastery experience, self-regulation can also include

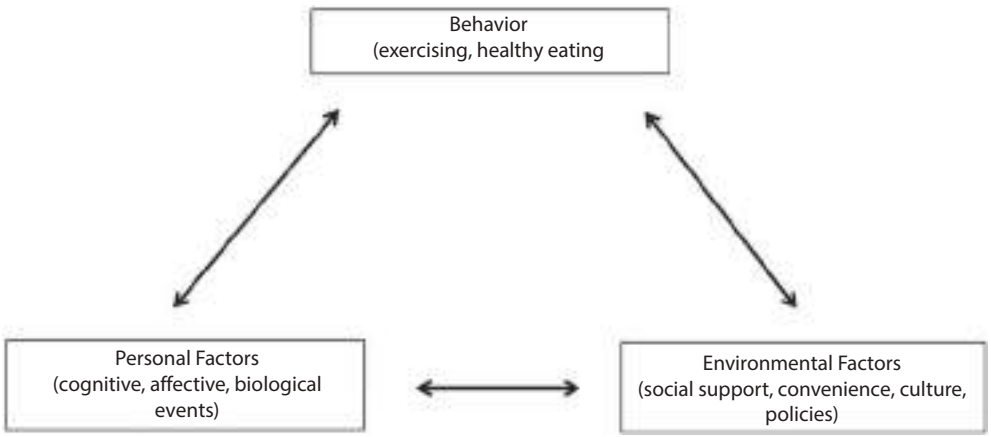


FIGURE 21.3 Social Cognitive Theory.

establishing rewards for meeting behavior change goals and enlisting social support from family and friends for performing target behaviors.[69]

Another important determinant of behavior according to the SCT is outcome expectancies.[3] This construct, defined as the influence that the outcomes anticipated from a health behavior exert on one's willingness to perform this behavior, makes intuitive sense and has been supported in numerous research studies.[73] According to SCT, one's expectations affect both initiation of and persistence of the behavior. Not only can perceived self-efficacy have direct effects on initiating activities, but by means of expectations of eventual success, it can affect continuing efforts once they are initiated. SCT posits that a health behavior is more likely to be performed if positive outcome expectancies are present, whereas negative outcome expectancies reduce the likelihood of the health behavior. For example, individuals will be much more inclined to run a mile if they anticipate that doing so will energize them rather than cause them to feel sore.

SCT offers a comprehensive model of the behavior change process and provides a strong foundation for health promotion research and practice, using numerous strategies to address diverse public health issues. Furthermore, SCT has been successfully applied to a variety of health behaviors (e.g., cardiovascular disease,[74–78] cancer screening,[79] tobacco use,[80–83] alcohol use,[42,84–86] diet,[87,88,138] weight management[139] and obesity,[89] physical activity,[73,87,88,90,91,140,141] diabetes prevention,[92,142] condom use[93,94]), in a wide range of ages (including children,[88] teens,[84] and elderly[90]) and underserved populations (e.g., African Americans,[80] Latinas,[89,92,143] low-income individuals[88,89]), and in several different countries (mostly in the United States, but also in China,[94] Sweden,[88] and Australia[90]).

21.6 ECOLOGICAL LEVEL

21.6.1 Socioecological Model

In more recent years, psychological theories and models have increasingly incorporated the broader contexts that affect health behaviors, recognizing that these external factors are often as influential as internal factors.[95–97] Socioecological models are based on four fundamental principles that are critical to understanding their application to health behavior change:[98–100] (1) the environmental and personal factors that influence health behavior dynamically interact with each other; (2) environments are multidimensional and complex; (3) people are multidimensional and complex, and intervention designs should consider both the individual and the groups with which the individual is affiliated; and (4) people–environment interactions exert multiple levels of influence, such that individuals often modify their settings, and social features of settings influence individuals. Based on these principles, the social ecological framework suggests that health behavior change strategies should consider both person-focused and environment-focused strategies for health behavior change.[99] Since multiple levels of factors influence behavior, interventions for health behavior change should also be multilevel.[101] Individual-focused strategies may include preventive screening programs, individual counseling, or participation in lifestyle interventions. Environmental strategies include both geographic (e.g., mixed-use communities) and sociocultural (e.g., integrating target health behaviors into organizational structures/cultures) aspects.

The SEM has recently grown tremendously in popularity, particularly in the public health realm. As the SEM has gained attention, intervention strategies have extended their target factors to other levels such as delivery of pediatric preventive care[144], physical activity and sedentary behavior during COVID-19[145], community participation,[102] health equity[146], organizational policies for smoking cessation,[103] neighborhood resources for physical activity[104] and healthy food,[105] children's obesity prevention and weight loss programs[147–149], and comprehensive programs for diabetes care.[106] The SEM differs from more traditional psychological models in that it explicitly incorporates not only the individual's immediate external influences (e.g., interpersonal relationships) but also more peripheral factors (e.g., community, environment). Furthermore, rather than predicting a specific order or direction in which influences exert themselves, the SEM depicts the individual in the center of increasingly broader circles of influence, which interact with one another in an ongoing process (see Figure 21.4).

The SEM has been applied in understanding, assessment, and intervention research on a variety of health behaviors and/or in diverse populations, including dietary behaviors in urban food environments in Africa[150], fruit and vegetable consumption among low-income African Americans,[107] church-based health promotion interventions,[108] diabetes prevention and treatment interventions for Native people in the USA and Canada[151], physical activity promotion and fruit and vegetable intake,[109] and physical



FIGURE 21.4 Socioecological Model.

activity assessment within a variety of different populations,[110–112] among others. The SEM has also been used to identify and classify barriers and facilitators individuals face in the adoption of health behaviors[113–115] and to participation of minorities in clinical trials.[116]

As with all of the aforementioned models and theories, some challenges arise in the application of the SEM to health behavior change interventions. Because the model is exceptionally comprehensive, its application is inherently complex. For example, addressing the SEM's multiple levels of influence, including regional (e.g., neighborhoods), structural (e.g., the physical environment), and institutional (e.g., government, worksite, family) factors, on health behaviors is challenging due in large part to limitations on control over these external variables. Despite its complexity, the SEM appears to be a promising model for an increasingly multidisciplinary scientific community.

21.7 THEORY-BASED HEALTHY LIFESTYLE INTERVENTION IN RESEARCH AND PRACTICE

Research and practice are both producers and consumers of theory-based interventions, contributing to the evidence base in lifestyle interventions, understanding the determinants of behaviors, testing behavior change strategies, and implementing and disseminating effective interventions.

In the selection of strategies to change lifestyle in research and practice, some focus on the most effective constructs, such as self-efficacy, intention, planning, and self-regulatory skills, and evaluate their mechanism and effectiveness regarding behavior change. Others follow a defined structure according to a specific theory or model such as HBM or SCT as a rationale for choosing constructs and arranging their relationships and mechanisms in the process of analyzing and assessing outcomes. The recognition of the wide range of health behavior determinants can make the design and evaluation of intervention strategies a complex process.

The use of psychological models or theories to better understand, predict, and change behaviors is widely accepted. Thus, they have been applied in the design of health promotion interventions in both research and practice. In the HBM, each step in the decision-making process is dependent on the previous decision or belief. The SCT is based on the assumption that psychological constructs, namely, self-efficacy and outcome expectancy, serve as predictors of individuals' behavior. The TPB postulates that a central factor to perform a given behavior is an individual's intention.[117] However, not all of those who have the intention would perform a health behavior.[118–120] This so-called *Intention Behavior Gap* is explicitly addressed in Part IV, Chapter 6 of this book.

Several behavioral constructs have been introduced to translate intentions to behavior, among which the most frequently used are goal setting,[121] implementation intention,[122] action and coping planning,[123] and self-monitoring.[124] Goals affect individuals' performance through four mechanisms: specifically, they (1) direct attention and effort toward relevant activities, (2) energize action and elicit greater effort, (3) increase persistence, and (4) affect action indirectly via motivation.[125] Goal-setting is consistent with SCT in the sense that both acknowledge the importance of goals and self-efficacy. The difference is that the emphasis of goal-setting theory is on the process of defining clear properties of an effective goal in order to make it more achievable.[121]

When a person is inclined to adopt a particular health behavior, the intention has to be transformed into detailed action plans of when, where, and how to perform the desired action, and coping plans on how to overcome the barriers.[123] Implementation intention[122] is another form of planning strategy, which typically requires that individuals specify their plans in an "if-then" format that explicitly links the anticipated situation to a specific response, specified in the "then" part of the plan.

After taking up a health behavior, one has to focus on maintaining the behavior for the long -term. This involves continuous self-management, meaning the person needs to monitor his/her adherence to the newly adopted health behavior. Self-monitoring is a concurrent self-management strategy, where the health behavior is continuously evaluated with regard to the person's behavioral goal or standard.

21.8 SUMMARY

In this chapter, we focused on some of the most frequently utilized models and theories that guide health behavior change interventions. Over the past few decades, the fields of behavioral medicine, public health, and medicine (among others) have been gradually shifting from a sole focus on the individual to a progressively greater focus on the local and to a growing extent, global environment in which the individual resides.[1,99] Although this shift recognizes and better accounts for the increasingly globalized world that undoubtedly influences individuals' behavior more than ever before, these new ecological models and theories are quite complex and somewhat generic.[98–100] Their numerous and relatively broadly defined variables are often difficult to measure, rendering these models as a whole difficult to assess. However, they relieve individuals of the responsibility that they should engage in target health behaviors regardless of the external barriers they may face. Moreover, the health problems and challenges for which health behavior change interventions are designed have also shifted from primarily acute and/or short-term illnesses (e.g., deadly viruses and infections) to predominantly chronic diseases (e.g., cardiovascular disease and diabetes). One-time or short-term problems appear to be adequately addressed by the individual-focused theories and models, whereas interventions for longer-term problems are more appropriately designed using interpersonal (and presumably ecological) ones.

We presented the constructs that have been shown to be most effective in translating behavioral intentions into actions. Many other theories not included in this chapter also incorporate key concepts that help explain and predict health behaviors. Perhaps the two biggest challenges in health behavior change are (1) to match health behavior goals with the models and theories that incorporate the most relevant constructs to design and implement effective interventions and (2) to systematically incorporate and account for the wide range of ecological factors that clearly influence health behavior to an increasingly great extent in the modern, global world.

CLINICAL APPLICATIONS

- The behavior change theories and models guide behavioral interventions, including addiction or obesity treatment.
- Self-monitoring intervention components are useful for disease prevention and health behavior promotions.
- For community health initiatives, the socio-economic model is very helpful because it involves all stakeholders in the process.
- Sometimes, it is more effective to focus on one construct, such as intention or self-efficacy, to improve healthy behavior.
- Lifestyle change is a process, and continuous monitoring and support are essential for the maintenance of changes made and encouragement for further changes.

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22 Motivational Interviewing and Lifestyle Change

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KEY POINTS

- Understand the key components of the Spirit of Motivational Interviewing and how it differs from more directive communication approaches.
- Learn the meaning of and how to use OARS (open-ended questions, affirmations, reflections, and summaries) when engaging with your patients.
- Understand the importance of ambivalence and how to intentionally focus on increasing change talk while minimizing sustain talk.

CLINICAL APPLICATION TAKE HOME POINTS

- MI is a strengths based approach, which maintains that clients have within themselves the capabilities to make lifestyle changes successfully.
- MI recognizes and accepts that patients who need to make changes in their lives approach lifestyle changes at different levels of readiness to change.
- Ambivalence is the patient's ability to see both the reasons for and the reasons against change: a normal behavior that should be expected when anyone considers making a change in their lives.
- Before thinking about increasing change talk and decreasing sustain talk, clinicians should focus their attention on creating therapeutic rapport with the patient.

22.1 INTRODUCTION

The United States spends more money per capita on healthcare than any other country in the world.[1] Considering that three of the top ten causes of death in the world (cardiac and respiratory disease, and stroke) are behaviorally related,[2] lifestyle medicine has the potential to fundamentally change healthcare. Clinicians are thinking outside their typical prescribing habits and writing more prescriptions for exercise and fresh food pharmacies, providing savings in healthcare costs.[3] This change, however, comes with a different kind of cost: the cost of individual effort. Patients are faced with hard decisions about how they live, including potentially changing major components in their lives. Subsequently, clinicians will have to modify the tools they use to treat patients, one of which must be the tool of communication regarding behavior change.

Making changes in our lives is inevitable. However, sometimes changes that appear simple in theory prove to be difficult to implement in practice. Think, for instance, about flossing. How many people floss their teeth as often as recommended; one to two times daily? Is it due to low supply of floss, a lack of knowledge about the importance of flossing, or even lack of time? Perhaps not. Most likely, it is due to a low intrinsic need or perceived importance of flossing. For years, doctors, nurses, teachers, consultants, and others have heavily favored a "directive approach" to change (i.e., telling folks what to do). While a directive approach may be indicated in certain situations (e.g., medical emergencies), this approach tends to backfire when addressing other situations; specifically those involving ambivalent patients. Although not always conscious about being directive, clinicians have often held the view that "I, the expert, have the key to change; which I will impart upon you, *when* and *if* you are ready." If behavior change did not result, patients were deemed to be unmotivated, uncaring, and non-compliant. Motivational Interviewing[4] is one clinical *tool* that allows a shift in how we "see" patients' attempts at making changes. With this change of view comes a change in language. Instead of being non-compliant, a patient is seen as ambivalent about changing, and the role of clinicians is to adopt a "guiding" approach" as opposed to the more directive approach mentioned above. Such a guiding approach provides hope that change is possible. Paradoxically, respecting a patient's autonomy and freedom not to change is sometimes what makes the change possible.

Motivational Interviewing (MI) is a therapeutic approach that targets language of change. Specific attention to the language of change offers an alternative view to addressing treatment readiness. Instead of passively waiting for the motivation and readiness to suddenly appear, or worse yet, aggressively pushing forward with a plan regardless of the individual's stage of change, MI allows an intentional and strategic focus on the client's readiness to change. Many MI practitioners hold the inherent view that they are only responsible for the interaction, not the outcome. This is rooted in the fundamental truism that clinicians can do very little to make a patient implement sustained behavior change unless they themselves want to do so. Clinicians

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can, however, assist with increasing and strengthening the patient's internal motivation and preparedness for the change. As Miller and Rollnick explained, MI "involves a collaborative partnership with patients, a respectful evoking of their own motivation and wisdom and a radical acceptance recognizing that ultimately whether change happens is each person's own choice, an autonomy that cannot be taken away no matter how much one might wish to at times."[4] MI offers clinicians an alternative lens through which to view the situation, which is proven to reduce burnout.[5]

Currently, *Motivational Interviewing: Helping People Change* is in its third edition. Numerous other supportive texts describe the use of MI in myriad settings, ranging from treatment of addictions and chronic illness to multiple offender programs and school systems. Since the first edition, MI has been cited in more than 25,000 articles and has been studied in over 200 randomized clinical trials.[4] Furthermore, there have been over 16 different books expounding on MI, ranging from treating addictions and psychological problems to managing classroom behaviors and interactions with dental patients. MI improved outcomes in 63% of the studies examined.[6] A recent review on the effects of MI found it to be effective in improving a wide range of medical outcomes, including blood pressure, cholesterol, HIV viral load, alcohol and marijuana use, abstaining from tobacco, and adhering to medical advice.[6] Impressively, the effects of MI hold regardless of the clinician's background (e.g., nurse, mental health clinician), as long as the clinician has sufficient training and supervision.[7]

22.2 WHAT IS MOTIVATIONAL INTERVIEWING?

To better understand MI, it is helpful to explore its origins. The foundation for MI was set during a clinical trial comparing treatment approaches for individuals with problem drinking.[8] As part of this trial, clinicians' empathic statements toward their patients were recorded by supervisors. It was noted that these empathic statements had a stronger effect on drinking behavior than the interventions being evaluated and that these improvements in drinking behavior were maintained for up to 24 months following the intervention.[9] The importance and utility of empathy were reinforced after Miller participated in a role-play process where he modeled his therapeutic style for a group of psychologists. Although his audience questioned his approach to treating alcohol problems, this led Miller to identify the framework that would later become MI.

Since then, MI has evolved into a clinical approach aimed at increasing an individual's motivation for behavior change.[10,11] This communication method is not the combination of a set of techniques to apply at random. It requires a clinician to purposely listen for two types of language: change talk and sustain talk. Simply put, change talk refers to statements focused on why a person should engage in the desired behavior change, while sustain talk is reasons why a person should continue their current behavior(s). Often, change and sustain talk occur in the same sentence, and the clinician's goal is to strategically evoke change talk while simultaneously minimizing sustain talk.

This natural process of seeing reasons to change, as well as reasons not to, is referred to as *ambivalence*.[4] For example, an obese individual with poorly controlled diabetes may express interest in increasing their consumption of fruits and vegetables to lose weight yet struggle to make healthy choices when presented with junk foods at work. The difficulty implementing behavior change persists despite an individual having the knowledge of why they should act differently. MI allows this ambivalence to be explored and possibly resolved.

Motivational Interviewing encourages clinicians to resist the "righting reflex," or the tendency to argue for the behavior changes they wish to see in the patient.[4] The desired effect of telling someone why they should change is for the patient to align with these reasons. However, what tends to happen is that the patient defends their choices, paradoxically strengthening their rationale for not changing. People, in general, tend to align with their own thoughts and opinions more strongly than those of others. When they verbalize their own reasons for sustaining their behavior, they may align with these beliefs more closely than they previously had.

MI differs from other treatment approaches in that it is necessary to understand and demonstrate the "spirit of MI" to effectively utilize it.[4,11] The spirit of MI differs from the techniques a clinician can employ as part of this approach. It is characterized by four key elements: partnership, compassion, evocation, and acceptance.

Partnership. MI is practiced as a true collaboration, maintaining that there are two experts in the room—the clinician and the patient. While the clinician may be an expert in smoking cessation, for example, the patient is an expert on themselves and on implementing the recommended plan in their own lives. Therefore, the clinician must work alongside the patient to best help them. A visual example of this was created by Jeff Allison,[4] who described MI as an opportunity to "dance with a patient, not wrestle." This metaphor suggests that while the clinician may guide the session in a goal-oriented fashion, they are not in the position to convince or force their patient to make any choices. Another distinction of this partnership is the understanding that the clinician is not responsible for all the answers, and the individual ultimately knows what is best for them. This is in direct contrast to training models emphasizing the role of a professional to have all the answers to problems their patients present to them. It is sometimes hard for clinicians to internalize that they may be more responsible for the intervention than the outcome.

Compassion. Compassion goes beyond having positive regard for another and an understanding of their experiences, to include purposely prioritizing what is in their best interest. The other three aspects of MI's spirit can be employed to serve the interests of the clinician, but with

compassion, the emphasis is placed on doing what is best for the patient. Compassion underscores the importance of being selfless and structuring communication around an individual's personal goals even if they do not align with the clinician's goals.

Evocation. One of MI's goals is to help the patient better understand and recognize their own reasons for behavior change. It suggests that the patient already has their own reasons for changing, and MI's role is to illuminate what these specific reasons are. By evoking and strengthening change talk and suppressing sustain talk, a patient's ambivalence may be resolved, allowing them to focus on the preparation and planning it takes to make and sustain change.

Acceptance. Four key components make up the principle of acceptance and are based on work by Carl Rogers.[12] Together, they explain that the clinician must accept a patient, their choices, and what they have the capacity to do.

Absolute Worth. Rogers identified absolute worth as unconditional positive regard. It communicates the importance of abstaining from judgment. Rogers suggested that when people feel judged, they are less likely to change. They may feel reluctant to attempt change when their environment feels unsafe. Contrasting this, when individuals feel valued, it provides an opportunity for them to explore themselves and the possibility of change.

Affirmation. Affirmations provide a way of communicating to another that you recognize their efforts as well as their positive attributes.[12] In many disciplines, clinicians are trained to evaluate their patients for deficiencies and inadequacies and to identify what is going wrong. However, affirmations intentionally focus on the opposite—the strengths and resilience of the patient. Clinicians are encouraged to share with the patient the characteristics, traits, or behaviors they already possess that will assist them in accomplishing their goals.

Autonomy Support. To fully accept an individual, their own attitudes and decisions must be appreciated and respected. Humans seem to possess a unique need to preserve their sense of autonomy, to maintain an internal locus of control, and to make decisions for themselves. Respecting and supporting autonomy is in direct contrast to convincing someone to act in a certain way. Ultimately, an individual will decide what changes to implement, and if they are maneuvered toward a direction they do not agree with, they will advocate for the opposite behavior as a way of demonstrating their free will.

Accurate Empathy. This is another "critical condition for change," per Rogers. Clinicians need to prioritize their patient's perspective and purposely ask questions to better understand their interests, views, and beliefs. It is important to distinguish our own opinions from our patients so that we can avoid imposing our views on others. Ultimately, it is difficult to respect patient autonomy if the clinician does not understand who they are, what they believe in, and what they hope for.

22.2.1 Research and Evidence

In the 30+ years since MI was described, it has had broad applicability, and the large body of MI research reflects this. MI has been utilized to address a wide variety of behaviors throughout the lifespan, across multiple settings, and by healthcare clinicians across training levels and disciplines. Concerning health behaviors, MI has demonstrated effectiveness for individuals with chronic pain, diabetes, HIV, poor contraceptive use, excess weight, alcohol, and substance use, as well as promotion of positive health behaviors (e.g., physical activity, self-care, treatment adherence).[13–23]

Meta-analyses suggest that MI improves outcomes by 10–20% in a variety of conditions compared with no treatment and is at least as effective as active treatments.[24] These effects hold across severity of problem, patient gender, age, and ethnicity. Motivational Interviewing also appears to be effective when delivered via telehealth.[17] Indeed, research has found that the style of MI might be a more culturally sensitive form of psychotherapy, which might explain the finding that MI is more effective in minority groups.[25] Interestingly, Motivational Interviewing is more effective when clinicians do not rigidly follow a manual, perhaps because sticking closely to a manual encourages clinicians into problem solving too quickly.[25]

Clinicians from a variety of backgrounds and training can attain proficiency in MI through a 2-day intensive training or the equivalent of 12–16 hours of in-person didactic and role-playing opportunities, followed by continued coaching and supervision/consultation.[24,26] Sustained proficiency in MI has been shown with 14–16 hours of training followed by modest yet prolonged (i.e., 4–5 hours over 6 months) supervision and coaching from an expert trainer.[7]

Motivational Interviewing first garnered attention as an effective technique for its use in alcohol use disorder in the early 1980s. Since then, meta-analysis suggests that MI has a small effect size in improving alcohol use[27] Further, it appears that for alcohol use disorder, MI is just as effective as, and in some cases more effective than, other treatments, particularly in the short term.[27] Additionally, MI appears to be an effective treatment for substance use disorders throughout the lifespan.[27,28,29]

The effects of Motivational Interviewing extend to other health behaviors, such as weight loss. Motivational Interviewing research suggests it can be utilized effectively to contribute to improvements in eating, exercise behaviors, and weight loss. In a review of 11 randomized controlled trials evaluating MI for weight loss in overweight and/or obese adults, MI demonstrated a medium effect size of 0.51 standard deviations for weight loss compared with control interventions.[30,31] A similar meta-analysis indicated that MI led to an increase in diet and exercise for overweight adults with an effect size of 0.56.

Motivational Interviewing has also been used to address population health issues, such as vaccine hesitancy, though this research is still in its infancy. One study suggested that MI improved vaccine rates at a large university health care center for some, but not all, vaccines.[32] The American Academy of Family Physicians has suggested that physicians utilize MI to increase rates of COVID-19 vaccination based on the theoretical underpinnings of MI.[33,34]

Although originally utilized for an adult population, the effectiveness of MI extends to children and teenagers. The impact of MI for children and teenagers depends on the target health behavior. A meta-analysis evaluating MI for pediatric health domains (e.g., risky sexual behavior, physical activity, substance use) suggests that MI has a small, but significant, effect across behaviors ($g = 0.16$) compared with alternative interventions and that these improvements are maintained across follow-up evaluations.[35] These findings are encouraging for the use of MI to improve health outcomes for children and teenagers.

22.3 FOUR PROCESSES

22.3.1 Introduction

Clinicians need to be mindful of the four processes of MI: Engaging, Focusing, Evoking, and Planning. The use of a metaphor is helpful in understanding the four processes of MI. First, imagine there is a boat; a vessel to hold both the practitioner and the patient. Through the process of engagement, the patient invites the practitioner into the boat. Together, via the use of MI skills, the practitioner begins rowing the boat. With the utilization of focus, the two occupants decide on a direction to row. As the journey towards the shared destination continues, evocation is utilized to enhance and reinforce the motivation to continue rowing. Once there has been substantial motivation established, the process of planning enables a continued journey in the direction of change behavior. Clinicians should keep in mind that the journey of rowing the boat together can be a linear process. However, most often, it is recursive; navigating and re-navigating the same exacting waters. The process becomes MI when the communication style follows the MI Spirit, there is a focused goal, and the practitioner evokes the patient's motivations for change. In practice, behavior change often requires that the four processes be repeated in an iterative fashion over many weeks, months, and even years.

22.3.2 Engaging

Motivational interviewing first seeks to create an appropriate interpersonal environment that sets the stage for the possibility of change to occur by intentionally working to create a strong and collaborative relationship between the patient and the clinician (e.g., by asking "shall we row together?"). According to Miller and Rollnick,[4] the goals of the engagement in MI are to establish a working relationship with the patient, create agreement on treatment goals, and collaborate on ways to achieve those goals. This contrasts with the medical model, in which the clinician takes on an authoritative, educator, or expert role. It should be noted that there are times when the educator or expert role is not only helpful but necessary in medicine and psychotherapy (e.g., when providing information about a medical procedure or diagnosis; addressing acute and emergent medical or psychiatric problems). An MI approach works best when a patient is in either the contemplative or the planning stage of change.[35] Focusing on engagement in the relationship, as opposed to a fact-finding mission, requires a different set of complex skills. OARS (i.e., open-ended questions, affirmations, reflections, and summaries) are a helpful tool set to develop engagement with the patient. These are described more fully in the following.

Open-ended questions. The difference between open-ended and closed-ended questions is relatively easy to spot, though much harder to change in communication patterns (Table 22.1). Open-ended questions elicit responses that require more than one- or two-word responses, and typically elicit full sentence responses. Open-ended questions encourage patients to give thoughtful and elaborate narrative-like responses to questions, and patients themselves must choose what to disclose. They also allow the patient to engage more collaboratively in the discussion. Closed-ended questions elicit one-to-two-word responses, often a "yes/no" or fact-base response. The use of closed-ended questions is helpful when a specific response is needed; however, relying too much on closed-ended questions can be inefficient, seem disingenuous, and reflect the clinician's agenda, rather than the patient's.

Affirmations. Affirmations are statements or reflections of an individual's strengths or efforts, and can be simple ("Thank you for coming in on time today") or complex ("You are a resourceful person for dealing with this stress for so long"). According to Miller,[9] the goal of making affirmative statements is to enhance the patient's self-esteem and self-efficacy. Increasing an individual's self-efficacy has been shown to improve motivation for change.[36] It is important that affirmations, as with any emphatic statement, are expressed genuinely. As well, it is best to avoid making the statements focused on your approval of a patient's behavior; these are considered compliments and not affirmations.

TABLE 22.1
Examples of Open versus Closed-Ended Questions

Open-ended questions	Closed-ended questions
What brings you in today?	You're here to talk about quitting smoking, right?
What is important to you about changing your diet?	Is your diet important to you?
How do you manage your stress?	Do you mind if I ask you a few questions about your health habits?
If you had to quit smoking, how would you do it?	Do you want to try the nicotine patch?

Where there is approval, there can be disapproval, and this could put undue pressure on the patient to perform for the clinician in the future. At times, it may be difficult to conjure an affirmation. Take, for an example, a patient who has unmanaged diabetes with a high A1C, is overweight, eats poorly, does not exercise, and albeit is late every visit, continues to show up. An affirmation for this individual could be, "You were determined to make it here today."

Additional examples of affirmations:

"You are very good at caring for others."
"It is hard to get you down for long."
"You are resilient."

Reflections. Reflections are one of the most frequently used skills in Motivational Interviewing (Table 22.2). The goal of using reflective statements is twofold. The first is to convey empathy and compassion to the patient. The second, and perhaps more unique, purpose of reflections is to strategically elicit and guide the discussion toward motivation for change. Reflections can range from simple to complex. Those who are just beginning to practice MI may choose to focus on simple reflections until they become more proficient. To best illustrate different types of reflections, let us first look at a case example.

Clinician: "Thank you for coming in today. Your primary care physician told me a little bit about you and that you might be interested in quitting smoking. Why don't you tell me in your own words what brings you in today."

Patient: "Well, I'd like to quit smoking and I've been thinking about it for a while, but I'm not sure I can. My doctor wants me to quit, but between work and being a single parent, smoke breaks are my only time to myself."

Simple: In a simple reflection, the clinician may repeat back what the patient stated, "You'd like to quit smoking and you've been thinking about it for a while." Simple reflections are best used in moderation, for they may become tiresome for both clinician and patient if repeated multiple times. Simple reflections might also involve the clinician reflecting back a statement very close to what the patient said and substituting synonyms or slightly rephrasing what the patient offered. For example, "Your doctor wants you to quit smoking and you don't have a lot of alone time besides smoke breaks." Clinicians might also utilize paraphrasing, which is when the clinician is listening for ways to infer the underlying meaning in what the patient is saying and to reflect that meaning back to the patient. When this is done well, it helps the patient to continue their own thought process, rather than starting a new one. Paraphrasing in this example might look like, "Tackling something like quitting smoking seems difficult as a single parent, and part of you recognizes that this is an important part of your health."

Complex: In complex reflections, clinicians are reflecting the feeling that highlights the emotional aspect of what the patient is discussing. These are often more complex versions of paraphrases. As clinicians become more skilled at this type of reflection, they use both feeling statements ("you are scared") as well as metaphors ("you feel like you are treading water"). In this example, the clinician might reflect back, "You are really stressed and worried about losing the only alone time that you have."

Summaries. The final component of OARS is summary statements. Summary statements are used to tie together everything discussed during the interaction and to ensure that there is clear communication. It is often helpful to let the patient know that a summary is coming by using statements such as, "Let me see if I understand so far," or "To summarize, on the one hand you feel … and on the other hand …" Summaries can also be used to link together statements that they have made in previous encounters or to include information you might have from other sources (e.g., medical chart, PCP, spouse if permission has been given, etc.). Summaries are a helpful device to transition focus to a different topic and to probe the patient's readiness to make a plan. It is helpful to end a summary statement with an invitation such as "Did I miss anything?" or "Anything you want to add or correct?" This encourages the patient to continue collaborating and to have autonomy. A particularly useful way to incorporate summaries is to offer patients a summary of their change talk, referred to as the "change talk bouquet," in which the change talk statements evoked are bundled into a summary. This could function as a transitional summary to move on to the key question or to conclude the interview by highlighting the positives.

Roadblocks for engaging. Despite our best efforts and intentions, barriers to effective patient engagement exist. Often in the form of how we communicate, these

TABLE 22.2
Additional Examples of Reflections

Type of reflection	Example
Amplified	"You were petrified"
Double sided	"Quitting will be hard, and you realize the change will benefit your family"
Affective	"It upsets you to hear yourself say that"
Metaphor	"It feels like you are drowning"
Continuing the sentence	"… and you have been waiting to say that for a long time"
Emphasizing personal choice	"… and you know you are the only one who can make this change"
Siding with the negative	"… and then there is always the choice to change nothing"

"roadblocks" can hinder effective listening and engagement with the patient. Motivational Interviewing is an approach that helps avoid these roadblocks. The following are 12 common roadblocks that hinder effective communication (adapted from Thomas Gordon's 12 Roadblocks): [4]

1. Ordering, directing, or commanding
2. Warning, cautioning, or threatening
3. Giving advice, making suggestions, or providing solutions
4. Persuading with logic, argument, or lecturing
5. Telling people what they should do; moralizing
6. Disagreeing, judging, criticizing, or blaming
7. Agreeing, approving, or praising
8. Shaming, ridiculing, or labeling
9. Interpreting or analyzing
10. Reassuring, sympathizing, or consoling
11. Questioning or probing
12. Withdrawing, distracting, humoring, or changing the subject

The communication styles outlined in this list rely on being directive, educating, or judging, rather than collaborating and supporting autonomy.

A helpful alternative to these roadblocks is the Elicit-Provide with Permission-Elicit (EPPE) model, a conversational structure that allows a clinician to provide education to a patient in an MI-consistent way. First, the clinician will *elicit* what the patient already knows about condition X, if they are interested in learning more, and if they have permission to share more information. This approach respects patient autonomy by asking permission and assessing interest. If permission is given, the next step is to *provide* affirmation, feedback, advice, or information to the patient. If permission is not granted (this may sound strange, but it happens), then do not continue with educating or risk damaging the relationship. Please keep in mind that the patient's presence in the room with you is not necessarily implied consent for providing information. For the last step, the clinician would again *elicit* reactions, questions, and possibly plan for next steps (Figure 22.1).[4]

An additional common trap is spending most of the time during the initial session *only* gathering information, as opposed to spending time connecting to and understanding the patient. This can be a challenging balance for clinicians when certain information is required to be answered in an intake session. When the clinician solely focuses on information gathering, they are more likely to be perceived as the expert in the relationship, which risks prematurely defining the focus of the interview or focusing on the clinician's agenda rather than the patient's.

An approach that can be used to safeguard against this is the MI assessment sandwich.[37] First, the clinician uses OARS to build rapport and engage with the individual (via the elicit-provide-elicit model). This allows the patient to join with the clinician while simultaneously providing an opportunity for the clinician to understand the patient's readiness for change. Then, the clinician leads into the information gathering portion of the session. This could include any number of assessment protocols. Finally, the clinician focuses on eliciting change talk, working with the patient's ambivalence, and ultimately, if appropriate, creating a change plan.

22.3.3 Focusing

The second process in MI is focusing. Clinicians and patients must know the direction toward which they are rowing the boat. Without a clear understanding of the goal or specific behavioral change, it can be difficult for both the patient and the clinician to know where to focus their attention. Learning how to collaboratively set an agenda becomes an important skill in this MI process. The clinician may have some clear ideas on how to proceed based on their own expertise; however, the client, being the expert in themselves, might also have clear ideas about how to proceed. Understanding that there can be two experts in the room is essential to moving forward. The true art of focusing comes in when the patient is less clear about their goal and how to move forward. The clinician should feel comfortable staying in the focusing process until a clear goal can be established. To help move along the process when there is an unclear goal, Miller and Rollnick[4] suggest a tool called agenda mapping, which they describe as being similar to "looking at a map and seeing the places you might go, perhaps like two people on a sailboat slowing down for a moment to agree on a new course (p. 106)." Agenda mapping starts by asking the patient for permission to take a step back to consider all the topics that the patient would like to discuss. This technique guides the patient to where you are going and supports their autonomy. Next, the patient and clinician create a list of possible options to talk about. Once this bird's eye view is created, the clinician guides the patient back toward a narrower, more specific focus.

Another challenge to focusing is when there is a preset goal to the visit (e.g., court ordered therapy). In these cases, it is important to acknowledge that the individual is being mandated to be at the appointment and might be reluctant to engage. It can be helpful for the clinician to acknowledge their dual role of being the patient's clinician while also making an importation recommendation about the patient. This type of honest and open conversation can help create the trust necessary to move forward in the interview. In these cases, the clinician taking a neutral stance regarding



FIGURE 22.1 Elicit-Provide with Permission-Elicit model

any desired outcome (equipoise)[4] is useful. Typically, in MI, the clinician is working toward moving the patient toward a particular goal, which is typically clear (e.g., smoking less; losing weight; going to treatment); in equipoise, the clinician would remain neutral and allow the patient to explore the pros and cons of each side of the potential outcome (e.g., to stay with a job or not; to leave a partner or not). A clinician in this situation might choose to complete a decisional balance with the patient (Figure 22.2).

22.3.4 Evoking

As a patient makes their way toward change (the direction they are rowing in), ambivalence is a natural and common place to get stuck. Concepts such as "change talk" and "sustain talk" help explain the two sides of ambivalence: reasons for changing and reasons for not changing. Miller and Rollnick[4] hypothesized that self-motivational speech (change talk) is one mechanism of action in MI, and there is a strong body of evidence reliably linking change talk to positive health outcomes.[38–40] Furthermore, there is evidence that MI-consistent clinician behaviors lead to change talk.[41–43] Moyers et al. suggests that change talk "[m]ediates the relationship between MI-consistent clinician behaviors and improved client outcomes."[40] Change talk is the verbalization of the patient's internal motivation to change. Statements that represent movement toward change are precisely the language clinicians should be focused on evoking, strengthening, affirming, and validating. Clinicians must first build their awareness and ability to recognize change talk and then work on responding to it.

Recognizing change talk: Although sustain talk is normal, focusing on it is not always helpful. Often, clinicians are habituated, or even trained, to identify the problems in a situation. With MI, it is necessary to shift the lens from a problem-centric approach (which may elicit sustain talk) to a solution-focused approach with hopes to elicit change talk. According to Miller and Rollnick,[4] change talk is divided into two categories: preparatory change talk and mobilizing change talk.

Preparatory Change Talk:

Desires: "I really want to" … "I'm hoping that if" … "I really wish life was different."

Ability: "I know I can do this if" … "I have changed like this in the past."

Reason: "If I could just lose ten pounds, I know I would feel better" … "I know what I'm doing is not healthy" … "If I could just get started, I would feel more confident in other ways."

Need: "The doctor said I need to quit" … "I need to do this for me and my family" … "I'm always so exhausted and I know it is affecting my work."

Mobilizing Change Talk:

Commitment: "I am willing to hear your advice on what to do next" … "I'm going to start tracking daily step count."

Activation: "I've been considering how to tackle this bad habit" … "I'm ready to start."

Taking Steps: "I have already bought a gym membership" … "I called the smoking cessation phone line and left a message" … "I talked to my wife about what she thinks."

It is important to remember that sustain talk is not fundamentally bad or non-therapeutic. In fact, it is completely normal. The clinician's goal, however, is to strategically evoke and respond to change talk when they hear it. Miller and Rollnick[4] state that "[s]killful MI significantly strengthens client change talk, which in turn predicts subsequent change (p. 155)." When responding to change talk, it is helpful to identify the type of change talk to facilitate movement forward. If the patient is providing preparatory change talk, the clinician targets increasing the change talk and moving toward a plan. If the patient is providing mobilizing change talk, the clinician then works on increasing the change talk toward next steps.



FIGURE 22.2 Decisional balance.

Evoking change talk is an essential part of MI, and scaling type questions are often used to facilitate this. To do this, use an imaginary scale ranging from 0 to 10. This *importance ruler* is integrated into conversations about change by inquiring how important it is to the patient to change the target behavior. For example, the clinician could ask:

> "On a scale from 0 to 10, where 0 is "not important at all" and 10 is "extremely important," how important is it to you to _____?"

This offers a baseline level of importance. From here, the clinician could begin eliciting change talk. Proceed by asking:

> "Tell me a bit about why you are at a (reported number) and not a (lower number)?"

Keep in mind to offer the patient-reported number first, followed by a lower number. When the clinician approaches in this manner, the patient will provide change talk by offering up reasons why it is important. If asked in reverse, this question elicits sustain talk and road blocks, as they would be rationalizing reasons to stay the same. This last question can be followed up by:

"What would it take to get you from (lower number) to (a number slightly higher)?"

The response will likely provide more change talk and support the efforts and/or successes in the past. The abovementioned ruler in Table 22.3 can also be used to investigate the patient's level of confidence. To do this, simply replace *importance* with *confidence.* The result will be the patient's confidence talk. Be sure to offer the patient's stated number first once again, followed by the lower number. When done in this manner, the patient will offer up reasons for their confidence, including wants, needs, and even past successes. Other provocative questions that could elicit change talk are:

- What is there about you that would help you do this?
- How might you go about it to succeed?
- How would you go about this change?
- What have you done successfully in the past that was like this in some way?
- What are the reasons for changing?

Responding to Change Talk is a critical component of MI. Given that change talk represents internal motivation for change, it can be further strengthened by strategically responding with OARS. Strategies for Evoking Change Talk[4] fall into a commonly used and easy to remember mnemonic: EARS.

- *Elaborate* by asking open-ended questions such as, "Why do you want to make this change or how might you go about it," or use the importance/confidence ruler. Clinicians can also inquire about what was successful in the past or what the patient hopes to achieve by this change in the future.
- *Affirmations* are given to agree with, encourage, or support the patient.
- *Reflect* on what the patient has already said. If possible, offer a complex reflection; one that elaborates on the change talk or emotional content.
- *Summarize:* Here, the clinician attempts to collect the "bouquets" of change talk and provide it back to the patient in summary form.

As mentioned earlier, sustain talk is the patient's argument to maintain the status quo. This is a normal behavior that should be expected during the change process. Sustain talk occurs when the patient has intrapersonal conflict (ambivalence) with changing a target behavior. Discord, however, is very different. Discord occurs when there is an interpersonal conflict between the patient and the clinician. Said otherwise, discord is behavior that reflects an issue or disharmony within the relationship. Discord shows up in numerous ways, including:

- Defensiveness
- Arguing
- Interrupting
- Ignoring

Discord can occur in any of the four processes of MI, be it discord in engaging, focusing, evoking, or planning. Discord is best addressed by returning to the first process of MI—engaging. There are numerous ways to approach the amelioration of discord. First, it can be done by simply apologizing for the disconnect. A simple "sorry" can go a long way in repairing the collaborative relationship. A statement such as "I'm sorry I overstepped my bounds. I should not be telling you what to do," can easily reduce the tension of discord. Affirming the patient is also an effective technique. A clinician who observes discord could offer, "You are very sure of what has worked in the past." Lastly, there is shifting focus. This technique is an implicit way for the clinician and patient to agree to disagree by shifting the conversation away from the contentious topic. An example of shifting focus is, "You are right, my opinion is not important here, tell me what is important about this to you."

TABLE 22.3
Importance Ruler

0<----------10
Not important at all — **Extremely important**

22.3.5 Planning

Once a significant amount of change talk is present, it may now be appropriate to investigate a plan, keeping in mind not to get ahead of the patient's level of readiness. The planning is an ongoing, ever-changing process that requires the clinician to assess potential approaches to addressing the target behavior. First, the clinician offers a summary in the form of a "change talk bouquet"—a collection of "flowers" (change talk statements) the clinician has collected and offered back to the patient like a bouquet. This can be followed by a simple question, such as "Where should we go from here?" This can transition the clinician and patient from processing to planning. This question may result in either a clear step forward, a multitude of options forward, or a step forward with no clear path. When there is a clear path to change, it is helpful to focus on clarifying the goal and summarizing your current understanding of the progress. From here, you begin troubleshooting hurdles and speed bumps impeding progress and narrowing down the details to attain more specific details regarding the plan. Although not MI specific, the acronym SMART is often helpful when creating goals:

Specific: Define the goal as much as possible, including interrogatives such as what, where, and when will this occur?

Measurable: Ensure the goal/behavior can be tracked. For example, "I will exercise for 30 minutes 3 days a week."

Attainable: Ensure that the goal can be accomplished. Try to make the goal not too high or too low below their standard performance.

Relevant: Is the goal in line with other goals they have?

Timely: Goals should have a start time, as well as a time limit to accommodate for evaluation. After a certain amount of time, such as one week, one month, or one year, the goal will be evaluated for success.

Sometimes, the path forward has many branches; the motivation is present, but there could be a multitude of options for the patient to choose from. After you have provided a summary and list of the different options, it is important to confirm the goal. Then, try to investigate the patient's preference and intuitions regarding next steps, asking questions such as, "If you could imagine being most successful in this task, what three options seem most likely to move you forward?" or simply, "Which one appeals to you most?" From here, continue evoking change talk and troubleshooting further tasks. Lastly, there is the scenario where there is no clear plan at all. As with the clear plan and the plan with many options, first, the practitioner clarifies the plan after offering a summary. From here, you engage in a brainstorming session with the patient, offering up any option that is plausible. At this point, you want to work with the patient's ideas from general to specific. The CATS mnemonic, under "Mobilizing Change Talk," can guide you as you continue working on the patient's change talk regarding commitment, action, and taking steps.

22.4 SUMMARY

Motivational Interviewing is a "collaborative conversation style for strengthening a person's own motivation and commitment to change."[4] In this chapter. we discussed the four processes of MI and basic MI skills such as OARS and how to respond to change talk, sustain talk, and discord. Proficiency in MI is attainable with training, coaching, and a lot of practice. As seen in research, using MI is typically better at improving outcomes than offering education alone, wait-listing, or treatment-as-usual interventions[6] and often better than using a directive style.[44] Clinicians are encouraged to explore how MI can influence change behaviors and how cultivating the relationship alone may positively influence outcomes. Keep in mind, you are often more responsible for the interaction than you are for the outcome.

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23 Transtheoretical Model

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KEY POINTS

- The importance of a healthy lifestyle
- Characteristics of people in each stage of change
- The principles and processes to apply at each stage
- Increasing impacts with multiple behavior change
- Challenges to the Transtheoretical Model (TTM)
- How TTM can increase well-being
- Multiple benefits of integrating TTM into practice

23.1 INTRODUCTION

Health risk behaviors, like smoking, inactivity, unhealthy diets, alcohol abuse, and ineffectively managed stress, account for about 70% of a population's morbidity, disability, mortality, reduced functioning and productivity, and escalating health care costs. In contrast, a healthy lifestyle, including abstinence from smoking, eating 5 servings of fruits and vegetables each day, adequate physical activity (e.g., walking 10,000 steps a day or doing 150 minutes of moderate exercise a week), and striving to maintain a body mass index (BMI) of less than 25, is being shown to increase life expectancy by up to 14 years.[1–3] However, having a healthy lifestyle of 0 (smoking), 1–2 alcoholic drinks per day, 5 (fruits and vegetables), 10 (10,000 steps), 20 (20 minutes of stress management), and 25 (<25 BMI) (0–1-5–10, 20, 25) has been an elusive goal for 97% of the population.[4] Why are these health risk behaviors so critical to health and well-being? They represent fundamental functions of life: breathing, drinking, eating, moving, and feeling. If we breathe toxins, we threaten our bodies. If we drink alcohol to toxic levels, we do damage to our minds and bodies. If we don't move enough, we don't remove enough toxins from our bodies.

To have a significant and sustainable impact on attaining these healthy behaviors, a model of behavior change is needed to address the needs of entire populations, not just the minority who are motivated to take immediate action for better health. The Transtheoretical Model of Behavior Change (TTM) is founded on stages of change that categorize segments of populations based on where they are in the process of change. Principles and processes are applied to initiate movement through the stages of change. Interventions based on TTM principles can produce programs that are interactive and broadly applicable for the treatment of entire populations. The programs include computer-tailored interventions (CTIs) delivered through various modalities, such as counselor guidance, telephonic coaching, the Internet, and texting.

23.2 STAGES OF CHANGE

The TTM postulates that change is a process that unfolds over time through a series of stages: Precontemplation, Contemplation, Preparation, Action, Maintenance, and Termination.

Precontemplation is a stage in which the individual does not intend to take action in the foreseeable future (usually measured as the next six months). Individuals may be at this stage because they are uninformed or underinformed about the consequences of a given behavior, or they may have tried to change a number of times and have become demoralized about their ability to do so. Individuals in both categories tend to avoid reading, talking, or thinking about their high-risk behaviors. In other theories, such individuals are characterized as "resistant" or "unmotivated" or "not ready" for health promotion programs. In fact, traditional programs were not ready for such individuals and were not motivated to match their needs.

Individuals who are in the Precontemplation stage typically underestimate the benefits of change and overestimate its costs but are unaware that they are making such mistakes. If they are not conscious of making such mistakes, it is difficult for them to change. As a result, many remain stuck in the Precontemplation stage, with considerable resulting harm to their bodies, themselves, and others. There appears to be no inherent motivation for people to progress from one stage to the next. The stages are not like stages of human development, in which children have inherent motivation to progress from crawling to walking, even though crawling works very well and even though learning to walk can be painful and embarrassing. Instead, two major forces can move people to progress.

The first is *developmental events.* In the authors' research, the mean age of smokers who reach the long-term Maintenance stage is 39 years. Those who have passed 39 recognize it as an age to reevaluate how one has been living and whether one wants to die from that lifestyle or whether one wants to enhance the quality and quantity of the second half of life. The other naturally occurring force is *environmental events.* A favorite example is a couple

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who were both heavy smokers. Their dog of many years died of lung cancer. This death eventually moved the wife to quit smoking. The husband bought a new dog. So, even the same events can be processed differently by different people.

A common belief is that people with health risks must "hit bottom" before they are motivated to change. So family, friends, and physicians wait helplessly for a crisis to occur. But, how often do people turn 39 or have a dog die? When individuals show the first signs of a serious physical illness, such as cancer or cardiovascular disease, those around them usually become mobilized to help them seek early intervention. Evidence shows that early interventions often are lifesaving, and so it would not be acceptable to wait for such a patient to "hit bottom." In opposition to such a passive stance, a third force that has been created to help individuals progress beyond the Precontemplation stage is called *planned interventions.*

Contemplation is a stage in which an individual intends to take action within the ensuing six months. Such a person is more aware of the benefits of changing but also is acutely aware of the costs. When a smoker begins to seriously contemplate giving up smoking, their awareness of the costs of changing can increase. There is no free change. This balance between the costs and benefits of change can produce profound ambivalence, which may reflect a type of love–hate relationship with risks and thus can keep an individual stuck at the Contemplation stage for long periods of time. This phenomenon often is characterized as "chronic Contemplation" or "behavioral procrastination." Such individuals are not ready for traditional action-oriented programs.

Preparation is a stage in which individuals intend to take action in the immediate future (usually measured as the ensuing month). Such persons typically have taken some significant action within the preceding year. They generally have a plan of action, such as participating in a weight-loss group, consulting a counselor, talking to a physician, buying a self-help book, or relying on a self-help approach. It is these individuals who should be recruited for action-oriented treatment programs.

Action is a stage in which individuals have made specific, overt modifications in their lifestyle within the preceding six months. Because action is observable, behavior change often has been equated with action. But in TTM, Action is only one of six stages. In this model, not all modifications of behavior count as action. An individual must attain a criterion that scientists and professionals agree is sufficient to reduce the risk of disease. With smoking, for example, only total abstinence counts. With alcoholism and alcohol abuse, many believe that only total abstinence can be effective, whereas others accept controlled drinking as an effective action.

Maintenance is a stage in which individuals are working to prevent relapse but do not need to apply change processes as frequently as one would in the Action stage. Such persons are less tempted to relapse and are increasingly confident that they can sustain the changes made. Temptation and self-efficacy data suggest that Maintenance lasts from six months to about five years. One of the common reasons for early relapse is that the individual is not well prepared for the prolonged effort needed to progress to Maintenance. Many persons think the worst will be over in a few weeks or a few months. If, as a result, they ease up on their efforts too early, they are at great risk of relapse.

To prepare such individuals for what is to come, they should be encouraged to think of overcoming a bad habit as running a marathon rather than a sprint. They may have wanted to enter the Boston Marathon, but they know they would not succeed without preparation and so would not enter the race. With some preparation, they might compete for several miles but still would fail to finish the race. Only those who are well prepared could maintain their efforts mile after mile. Using the Boston Marathon metaphor, people know they have to be well prepared if they are to survive Heartbreak Hill, which runners encounter at about mile 20. What is the behavioral equivalent of Heartbreak Hill? The best evidence available suggests that most relapses occur at times of emotional distress. It is in the presence of depression, anxiety, anger, boredom, loneliness, stress, and distress that humans are at their emotional and psychological weak point.

How does the average person cope with troubling times? He or she drinks more, eats more, smokes more, and takes more drugs to cope with distress. It is not surprising, therefore, that persons struggling to overcome risky behaviors will be at greatest risk of relapse when they face distress. Although emotional distress cannot be prevented, relapse can be prevented if individuals have been prepared to cope with distress.

If so many Americans rely on oral consumptive behavior as a way to manage their emotions, what is the healthiest oral behavior they could use? Talking with others about one's distress is a means of seeking support that can help prevent relapse. Another healthy alternative is exercise. Physical activity helps manage moods, stress, and distress. Also, 150 minutes per week of exercise can provide a person with more than 70 health and mental health benefits.[5] Exercise thus should be prescribed to all sedentary individuals. A third healthy alternative is some form of deep relaxation, such as meditation, yoga, prayer, massage, or deep muscle relaxation. Letting the stress and distress drift away from one's muscles and one's mind helps the individual move forward at the most tempting of times.

Termination is a stage in which individuals have zero temptation and 100% self-efficacy. Whether they are depressed, anxious, bored, lonely, or stressed, such persons are certain they will not return to their old unhealthy habits as a method of coping. It is as if they had never acquired the habit in the first place. In a study of former smokers and people with alcohol use disorders who were abstinent for less than five years, about 20% of each group had reached the stage of no temptation and total self-efficacy. This is an ideal stage that only a minority might reach.[6]

23.3 PRINCIPLES AND PROCESSES OF CHANGE

To help motivate patients to progress from one stage to the next, it is necessary to know the principles and processes of change that can produce such progress.

23.3.1 Principle 1

The benefits of changing must increase if clients are to progress beyond Precontemplation. In a review of 12 studies, all showed that the perceived benefits were higher in the Contemplation than in the Precontemplation stage.[7] This pattern held true across 12 problem behaviors: use of cocaine, smoking, delinquency, obesity, inconsistent condom use, unsafe sex, sedentary lifestyles, high-fat diets, sun exposure, radon testing, mammography screening, and physicians practicing behavioral medicine.

A technique that can be used involves asking a client in the Precontemplation stage to describe all the benefits of a change such as quitting smoking or starting to exercise. Most persons can list four or five. The coach can let the client know that there are eight to ten times that number and challenge the patient to double or triple the list for their next meeting. If the client's list of benefits of exercise begins to indicate many more motives, such as a healthier heart, healthier lungs, more energy, healthier immune system, better moods, less stress, better sex life, and enhanced self-esteem, he or she will be more motivated to begin to seriously contemplate such a change.

23.3.2 Principle 2

The "cons" of changing must decrease if clients are to progress from Contemplation to Action. In 12 of 12 studies, the authors and colleagues found that the perceived costs of changing were lower in the Action stage than in the Contemplation stage.[8]

23.3.3 Principle 3

The relative weight assigned to benefits and costs must cross over before a client will be prepared to take action. In 12 of 12 studies, the costs of changing were assessed as higher than the rewards in the Precontemplation stage, but in 11 of 12, the rewards were assessed as higher than the costs in the Action stage. It should be noted that if raw scores are used to assess these patterns, it would appear that the rewards for changing are seen as greater than the costs, even by persons in the Precontemplation stage. It is only when standardized scores are used that clear patterns emerge, with the costs of changing always perceived as greater than the rewards. This suggests that compared with their peers at other stages of change, persons in the Precontemplation stage underestimate the rewards and overestimate the costs of change.

23.3.4 Principle 4

The strong principle of progress holds that to progress from Precontemplation to effective Action, the rewards for changing must increase by one standard deviation (SD).[8]

23.3.5 Principle 5

The weak principle of progress holds that to progress from Contemplation to effective Action, the perceived costs of changing must decrease by one-half an SD.

Because the perceived benefits for changing must increase twice as much as the perceived costs decrease, twice as much emphasis must be placed on the benefits as on the costs of changing. What is striking here is that the authors and colleagues believe they have discovered mathematical principles for the degree to which positive motivations must increase and negative motivations must decrease. In a recent meta-analysis of nearly 140 studies on 48 behaviors, the pros of changing increased by exactly 1.00 SD, whereas the cons decreased by 0.54 SD.[9] Such principles can produce much more sensitive assessments to guide interventions, giving coaches and clients feedback for when coaches' efforts are producing progress and when they are failing. Together, they can modify methods if movement is needed for the client to become adequately prepared for the Action stage.

23.3.6 Principle 6

It is important to match particular processes of change with specific stages of change. Table 23.1 presents the empirical integration found between stages and the principles and processes of change. Guided by this integration, the following processes would be applied to clients across the stages of change:

1. *Consciousness raising* (get the facts) involves increased awareness of the causes, consequences, and responses to a particular problem. Interventions that can increase awareness include observations, confrontations, interpretations, feedback, and education. Some techniques, such as confrontation, pose considerable risk in terms of retention and are not recommended as highly as motivational enhancement methods such as personal feedback about the current and long-term consequences of continuing the unhealthy behavior. Increasing the costs of not changing is the corollary of raising the benefits of changing. So, consciousness raising should be designed to increase the perceived gains from changing.
2. *Dramatic relief* (pay attention to feelings) involves emotional arousal about one's current behavior and the relief that can come from changing. Fear, inspiration, guilt, and hope are some of the emotions that can move persons to contemplate

TABLE 23.1
Integration of the Stages, Principles, and Processes of Change

Precontemplation	Contemplation	Preparation	Action	Maintenance
Consciousness raising				
Dramatic relief				
Environmental reevaluation				
	Self-reevaluation			
		Self-liberation		
			Reinforcement management	
			Helping relationships	
			Counter conditioning	
			Stimulus control	
Pros of changing increasing				
	Cons of changing decreasing			
		Self-efficacy increasing		

Note: Social liberation has been found not to have differentiated emphasis across all five stages.

changing. Psychodrama, role playing, grieving, and personal testimonies are examples of techniques that can move people emotionally. It should be noted that earlier literature on behavior change concluded that interventions such as education and fear arousal did not motivate behavior change. Unfortunately, many interventions were evaluated in terms of their ability to move people to immediate action. However, processes such as consciousness raising and dramatic relief are intended to move people to the Contemplation stage rather than the Action stage. Therefore, their effectiveness should be assessed according to whether they lead to the expected progress.

3. *Environmental reevaluation* (notice your effect on others) combines both affective and cognitive assessments of how an unhealthy behavior affects one's social environment and how changing would affect that environment. Empathy training, values clarification, and family or network interventions can facilitate such reevaluation. For example, a brief media intervention aimed at a smoker in the Precontemplation stage might involve an image of a man clearly in grief saying, "I always feared that my smoking would lead to an early death. I always worried that my smoking would cause lung cancer. But I never imagined my wife would die from lung cancer." Beneath his grieving face appears this statistic: "50,000 deaths per year are caused by passive smoking." In 30 seconds, this message achieves consciousness raising, dramatic relief, and environmental reevaluation.
4. *Self-reevaluation* (create a new self-image) combines both cognitive and affective assessments of an image of one's self free from an unhealthy behavior. Imagery, healthier role models, and values clarification are techniques that can move individuals in this type of intervention. Individuals first look back and reevaluate how they have lived as unhealthy individuals. As they progress into the Preparation stage, they begin to develop a focus on the future as they imagine how life could be if they were free of the unhealthy habit.
5. *Self-liberation* (make a commitment) involves both the belief that one can change and the commitment and recommitment to act on that belief. Techniques that can enhance such willpower include public rather than private commitments. Motivational research also suggests that individuals who have only one choice are not as motivated as they could be when they have two choices.[10] Three choices are even better, but four choices do not seem to enhance motivation. Wherever possible, then, clients should be given three of the best choices for applying each process. With smoking cessation, for example, there are at least three good choices: quitting "cold turkey," using nicotine replacement therapy, and using nicotine fading. Asking clients to choose which alternative they believe would be most effective for them and to which they would be most committed can enhance their motivation and their self-liberation.
6. *Counter conditioning* (use substitutes) requires the learning of healthier behaviors that can substitute for the unhealthy behavior. Counter conditioning techniques tend to be quite specific to a particular behavior. They include desensitization, assertion, and cognitive counters to irrational self-statements that can elicit distress.
7. *Reinforcement management* (use rewards) involves the systematic use of reinforcements and punishments for taking steps in a particular

direction. Because successful self-changers rely much more on reinforcement than on punishment, it is useful to emphasize reinforcements for progressing rather than punishments for regressing. Contingency contracts, overt and covert reinforcements, and group recognition are methods of reinforcement and incentives that increase the probability that healthier responses will be repeated. To prepare clients for the longer term, they should be taught to rely more on self-reinforcements than on social reinforcements. Clinical experience shows that many individuals expect much more reinforcement and recognition from others than they actually receive. Relatives and friends may take the Action stage for granted. They typically generate only a few positive consequences. Self-reinforcements, obviously, are much more under self-control and can be given more quickly and consistently when temptations to lapse or relapse are resisted.

8. *Stimulus control* (manage your environment) involves modifying the environment to increase cues that prompt healthy responses and decrease cues that lead to relapse. Avoidance, environmental re-engineering (such as removing addictive substances and paraphernalia), and attending self-help groups can provide stimuli that elicit healthy responses and reduce the risk of relapse.
9. *Helping relationships* (get support) combine caring, openness, trust, and acceptance, as well as support for changing. Rapport building, a therapeutic alliance, coach calls, buddy systems, sponsors, and self-help groups can be excellent resources for social support. If clients become dependent on such support to maintain change, the support will need to be carefully faded, lest termination of coaching becomes a condition for relapse.
10. *Social liberation* (notice public support) is the process by which changes in society increase the options and opportunities to have healthier and happier lives freer from risky behaviors. Social networks are examples of a dramatic increase in being able to participate in positive interactions free from pressures to rely on unhealthy habits.

23.3.7 Principle 7

Self-efficacy is the situation-specific confidence that people have while coping with high-risk situations without relapsing to their unhealthy behavior. Self-efficacy increases as people move through the stages of change.

What is the result when all of these principles and processes of change are combined to help clients and entire populations move toward the Action stage to reduce their health risks? A series of clinical trials applying stage-matched interventions offers lessons about the future of behavioral health care generally and treatment of the bad habits specifically. In a large-scale clinical trial, the authors and colleagues compared four treatments: (a) a home-based action-oriented smoking cessation program (standardized), (b) stage-matched manuals (individualized), (c) a CTI plus manuals (interactive), and (d) counselors plus CTI (personalized). Clients (739 smokers) were randomly assigned by stage to one of the four treatments.[11]

In the CTI treatment, participants completed 40 questions by mail or telephone. Their responses were entered into a central computer, from which tailored feedback reports were generated. These reports informed participants about their stage of change, the pros and cons of changing, and change processes appropriate to their stages of change. At baseline, participants were given positive feedback on what they were doing correctly and guidance on which principles and processes they needed to apply to progress. In two progress reports delivered over the following six months, participants also received positive feedback on any improvement in any of the variables relevant to progress. Thus, demoralized and defensive smokers could begin to progress without having to quit and without having to work too hard. Smokers in the Contemplation stage could begin to take small steps, such as delaying their first cigarette in the morning for an additional 30 minutes. They could choose small steps that would increase their self-efficacy and help them become better prepared for quitting.

In the personalized treatment, smokers received four proactive counselor calls over the six-month intervention period. Three of the calls were based on the CTI reports. When they didn't have a CTI report, counselors reported much more difficulty in interacting with participants without any progress data. Without scientific assessments, it was more difficult for both clients and counselors to know whether any significant progress had occurred since their last interaction.

Figure 23.1 presents point prevalence abstinence rates for each of the 4 treatment groups over 18 months, with treatment ending at 6 months. Results with the 2 self-help manual conditions were parallel for 12 months, but the individualized stage-matched manuals achieved better results at 18 months. This is an example of a *delayed action effect*, which often is observed with stage-matched programs. It takes time for participants in early stages to progress all the way to Action. Therefore, some treatment effects as measured by action will be observed only after considerable time has elapsed. But, it is encouraging to find treatments producing therapeutic effects months and even years after active treatment has ended. The CTI alone and personalized counselor calls plus CTI treatments produced comparable results for six months. The CTI alone produced delayed action effects through 18 months. The effects of CTI plus counselors leveled off. One hypothesis is that clients can become dependent on counselors. Counselors may need to phase out treatment gradually to reduce such dependence and enhance the self-efficacy of clients.

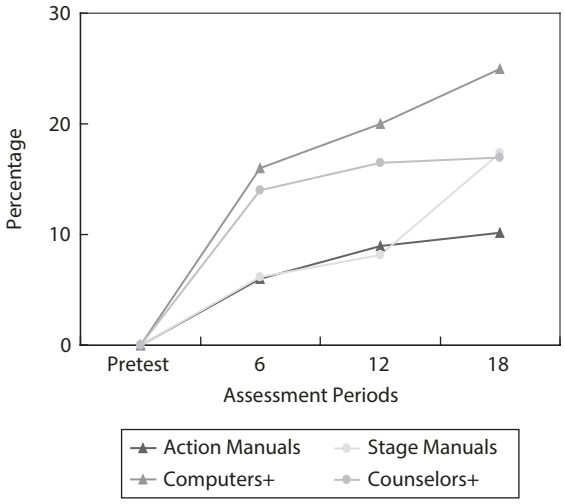


FIGURE 23.1 Point prevalence abstinence (%) for treatment groups pretest and at 6, 12, and 18 months.

23.4 CRITICAL ASSUMPTIONS OF THE TTM

The TTM is also based on critical assumptions about the nature of behavior change and population health interventions that can best facilitate such change. The following are a set of assumptions that drive transtheoretical theory, research, and practice:

1 Behavior change is a process that unfolds over time through a sequence of stages. Effective health promotion interventions need to match their help to individuals' stages as they progress over time.
2 Stages can be both stable and subject to change, just as chronic behavioral risk factors are both stable and subject to change. Health initiatives can motivate change by enhancing the understanding of the pros and diminishing the value of the cons.
3 The majority of at-risk populations are not prepared for action and will not be served by traditional action-oriented prevention programs. Helping individuals set realistic goals, like progressing to the next stage, will facilitate the change process.
4 Specific principles and processes of change need to be emphasized at specific stages for progress through the stages to occur.

These critical assumptions need to be taken into consideration when developing health promotion interventions for behavior change that can facilitate progress through the stages.

23.5 INCREASING IMPACTS WITH MULTIPLE BEHAVIOR CHANGE PROGRAMS

One of the greatest challenges for the application of any theory is to keep raising the bar, that is, to be able to increase the theory's impact on enhancing health. One potential is for TTM to treat multiple behaviors in a population, since most populations have multiple behavior risks and are at risk for both chronic disease and premature death. Those multiple-comorbid populations also account for a disproportionate percentage of health care costs. One estimate is that about 60% of health care costs are generated by about 15% of populations who have multiple behavior risks and medical conditions.[12]

Historically, studies conducted on multiple behavior changes have been limited by reliance on the action-oriented treatment and the lack of applying the most promising interventions, such as interactive and individualized TTM-tailored interventions.[13] From a TTM perspective, applying an action paradigm to multiple behaviors would indeed risk overwhelming populations, since Action is the most demanding stage, and taking action on two or more behaviors at once could be overwhelming. Furthermore, among individuals with four health behavior risks, like smoking, diet, sun exposure, and sedentary lifestyles, fewer than 10% of the population were ready to take action on two or more behaviors.[14] The same was true of populations with diabetes who needed to change four behaviors.[15]

With a population of 1,277 overweight and obese patients proactively recruited in the United States, we applied our first strategy for multiple behavior change. We call this the modular approach, where participants receive a separate TTM CTI module for each of their risk behaviors related to healthy weight management. The treatment groups had significant changes at 24 months on healthy eating, exercise, and emotional eating. This study was the first to report results showing significant coaction in the TTM CTI group and significant changes in fruit and vegetable intake that were not treated. Also, this study reported a mean of about 0.8 behaviors changed per participant in the TTM group, which was 60% greater than the 0.5 behaviors in the control group.[16]

One of the most exciting developments in our knowledge of simultaneously changing multiple behaviors is the phenomena of coaction. Coaction is the increased probability that if individuals take effective action on one behavior (like exercise), they are more likely to take action on a secondary behavior (like diet). We have found that significant coaction typically occurs only in our TTM treatment groups and not in control groups, suggesting it is likely to be treatment-induced.[16–18]

With a population of 1,400 employees in a major medical setting, the authors and colleagues made available online modular TTM CTIs for each of four behaviors (smoking, inactivity, BMI >25, and stress) and three Motivational Interviewing (MI) telephonic or in-person sessions. Employees chose which behaviors to target and how much time and effort would be spent on any behavior. At six months, both treatments outperformed the Health Risk Intervention (HRI), which included feedback on the person's stage for each risk and guidance on how they could progress to the next stage.[19]

With a population of 1,800 students recruited from 8 high schools in 4 states, Mauriello et al. applied a second-generation strategy with exercise as the primary behavior receiving three online sessions of fully tailored CTIs.[20] The secondary behaviors of fruit and vegetable (F&V) intake and limited TV watching alternated between moderate and minimal (stage only) tailoring. Over the course of the 6-month treatment, there were significant treatment effects in each of the three behaviors, but only changes in F&V were sustained at 12 months. Significant coaction was found for each pair of behaviors in the treatment group but not in the control group.

23.6 STUDIES CHALLENGING THE TRANSTHEORETICAL MODEL

Critics of the TTM have several core concerns. These include how well TTM constructs predict outcomes compared with non-TTM variables and whether TTM constructs (like processes of change) predict progress across stages of change in the way that TTM should predict. Their concerns are supported by some empirical studies, but some of the negative results in these studies can be explained by inappropriate methodology. Others have stronger methodology and provide useful detail that can be used to refine the TTM.

Farkas et al. and then Abrams et al. compared addiction variables with TTM variables as effective predictors of cessation over 12 to 24 months.[21,22] Addiction variables, including the number of cigarettes smoked and duration of prior quits (e.g., more than 100 days), were more effective than TTM variables in predicting cessation rates, suggesting that addiction models were preferable to TTM. Responses to these comparative studies have included concerns that Farkas et al. compared 14 addiction-type variables with just the single-stage variable from TTM.[23,24] The Abrams et al. study included self-efficacy and the Contemplation Ladder—an alternative measure of readiness or stage—as part of their addiction model but failed to acknowledge that both of these constructs are part of TTM.[22] Also, from an intervention perspective, the amount of variance accounted for by predictor variables is less important than the amount of variance that can be controlled or changed through an intervention. For example, duration of previous quits (e.g., more than 100 days) may be more predictive than stage; little can be done to change this historical variable, while a dynamic variable like stage is responsive to interventions.

In the first of a series of studies, Herzog and colleagues found that six processes of change were not adequate predictors of stage progress over a 12-month period.[25] In a second report, processes predicted stage progress but only when the Contemplation Ladder was used.[26] In the third report, TTM measures predicted 12-month outcomes, but self-efficacy and the Contemplation Ladder were not counted as TTM variables.[22] These findings conflict with other research that has found change processes and other TTM variables predict stage progress.[27–34] Johnson, J. L. et al. in their study explained some of the inconsistencies in previous research by demonstrating better predictions over 6 months versus 12 months, and better predictions using all ten processes of change instead of just a subset.[33]

One of the productive responses to studies critical of the TTM is to conduct further research. In response to the criticism that addiction severity levels are better predictors of long-term outcomes than stage of change, a series of studies was conducted to determine which types of effects predict long-term outcomes across multiple behaviors. To date, four such effects have been found.[35] The first is **severity effect**, in which individuals with less severe behavior risks at baseline are more likely to progress to the Action or Maintenance stages at 24-month follow-up for smoking, diet, and sun exposure. This effect includes the severity of addiction that Farkas et al. and Abrams et al. preferred.[21,22] The second is **stage effect**, in which participants in the Preparation stage at baseline have better 24-month outcomes for smoking, diet, and sun exposure than those in the Contemplation stage, who do better than those in the Precontemplation stage. This effect is what Farkas et al. and Abrams et al. criticized. The third is **treatment effect**, in which participants in treatment do better at 24 months than those randomly assigned to control groups for smoking, diet, and sun exposure. The fourth is **effort effects**, in which participants in both treatment and control groups who progressed to the Action and Maintenance stages at 24 months were making better efforts by using the TTM variables like pros and cons, self-efficacy, and processes at baseline. There were no consistent demographic effects across the three behaviors, indicating that no single demographic group did better across these multiple behaviors. What these results indicate is that either/or thinking (such as either severity or stage) is not as helpful as a more inclusive approach that seeks to identify the most important effects, whether they are based on TTM or on an addiction or severity model. These four effects are now being applied in TTM-tailored interventions for employees and other populations.

23.7 MULTIPLE DOMAINS OF WELL-BEING: FROM SUFFERING OR STRUGGLING TO THRIVING

Motivated by a risky test philosophy of science, we keep raising the bar to have increasing impacts with vulnerable populations, such as moving from changing a single behavior to a riskier goal of changing multiple risk behaviors.[36] One of our most recent challenges has been to simultaneously enhance multiple domains of well-being, e.g., physical, emotional, social, and work well-being. Prochaska et al. conducted a project with 3,391 participants from 39 states who had an average of almost 4 chronic conditions and almost 4 risk behaviors, with 40% obese, 35% overweight, and 0% exercising adequately or managing stress

effectively. A majority had poor diets, were or had been smokers, and had problems with depression.[37]

Compared with national norms, this population, with 59% women, a mean age of 48, and 48% unemployment, had much lower scores on each domain of well-being. Most striking was that a majority were suffering or struggling, and only a minority were thriving. The only time this pattern had been seen in the United States as a whole was during the economic crash of 2008.[38]

Random assignment to treatment groups and one control group was made. One group had telephonic TTM CTI coaching with exercise as the primary target and stress management as secondary. The second group received CTI coaching with stress as the primary target and exercise as secondary. Compared with controls, both treatment groups produced more multiple behavior change than controls and more improvement on multiple domains of well-being. In all comparisons, the telephonic coaching, which spent most of the time on exercise, produced more positive changes than the CTI coaching, which treated stress primarily and exercise secondarily.[37]

What was most rewarding was that the majority of both treatment groups, but not the control groups, had progressed from suffering or struggling to thriving. These results led us to produce a follow-up book to *Changing for Good*, which for over 20 years has been a guide for many health coaches.[39] Our new book, *Changing to Thrive*, is designed to help professionals, their clients, and other populations to reduce multiple risk behaviors, enhance multiple domains of well-being, and progress from suffering or struggling to thriving.[5]

23.8 CONCLUSIONS

It seems clear that the future of health promotion programs lies in stage-matched, proactive, interactive interventions. Much greater effects can be generated through the use of proactive programs because participation rates are increased, even if efficacy rates are lower. But, proactive programs also can produce outcomes comparable to those of traditional reactive programs. Although it is counterintuitive to suggest that outcomes for groups that are proactively recruited can match those of individuals who reach out for help, that is what informal comparisons strongly suggest. For example, in a comparison of results at 18-month follow-ups for all subjects who received three CTIs in a study of reactive intervention and a study of proactive intervention, the abstinence curves were remarkably similar.[40] The results with the counseling plus CTIs were even more impressive. Proactively recruited smokers, working with both coaches and the CTI, achieved higher rates of abstinence at each follow-up than did the smokers who had called for help. These results are partially attributable to the fact that the proactive coaching protocol has been revised and, it is to be hoped, improved on the basis of previous data and experience. But, the point is that if it is possible to reach out and offer people improved behavior change programs that are appropriate for their stage of readiness to change, it ought to be possible to produce efficacy or abstinence rates at least equal to those seen with individuals who reach out for help. Unfortunately, there is no experimental design that would make it possible to assign study subjects randomly to proactive versus reactive recruitment programs. Thus, one is left with informal but provocative comparisons. Results with multiple behavior interventions using some type of TTM tailoring and proactive recruitment have found effects as good as when smoking alone is treated. The results with the other treated behaviors were even better.

If these results continue to be replicated, programs will be able to produce unprecedented effects on entire populations. To do so will require scientific and professional shifts: (a) from an Action paradigm to a stage paradigm, (b) from reactive to proactive recruitment, (c) from expecting participants to match the needs of programs to having programs match the needs of clients, (d) from single- to multiple-behavior interventions, (e) from clinic-based to population-based programs that apply individualized and interactive intervention strategies, and (f) reducing multiple problem behaviors to enhance multiple domains of well-being to help vulnerable populations to progress from suffering or struggling to thriving.

With the knowledge and tools needed to move forward, we end with a final question for your consideration.

How ready are you to integrate a stage approach in your work?

1. I don't intend to integrate a stage approach in my work in the next six months (Precontemplation).
2. I intend to integrate a stage approach in my work in the next six months (Contemplation).
3. I intend to integrate a stage approach in my work in the next month (Preparation).
4. I have been integrating a stage approach in my work for less than six months (Action).
5. I have been integrating a stage approach in my work for more than six months (Maintenance).

Some ideas to guide your next steps:

1. If you are in Precontemplation, look for more information on using a stage approach and consider how your work, your client interactions, and your colleagues might benefit by your adopting a stage approach. (See Table 23.2 regarding some of the benefits.)
2. If you are in Contemplation, learn more about using a stage approach by talking with others who use it and seeking additional training in the approach at www.prochange.com/elearning. Identify what barriers might be in your way and consider ways to overcome them. Feel inspired by how the stage approach has helped others to engage patients more successfully.

TABLE 23.2
There are Many Benefits of Integrating TTM into Your Practice

TTM:

- Prepares you to work with entire populations wherever they are in the stages of change
- Helps you reduce resistance among your clients
- Allows you to see and appreciate how your clients are making progress in stages
- Enables you to set stage-matched goals with clients
- Gets you to offer and prescribe behavior change programs that are stage-appropriate
- Teaches you the principles and processes of change that are applicable across all health behaviors
- Shows you an approach that's successful at increasing engagement, increasing healthy behaviors, reducing multiple risks, and enhancing multiple domains of well-being and productivity

3. If you are in Preparation, make a commitment to begin using a stage approach, and share that commitment with others. Build your confidence by role playing or practicing the approach with clients. Ask colleagues to support and assist your efforts, and notice the benefit.
4. If you are in Action or Maintenance, keep this chapter and other training materials visible to make it easy to use a stage approach. Appreciate the benefits TTM offers you and your clients. Boost your confidence by using the approach even with resistant clients.[41] See a demo of a CTI at www.prochange.com/demo. The authors cofounded Pro-Change Behavior Systems, Inc., in 1997 and sold it to the two lead staff in 2015. They now act as consultants from time to time.

TTM has a broad range of clinical applications:

- Multiple behavior change for the prevention and management of chronic diseases, like type 2 diabetes
- Medication adherence for lipids, changing diet, and increasing exercise to prevent and manage cardiovascular disease
- Prevention and management of clinical depression
- Changing multiple behaviors and enhancing multiple domains of well-being in populations with multiple chronic conditions
- Changing multiple behaviors to prevent severe types of cancer

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24 The Impact of Positive Psychology on Behavioral Change and Healthy Lifestyle Choices

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KEY POINTS

- The goal of positive psychology, a science that focuses on human strengths, is to increase well-being and flourishing in individuals and groups. Psychological well-being is a "health asset," protecting against risk of physical illness.
- A substantial and growing body of evidence connects positive emotions, optimism, and subjective well-being with better health and longevity outcomes, even in the context of adversity.
- Positive psychology practices can influence health and wellness by encouraging patients' use of their strengths to manage stress and emotions, and to work toward healthy habits and lifestyle changes.
- Positive psychology interventions (PPIs), which can be prescribed, have been developed and tested in randomized controlled trials. PPIs have been demonstrated to be effective in improving positive emotions and well-being, and reducing depressive symptoms.

"Treatment is not just fixing what is broken; it is nurturing what is best."[1]

24.1 INTRODUCTION

Positive psychology is defined as the scientific study of the "conditions and processes that contribute to the flourishing or optimal functioning of people, groups, and institutions."[2] Patients who seek healthcare services, from yearly check-ups to treatment for serious illnesses such as diabetes and cancer, can benefit from incorporating positive psychology principles into their lives. As healthcare professionals, we can assist patients in improving their overall well-being by promoting positive psychology tenets during office visits and throughout treatment protocols. We can inquire about what is going right for them and point out personal strengths that we observe in them. There is a growing body of evidence indicating that positive psychology practices can influence health and wellness by encouraging patients' use of their strengths to manage stress and emotions, and to work toward healthy habits and lifestyle changes. We can assist patients to tap into these practices to improve their comfort, treatment compliance, and resilience.

In this chapter, we will examine the major tenets of positive psychology, review the evidence-based research on how positive psychology factors impact a variety of physical health issues, and offer suggestions on how positive psychology principles and interventions can be incorporated into any lifestyle medicine practice.

24.2 POSITIVE PSYCHOLOGY: A BRIEF OVERVIEW

The term "positive psychology" was first used by Abraham Maslow in his 1954 book *Motivation and Personality*.[3] Maslow and other psychologists of the humanist tradition, who believed in the self-actualization tendencies of humans and the nobility of the human spirit, deeply influenced the field of positive psychology as it exists today. However, as a structured discipline, positive psychology is very young; most scholars trace its beginnings to Martin Seligman's presidential address to the 1998 American Psychological Convention in San Francisco. In that address, Seligman argued that psychology had become a science focused primarily on improving symptoms of mental illness while neglecting research into what constitutes human flourishing and "what makes life worth living."[4] Although reducing suffering is a worthy goal, Seligman suggested it was incomplete; he called for an additional new psychological science, one that would focus on human strengths and the prevention of symptoms, rather than just the repair of human weaknesses.

Since 1998, scientific centers for the study of positive psychology have investigated factors leading to optimal self-regulation, well-being, flourishing individuals, and thriving communities. To counter criticism that positive psychology focuses too much on the positive and fails to recognize the negative realities of individual situations, a movement dubbed Second Wave Positive Psychology has sought to situate the original positive psychology principles within contextual and cultural concerns, and relate

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positivity to real-world negative circumstances and suffering.[5,6] The application of these principles has resulted in the development of rigorously tested interventions to promote human strengths, realistic optimism, and competencies, thus improving well-being and self-regulation, and buffering against disease.

24.2.1 The PERMA Model

The main goal of positive psychology, according to Seligman,[7] has been to increase well-being and flourishing in individuals and groups. The major elements of well-being can be summed up in the PERMA model (see Table 24.1).

Each of the five elements of the PERMA model not only contributes to overall well-being but is sought after for its own sake.[7] As we shall see throughout this chapter, not only do these elements contribute to well-being, but they measurably contribute to lifestyle medicine outcome goals as well.

Positive Emotions. Positive emotions include, but are not limited to, joy, hope, pride, love, and gratitude. In addition to increasing levels of happiness and overall well-being, positive emotions have been found to predict emotion regulation skills and to help individuals find meaning in personal struggles.[8] Positive emotions have also been shown to facilitate the physiological components of recovery from stress, a major contributor to long-term health.[9]

Engagement. Much of the work on the importance of engagement for human flourishing centers on Mihaly Csikszentmihalyi's work on the psychological state of flow.[10] In the flow state, a person is fully immersed in, energized by, and focused on a current challenging activity. Relative to health, the flow state is associated with overall well-being, reduced symptomatology, and positive changes in both therapeutic and rehabilitation processes.[11]

Relationships. Having healthy, positive relationships with other people is one of the best predictors of well-being. A robust body of research indicates that close relationships contribute to stress reduction, health, and longevity.[12–14]

Meaning. In his iconic book *Man's Search for Meaning*, Victor Frankl[15] argued that our ability to find meaning in our lives is central to our ability to survive and thrive as human beings. Since the publication of Frankl's book, a growing body of research has found meaning in life to be associated with greater physical health[16] and longevity.[17]

Accomplishments. Setting goals and accomplishing them, even when they are small goals, provides us with a sense of fulfillment, satisfaction, and confidence in our ability to meet life's challenges. Accomplishment, measured as progress toward goals that are important to the individual, is also correlated with subjective well-being in a meta-analysis of 85 studies.[18] Self-efficacy, our belief in our ability to accomplish the tasks we have before us, is associated with stress reduction and lower vulnerability to stress, including stress associated with the COVID-19 pandemic.[19]

TABLE 24.1
Seligman's PERMA Model of Well-Being

Positive Emotions	Experiencing emotions such as love, joy, gratitude, serenity, hope
Engagement	Being completely absorbed in an activity (state of flow)
Relationships	Developing positive connections with others
Meaning	Believing in and serving something that is bigger than yourself
Accomplishment	Achieving incremental steps toward identified goals

Source: Adapted from Seligman, M., *Flourish: A visionary new understanding of happiness and well-being*, Free Press, New York, NY, 2011.

24.3 POSITIVE PSYCHOLOGY AND POSITIVE HEALTH

The Constitution of the World Health Organization encourages us to consider health as a "state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity."[20] Positive health, as an aspect of positive psychology, describes a state beyond the mere absence of illness, and focuses on three independent health variables: subjective, biological, and functional.[21] Positive subjective health describes the state when an individual feels great and frequently experiences vigor, hardiness, an internal health-related locus of control, optimism, positive emotion, and high life satisfaction. The state of positive biological health looks at variables relevant to health, such as optimum heart rate variability, high levels of high-density lipoprotein (HDL), and cardiorespiratory fitness. Positive functional health includes both physical functionality (e.g., fitness and flexibility) and personal functionality (e.g., close friends and family, meaningful work, and the ability to meet the demands of one's chosen activities).

Positive health works to empirically identify and enhance *health assets* that predict health and illness over and above conventional risk factors. According to Seligman et al.,[22] a health asset is "an individual factor that produces longer life, lower morbidity, lower health care expenditure, better prognosis when illness does strike, and/or higher quality of life." Positive health adds to the preventive medicine model by fostering health assets, such as psychological well-being and the five aspects of the PERMA model, that contribute to health promotion and protect against the risk of physical illness.

In recent years, there has indeed been an increasing pool of research evidence supporting a correlation between such health assets and physical health outcomes. For example, psychological well-being[23, 24] and positive social relationships[13] have been shown to predict positive health outcomes in both cross-sectional and longitudinal studies.

24.3.1 Positive Psychology Factors and Cardiovascular Disease

A number of chronic disease studies have demonstrated associations between psychological well-being and

improved health outcomes for patients with cardiovascular disease. Three recent reviews of the literature, including one from the American Heart Association, found that elements of subjective well-being consistently protect against cardiovascular disease (CVD), even after controlling for traditional risk factors.[25–27] In addition, a prospective study of almost 7,000 participants found that higher optimism was associated with a lower risk of heart failure after adjusting for sociodemographic, behavioral, biological, and psychological covariates,[28] while another study of over 5,000 Hispanic/Latino participants found that dispositional optimism predicted better overall cardiovascular health.[29]

An additional study that examined cardiometabolic measures (including diastolic and systolic blood pressure, HDL and low-density lipoprotein (LDL) cholesterol, triglycerides, glycosylated hemoglobin, waist circumference, and C-reactive protein) in 800 adults over an 8–11-year time period found that both positive emotions and life satisfaction at Time 1 predicted lower cardiometabolic risk at Time 2, with life satisfaction possibly being the more robust predictor.[30] Finally, a review of 11 experimental studies concluded that gratitude, a positive psychology factor, positively impacts biomarkers of cardiovascular health, including endothelial dysfunction and prognostic inflammatory markers, as well as improving adherence to health behaviors.[31]

24.3.2 Positive Psychology Factors and Diabetes

Positive health outcomes related to diabetes have also been reported. A meta-analysis of 80 studies that looked across diverse populations of age, race, geography, and diabetes type concluded that across the lifespan, positive psychology characteristics (e.g., self-efficacy, self-esteem, adaptive coping, social support) were associated with improved diabetes management and glycemic control.[32] An additional study that focused on preadolescent youth with Type I diabetes found that psychological well-being was associated with lower depressive symptoms and better glycemic control.[33] In a prospective study of 7,800 middle-aged British citizens (562 of whom developed diabetes over the course of the study), life satisfaction and emotional vitality, but not optimism, were associated with reduced risk of physician-diagnosed diabetes.[34]

24.3.3 Positive Psychology Factors and Mortality

Ultimately, subjective well-being has been found to be associated with health, longevity, and reduced mortality.[35–37] An important review and meta-analysis of 62 studies examining over one million participants found that subjective well-being was associated with a decreased risk of mortality, and that the decreased risk was slightly more protective for men.[36]

A French study[38] that examined the influence of positive affect, negative affect, and life satisfaction on mortality in a cohort of 3,777 older adults found that positive affect predicted longevity. A British observational study obtained subjective well-being measures from a sample of over 9,000 men and women aged 50 and older at three time periods over a decade.[39] Individuals in the group with the highest well-being at Time 1 had the fewest deaths at Time 3, while the group with the lowest well-being at Time 1 had the greatest number of deaths at Time 3. While no claims of causality can be derived from this observational study, it contributes to the growing body of evidence that links well-being and life satisfaction with longevity.

A large prospective study[40] analyzed the incidence of stroke over a mean of 16 years in over 6,000 individuals. This study found that higher emotional vitality (a subscale of general well-being including optimism, mastery, and positive emotions) was associated with lower stroke incidence.

Two sytematic reviews looked specifically at the effect of optimism on mortality, one including 15 studies and over 200,000 participants and the other including 25 studies encompassing over 200,000 participants. Both concluded that optimism was associated with lower risk of all-cause mortality.[41, 42]

Not all studies, however, support the association between well-being and longevity. The UK Million Women Study, which followed over 700,000 women in a prospective study over a 12–16-year period, reported no connection between mortality and positive affect.[43] Four percent of the sample died during the study period. The authors reported that unhappiness was associated with self-rated poor health, but when this relationship was controlled for, happiness and well-being did not directly predict mortality.

In summary, however, the preponderance of research indicates that factors associated with positive psychology and well-being have a beneficial effect on a variety of health conditions, including cardiovascular health, diabetes, general mortality, and risk for stroke. Many major reviews within the past decade have examined the topic.[25–27, 36, 41, 42] All have shown that positive affect and subjective well-being have a beneficial effect for healthy populations or those who are mildly ill, suggesting that these factors should be promoted as protective factors for public health. While the evidence associating these well-being factors with positive health is impressive, we must be mindful that many of the studies are correlational, and reverse causation (that is, that better health is leading to psychological well-being rather than vice versa) is a concern.[44]

24.3.4 Positive Psychology Factors and COVID-19

The COVID-19 pandemic was a major public health crisis, resulting in over 770 million confirmed cases and 7 million deaths worldwide as of this writing.[45] Although there is currently no direct evidence that psychological well-being impacts the incidence of COVID, there is indirect evidence that aspects of psychological well-being can ameliorate negative physiological and psychological factors of the

disease and the pandemic. First, the risk for both hospitalization and mortality related to COVID-19 is elevated in persons suffering from mental health issues such as depression and stress disorders.[46–48] Psychological well-being is negatively associated with mental health issues related to the COVID pandemic,[49,50], and PPIs demonstrate reduction in mental health symptoms.[51]

Two factors, gratitude and social support, have been shown to be particularly salient in the face of COVID-related negative mental health. A diary study conducted by Chinese researchers reported that perceived positive health and reduced COVID-related stress were predicted by experiences of gratitude.[52] And, a large British study of over 70,000 participants reported that those individuals who had more positive social relations and support, as indicated by social contact during the pandemic, displayed fewer depressive symptoms.[53]

Finally, research indicates that as factors of psychological well-being increased during the pandemic, so did health behaviors, such as getting adequate exercise.[54,55] Another study of over 1,500 Korean citizens found that the factors of self-efficacy and social support were associated with positive health behaviors during the pandemic.[56] In general, the body of research associating positive psychological factors with positive outcomes from COVID is primarily correlational but appears to be growing in scope.

24.3.5 Positive Psychology Factors and Additional Health Considerations

In addition to the direct effects on health reviewed so far, positive psychology factors appear to confer other health benefits, including pain modulation and higher reported quality of life in persons with chronic illness. A number of studies have found that positive affect can reduce the experience of chronic pain. In a longitudinal study of over 9,000 adults, researchers found that positive well-being at Time 1 predicted lower levels of severe pain distress at Time 2 in persons with and without chronic pain. Less severe pain at Time 2 was also predicted by Time 1 life satisfaction in the group with chronic pain.[57] A study of 96 patients with severe pain indicated that subjective well-being had a beneficial effect on pain control, pain catastrophizing, and pain interference.[58]

A rather large body of research has now investigated the effect of positive psychology factors on increasing the quality of life in patients with chronic diseases. The results are fairly consistent in finding that positive emotions, well-being, and meaning-making decrease negative emotions, reduce the risk for depression, increase functionality, help maintain positive relationships, and help maintain compliance with medical regimens.[59–61]

While a positive attitude and positive emotions have been shown to help patients maintain a higher quality of life while dealing with severe health issues, other voices within the research field have suggested caution in interpreting or promoting positive psychology factors as "cures" for serious illness.[62] The research supporting positive psychology factors as health assets is strong. However, patients who are facing difficult health issues may feel frustrated, misunderstood, or even hopeless if confronted with what Aspinwall and Tedeschi have called the "tyranny of optimism."[62] This argument has been heeded and addressed by second wave positive psychology.[5,6] The goal of the field is to help patients raise their level of positive emotions within the bounds of the reality of their current situation. The next section describes PPIs that have been empirically tested, many in randomized controlled trials.

24.4 POSITIVE PSYCHOLOGY INTERVENTIONS

We have seen that factors related to positive psychology do in fact predict positive health conditions. However, can these positive psychology factors be purposely enhanced to benefit health? To date, a number of positive psychology interventions (PPIs) have been identified and tested. The field of positive psychology thus provides both a theoretic framework within which to approach patient health and a wide range of interventions that can be effective in the enhancement of psychological well-being.

Several meta-analyses indicate that PPIs have demonstrated small to moderate improvements in well-being, increased optimism and happiness, as well as decreased depressive symptoms. Results have been maintained for follow-up periods of up to six months.[63–68] Mental health and well-being factors are generally assessed with validated self-report tools (see Table 24.2 for a list of commonly used measures in PPIs).

PPIs can be delivered through a variety of modalities: web-based self-help programs, apps delivered on various technology devices, group training, or individual therapy/face-to-face meetings. The majority of interventions are delivered in a self-help format. While all formats have demonstrated effectiveness, interventions that are more intensive and include face-to-face interactions have been shown to generate larger positive effects.[63,64,66,67]. Further, PPI interventions have beneficial effects in both children and adults.[69]

In the following, we describe the most widely used evidence-based PPIs:

Gratitude. Two types of gratitude interventions have been widely studied. These include the *Gratitude visit*, in which individuals have one week to write and then deliver a letter of gratitude in person to someone who has been especially kind to them but whom they have never properly thanked,[78] and the *Gratitude list (Counting blessings)*, in which individuals are instructed to write down between three and five things in their lives, large or small, that they are grateful for, either each night for a period of two weeks or every week for a period of ten weeks.[81] Individual studies indicate that these short interventions increase positive emotions and mood extensively enough to be noticed by others, and also improve sleep quality.[78,81,82] Meta-analyses

TABLE 24.2
Self-Report Measures Commonly Used to Test Positive Psychology Interventions

Measure and Reference	Category	Description
Center for Epidemiological Studies–Depression Scale (CES-D)[70]	Depression	20 items on 4-point scale
Flourishing Scale[71]	Well-Being	8 items on 7-point scale
Gratitude Questionnaire (GQ-6)[72]	Gratitude	6 items on 7-point scale
Mindful Attention Awareness Scale (MAAS)[73]	Mindfulness	15 items on 6-point scale
Life Orientation Test-Revised (LOT-R)[74]	Optimism	10 items on 5-point scale
Positive and Negative Affect Schedule (PANAS)[75]	Emotions	20 items on 5-point scale
Psychological Well-Being Scales[76]	Well-Being	18 items on 6-point scale
Satisfaction with Life Scale (SwLS)[77]	Well-Being	5 items on 7-point scale
Authentic Happiness Inventory (AHI)[78]	Emotions	24 items on 5-point scale
Subjective Happiness Scale[79]	Emotions	4 items on 7-point scale
Values in Action Inventory of Strengths (VIA-IS)[80]	Personal Strengths	240 items on 7-point scale

that capture the cumulative results of multiple studies suggest that gratitude interventions are modestly effective in improving positive affect and psychological well-being in the short term, but more evidence needs to accrue before long-term effects of these interventions can be established.[83–85]

Three good things. Individuals are instructed to write down three things that went well each day for one week. They are also asked to explain why each good thing happened.[78] Both the original test of this intervention[78] and a later replication showed long-lasting increases in positive emotions.[86]

Using signature strengths. Individuals take an online inventory of 24 character strengths that was developed by Christopher Peterson and colleagues[80] and receive feedback about their top 5 "signature" strengths. They are then instructed to use one of these signature strengths in a new and different way each day for one week. A meta-analysis of 14 studies indicated that this intervention improved positive emotions and life satisfaction, as well as decreasing depression.[87]

Best possible self. Individuals are instructed to think about their life in the future and imagine that everything has gone as well as it possibly could. They are to imagine that they have worked hard and been successful at accomplishing their life goals. They are then instructed to write about what they have imagined for 20 minutes a day for 4 consecutive days.[78] A meta-analysis of 29 studies indicated that this intervention improved positive emotions, optimism, and well-being.[88] A second meta-analysis of 34 studies found small but important effect sizes for improvements in positive emotions and optimism.[89]

Acts of kindness. Individuals are instructed to perform five acts of kindness—all within one day of the week—for six weeks. The acts can be anything that makes others happy or that benefits others (such as donating blood, visiting an elderly relative, etc.)[79] This intervention is associated with increased positive emotions immediately following the acts as well as sustained increases in subjective well-being.[79,90]

Mindfulness meditation. Some reviews also include mindfulness interventions in their list of PPIs.[64] Mindfulness interventions cultivate nonjudgmental awareness of the present moment through daily or weekly meditation. Individuals are generally instructed to relax and focus on the flow of their breath or some other aspect of their current environment for a period of 20 minutes, nonjudgmentally acknowledging any passing thoughts and then letting them go.[91] While the topic of mindfulness is often associated with positive psychology,[92] it is too extensive to review in this chapter and is covered elsewhere in this volume. Numerous reviews have shown that mindfulness interventions can improve well-being in both patients and healthcare providers;[93–95] therefore, mindfulness meditations, along with PPIs, are recommended additions to any lifestyle medicine practice.

24.4.1 PPIs and Moderating Factors

Several factors impact the effectiveness of PPIs, including the patient's level of depression at the beginning of the intervention, age, motivation to improve, the format of the intervention, and the appropriate patient/intervention match. Sin and Lyubomirsky[64] found that patients who had symptoms of depression at the start of the intervention benefitted more from PPIs than those who were not depressed, and that PPIs were effective in preventing relapse in previously depressed patients. These same researchers found that patients who were older benefitted more than those who were younger, and that patients who demonstrated a greater motivation to improve benefitted more from the interventions than those who were less motivated. A German study found that those individuals who believed in the malleability of well-being benefitted more from PPIs than those who did not believe that well-being could be changed.[96] Finally, research suggests that patient characteristics such as personality and cultural background may impact the effectiveness of interventions.[64,97] However, there is a continuing need for research that better addresses racial, ethnic, and

gender differences in the implementation and effectiveness of PPIs.[98]

24.4.2 Positive Psychology Technological Devices

The delivery of health-related information and tools through apps that are available on a wide variety of technological devices provides healthcare and support that are not always geographically, financially, or socially accessible. There are many types of positive psychology assessment and intervention tools offered through mobile device apps. Most health-based assessment and intervention tools fall under two broad categories: *active* or *passive*. Active apps require direct participation, such as completing mood logs or recording subjective experiences. Passive apps do not require active participation and can automatically gather data (e.g., calories burned, heart rate, steps taken) through a smartphone's GPS, accelerometer, or other sensors.[99] Most positive psychology tools tend to fall in the active category of tools.

As of 2021, the American Psychological Association estimated there were betweeen 10,000 and 20,000 mental health apps,[100] with the number skyrocketing since COVID began. While not all of these apps are associated with positive psychology, few of them have been vetted. According to Torous and Powell,[99] any assessment or intervention tool should be empirically validated, be widely used, focus on some aspect of positive human functioning, be appropriate to the setting, and be easy to interpret/administer. While the current wide variety of positive psychology apps may enhance motivation, promote positive affect and well-being, or improve compliance with intervention protocols, practitioners should be cautious when deciding which intervention tools to recommend for their patients. Many apps have not been validated through empirical research, and most of the validation for these apps that does exist was completed by the app developer rather than an independent source.[101]

In summary, a number of PPIs have been developed and tested, and have been shown to be effective in improving positive emotions and well-being, and reducing depressive symptoms. Several moderating factors that impact effectiveness have also been identified, including the method of delivery. While the most effective method is one-on-one therapy, other methods (including web-based self-help), although less effective, are still beneficial. New delivery methods, including mobile apps, are being developed and with adequate testing, may also offer a beneficial form of positive psychology intervention delivery.

24.5 Incorporating Positive Psychology into Lifestyle Medicine Practice

There are several methods for incorporating positive psychology into the practice of lifestyle medicine. We discuss four methods here: 1) modeling positive psychology principles in your practice; 2) having positive health conversations with patients; 3) prescribing PPIs; and 4) incorporating a health coach trained in positive psychology principles into your practice or clinic.

24.5.1 Modeling Positive Psychology Principles

Since Albert Bandura first introduced social learning theory over a half-century ago, research has supported the concept that people learn through observing and modeling other people's behavior, attitudes, and emotional reactions.[102] In a healthcare setting, modeling health behaviors is a valuable method of promoting behavior change in others. Effective ways to model positive psychology principles in your practice include:

- Displaying *positive emotions* during interactions with patients and with other staff (contentment, hope, serenity, interest, amusement, inspiration) unless inappropriate to the situation
- Expressing *gratitude* to staff within earshot of patients for their positive work
- Determining your own signature *character strengths* and using them on a regular basis in your work

24.5.2 Having Positive Health Conversations with Patients

One method of introducing positive psychology principles into a lifestyle medicine practice is through both incidental and more focused conversations that occur throughout the patient visit. Here are some examples:

- During examinations, ask open-ended questions that focus on the patient's strengths:
  - What aspects of their health do they feel good about?
  - What is their overall level of well-being?
  - What capacities—strengths, interests, and resources—can they bring to the table if need be to help improve their health?
  - What are their situational benefactors (e.g., supportive family, friends, good job)?
- Here are a few good questions to ask patients in order to encourage them to explore and share their positive health attitudes and behaviors:
  - "When was the last time you felt well?"
  - "What have you done in the past that made you feel better?"
  - "Can you tell me about a time when you were at your best? What strengths were you using at that time?"
  - "It seems like this is very important to you. How do you imagine your life would be different if you [lost weight]?"
  - "What would be possible for you if you [quit smoking]?"

- When patients speak, employ *active* listening:
  - Face your patients and put down any papers, pencils, or equipment while they speak to you. Make eye contact and nod to express that you hear them. Reflect back to them in your own words what you heard them say (e.g., "If I understand you correctly …," "It sounds like you're feeling …," "What I hear you saying is …," "Is this correct?").
  - Active listening allows patients to feel heard and often helps them to understand their own symptoms, condition, and potential for habit change more clearly.
- Encourage patients to avoid social comparisons (including comparisons with themselves as they used to be when they were younger) and to focus on their own current strengths.
- Remind patients that they can make *mindful* choices: every step we take, every bite we eat, every activity we perform, every reaction to an event we have, is a choice. Sometimes we forget that. It's liberating to know we can mindfully *choose* so much about our lives!
- Engage in a short realistic optimism process with patients:
  - First, help them to see their current health situation objectively rather than catastrophically.
  - Second, help them brainstorm the best possible outcomes given their current situation.
  - Third, help them plan to move confidently and positively toward those best possible outcomes.

24.5.3 Prescribing Positive Psychology Interventions

Just as exercise can be prescribed for its health-enhancing and disease-preventing effects,[103] PPIs can be prescribed for the same reasons.[104] Table 24.3 presents sample prescriptions for evidence-based PPIs mentioned in the previous section. These PPIs have been shown to increase positive emotions, decrease negative emotions, and increase overall well-being.

When prescribing a PPI, as research indicates, it is important to consider patient characteristics such as personality and cultural background.[64,105] For example, Nelson and Lyubomirsky[105] have pointed out that introverts may benefit more from reflective activities such as counting blessings or meditation, while extraverts may prefer more outgoing activities, such as acts of kindness. Likewise, patients from a collectivist cultural background (e.g., some Asian cultures), where group happiness is emphasized, may benefit more from one of the prosocial interventions, such as acts of kindness or writing a gratitude letter, than from an intervention targeting the individual, such as best possible self.[64,97] Some research suggests that patients may have better results when matched with a self-selected intervention with which they feel comfortable.[106]

It is also important to consider the modality of the prescription. Self-motivated patients may benefit from a prescription to simply perform an action, such as those listed in Table 24.3. However, less motivated patients may derive more benefit from a prescription to work one-on-one with a trained positive psychology health coach.

24.5.4 Incorporating a Health Coach Trained in Positive Psychology Principles into Your Practice

As an important part of an effective collaborative care team model, health coaches in primary care practices offer positive psychology skill building for patients who would benefit from lifestyle changes to improve their health condition. Health coach job tasks include assessing readiness for change, collaboratively establishing client goals, evaluating successful steps and self-limiting patterns, re-assessing and modifying goals, articulating insights gained, and

TABLE 24.3
Examples of Prescriptions for Positive Psychology Interventions

Name	Rx	Evidence for Effectiveness
Gratitude Letter and Visit	Write and deliver in person a letter of appreciation to someone who has been kind to you but whom you have never properly thanked.	76, 78, 82
Three Good Things	Write down three good things that happen each day for one week, together with an explanation for why each good thing happened.	78, 86
Use Your Signature Strengths	Take the survey at viacharacter.org. Use one of your five signature strengths in a new and different way for a week.	78, 87
Gratitude List	Write down three new things (small or large) you are grateful for each night for two weeks. At the end of each week, read your entire list.	76, 83–85
Best Possible Self	Imagine as vividly as possible that you have worked hard and been successful at accomplishing your life goals. Write about what you have imagined for 20 minutes a day for 4 consecutive days.	78, 79
Acts of Kindness	Pick one day of the week for the next six weeks, and on that day each week, perform *five* acts of kindness (large or small) for other people that you would not have otherwise performed.	90

formulating a post-coaching plan to sustain changes that promote health and wellness.[107]

Research has shown that patients who received coaching services demonstrated significant improvements in both physical and mental health, with reductions in chronic disease markers (HbA1c, blood pressure, LDL cholesterol) that persisted one year after completion of the health coaching intervention.[108] Health coaching with a positive psychology emphasis has been found to improve overall patient health, with a 19% decrease in patient-reported medical symptoms and enhanced mental health strengths, including improved quality of life and increased mastery of areas of well-being, such as maintaining trusting relationships and realizing one's potential.[109] In addition, primary care clinicians reported that patients who received health coaching were more empowered and less demanding.[110] Health and wellness coaches are becoming fixtures in hospitals, clinics, private practices, and health clubs.

24.6 CONCLUSION

The advancement of positive emotions and well-being is synergistic with the advancement of physical health. In this chapter, we have reviewed the evidence for a connection of positive emotions, optimism, and well-being with better health and longevity outcomes. In particular, there are growing bodies of research that connect positive emotions, optimism, and well-being with better cardiovascular health, better diabetes management and glycemic control, lower pain levels, and lower mortality among healthy persons.

While individual levels of optimism and well-being are, to an extent, trait-like factors, research has provided evidence that these factors can be enhanced through PPIs. These interventions have centered on increasing positive emotions, self-efficacy, and life satisfaction while decreasing negative emotions and stress. Some of the mechanisms employed in these interventions include expressing gratitude, understanding and using one's strengths to achieve goals and solve problems, focusing on and savoring positive events, and completing small acts of kindness.

We have suggested several methods for implementing positive psychology principles and interventions in a lifestyle medicine practice, including modeling these principles in yourself and your practice, incorporating the principles in discussions with patients, prescribing PPIs as part of preventive or palliative care, and adding positive psychology coaching to your practice or clinic. There is growing evidence for the physical health benefits of positive psychology practices for both physical and mental well-being. Practitioners of lifestyle medicine are in an excellent position to promote overall well-being as an important part of comprehensive healthcare.

SUMMARY OF CLINICAL APPLICATION POINTS

1. Have Positive Health Conversations with Patients	• During examinations, ask open-ended questions that focus on the patient's strengths. • When patients speak, employ *active* listening. • Encourage patients to avoid social comparisons (including comparisons with themselves as they used to be when they were younger) and to focus on their own current strengths. • Remind patients to make *mindful* choices: every bite we eat, every activity we perform, every reaction to an event we have, is a choice. It's liberating to know we can mindfully *choose* so much about our lives! • Engage in a short realistic optimism process with patients.
2. Model Positive Psychology Principles	• Display *positive emotions* during interactions with patients and with other staff (contentment, hope, serenity, interest, amusement, inspiration) unless inappropriate to the situation. • Express *gratitude* (for example, to staff) within earshot of patients for their positive work. • Determine your own signature *character strengths* and use them on a regular basis in your work. • Discuss the personal *meaning* of health in your own life (e.g., lifestyle challenges you may have struggled with in the past and how you may have used positive psychology principles to help effect positive lifestyle changes).
3. Prescribe Positive Psychology Interventions	Just as exercise can be prescribed for its health-enhancing and disease-preventing effects, positive psychology interventions (PPIs) can be prescribed for the same reasons (e.g., gratitude letter, three good things journal, acts of kindness).

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25 The Intention–Behavior Gap

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KEY POINTS

- Intention indicates how hard a patient is willing to try, or how much effort they are willing to put toward any given behavior.
- Intention, alone, is generally found to not be a reliable predictor of physical activity or dietary behavior—even if intention is high (the intention–behavior gap).
- Thus, the practitioner should consider the factors that have been shown to moderate or affect the strength of the intention–behavior relationship, which include:
- Action and Coping Planning: Forms of planning that specify a critical condition linked to goal-directed responses (e.g., "if-then" statements), and when an individual imagines a scenario that might hinder them from performing an intended behavior (e.g., barriers), respectively
- Self-Efficacy: A personal expectation or judgment regarding one's competence to accomplish a specific task in a particular context
- Capacity (Executive Function): A concept that describes the neurocognitive faculties of higher-order supervisory abilities to direct cognitive functions toward a goal
- Emotional Response: The affective reaction to some type of internal or external stimuli
- The practitioner and healthcare team can play a key role in helping to bridge the intention–behavior gap with their patients by improving the utilization of action and coping planning, building self-efficacy, or identifying anticipated affective responses (e.g., regret).
- Understanding of the intention–behavior gap allows modification of lifestyle prescriptions and development of practice models that maximize lifestyle adherence when lifestyle is the medicine.

25.1 INTRODUCTION

Two common scenarios are experienced by practitioners with lifestyle prescriptions:

1. The patient has *no* intention to adopt the lifestyle prescription, or
2. The patient has intention to adopt the lifestyle prescription but does not follow through with it.

Both scenarios of non-compliance can be frustrating to the patients and the practitioners, who truly desire the best for their patients. This chapter hinges on the realization that lifestyle medicine only works if patients take their medicine. As a result, practitioners are very interested in medication adherence, especially the aspects of evidence-based factors that might contribute to increasing adherence to the prescription.

Thus, the purpose of this chapter is to introduce and elucidate the intention–behavior gap (IBG). In addition, we aim to investigate the efficacy of current proposed solutions to the IBG to provide the practitioner with options to increase medication adherence when lifestyle is the medicine.

25.1.1 What Is the Intention–Behavior Gap?

Traditionally, intention has been conceptualized as the immediate antecedent to behavior. In other words, we have intention to do something, then we do it (behave). However, early examinations of behavior highlighted that intention did not always translate to behavior. Early theories to explain this phenomenon were the predecessor of the more widely utilized Theory of Planned Behavior (TPB) by Drs. Ajzen and Fishbein, which shed light on potential factors that either moderated or mediated the relationship of intention with behavior (e.g., habit, facilitating or constraining conditions, or social and affective factors). However, the intention–behavior gap remains enigmatic as it relates to physical activity (PA) or healthy eating.

After observing the IBG in practice, researchers uncovered that intention, even if it was high, was not a reliable predictor of PA or dietary behavior. [1] Clearly, there is variation in behavior—with some doing more, some doing less, and some not changing over time. In an ideal scenario, intention would explain all (100%) of this variation, accounting for why some people increase, some decrease, and some do not change their behavior. We would be able to measure intention level and predict, perfectly, how much their behavior would change. However, the TPB, which includes intention, was found to predict only 24% and 21% of the variation in physical activity and dietary behavior, respectively.[2] In other words, somewhere between 75% and 80% of the variation in behavior is not explained by intention and its related predictors.

In response, Rhodes and de Bruijn set out to explain how big the IBG gap was with leisure-time, moderate-to-vigorous physical activity that met current public health

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guidelines.[3] They discovered that across ten studies presented, on average, approximately:

- 21% were non-intenders and were *unsuccessful* in performing the behavior,
- 2% were non-intenders but were *successful* in performing the behavior,
- 36% were intenders but were *unsuccessful* in performing the behavior, and
- 42% were intenders and were *successful* in performing the behavior.

If these results translate to practice, we can assume that about seven out of ten patients will have intention to be more physically active, while the rest (three out of ten) will not have intention: "The results suggest that, while some people still require interventions changing intentions, much of the inactive population has positive intentions."[3] However, of those who did have intention to get more physical activity, only 54% were successful in performing the behavior, which would translate to about one out of every two patients who intend to be more physically active following through with their intention. The rest, 46% of the intenders who did not follow through with their intention, epitomize the IBG.

We find similar IBGs with fruit and/or vegetable (FV) consumption. For example, the authors of a systematic review found that intention only predicted or explained 34%, 43%, and 31% of the variation in total FV intake, fruit intake, and vegetable intake, respectively. Other studies have examined the relationships or correlations (r) between intention and FV behavior, such as achieving previous public health recommendations of consuming 5 FV per day. Generally, on average, these correlations are weak: $r_+ = 0.27$ in children/adolescents,[4–8] $r_+ = 0.36$ in college students,[9–11] $r_+ = 0.41$ in adults,[12, 13] and $r = 0.40$ in older adults.[14] As a reminder, strong correlations typically surpass $r \geq 0.50$ on the 0 to 1 scale.

A more recent review of studies of healthy eating found that on average across all studies, intention and behavior were only moderately correlated ($r_+ = 0.45$).[15] Also, studies were separated into those that directed participants to consume health-promoting foods versus avoiding health-compromising foods. Interestingly, the intention–behavior relationship was weaker for *avoiding unhealthy* food ($r = 0.28$) than *promoting healthy* food ($r = 0.43$). These findings suggest that patients could have a higher probability of overcoming the IBG with healthy food–promoting prescriptions (e.g., add another vegetable to your day) than with prescriptions aimed at avoiding unhealthy foods (e.g., eat less sugar). Clearly, both prescriptions are important in lifestyle medicine practice, but the nuances of the IBG can help explain variation in medication adherence within patients.

The IBG remains large, as intentions only get translated into action about half of the time, [1] which equates to the fact that 1 in 2 patients will succeed. In response, additional theories have been utilized to help explain the IBG, such as the Action Control Theory, the Precaution Adoption Process Model, the Temporal Self-Regulation Theory, and the Volitional Model of Goal-Directed Behavior. Rhodes and Yao have provided an excellent review of 16 models, hoping to better explain the IBG in physical activity, concluding: "Whether these models will serve to improve our interventions and/or explain [physical activity] better than the current state of research is unknown."[16] In other words, we have several models and factors that can help us, but the future is bright with opportunity to innovate and properly evaluate old and new models to further our understanding of the IBG. Until then, we can begin to put the known concepts into practice, reducing the probability of IBG occurrence in our patients. Many of the leading concepts are summarized later in this chapter, alongside practical applications for you to implement—if you have intention to do so.

25.2 INTENTION IN PRACTICE

25.2.1 What Is Intention?

As it relates to the IBG, intention indicates how hard a patient is willing to try, or how much effort they are willing to put toward any given behavior.[17] The assumption is that "[t]he stronger a person's intention, the more the person is expected to try, and hence the greater the likelihood that the behavior will actually be performed."[18] Also, with such desire and willingness, intention to do a behavior indicates a more proximal time frame. They intend to behave very soon, not later or in the coming months/years.

25.2.2 Intention in Practice

In practice, patients might relay that they "intend" to be more active or start eating more healthily. However, this might resemble a statement of hope for some time in the future rather than an actual dedication to change. In this case, they are not indicating that they are willing and ready to put forth vast amounts of effort to be more active and eat more healthily in the immediate future. So by definition, they do not have true intention to change. In a way, they are saying, "I intend to," but really mean "I would like to," or "I hope to." This is supported by Rhodes and Rebar's 2017 study, in which they advise investigators to be cautious, noting that "intention" can be interpreted both as a decision taken toward performing a certain behavior and/or the commitment to enact a behavior. [19] They found that these two concepts are not equal predictors of physical activity. Instead, the authors recommend using the terms *decisional intention* to denote the direction meaning of intention and *intention strength* to denote the intensity of commitment. The semantics here are important, as this gives insight into intention strength and the IBG in practice.

For example, Dr. Ajzen has provided instructions for developing questionnaires to assess intention with the context of the TPB; these instructions are accessible online at http://people.umass.edu/aizen/pdf/tpb.measurement.pdf. First, the behavior must be clearly defined in its target,

action, context, and time elements. In other words, we cannot simply ask patients about their intention be more physically active. That is too general. We would need to more specifically define physical activity, such as "at least 30 minutes per day, 5 days per week for the next 4 weeks." Since intention is assuming a level of likelihood of effort toward performing the behavior, "likely" or "unlikely" anchors are applied. Here is a final item that a patient could be asked to answer.

"*I intend to exercise for at least 30 minutes per day, 5 days per week for the next 4 weeks.*"

Unlikely : 1 : 2 : 3 : 4 : 5 : 6 : 7 : Likely

As you can see, the specifics of the behavior, including the type of behavior, the amount of the behavior, and the time frame could greatly impact a patient's level of intention. Although not of direct focus within this chapter, it is important to note that lifestyle prescriptions can and should be modified to accommodate an inadequate level of important factors, such as intention or self-efficacy (discussed later in the chapter).

25.2.3 Intention Stability

Intention strength has also been conceptualized as *intention stability*, which refers to the fluctuations in intention across time.[20,21] In those with high intention to engage in more physical activity, for example, having more intention stability could help.[21] Those with high intention–high stability achieved twice the amount of physical activity as those with high intention–low stability. In other words, if a patient has high intention, ensuring that the intention remains stable over time can be beneficial for behavior. If intention slips over time, then behavior could be negatively impacted—even if the patient initially had high intention to follow the lifestyle prescription.

The largest effect, however, was seen in those with low intention. Low intention—high stability participants did not increase physical activity from baseline, as expected. They did not have much intention to change and were stable with their low intention over time. Yet, low intention–low stability participants were more willing to change as their physical activity behavior increased. In this case, their instability of intention was beneficial. These findings highlight individual differences in intentional response, as well as the complexities of self-regulatory factors that could influence intention and subsequent behavioral success.[22–24] Thus, there is the need for the practitioner to better understand what other factors or concepts could moderate or affect the strength of the intention–behavior relationship.

25.3 SOLUTIONS FOR THE IBG

25.3.1 Action and Coping Planning

25.3.1.1 Introduction

The health action process approach (HAPA; Figure 25.1) model is a behavior change framework that allows for additional explanatory variables beyond the TPB. More specifically, it is a model "that explicitly includes post-intentional mediators to overcome the intention-behavior gap."[25] The motivation phase includes factors that lead up to intention, while the volition phase describes the variables helping connect intention to behavior. A generic model example is shown in Figure 25.1.

When a patient has intention to adopt a particular health behavior, the action must be initiated and subsequently maintained. As previously mentioned, the ensuring process of connecting intention and behavior requires multiple factors and skills that facilitate successful self-regulation of one's own behavior. The HAPA could allow an open architecture for multiple factors but emphasizes self-efficacy (discussed in the next section) and planning. The hypothesis

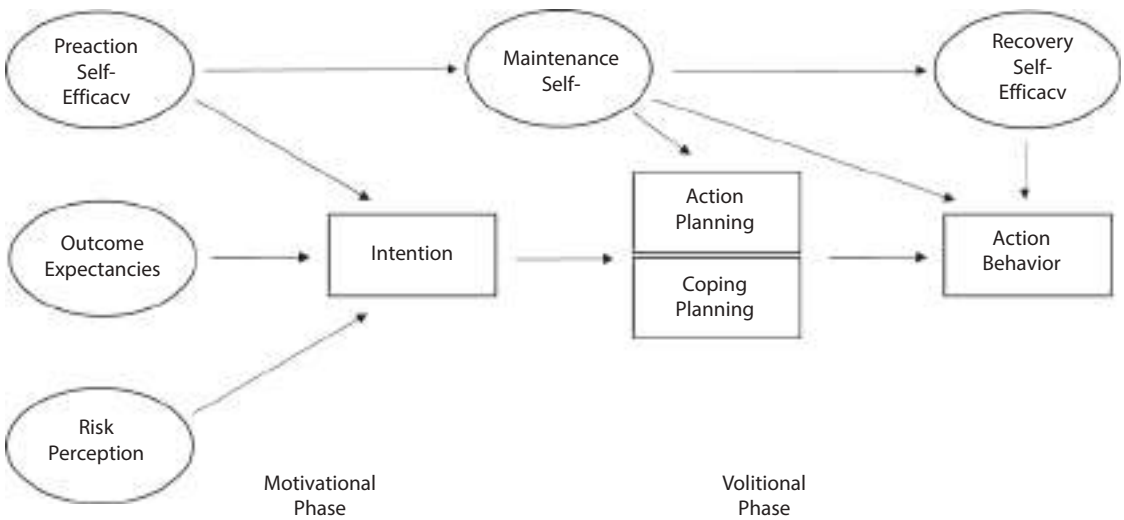


FIGURE 25.1 Health Action Process Approach Model. (From Schwarzer, R., ***Appl. Psychol.***, 57(1), 1–29, 2008)

relays that "good intentions are more likely to be translated into action when people develop success scenarios and preparatory strategies for approaching a difficult task."[25] Such planning is accomplished through action planning and coping planning.

Action planning, or implementation intentions, is "a form of planning that specifies a critical condition linked to goal-directed responses."[26] Such plans provide "if-then" statements to help connect a patient's intention to following through with the behavior. For example, "*If I wake up at 6:00 am tomorrow morning, then I will get ready and immediately go jogging in the neighborhood*."

However, as with any plan, problems will be encountered, and strategies are needed to invest conscious effort for the purpose of solving problems or responding to perceived discrepancies in behavior. So, in relation to HAPA and implementation-intention strategies, *coping planning* takes place when an individual imagines a scenario that may hinder them in performing an intended behavior. Coping planning is making a plan that anticipates difficulties or barriers that might hinder the patient's implementation of their intentions to live a healthy lifestyle.[27,28] A coping planning statement might look like, "*If it is raining or too cold in the morning, then I will go to the gym instead of jogging in the neighborhood*."

25.3.1.2 Review

Of all the potential moderators of the IBG, implementation-intention (action planning) research is perhaps the most robust. For PA, a 2013 review examined 26 independent studies and concluded that action planning could help promote PA, but the effect size was relatively small (d = 0.31) for measures of PA post intervention and even smaller for longer-term follow-up measures (d = 0.24).[29] The authors conclude that

> although implementation intentions are viewed as a powerful strategy to overcome the above self-regulation problems, individuals might have to formulate specific plans not only for their [behavioral] resolution (e.g., if it is Sunday morning, then I will go to the gym) but also for the management of barriers. Thus, this aspect can lower the efficacy of implementation intentions for complex [behaviors], particularly if the manipulation of implementation intentions is less elaborate (i.e., only planning when, where and how).[29]

A 2011 review and meta-analysis on healthy eating and implementation intentions highlighted 14 studies that investigated the efficacy of implementation intentions in increasing healthy eating behaviors, while 8 studies were designed to reduce unhealthy eating behaviors.[30] For healthy eating patterns, implementation intentions appear to be more effective in promoting the inclusion of healthy food items (d = 0.51) than they are for diminishing unhealthy eating patterns (d = 0.29). However, the authors note that the overall effect sizes of the results were small, perhaps due to poor control groups or weak outcome measures. A 2017 review and meta-analysis of 12 empirical studies examining the effect of implementation intentions on reducing fat intake found a moderate effect size (d = 0.49),[31] which fared better than the effects found by Adriaanse and colleagues[30] on reducing unhealthy eating behaviors (d = 0.29).

Coping planning, on the other hand, could help account for the weak effect sizes found with action planning's effect on PA and healthy dietary behavior, since the coping plan anticipates personal challenges or barriers to completing the action plan. In this way, the patient can create a sense of control over unwanted concerns or distractions to their behavior. Also, coping planning implies action planning.[32] Research in physical activity suggests that both action and coping planning could be used to help individuals connect intention to behavior in the short term; however, coping planning appears to have a larger effect on behavior over time.[28]

25.3.1.3 Practical Application

The practitioner can help the patient develop action and coping plans. From this section, the main actionable ideas are that action control and action planning are related to exercise.[33] A beneficial way to employ this strategy would be, for example, to instruct the patient to write down how they plan to exercise, where they plan to exercise, and when they plan to exercise. Similarly, this formula could be followed for planning how they will prepare vegetables, where they plan to obtain them, and when they plan to consume them (meal time). Next, they can form coping plans to help clarify, specifically, how they will deal/cope with upcoming problems. Doing so is clearly beneficial. If a patient likes to walk outside, ask them what they will do if it is a rainy day. If they go to a restaurant with friends, what will they order to be the healthiest? In this vein, conversations are somewhat endless; however, having a few discussions to plan and set up some contingencies could help the patient stay on their journey toward health.

Here is a sample template for use in practice.[34]

---

1. My Goal _____

"To eat 2 more fruit and vegetables per day this week."
"To walk 3 afternoons this week."

2. My Plan

If/When I _____ I will _____

"When I have lunch at work, I will have a piece of fruit."
"When I get off work, I will walk around the block."

3. My Backup Plan

If I _____ I will _____

"If I go out to eat for lunch, I will eat the piece of fruit before I leave."
"If it is raining or too cold outside, I will walk on the treadmill in the office gym."

25.3.2 Self-Efficacy

25.3.2.1 Introduction

Self-efficacy is a mixture of value and personal belief in one's ability (i.e., confidence) to achieve intended results.

Put another way, it is a personal expectation or judgment regarding one's competence to accomplish a specific task in a particular context. In relation to the IBG, the HAPA provides three separate self-efficacy constructs:[25]

1. *Pre-action or Action Self-Efficacy*: This type of efficacy occurs before individuals have yet acted and helps develop a motivation to do so. Individuals who are high in pre-action self-efficacy imagine success, anticipate potential outcomes of diverse strategies, and are more likely to initiate a new behavior.
2. *Maintenance or Coping Self-Efficacy*: Represents optimistic beliefs about one's capability to deal with barriers that arise during the maintenance period.
3. *Recovery Self-Efficacy*: Addresses the experience of failure, lapses, and setbacks.

25.3.2.2 Review

The HAPA model (Figure 25.1), with the various self-efficacy constructs, is generally able to account for additional variance of behavior beyond intention. For example, in adults classified as obese, self-efficacy was found to be the main direct and indirect predictor of both intention and physical activity.[35] Pre-action self-efficacy had a direct effect on intention, and in combination with outcome expectations, predicted 30% of the variance in intention. Consistently with the model, maintenance/coping self-efficacy predicted coping planning, which did not predict physical activity behavior. However, recovery self-efficacy did, and in combination with social support, accounted for 18% of the variation in physical activity. In other words, approximately 82% of the variation in physical activity is unaccounted for by this model despite self-efficacy being a leading determinant.

The HAPA model was also applied to patients classified as overweight and obese regarding intention to eat high-fat foods and their subsequent consumption two months later.[25] Recovery self-efficacy was the main predictor of consumption, with contribution from planning. This overall model accounted for 46% of the variation in high-fat food consumption, which is a more substantial predictive model than we saw with the previous physical activity example at 18%.

Additional studies have investigated self-efficacy in regard to PA and the IBG.[36–39] Only two of the four have shown higher self-efficacy to be related to greater intention for PA.[36, 37] Rhodes and colleagues[31] did show that self-efficacy varied across various intention–behavior profiles. Because self-efficacy is context specific, one's confidence in being physically active was wisely assessed with these contexts in mind (e.g., when a little tired, in a bad mood, when it becomes boring).[36] When measured in this way, "successful maintainers" of PA have a mean self-efficacy of 3.68 (on the 1 to 5 scale), indicating moderate–high confidence in their abilities. The "non-intenders" and the "unsuccessful adopters" had low–moderate self-efficacy ratings of 2.45 and 2.54, respectively.

Self-efficacy also has an effect on planning, which mediates the intention–behavior relationship. For example, Luszczynska and colleagues showed that a six-month intervention to boost self-efficacy or self-efficacy combined with action planning (i.e., specific plans outlining actions to meet particular goals) led to similar increases in FV consumption.[40] Interestingly, Richert and colleagues investigated the outcome of FV intake following a planning intervention in 411 employees.[41] The effectiveness of the planning intervention was found to be contingent on self-efficacy. In other words, those with low self-efficacy did not benefit from the planning. Similarly, Luszczynska and Schwarzer examined the influence of self-efficacy on intention and subsequent breast self-examination.[42] They first found that planning mediated the relationship between intention and behavior. Pre-actional self-efficacy had a positive effect on both their intention to conduct and their planning for conducting a breast self-examination, but not the actual behavior. However, their maintenance self-efficacy, which was assessed 12–15 weeks later, had a weak but positive effect on actual breast self-examination behavior.

25.3.2.3 Practical Application

Currently, the evidence for self-efficacy to bridge the IBG is generally supportive, yet still somewhat speculative, despite the growing literature in support of the importance of self-efficacy in health behavior. Interventions to reduce the IBG continue to arise, some of which lend potential support to the importance of self-efficacy. For example, when brief text messages were sent to participants to remind them of their action plans in addition to a standard psychoeducational intervention, self-efficacy increased slightly, while the psychoeducational intervention alone resulted in a significant decrease in self-efficacy.[43] The authors conclude with considerations for application, suggesting that

> individuals in the standard intervention group became discouraged by the experience that they could not fully transform their intentions into action. On the contrary, the text message reminders in the augmented intervention group might have assisted sedentary individuals to strengthen the confidence to become more active. Importantly, there is robust evidence that self-efficacy is a prerequisite for successful behavior change throughout a variety of health-related domains, including physical activity.[43]

Thus, the practitioner should consider the common determinants of perceived self-efficacy in their patients[44] as well as novel methods or technology to enhance patient self-efficacy.

Planning is also another key factor that can be facilitated in practice, but it hinges, at least in part, on self-efficacy. In other words, proper planning can help patients connect intention to behavior *if* they feel confident in their abilities to be physically active or eat healthfully across various contexts, especially when faced with certain barriers or when

resuming healthy behavior following a break from it. In summary,

> self-efficacious individuals are optimistic about their capability to resume an exercise regimen after a break, which might help them enact their plans. Therefore, self-efficacious people might be more likely to translate their intentions into action. In other words, action plans do not convert intentions into behavior if a person harbors self-doubts.[45]

These findings also highlight (1) the need to ensure each type of self-efficacy in patients and (2) the importance of understanding predictors in theoretically based path models (e.g., working left to right in the HAPA model).

25.3.3 Capacity (Executive Function)

25.3.3.1 Introduction

Self-regulation of behaviors, especially those behaviors that have been ingrained over time, can be quite difficult—even for those who might have the utmost intent to follow a prescription. This paradox highlights an important need for an adequate capacity of our brains to control and manage our thoughts, attitudes, and behaviors. This capacity, which is a foundation for self-regulatory abilities, is collectively known as the executive functions (EF). EF is a concept that describes the neurocognitive faculties of higher-order supervisory abilities to direct cognitive functions toward a goal.[46] When disassembled, the aspects of EF generally include attentional control, response inhibition, planning and problem solving, working memory, and cognitive flexibility (see Table 25.1). Put simply, EF appears to be the capacity for an individual to control their actions and thus, is a theoretically pertinent attribute to help bridge the IBG.

25.3.3.2 Review

First, the EF capacity of an individual might determine the strength of the connection between intention and behavior. For example, Hall and colleagues investigated the relationship of attentional/inhibitory control and intention for vigorous PA and FV intake.[52] Such measures, (e.g., Go/No-Go task), "predominantly tap one facet of executive function that may be particularly pertinent to behavioral self-regulation: the ability to suspend prepotent responses to external cues."[52] Clinically, such suspension of cues, thoughts, or actions that have been ingrained over time could be very helpful when overriding unhealthy habits to allow healthier choices.

Based on results from the Go/No-Go task, participants were classified as having either strong or weak EF (i.e., attention/inhibitory control). Those with low intention to increase PA or FV intake did not augment behavior regardless of their EF categorization. In other words, when someone has low intention to change, whether they have strong or weak attention/inhibition, there was no increased consumption of FV or minutes of PA. Only those with both high intention strength and strong EF scores bridged the IBG with an increase in PA and FV intake.

In another study, Hall and colleagues[53] investigated the role of EF with a sample of postmenopausal women undergoing a self-regulation enhancement intervention of implementation intentions (discussed earlier). They found that higher EF capacity in areas of inhibitory control, working memory, and task switching (i.e., subconscious ability to shift attention between one task and another) was associated with an increased ability to employ the self-regulatory strategy, which led to higher self-reported PA. In corroboration of these findings, poorer inhibitory control is associated with higher saturated fat intake, whereas higher working memory was found to be associated with greater FV consumption.[54]

However, inhibitory control has not been consistently associated with health behaviors. For example, Wong and Mullan reported that inhibitory control was not related to breakfast consumption.[55] Wong and Mullan did report, however, that abilities to plan and problem solve, as measured with the Tower of Hanoi task, moderated the IBG for those with low intention. Thus, breakfast consumption was not shown to be due to a deficit in inhibitory control; it is, instead, related to an individual's capacity to plan. However, these data on breakfast consumption indicate that some behaviors might be pliable through some aspects of EF rather than others, even within the same category of behaviors, such as healthy eating (i.e., breakfast consumption vs. increasing FV).

Like inhibitory control, planning and problem solving have proposed implications for healthy behaviors in that

TABLE 25.1
Common Executive Functions and Their Definitions (with Citations)

Executive Function	Definition
Attentional Control[47]	The ability to willfully direct one's focus on a given topic/subject
Response Inhibition/Inhibitory Control[48]	The ability to stop dominant or prepotent responses
Planning[49]	The formulation, evaluation, and selection of a sequence of actions to achieve a desired outcome
Problem Solving[50]	The procedure of deriving solutions to complex issues
Working Memory[48]	A limited capacity system that is responsible for manipulating and holding temporary information, especially when new information is presented
Cognitive Flexibility[51]	Ability to adapt to face new and unexpected conditions in the environment

greater inhibitory control and/or greater capacity for planning and problem solving should lead to a higher probability of follow-through of health behaviors. "The ability to plan efficiently may be especially useful in health-protective [behaviors], for example setting aside time to prepare meals, and making plans to exercise."[55] Norman and Conner reported that one's self-reported ability to plan was positively associated with exercise frequency in younger and older men and women.[56] Reuter and colleagues used a volitional planning intervention within an ongoing employee health promotion program.[57] Participants were asked to plan by simply writing down "when, where, and how you will eat five portions of fruit and vegetables a day," which led to increased FV intake one month later.

However, the results of planning as a moderator are rather ambiguous, with other investigations reporting null findings regarding PA.[58,59] Luckily, the research is relatively nascent regarding the different facets of EF as they relate to healthy behaviors. More investigation is warranted to further clarify the relationship of some aspects of EF with certain health behaviors. One could hypothesize that some EFs are more intuitively related to certain endeavors than others. For example, the ability to pass on donuts at the office could be related to inhibitory control. Planning/problem solving could be related to scheduling a week with sufficient time to attain 150 minutes of moderate exercise. However, there could be overlap. Proper planning/problem solving could mitigate the desire to even eat a donut, as in the case when an individual eats a breakfast filled with numerous fibrous fruits and vegetables, which helps control their blood sugar, subsequently leading to an attenuated hunger response.

25.3.3.3 Practical Application

For the practitioner, it is important to have a sense of a patient's EF capacity. If a practitioner was so inclined, they could download a free software that offers numerous EF-related tests from http://pebl.sourceforge.net/. Many of the tests only take a few minutes to administer, the software is relatively user-friendly, and the results are generally simple to interpret. However, computerized tests are not compulsory to assess EF capacity. There are a few questionnaires that can provide a quick assessment concerning where an individual lies on the EF capacity spectrum, such as the Web-Ex[60] and the EF index.[61]

Also, it is possible for EF to be improved. Computerized, home-based interventions have been successful for improving EF in long-term breast cancer survivors.[62] Acute exercise, chronic exercise, and plant-based diets also improve EF in a host of ages.[63–66] Researchers have also found that prayer,[67] tai chi and meditation,[68] positive feelings,[69] self-affirmation,[70] and even a short visit with nature[71] can provide acute enhancement of various aspects of EF and self-control. Alternatively, more Westernized diets and inactivity can negatively affect EF.[72–74] Since unhealthy behaviors can decrease EF, there is concern for a cycle whereby unhealthy actions decrease one's capacity to implement healthy actions, which in turn, can make self-regulation of healthy behavior more difficult.

These ideas are focused on improving EF, which will likely take an extended period of time. Rather, the practitioner should consider how prescriptions could be modified. For example, the Maintain IT model poses that it is essential to link desired health behavior changes to an individual's identity, beliefs, or personal values to achieve success, a process known as *centered identity*.[75] Over time, this process can reduce the patient's reliance upon EF, as enacting the health behavior becomes increasingly routine. However, individuals with lower EF might require more guidance and planning than those with higher EF scores. If EF is a constraint, then it is imperative to configure an individualized plan where EF is not a limiting factor: for example, providing a patient who is weak in planning and problem solving with a simpler food log to self-monitor food intake, as a more complex version might be too difficult. However, if a patient is quite strong in planning, then a more detailed logging plan might be suitable. At this time, such individualized prescriptions are speculative. Nevertheless, as the research continues to provide insight into EF and its role in the IBG, the practitioner can incorporate EF into clinical practice when appropriate.

25.3.4 Emotional Response

25.3.4.1 Introduction

Consider doing a behavior that you believe will produce negative or adverse feelings. Would this anticipation affect your intention? Intention does not predict behavior as well when a strong affective component (i.e., feelings) is present.[76] Theoretically, an anticipation of the feelings that a behavior might produce could influence one's intention to perform that behavior. This assumption is behind "anticipated affective reactions" (AAR) or the positive affect (e.g., exhilaration) or negative affect (e.g., regret) that is anticipated to follow performance or non-performance of a behavior.[77, 78] AAR is considered an emotional dimension of attitude (see TPB)[79] but is proposed here with a possible role in moderating the IBG.

25.3.4.2 Review

Conner and colleagues put this possibility to the test. They found that when intentions to perform various health behaviors (e.g., eat five fruits/vegetables a day, exercise regularly, use sunscreen) were based on anticipated affective reactions to those behaviors,[77] "[i]n other words, the stronger the correlation between the feeling of regret associated with performing the behavior and intention, the more likely that intention was to predict health behaviors."[77] These findings corroborated an earlier review, which found that the anticipation of negative affect following a behavior (or not performing a behavior), such as regret, worry, tension, and anxiety, was a significant correlate ($r_+ = 0.43$) with intention and predictor of an additional 7% of the variation in intention beyond TPB variables ($R^2\Delta = 0.07$).

Regret, in particular, has similar support for other health-related behaviors.[80,81] A more recent study found that anticipated regret was a significant correlate of COVID-19 vaccination intention.[82] This study analyzed both *inaction regret*, regret for *not* getting the COVID-19 vaccine, and *action regret*, regret *for* getting the vaccine. Inaction regret was positively correlated with intention ($r = 0.82$), and action regret was negatively correlated with intention ($r = -0.42$). It is currently unknown whether action or inaction regret might better moderate the IBG. Although a wealth of research has been conducted over the IBG within PA and dietary behaviors, there is still much to be learned about the IBG and vaccination. Brewer and colleagues have provided a clear overview of the hypothesized relationships between anticipated regret and health behavior (Table 25.2).[80]

Abraham and Sheeran manipulated anticipated regret by having participants in an experimental condition focus on it through answering an anticipated regret item, "Would you regret it if you did not exercise in the next two weeks?"[83] Participants were then asked about their intention to exercise over the following two weeks. A control group was asked their exercise intention and then their anticipated regret. Those in the experimental condition had nearly double the intention ($M = 6.18$ on an 8-point scale) as the control group ($M = 3.67$). In this way, anticipating regret, a negative feeling, had a positive effect on intention when made salient before exercise intentions were considered. The authors conclude that highlighting anticipated regret in relation to not exercising could enhance future interventions.

Similar results could be achieved in the FV domain, as a brief, leaflet-based motivational intervention of implementation intentions with anticipated regret (of not meeting daily recommended intake of FV) was able to predict intention to meet the intake of FV but was not related to FV intake.[84] However, Godin and colleagues found that anticipated regret was positively correlated with FV consumption ($r = 0.34$) and intention ($r = 0.59$) in a sample of adult men and women classified as obese.[13]

Although receiving little attention in the literature, negative anticipated affect or negative affective responses to healthy behaviors could theoretically reduce intention. For example, I have heard negative anticipatory response with both whole food, plant-based diets (e.g., "It will taste like cardboard and grass") and exercise (e.g., "It will hurt me," or "It will be boring"). Also, if I try the healthy meal, and I do not enjoy it, then my intention might be lower to try another healthy meal in the future. Similarly, if I respond to a bout of exercise in a negative way, then I might have less or no intention to try it again. Such responses are very feasible, as the affective and exercise relationship has been examined for decades,[85] and the affective response using the single-item Feeling Scale (very bad to very good)[86] to a single bout of exercise in sedentary adults was able to predict their physical activity level 12 months later.[87]

The exercise–affect relationship might help explain how exercise intensity could moderate the IBG. For example, Rebar and colleagues found that it takes more intention to follow through with vigorous-intensity physical activity than with moderate-intensity activity or walking.[88] This could be due to numerous reasons, one of which could be the physical demands of and affective responses to more vigorous forms of physical activity. However, for the practitioner, this distinction could be helpful. As the authors state, "The results of this study suggest that focusing on activities of lesser intensity may help bridge the intention-behavior gap, thereby potentially enhancing the effectiveness of intention-enhancing physical activity intervention."[88]

25.3.4.3 Practical Application

In summary, anticipated affective responses to performing (or not performing) a behavior have been shown to predict intention across multiple health behaviors, including PA and FV. Practitioners, then, should consider assessing and highlighting perceived regret, in particular, within their patient interventions. As previous authors suggested, "[I]f we want to help individuals act on their intentions then promoting greater correspondence between intentions and underlying anticipated affective reactions to the target behavior, may be a useful approach."[77] In support, Brewer and colleagues conclude that anticipated regret should be a standard variable assessed in studies of health behaviors.[80] They also offer that anticipated regret should be measured with the following guidelines:

TABLE 25.2
Hypothesized Relationships between Anticipated Regret and Health Behavior

Anticipated regret of	
Action	**Inaction**
Discourages health behavior *Example*: anticipated regret of vaccination (if it led to side effects) discourages vaccination.	Encourages health behavior *Example*: anticipated regret of not getting the flu vaccine (if the person later got the flu) encourages vaccination.
Discourages risk behavior *Example*: anticipated regret of smoking (if it caused cancer) discourages smoking.	Encourages risk behavior *Example*: anticipated regret of not trying cigarettes (if it led to being shunned by friends) encourages trying cigarettes.

Source: Recreated from Brewer, N.T., et al., *Health Psychol.*, 35(11), 1264–1275, 2016.

1. Specify a negative consequence of the action or inaction.
2. Assess regret of the action or inaction but not the health consequence.
3. Examine only anticipated regret without also assessing other expected negative emotions.
4. Have separate subscales for action and inaction.
5. Include multiple items in each subscale, if possible.

They also provide an example item that would meet the first three criteria: "Imagine that you had an abnormal Pap test, but the HPV vaccine might have prevented it. How much would you regret that you did not get the HPV vaccine?"[80]

It is also important to manage emotional states so that a patient will stick with a prescription. The practitioner might ask the patient about their anticipated expectancies and feelings surrounding the lifestyle prescription. The prescription can then be modified to encourage positive feelings, feelings of self-efficacy, or even anticipated regret, depending on the specific behavior. Making prescriptions without consideration of the anticipated feelings of the patients, for both new behaviors and past behaviors they are being asked to do again, could be detrimental and ineffective in increasing intention and bridging the IBG.

25.4 SUMMARY

A phenomenon exists where intention to perform healthy behaviors does not translate into behavior, called the "intention–behavior gap." Patients are faced with a challenge of (1) building intention to initiate healthy lifestyle behaviors and (2) acquiring the self-regulatory abilities to follow through with their intention. Unfortunately, left alone, most patients will succumb to the intention–behavior gap, frustrating themselves and the practitioners who desire to help them succeed with lifestyle medicine prescriptions. This chapter provided initial insight into how the practitioner and the healthcare team can play a key role in helping bridge the intention–behavior gap with their patients, such as the use of action and coping planning, building self-efficacy, or identifying anticipated affective responses (e.g., regret). An awareness and better understanding of the intention–behavior gap allows modification of lifestyle prescriptions and development of practice models that maximize lifestyle adherence when lifestyle is the medicine.

CLINICAL APPLICATIONS

- Action and Coping Planning
  - Instruct the patient to write down how they plan to exercise, where they plan to exercise, and when they plan to exercise. This can also be done in regard to more healthful dietary choices.
  - Assist the patient in formulating coping plans to help clarify, specifically, how they will deal/cope with upcoming problems, such as how to still exercise on a rainy day.
- Self-Efficacy
  - The practitioner should consider the common determinants of perceived self-efficacy in their patients. This can be done by using peer models, giving frequent and focused feedback, and also encouraging accurate attributions.
- Capacity
  - Test the individual's EF and determine where they fall on the spectrum. Individuals with lower EF may require more guidance and planning than those with higher EF scores. If EF is a constraint, then it is imperative to configure an individualized plan where EF is not a limiting factor.
- Emotional Response
  - Practitioners should consider assessing and highlighting perceived regret, in particular, within their patient interventions.
  - The practitioner might ask the patient about their anticipated expectancies and feelings surrounding the lifestyle prescription. The prescription can then be modified to encourage positive feelings, feelings of self-efficacy, or even anticipated regret, depending on the specific behavior.

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26 Cognitive-Behavioral Change Approaches to Enhancing Physical Activity Participation and Decreasing Sedentary Behavior in Adults

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KEY POINTS

- Systematic evaluations of the use and effectiveness of behavior change techniques in physical activity interventions support the value of basic cognitive and behavioral strategies for promoting and maintaining physical activity.
- Wearable activity trackers are popular and effective interventions and are likely enhanced with goal-setting and self-monitoring strategies.
- High quality internet-based physical activity information and motivational materials have the potential to reach high-risk groups previously underrepresented in health promotion efforts. Online and social media physical activity interventions using cognitive-behavioral strategies may not be sufficient on their own to sustain activity gains over time.
- Structured telephone contacts and smartphone apps providing activity prompts can be effective, particularly when the content and timing of messaging are personalized to address individual preferences and other factors such as physical and emotional status.
- Sedentary behavior is distinct from moderate and vigorous activity, and assessment benefits from objective measurements. Interventions have been most successful when specifically targeting sedentary behavior rather than combining this with efforts to also target physical activity increases.
- Physical activity interventions can have a wider and more representative reach by planning recruitment and interventions across gender, income, and racial/ethnic groups, considering barriers to engagement, community access, and neighborhood settings along with behavior change approaches.

26.1 INTRODUCTION

Numerous reviews and meta-analyses of the research literature have now confirmed the results of many individual clinical trials demonstrating that interventions can increase physical activity (PA). In recent years, evidence has also begun to accumulate on interventions designed to decrease sedentary behavior (SB) as a related but separate and significant health concern. These reviews of PA and SB interventions have contributed to increasingly specific understanding of optimal approaches for promotion of PA and SB behavior change and maintenance, including which techniques and conditions might be effective,[1,2] by whom,[3] and for whom,[4,5] as well as identifying key areas in need of future research.[6, 7]

In this chapter, we will provide an overview of frequently used cognitive-behavioral interventions for increasing PA and decreasing SB at the individual level. Our purpose is to identify intervention approaches that have consistently shown efficacy in promoting PA and in attempts to reduce SB. We also include discussion of the influence of emerging technologies on PA assessment and interventions and recent attempts to increase the diversity of participants and to enhance community outreach in this area of scientific inquiry. We do not attempt to provide another critical review of the literature, since timely reviews are already available for the interested reader.

26.2 OVERVIEW OF EFFECTIVE COGNITIVE-BEHAVIORAL CHANGE APPROACHES TO PHYSICAL ACTIVITY INTERVENTIONS

The "behavioral" and "cognitive" interventions we use today for promoting physical activity (PA) and decreasing sedentary behavior (SB) are derived from experimental psychology and theories of behavior change. Behavioral intervention methods are characterized by a focus on specific observable behavior and factors that can be manipulated to influence the behavior that is the target of change. Cognitive interventions focus on changing the cognitions that are thought to facilitate or hinder behavior and rely on verbal or written reports to assess the otherwise unobservable events. Different cognitive-behavioral theories, such as Social-Cognitive Theory, the Transtheoretical Model, and

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the Theory of Planned Behavior, attempt to explain how cognitions influence behavior and how factors from different levels (such as individual biology and learning experience as well as physical and social environments) influence cognitions and behavior. Most successful health promotion behavior change intervention programs today are based on one or more cognitive-behavioral theories and use a combination of behavioral and cognitive change methods.[8] Table 26.1 shows examples of some frequently used methods in PA promotion. While early studies of behavioral and cognitive interventions to promote healthy PA often focused on only one or two methods, many interventions used today have several components designed to complement each other and produce stronger and more sustainable effects.

Reviewers have used different approaches to attempt to identify which cognitive-behavioral interventions and combinations of methods produce the best results. A systematic review of 129 analyses of intervention components for diet and PA found that specific goal-setting, feedback on performance, use of prompts to be active, and individual tailoring via provision of information or counseling were all associated with greater PA intervention effectiveness.[9] Another study used a meta-analysis of PA interventions, including more than 100,000 healthy adult participants,[10] with a wide variety of interventions and experimental designs in both published and nonpublished studies. Findings were similar to the previous review: goal-setting, contracting, self-monitoring, and using cues or rewards were effective interventions; they also revealed demographic limitations of the literature, as the vast majority of participants were middle aged, female, and only rarely ethnic minority. Conclusions from the expert review of PA intervention research for the 2018 PA public health guidelines[7,11] were also consistent with previous reviews, i.e., that commonly used theory-based intervention components such as self-monitoring, forming intentions or goal-setting, demonstrating or modeling PA, changing the environment to facilitate PA, and rewards for behavior change are effective for increasing PA. The expert reviewers also emphasized that PA interventions can be effectively delivered using a variety of methods, including face-to-face individual and group sessions, by phone, and through internet programs, as well as in a wide variety of settings.

The recent development of taxonomies and coding systems related to behavior change techniques has facilitated comparison of intervention components[12] across studies of PA and SB interventions.[13] A recent large-scale systematic review and meta-analysis examined PA and SB interventions for behavior change *and maintenance*[14] in randomized controlled trials and made use of these state-of-the-art methods, including the Behavior Change Technique (BCT) Taxonomy,[12] for evaluating active intervention ingredients using standardized definitions and descriptions. Additionally, to evaluate aspects of the interventions such as delivery mode, treatment delivery (and fidelity), duration, and frequency, the researchers used the Template for Intervention Description and Replication (TIDieR), a checklist detailing the intervention delivery approaches.[15] Also of note, studies included in the review were conducted in a diverse representation of countries, and intervention providers were mixed, most frequently an instructor or student interventionist. The most common intervention settings were primary care, exercise facility, or mail delivery. Theoretical approaches varied, with the Transtheoretical Model used the most. A wide range of contact frequency and duration was observed, ranging from 1 print contact to 33 sessions over 14 months (mean length 21 weeks). Unfortunately, only 12 of the 26 studies reported ethnicity, with three-quarters of those reporting a majority of White participants.[13] The most frequently reported behavior change techniques were goal-setting behavior and social support. Immediate post-intervention PA data suggested that participants randomized to intervention conditions had significantly more PA compared with control participants, with interventions yielding improvements ranging from 606 to 1,849 steps per day and from 31 to 247 minutes of PA per week. Evaluation of follow-up data indicated that participants randomized to interventions continued to engage in more PA, but the effect was smaller, with follow-up improvements ranging from 421 to 1,370 steps per day and from 5 to 95 minutes of PA per week. Intervention effectiveness for PA maintenance was associated with the presence of BCT Taxonomy–indicated use of action planning, specific performance instruction, use of prompts/cues, behavior practice and rehearsal, graded tasks, and self-rewards.[13] Only one of the studies reported intervention treatment fidelity; the authors accordingly highlighted this as an important need in future examinations of PA intervention approach effectiveness.

The reviews mentioned in this section are only a few among many supporting the value of basic cognitive-behavioral strategies in promoting PA. Emerging standardized taxonomies for comparing and summarizing evidence across studies will facilitate future reviews and meta-analyses. Improvements in future clinical trials of PA and SB interventions are likely if they include evaluation of adherence to intervention protocols (fidelity), adequate sample sizes, representation of diverse ethnicities and racial groups, complete sets of findings, and testing of different theoretical frameworks and cognitive approaches.

26.3 TECHNOLOGY IN PHYSICAL ACTIVITY MONITORING AND INTERVENTIONS

26.3.1 Activity Monitoring

Accurate information about performance is an essential component of many theory-based cognitive-behavioral change strategies, and the rapidly expanding access to technology for physical activity monitoring is now a major influence on current cognitive-behavioral PA intervention programs and research. Widespread adoption of wearable devices and mobile apps to promote PA is extending our knowledge of the benefits of self-monitoring on PA and

TABLE 26.1
Examples of Cognitive-Behavioral Methods in PA Promotion

METHOD	DEFINITION (excerpted/adapted from BCT Taxonomy[12])	EXAMPLE
Goal-setting	Set or agree on a goal defined in terms of the behavior to be achieved	Set a goal to walk in the neighborhood for 30 minutes
Action planning and intention formation	Detailed planning of performance of the behavior (must include at least one of context, frequency, duration, and intensity)	Plan to walk at a moderate pace in a nearby park for 30 minutes at lunchtime 4 days a week
Monitoring	Observe or record behavior with the person's knowledge as part of a behavior change strategy	Record attendance at a cardiac rehabilitation program group exercise classKeep a daily paper and pencil diary of exercise completedReview step count data displayed by a fitness smartwatch
Self-monitoring	Establish a method for the person to monitor and record their own behavior(s) as part of a behavior change strategy	
Feedback	Monitor and provide informative or evaluative feedback on performance of the behavior *(e.g., form, frequency, duration, intensity)*	Personal trainer reviews with client details of how performance has changed during past monthReceive notifications on a mobile phone or other device when specific activity goals have been accomplished
Biofeedback	Provide feedback about the body *(e.g., physiological or biochemical state)* using an external monitoring device as part of a behavior change strategy	Wearable device vibrates to indicate a target activity heart rate has been reached
Prompts or cues	Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behavior. The prompt or cue would normally occur at the time or place of performance	Leave exercise shoes in front of the door as reminder to walkDog barks and looks expectantly at the door at usual walking timeSign near stairs encourages walking upstairs rather than taking the elevator
Behavioral practice/ rehearsal	Prompt practice or rehearsal of the performance of the behavior one or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Practice a yoga pose guided by instructor
Graded tasks	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Weight training program begins with light weights and gradually progresses over time to heavier weights and/or more repetitions
Social support	Advise on, arrange, or provide social support *(e.g., from friends, relatives, colleagues, buddies, or staff)* or non-contingent praise or reward for performance of the behavior. It includes encouragement and counseling, but only when it is directed at the **behavior**	Arrange to meet a friend to exercise togetherForm a group of work colleagues who will encourage each other to interrupt sedentary work with brief activity
Instruction on how to perform the behavior	Advise or agree on how to perform the behavior	Recommendations for exercising safely and effectively are provided on a government website for persons with osteoarthritis
Demonstration of behavior/modeling	Provide an observable sample of the performance of the behavior, directly in person or indirectly, e.g., via film or pictures, for the person to aspire to or imitate	Fitness instructor bikes with class
Rewards, material reinforcement	Arrange for the delivery of money, vouchers or other valued objects if and only if there ***has been*** effort and/or progress in performing the behavior	Fitness program gives participants a tee shirt upon completion of a specified goalHealth insurance program offers monetary incentives for participants who report regular exercise for a specified period of time
Social reward	Arrange verbal or non-verbal reward if and only if there ***has been*** effort and/or progress in performing the behavior	Fitness instructor praises class members who bring their exercise diaries to the class
Self-rewards	Plan to reward self in future if and only if there has been effort and/or progress in performing the behavior	Purchase a new workout outfit after completing a workout at the fitness center
Problem-solving	Analyze, or prompt the person to analyze, factors influencing the behavior, and generate or select strategies that include overcoming barriers and/or increasing facilitators	Examine activity data for patterns that may help understand successes and failures to meet goals

creating opportunities for novel and highly individualized interventions.[16]

Modern pedometers, with their electromechanically based systems, are easy to use, still relatively inexpensive, and can produce objective, reliable, and valid estimates of normal gait walking–related PA.[17]. More technologically sophisticated activity trackers now available for research and commercially to the public offer many advantages and features that are engaging for wearers and valuable for researchers, including the ability to detect both PA and SB and activity intensity from light to vigorous, assess lateral and vertical movement, accumulate data over time, and provide in-the-moment as well as cumulative feedback.[2] Some trackers also have a GPS location capability built in or when linked to a smartphone. Validation studies consistently indicate that most commercially available trackers compare well for accuracy with research-level activity monitors and direct observation.[16]

A carefully conducted study with research-quality accelerometers found that total activity counts (TAC) as well as activity meeting criteria for moderate and vigorous intensity PA (MVPA) correlated significantly with more favorable levels of a variety of cardiometabolic and endocrine biomarkers in a sample of more than 500 women.[18] The correlations were attenuated but not eliminated by including self-reported PA in the statistical models. This result is what is expected if accelerometer data are a more accurate assessment of the activity that influences the biomarkers. Importantly, several more recent studies and a meta-analysis have found significant linear associations between higher daily step counts and all-cause mortality in a variety of populations. [19,20] In the meta-analysis, the association of steps per day with mortality was observed to vary by age: for those under 60, the association was attenuated after 8,000–10,000 steps per day, and for those 60 and older attenuated at 6,000–8,000 steps per day. Analyses of activity intensity measured by steps per minute showed association with mortality in some, but not all, studies.[20]

A 2022 study that followed 4,838 older women (average age 78.9 years) for 7 years to assess their walking PA and health risks[21] found that for every 1,000 steps per day added, there was a 6% lower incidence of developing diabetes; the relationship was stronger for MVPA steps than for light intensity steps per day. Interestingly, body mass index (BMI) was not a significant mediator of the association between steps and diabetes.

Another recently published meta-analysis examined the important question of the effects of interventions using accelerometers on PA and weight loss.[2] Data from 14 clinical trials were analyzed for PA and from 11 trials for weight loss; both sets of analyses showed small but significant positive effects. The authors noted that there was substantial variation among studies; qualitative findings suggested that effects were greater when the interventions included stronger emphasis on using device-driven feedback. The results suggested diminishing effects of accelerometer use over time, which would be consistent with other types of self-monitoring research. Another finding of note was that the results did not suggest accelerometers produced better effects than simple pedometers; this finding is encouraging for interventionists concerned about using the simplest and least expensive tracking devices.

Commercially available activity trackers are generally well liked by users, despite some technical issues,[22] but the accuracy of their data varies among models and is affected by where they are worn on the body and the gait of the user.[23,24] One validation study[25] found that although daily counts between a commercially available and a research tracker did not agree, over seven days, the results for active minutes were comparable. Another[26] found strong correlations between a commercial tracker and a research-quality tracker, but the commercial tracker tended to overestimate step counts. Health and fitness professionals who are evaluating activity using commercially available trackers should not rely on only a single day's data; users should consider at least one week's data and be aware that actual activity may be less than that indicated by a commercial tracker for healthy people and greater for those with slow or impaired gaits. Reviewers[9,27] agree that the use of activity trackers is an effective intervention for increasing physical activity but have noted that many of the interventions also included goals related to steps and/or diaries, highlighting the self-monitoring aspects of activity tracker use and the likely importance of coupling monitoring devices with goal-setting strategies in order to achieve optimal results.

26.4 COMPUTER AND WEB-BASED INTERVENTIONS

The rapid increase in the use of web-based interventions for PA promotion during the past two decades is not surprising given the many potential advantages, including the convenience of access at almost any place and time by large numbers of participants who may live far away from the original source, opportunities to utilize multimedia components, cost savings when interventions are based on interaction with computer algorithms rather than paid professionals, and the anonymity and self-paced nature of websites. A review of early studies (published before 2010[28]) concluded that web-based formats were feasible and engaging and yielded success rates similar to those of more traditional methods such as print and telephone outreach, although some studies noted greater satisfaction with some face-to-face content.[29] Examples of free, high-quality PA promotion intervention materials that utilize cognitive-behavioral approaches can be found on the websites of the United States Centers for Disease Control and Prevention and the National Institutes on Aging. Browsing these websites, any interested consumer can read and print PA information and motivational materials, watch videos of age-appropriate exercise, and use interactive PA tracking tools. It should be noted that these websites are now attempting to be more inclusive of at-risk groups that have often been underrepresented in health promotion efforts;

for example, most materials are available in Spanish as well as English, and the National Center on Health, Physical Activity, and Disability has a YouTube channel dedicated to exercise at home videos.[30]

Much of the research on web-based interventions is now focused on trying to answer more specific questions of how to reach and optimize PA interventions for population groups differing in characteristics such as age, culture, and health conditions. These research directions should in the future provide helpful guides to building acceptable and effective intervention programs for diverse groups, but at the present time, there are too few studies within specific groups to allow more than preliminary conclusions. For example, a review and meta-analysis including 11 studies[31] examined the use of web-based distance physical rehabilitation interventions on PA and walking in persons with multiple sclerosis. The analyses showed large positive effects for interventions using the internet, telephone, exergaming, and pedometers compared with no treatment, but the amount of data was too small to determine whether there were differences in effectiveness between these methods.

As noted earlier, cognitive-behavioral theories highlight the importance of goal-setting and some type of monitoring and performance feedback. Many web-based interventions depend only on self-reported data from users, but a group of Australian researchers[32] conducted a study to determine whether the effects of a web-based PA promotion intervention with no face-to-face contact would be improved by adding objective performance data using Fitbit trackers. After 3 months, the Fitbit users had greater increases in MVPA (163 vs. 77 minutes/week). They also completed more of the web modules and gave the website higher ratings than the control users. Other researchers have reported similar findings of stronger results when objective PA measures are used to evaluate performance.

26.5 MOBILE PHONES AND DEVICES

With even greater accessibility than computers, mobile phone messaging and apps are now increasingly used for interventions across a variety of preventive behaviors. Careful reviews of clinical trials using texts and/or apps indicate that texting can increase activity in adults in the short term,[33,34] but the effects in some projects have been disappointing. For example, a large, randomized control trial that offered free text messaging to deliver health-related information to pregnant women (Txt4baby) included an evaluation of the effectiveness of PA promotion messaging.[35] Inactive pregnant women were randomly assigned to one of four groups differing in dose and timing of messaging, and PA was measured using Fitbits. Unexpectedly, no increases in PA were observed regardless of message frequency or time, and participants who received the highest number of messages (six per week) unexpectedly had greater decreases in PA and increases in sedentary time. The authors concluded that "more is not better," that the frequency of messaging might have been aversive, and suggested that future interventions may need to incorporate more choice, utilize more behavioral strategies, and focus more on self-efficacy and beliefs.

A review of nine studies of smartphone apps that used steps or minutes of MVPA per day as outcomes[36] reported that the experimental interventions ranged from six weeks to six months in duration and included features such as PA performance summaries, goal achievement, and motivational prompts; some also included social comparisons and text messages. Steps per day increased in six studies, but the two studies looking at MVPA did not find significant differences favoring the app. Sensitivity analyses suggested the best results were for the short term (less than three months) and for interventions that targeted PA alone. Another review and meta-analysis of 11 studies[37] that compared a PA intervention app with no treatment or a more traditional intervention also found that the apps helped produce better short-term results in steps per day, but the authors noted that the quality of the research was generally low.

According to cognitive-behavioral theories, prompts or cues should increase behaviors, so researchers are exploring how both the content and timing of mobile messaging may need to be personalized for better results. One recent study[38] tested three kinds of messages (prompt to move more, prompt to sit less, or an inspirational quote) and different message frequencies from zero to six per day. Responses, measured by step counts, were quite varied between individuals, differed on weekdays versus weekends, and there was no "average" best combination. "Move more" and "sit less" messages generally had a greater effect on warm than on cold days, but this was not true for all participants. Optimal tailoring of messaging for individuals may be very complex, but as technology and understanding of key factors advance, might in the future not only include personal variation in the timing and content of mobile interventions, but also take into consideration factors that vary from day to day and from time to time, such as pain level, emotional state, and reactions to meeting or failing to meet exercise goals.[39]

Health professionals and interventionists desiring to use smartphone apps to promote PA should keep the limitations noted by researchers in mind and also be aware that the quality of apps is highly variable.

26.6 SOCIAL MEDIA

Online social networks offer a unique vehicle for PA intervention, and interventionists have utilized Facebook, Twitter, WeChat, and other programs widely available to consumers as well as study-specific platforms.

To date, reviews of attempts to use social media for increasing PA indicate that additional studies are needed to improve the effectiveness of the interventions. One review of 53 intervention studies using social media[40] found that only one-third reported positive effects on PA; two more critical reviews also found limited success for these interventions when compared with controls.[41, 42] These results

are consistent with other studies suggesting that the online and social aspects of social media PA interventions in tandem with known tools of self-monitoring and goal-setting can be engaging and effective for increasing activity, but that effects of PA interventions using social media that have been tested thus far are typically small and are not sustained over time.

26.7 EXPANDING THE TARGETS OF ACTIVITY PROMOTION: ASSESSING AND TARGETING SB

Accumulating evidence suggests that SB is distinct from a lack of MVPA, and studies increasingly examine MVPA, inactivity, and SB separately.[43] Examples of SB often examined in the research literature include screen time (e.g., computer use, television viewing), video games, time spent in transportation, and reading;[44] SB measurement has yet to catch up with the rapid growth in use of tablet and mobile devices with screens.[45, 46] There are also a number of components of SB that require separate examination in relation to health impact and intervention potential, including total sedentary time, durations of sedentary bouts, and frequency and duration of interruptions. Self-report measures of SB have been used in assessment and interventions studies[47] and may provide useful information, but objective measures such as accelerometers and inclinometers are probably necessary to accurately capture time spent engaging in. and patterns of, SB.[43]

Some intervention studies have attempted to focus on both decreasing SB as well as increasing PA. Overall, those focused specifically on SB seem to have been more successful in reducing SB relative to those that have included both foci.[48,49] Studies also differ in whether the intervention aimed to reduce time spent in sedentary activities or targeted breaking up periods of sedentary time, such as by providing prompts to stand up or and move after periods of sedentary time. A systematic review of *non*-worksite interventions to reduce SB (targeting sitting time and/or breaks in prolonged inactivity[50]) found that a combination of self-monitoring and technological feedback may be useful SB reduction strategies; however, providing real-time SB feedback using technology without other interventions may not be enough to change SB patterns.[51,52]

The majority of interventions for SBs in adults have targeted the workplace. A meta-analysis[53] found successful reductions in both self-reported and objectively measured workplace SB, with an average difference of 91 minutes per day spent in sedentary activities between intervention and control groups.[43] A more recent review of SB interventions and their impact on sitting time and screen time utilized an umbrella review of systematic reviews with both children and adults.[49] All of the reviews of SB interventions in workplaces showed reductions in sitting at work time (39.6- to 100-minute reductions per 8-hour workday). Individual components associated with effective SB changes were environmental changes such as use of sit-to-stand desks and active workstations. The use of active workstations such as sit-to-stand desks, treadmills, and portable pedal machines has been evaluated in a wide range of settings; a recent meta-analysis found that 14 of 15 studies reported significant changes in SBs.[54] Point of choice prompting technology to take standing breaks or get up and move (via prompting wristwatches or computer prompting software installed onto desktops) has also been reported.[54] Most of the interventions were shorter than 90 days in duration, so the maintenance of reductions in SBs in the workplace over time is unclear. The degrees to which roles of employer or coworker support or internal versus external factors influenced behavior change in these worksite settings are also unknown and important areas for further exploration, since social support and monitoring have independently been shown to influence PA.

Gardner and colleagues reviewed behavior change strategies used in published SB reduction interventions with adults.[55] Twenty-six studies and 38 interventions (53% worksite-based) were coded for use of discrete behavior change techniques in the interventions, using a BCT Coding Taxonomy.[56] The most commonly used behavior change techniques were goal-setting, provision of social support, adding objects to the environment, and action planning. Intervention approaches were categorized as very promising, quite promising, or non-promising according to the level of SB changes observed. Very or quite promising interventions were more likely to directly target SB rather than PA. The greatest degree of behavior change was noted for approaches that used environmental restructuring education or persuasion techniques. More information is needed regarding effective SB intervention strategies in older adult populations and how to best achieve maintenance of changes in SB over time.

26.8 PHYSICAL ACTIVITY INTERVENTIONS IN RACIAL/ETHNIC UNDERSERVED SAMPLES

Reviews of both PA and SB interventions continue to highlight the need for additional studies that are more representative of the population and extend the evidence base. While lower levels of MVPA are often observed in low socioeconomic status (SES) populations and in individuals from minority racial/ethnic backgrounds, these groups are still underrepresented in PA interventions and evaluations due to inadequate planning and conceptualization of recruitment approaches, barriers to engagement and intervention response, and limited interventions that have been specifically developed for minorities or culturally adapted.[57] Whitt-Glover and colleagues conducted one of the first systematic reviews of interventions to increase activity and fitness in African Americans.[58] The majority of studies were conducted with women. Interventions included community-based approaches such

as delivering the intervention in community settings such as the YMCA, community centers, church, worksites, and public housing projects. Cultural adaptations were included in many of these studies, for example, a church setting, activity instructors from the African American community, gospel, soul and hip-hop music and dancing, and incorporated prayer. The culturally adaptive methods of intervention were frequently paired with familiar behavior change approaches, including monitoring, use of pedometers, peer phone contacts, supervised exercise sessions, and social support via group walks in the local neighborhood. The multiple approaches and study design limitations made it difficult to evaluate the specific influences of these culturally tailored approaches. However, examination of findings from individual studies indicates that common factors associated with the effectiveness of individual studies of PA interventions in African Americans are similar to those noted in previous reviews of PA interventions, such as using a randomized controlled trial design, assessing PA using an objective measure, providing specific PA goals to participants, and including structured activity programs.

A recent systematic review and meta-analysis reviewed randomized controlled trials of behavior change interventions targeting men's PA, considering both pre-post intervention changes in PA and sustained change at a year or longer.[59] This review considered 24 eligible studies with men only and those in which the data was disaggregated by sex. Findings indicated a PA intervention effect size that is consistent with approximately 980 steps per day and an increase of 97 minutes of total PA per week. The review found that the moderating factors associated with greater increases in PA included having a gender-tailored design, using a theoretical framework, using four or more behavior change techniques, frequent contact with participants, and a program of ≤12 weeks' duration.

A small adaptation of the Diabetes Prevention Program lifestyle change intervention was developed to target PA in men from underserved communities in New York City.[60] This men-only program, Power Up for Health, integrated individual and community-level approaches. Five New York Park and Recreation sites across Bronx, Harlem, and Brooklyn were randomized to intervention arms, and coaches, participants, and community advisors provided input on programming. The outcome of this pilot program indicated increases in PA, particularly when PA sessions were added to the end of face-to-face education sessions. Stakeholders recommended phone sessions as an option to reduce participant burden.

Family-based PA interventions may also be beneficial for enhancing engagement and benefits for ethnic minority and underserved populations. Project SHINE, a family-based intervention with African American families, originally targeted adolescents using family-based, interactive sessions with PA goal-setting and self-monitoring with session content addressing lifestyle change motivation, sense of belonging, and family communication about maintenance of changes. Community speakers also presented information about norms for African American families.[61] The program had a beneficial impact on adolescent PA behavior. Subsequent follow-up analyses with participating caregivers indicated that they also improved MVPA, while control group caregivers showed decreases in PA.[61]

Promotion of PA in racial and ethnic minority populations has also successfully incorporated cultural values and models by employing ethnically matched health educators and interventionists.[57] Community-based outreach and bridging neighborhood and community approaches with the use of community health workers who are from the target population has also been successful; these *promatoras* have been widely used in culturally sensitive health interventions in U.S. Latina PA promotion efforts.[57,62] Carefully controlled intervention studies are needed to examine the specific influences of culturally adapted PA intervention approaches more thoroughly.

A six-month, culturally adapted, individually tailored, internet-based PA intervention with sedentary, Spanish-speaking U.S. Latinas was successful in increasing MVPA and achievement of national guidelines for PA.[63] Increased MVPA was maintained at a 6-month follow-up, 12 months following the baseline.[64] Acculturation and health literacy were not significant moderators of the impact of the intervention,[64] highlighting the range of participants benefiting from this web-based intervention approach.

An e-health intervention aimed at preventing weight gain in a sample of low-income African American women in a primary care setting used telephone-based interactive voice technology (IVT) for self-monitoring behavior change goals, including walking 10,000 steps/day.[65] This monitoring technology entailed listening to a voice prompt and responding with a simple numerical answer and had the advantage of brief duration, low cognitive demand, and dynamic and immediate feedback messages, without the need for internet connectivity.[65]. Participants' engagement in calls and adherence to weekly IVR monitoring was high and associated with positive study outcomes.

While studies have shown that technology-based PA interventions and different kinds of settings may be helpful in delivery of PA interventions with low-income, minority populations, care must be taken to understand which approaches might provide the best reach and acceptability. In some demographic groups, omnipresent internet access and mobile phone usage makes these modes of intervention delivery ideal; however, technology adoption gaps remain for many lower-income groups. Pew Research data from 2021[66] showed that the percentages of Americans in each tier of income who have broadband at home or own a smartphone did not significantly change between 2019 and 2021. Approximately one-quarter of adults with household incomes below $30,000 reported that they did not own a smartphone, 40% of adults in lower-income groups did not have home broadband, and 43% did not have a home computer or laptop. In contrast, adults living in homes with income above $100,000 owned nearly all of those devices

and were much more likely to have multiple devices. Pew data from 2021 indicated that 27% of adults in low-income households are smartphone-only internet users and used the phone for activities that are intended to be done on larger screens, such as applying for jobs or completing schoolwork.[66] This technology gap has important implications for the development of PA and SB interventions aiming to reach underserved, low-income participants.

The potential reach of home-based resources and community-centered approaches to further impact public health across a wide range of individuals, including those from disadvantaged groups, has led to efforts to translate what is known about effective components and delivery approaches of PA interventions into accessible community settings and dissemination formats. Strategies that appear to be effective for PA promotion in underserved populations include those that are delivered through home, church, or community-based channels, utilize technologies appropriate to the population, include cultural adaptations, incorporate staff or peer interventionists who reflect the community, and take advantage of opportunities for environmental interventions.[57]

26.9 COMMUNITY-WIDE PA INTERVENTIONS

As described in the preceding sections, print, telephone, internet, mobile device, and peer delivery modalities all offer opportunities for reaching a wide variety of individuals who may benefit from dissemination of these supported intervention approaches. A 2015 Cochrane review examined 33 studies of community-wide interventions aimed at increasing PA to evaluate their influence on population-level health;[67] 25 were conducted in high-income countries and 8 in low-income countries. The authors concluded that methodological issues precluded reaching clear conclusions regarding the effectiveness of community interventions; however the methodological review offered instructive information about the types of community interventions that have been conducted and suggestions for future intervention programs and research. A major concern identified in the community-wide PA intervention literature was selection bias, particularly limited use of community comparisons and randomization, and the quality and validity of assessments used to measure outcomes. Despite these limitations, it is encouraging to see that the majority of interventions included establishing partnerships with local government or non-government local organizations. Community strategies generally involved planning initiatives with the aim of producing long-lasting benefits for the community. They also operated at a series of levels to attempt to influence activity, such as environmental changes, policy changes, and use of the media. Some studies found significant increases in the use of community resources such as trails and pathways, indicating that programs reached some segments of the targeted population, but the effects did not translate to changes in the population levels of PA. The review also provides a description of community-level strategies for outreach to many types of disadvantaged groups. Many of the studies included some form of individual behavior change counseling delivered by a health professional, social marketing through local mass media, other communication outreach (posters, flyers, information booklets, websites, maps) to raise awareness of the intervention program and provide specific information, and working within specific settings that might facilitate contact with individuals who have social disadvantages such as lack of transportation and might otherwise be missed by traditional outreach, for example, schools, senior centers, workplaces, community centers, homeless shelters, and shopping malls. Environmental change strategies such as creation of walking trails and partnering with legislative and fiscal leaders to promote planning for outreach to the broader population were also undertaken.

The Cochrane Review[67] also provides a useful overview of the types of recent community approaches and highlights the challenges inherent in attempting to identify key components of effective community-based PA interventions that broadly impact population-level PA. The conclusions noted that many authors of the studies included in the review identified reasons for lack of efficacy as due to being unable to penetrate the community as well as a relatively short intervention duration, limited methodologies, and limited resources. Considering the recognized need for studies of adult PA promotion representing diverse population groups, these types of community-wide intervention approaches offer tremendous potential to promote activity, especially if advances in PA assessment methodologies and in technology use for outreach allow researchers to improve upon study designs and recruitment. More well-controlled evaluations of these approaches are needed and offer challenges for future community-wide PA intervention evaluations. Additionally, careful consideration of the method of outreach to and communication with community stakeholders is needed to ensure that the intended audience has been reached by the intervention and is able to maintain changes in PA over time.

Since the publication of the Cochrane Review,[67] several large-scale community intervention studies have provided information about adoption and maintenance of PA changes over time. A large community study conducted in Japan that showed significant increases in walking across all categories of age, sex, and market segments found that those who had higher cumulative awareness had greater uptake of the intervention.[68] Follow-up evaluations two and five years post a city-wide community PA intervention with 3 independent samples of 3,000 adults found that continued participation over time was challenging and that while PA knowledge was maintained at two years, that did not translate to maintained PA behavior.[69] Moving from a broad approach to targeting a specific population of older adults, and adding specific, manageable goals and self-monitoring tools, improved participation and engagement.[69]

26.10 ENVIRONMENTAL FACTORS IN PA

An additional approach to addressing the needs of the broader community when developing successful cognitive-behavioral PA interventions is to consider the role of the built environment and neighborhood, which has the potential to facilitate or create barriers to behavior change and maintenance. The last decade has produced a body of studies documenting that the physical environment and neighborhood factors play an influential role in PA.[70,71] Reviews have found that neighborhoods that are characterized as walkable (those with mixed land use, such as having homes, schools, workplaces, and areas to shops accessible) can encourage walking to multiple destinations.[70] King and colleagues evaluated both social and built environment influences in the context of PA interventions across five intervention trials.[72] Features of the built environment were assessed with a Neighborhood Walkability Scale. Activity guidelines were more likely to be met by participants living in neighborhoods with more attractive scenery and ease of walking, and traffic safety was related to both facilitating and impeding activity. The role of environment and neighborhood in PA may be a particularly important consideration when developing individual or group interventions for low-income or underserved populations and minority racial/ethnic groups.[73] A multilevel *promatora*-led intervention, aimed at promoting PA in a sample of 319 Latina women recruited from 16 churches, examined the influence of neighborhood environment variables on intervention effectiveness,[74] Participants' perception of their neighborhood esthetics moderated intervention effects on both self-reported leisure time PA and accelerometer-derived moderate to vigorous activity, with those reporting more favorable esthetics benefiting more. The authors of this study noted that less satisfying neighborhood esthetics could be associated with greater poverty and disorder and hinder motivation for PA in this context.

Other studies have reported what may seem to be an unexpected finding, that PA interventions were more likely to help those who perceived more environmental *barriers* to increase their activity. In an examination of two randomized activity trials conducted with similar methodologies and recruitment, Kerr et al. explored the interactions between changes in walking over time, lifestyle PA intervention conditions, and the walkability of participants' neighborhoods.[70] Examination of the interactions between the built environment and interventions revealed that men who resided in less walkable neighborhoods (as assessed with a walkability index) who were in the intervention group significantly increased their walking time, while men who resided in highly walkable neighborhoods decreased their walking over the course of the study. Men in the control condition did not increase their walking time. For women, results showed similar trends, with women living in low walkable neighborhoods who were in the intervention group increasing their walking the most, although results did not reach statistical significance. Women who perceived an unsafe volume or speed of traffic had decreased walking time (22-minute daily decrease), while women who perceived that the traffic in their neighborhood was safer had increased walking time (increased by 17 minutes) over the course of the study. The findings of this study may reflect a ceiling effect of living in a highly walkable neighborhood.

These mixed findings on interactions between built and neighborhood environment highlight the need for additional research to understand these results. Differences in use of self-reported perceptions of neighborhood factors and structured environmental space ratings and noted gender differences in interactions between built environment issues and activity outcomes are intriguing and suggest that personal appraisals of the neighborhood environment are important to consider. Men and women may have different perceptions of, and responses to, changes at the built environment level. The authors observed that one encouraging implication of the study findings is that the pattern of results shows that behavior change interventions can encourage walking even in less supportive environments.

One aspect of the built environment that has been studied for the potential for low-cost PA intervention is the use of stairs in community and workplace settings. The presence of stairs across a variety of settings has offered researchers the opportunity to assess the viability of using simple prompts to promote PA in public settings. A Norwegian intervention study, "Romsas in Motion," used theoretically developed, comprehensive approaches to addressing individuals, groups, and the environment, with tailored strategies accounting for readiness for change in PA in a low-income, ethnically diverse population.[75] PA levels increased, particularly in those with the greatest needs, and simple exposure to low-cost, poster prompts to use stairs and walk an available path was highly effective. A recent systematic review of 50 eligible studies examined the effectiveness of stair-use interventions[76] and found that they increased PA in 64% of worksite and 75% of public settings. Combining directional and motivational signs in worksite settings increased stair climbing by 83%, and conducting a second phase in public settings increased stair climbing by 86%. A quasi-experimental study comparing the use of general and specific stair messages to promote PA found that specific messages were more effective.[69] Future evaluations of this cost-effective approach in tandem with other known influences on PA may further assist efforts to increase PA adoption and maintenance across community settings using low-cost and practical approaches.

Programs that move beyond examining associations between built environment and PA to consider how and when and for whom behavior change intervention techniques promote PA or reduce SB in the environmental context will further our understanding of how to best promote neighborhood and physical environment climates that are conducive to the adoption and maintenance of consistent PA.

26.11 MAINTENANCE OF PA OVER TIME

Several recent studies and reviews have addressed the ongoing question of how to best promote consistent and sustained PA.[7] A systematic review and meta-analysis evaluated the effect of randomized clinical trial PA interventions and the trial strategies on at least six months of PA maintenance in community-dwelling older adults.[77] This review found that while some strategies to enhance PA maintenance were discussed in the individual studies, most were not designed with a focus on PA sustainability. Overall, PA interventions improved time spent in PA relative to control conditions at six months but not at one- or two-year follow ups, with heterogeneous findings regarding specific cognitive and behavioral strategies.[77]

Another recent systematic review and meta-analysis approached understanding PA behavior change and maintenance by focusing on intervention impact on self-efficacy for PA and the maintenance of PA self-efficacy post intervention.[78] The review encompassed 180 randomized trials that reported data on changes in and maintenance of PA self-efficacy. Behavior changes techniques used in the studies were coded using the BCT Taxonomy, and their associations with PA self-efficacy were evaluated. Significant associations were found between the number of behavior change techniques used and PA self-efficacy at the end of the intervention but not for maintained changes in PA self-efficacy. Examination of specific behavior change techniques found that behavioral practice was associated with larger effects for maintenance of PA self-efficacy, while practical social support was associated with lower maintenance of PA, and interventions delivered in person and within church/community settings led to higher effect sizes in maintenance of changes in PA self-efficacy. This pattern of findings highlights the complexity of the relationships between behavioral techniques and PA self-efficacy. The authors note that this pattern supports other reviews suggesting that planning social support and social change are associated with lower effect sizes for PA self-efficacy and may be related to social comparisons and relative personal judgements about PA abilities.[78] This emphasizes the need for ongoing evaluations of the optimal approaches to integrating social support elements within interventions and suggests that interventionists should not assume that increased social support will always be helpful.

26.12 CONCLUSION

Promotion of healthy PA and SB behavior change and maintenance is a popular topic for cognitive-behavioral researchers. Early studies aimed at understanding the utility of behavior change approaches to enhancing exercise participation have been extended by exciting and creative developments in research approaches. Advances in behavioral science taxonomies for evaluating specific cognitive-behavioral behavior change techniques used in interventions have led to greater ability to evaluate effective mechanisms of action in PA interventions. Cognitive-behavioral interventions such as self-monitoring, social support, goal-setting, and feedback with individual tailoring of content appear to be effective techniques across PA intervention studies and populations. Technology has greatly enhanced the methods available for PA monitoring and communications between interventionists and program participants. The use of written diaries and logs is now often accompanied or replaced by accelerometers, step counters, and a variety of wearable devices. Activity program participants may access interventions through peers, the internet, mobile phones, and various types of structured telephone contact approaches in addition to—or instead of—face-to-face contacts and printed materials. Efforts to improve intervention approaches to encourage adoption of exercise are now enhanced by a renewed emphasis on the importance of interventions that promote maintenance of activity once it has been established. Recent advances in ecological momentary analysis have allowed longitudinal examination of the usefulness of specific aspects of theoretically based intervention approaches, aiding in efforts to longitudinally examine the process of activity maintenance, cognitions and affect, and relationships to intervention components. Recent intervention studies have also addressed not only activity per se but also changes in the SBs that are encouraged, if not enforced, by our modern lifestyles.

Technological changes continue to introduce new ways of replacing active living with SB and suppress opportunities for PA in almost every domain of modern life. The obesity epidemic now threatens almost all population subgroups and even less technologically advanced cultures. Although these public health challenges are undoubtedly powerful adversaries, new discoveries of the benefits of PA are a continuing source of inspiration to researchers, healthcare providers, and others committed to finding more effective ways of encouraging all people to be physically active and healthy. Interventionists may employ effective PA counseling techniques in a variety of settings and take advantage of a variety of free and commercial materials based on empirical evidence.

The advances and limitations highlighted in this review of behavioral and cognitive interventions for promoting PA suggest some of the important directions for future work. In particular, we expect to see more studies that translate findings of efficacious interventions into a wide variety of settings and populations. New technologies are likely to make monitoring of the spectrum of activity, from complete rest to the most vigorous exertion, more accurate and less expensive. Telecommunications, internet, and mobile communications will continue to provide new opportunities to connect people to PA promotion interventions, and we need to learn how to effectively and efficiently combine the technology with the personal contacts that many people still desire. Consideration of how to best extend the evidence base to a wider range of adults, including older adults and representation of diverse racial and ethnic minorities and underserved communities, will further our understanding

of effective intervention approaches for larger segments of the population. Additionally, much remains to be learned about how to promote sustained activity over time and how to consistently reduce SB. Best practices for integrating across individual and community levels of intervention are still unknown, and the range of approaches now available offer exciting opportunities for the development of multicomponent intervention programs. There will also be unexpected challenges, but the scientific and creative advances of the past decade suggest that there will be exciting new progress to report in future years.

CLINICAL APPLICATIONS

- The use of established cognitive-behavioral approaches, such as self-monitoring, goal-setting and feedback, individual tailoring of content, and social support, appears to enhance PA interventions and should be incorporated when promoting PA change.
- PA assessment and promotion can be enhanced with widely available technology such as wearable activity trackers, websites, structured telephone contacts, social media, and mobile apps. These may also be used to promote communication between interventionists and program participants and used in addition to or instead of face-to-face contacts and printed materials.
- SB poses health risks independent of MVPA and is a useful target for intervention. Approaches specifically targeting SB, rather than simply including SB as a component of broader PA interventions, may be most successful in reducing SB.
- PA interventions may be more acceptable and effective when tailored to specific populations, such as different gender and age groups, different cultures, and different neighborhood environments.
- Home-based and community settings can provide greater reach to at-risk and underserved populations and help to translate evidence-based intervention approaches for promoting PA and decreasing SB in real-world settings.

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27 Enhancing the Nutrition Prescription Using Behavioral Approaches

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KEY POINTS

- The nutrition prescription is one of the most important components of lifestyle intervention.
- Empowering patients with basic nutrition knowledge can help with nutrition prescription adherence.
- When prescribing nutritional lifestyle interventions, it is important for the practitioner to take into account the various cultural and social factors involved in the individual's or group's dietary habits.
- A coaching approach built on a solid coach–client relationship can promote positive behavioral change as it relates to nutrition.
- Group medical visits can be a cost efficient and productive tool to implement nutritional prescription within a lifestyle medicine program.
- In order to effectively comply with a nutrition prescription, it is vital for patients to possess fundamental culinary skills so they can prepare health promoting meals at home.

27.1 OVERVIEW

Recent studies have shown that most patients suffering from chronic medical conditions do not follow lifestyle recommendations (i.e. tobacco cessation, healthy eating, exercise, etc.) despite the fact that doing so could significantly alter the underlying disease process in a positive manner.[1] Adopting healthy behaviors centered on optimal diet, sufficient physical activity, and reduction or elimination of substance use thus becomes vital in the overall treatment of many chronic diseases. Therefore, when considering the lifestyle medicine prescription, emphasis on changing a patient's behavior becomes a key component in the treatment plan. This chapter will focus on nutrition. It will review nutrition prescription and its importance, the art and science of coaching for behavior change in nutrition, as well as culinary skills and strategies to use for optimal nutrition.

27.2 THE IMPORTANCE OF NUTRITION PRESCRIPTION

Perhaps the most important modifiable lifestyle factor involved in the overall maintenance of health and prevention of disease is diet. It is clear that sub-optimal nutrition plays a direct role in the development and propagation of chronic diseases such as obesity, diabetes, hypertension, cancer, and cardiovascular disease.[2] The most recent U.S. Dietary Guidelines, made available to the American public in 2020, emphasize a dietary pattern rich in a variety of whole grains, fruits, and vegetables while simultaneously limiting consumption of added sugars, saturated fat, and sodium.[3] These guidelines were derived from scientific data that support a whole-food, mostly plant-based diet as the overall pattern of eating involved in health promotion and disease prevention. These efforts remain consistent and are evolving into primary prevention practices in order to reduce the incidence of overweight and obesity, Type II diabetes, cardiovascular disease, and cancer.[3] The evidence continues to accumulate on how a diet that is lower on the food chain can dictate the health of a population.[4] The United States Preventive Services Task Force (USPTSF) recommends that nutrition counseling be intensive and focused on behavioral interventions. A good nutrition prescription increases both the intensity and the ability to apply a focused behavioral intervention. Based on the latest U.S. Dietary Guidelines and scientific evidence, most would agree that the overall dietary pattern recommended for health promotion would be one that is plant centric—including half of a plate of a colorful variety of vegetables. Furthermore, emphasis should be placed on eating whole foods in the "pure" form as opposed to foods that have been processed. However, possessing knowledge on the most health promoting dietary pattern is meaningless without tools in place or a mechanism to put this knowledge into action. Dietary habits are largely controlled by the complex interaction of human behavior, cultural practices, and societal norms. Therefore, for clinicians to effectively intervene from a nutritional perspective, they must also know how to help change human behavior. Such behavior can be both

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learned or acquired and reinforced by the interplay of social interactions, cultural norms, and or societal factors, making it difficult to change over a short-term period.

Since it is now widely accepted that dietary pattern has a profound effect on overall health, the necessity of incorporating behavioral strategies to promote health and healing becomes even more vital to the lifestyle medicine practitioner. Among the major barriers to implementing such strategies are lack of confidence in behavior change counseling, inadequate provider training in behavioral counseling, and lack of time and or reimbursement for counseling services. Lack of confidence in behavioral counseling abilities seems to rank highest among healthcare providers as the reason for not implementing behavioral change strategies into their practice.[5] This lack of confidence is not surprising when one considers that physicians are offered little to no training in counseling techniques and most medical schools do not incorporate behavioral modification into their curricula. There is an entire chapter on health coaching, which can serve to amplify the behavior change information in this chapter.

Another barrier is the lack of standardization of behavioral counseling techniques. Currently, rigorously tested behavioral change strategies do not exist. One reason for this could be that it is challenging to design and conduct randomized controlled trials that can effectively evaluate the efficacy of behavioral techniques. The lack of concrete evidence supporting specific behavioral tools designed to improve lifestyle habits leads to inadequate advice given by providers, long counseling sessions, inappropriate methods of behavioral advice delivery, and poor follow-up.[6] Furthermore, most behavioral programs fail to incorporate specific guidance based on an individual's unique ethnic, cultural, and socioeconomic status. This lack of a personalized approach makes adherence to behavioral change much more difficult to sustain.

As healthcare continues to change from an economic standpoint, more physicians are finding themselves under more pressure to produce viable bottom-line numbers to meet growing healthcare costs and overhead, and to earn a living. Therefore, many clinicians feel that the time they have with patients, already limited, must be spent addressing symptoms rather than focusing on root causes such as sub-optimal lifestyle habits. Additionally, reimbursement for lifestyle counseling is either non-existent in many healthcare plans or simply not sustainable for most physicians when considering "bottom lines."

Influences that help shape decisions made on health behavior occur within an individual's personal life. Many of these decisions are directly influenced by relatives, friends, co-workers, and community members.[5,6] Thus, all these influences must be considered when constructing a nutrition prescription with motivation for behavior change as its foundation.

The nutrition prescription must be goal oriented for it to be successful. The acronym SMART has been used in helping physicians to set such goals for their patients. It is categorized as follows: S, specific; M, measurable; A, action oriented; R, realistic; and T, time sensitive. It has been found that when these SMART goals are aligned with an individual's life goals, the individual will be more motivated to change behavior.[5,6]

This chapter covers the key aspects of achieving a successful nutritional prescription to achieve lasting behavior change. Effective nutrition prescription implementation can only occur when patients are motivated to change. Various strategies to achieve optimal motivation will be discussed. Behavioral change theories for the lifestyle medicine practitioner are reviewed. Strategies for incorporating these principles, along with effective behavioral counseling techniques within the clinic setting, are highlighted throughout the chapter. Since health behavior is dynamic and dependent upon various cultural, social, and community factors, content related on how to integrate these aspects into a behavioral plan to facilitate nutrition goals is included. This chapter is unique as it includes information from a professional chef. Daniel Clarke shares his practical strategies to implement culinary skills. Empowering patients to adopt healthy eating patterns involves empowering them to cook at home. This chapter will help clinicians guide their patients on real life, hands-on cooking techniques and recipe planning while helping to promote positive behavioral changes.

27.3 EDUCATING PATIENTS ON NUTRITION BASICS: LAYING THE FOUNDATION

27.3.1 Nutrition, a Snapshot

The challenge of teaching nutrition is that the message is somewhat dull. Balance and moderation is certainly not as exciting or enticing as the new mocha-choco-pumpkin flavored iced coffee, or the influencer promoting just these 5 easy steps that promise to have you looking like you did at 17, complete with carefully curated photos. Herein lies possibly the most important lesson: ignore the marketing and outside influences, and listen to your body. This is a difficult lesson, particularly in America, but for most, knowledge is power.

Macronutrients, or the large building blocks of our nutritional intake, are Carbohydrates, Protein, Fat, and Water. Carbohydrates come in two forms, complex and simple; they are an extremely important source of energy for our bodies and our brains.[7] The vast majority of carbohydrates we consume should be complex for maximum nutrient density, slower digestion/energy absorption, and feelings of satiety.[7] Protein is found in many foods, from grains to meats. Protein is important for building and repairing tissues as well as a building block of hormones and enzymes.[7]. When educating about protein, encourage plant proteins. If people choose to eat fish, warn them of the high mercury levels in large fish like swordfish, tuna, mackerel, marlin, and others. If people do eat meat, warn them about processed meats and their link to cancer. If they desire meat,

recommend poultry or lean meats in limited quantities, such as one serving a week, maximum. Saturated fats in red meat can lead to high cholesterol. Fats have gotten a bad reputation in recent history, but fats are important for providing energy, transporting vitamins, and helping you feel satisfied after meals. Some fats are better than others for health; unsaturated fats and fats found in plants should be included in a healthy diet where saturated and "man-made" fats such as trans fats should be avoided.[7,8] Lastly, water is not always included as a macronutrient, but it is at that level of importance. One cannot survive without water for longer than a few days.[8] The human body needs proper hydration for cells to work properly, maintain temperature, and lubricate joints. When discussing fluids, unsweetened beverages should be encouraged.

Micronutrients, or the small building blocks of our nutrition intake, are all the vitamins and minerals. These nutrients, along with phytonutrients, work together to ensure that numerous body functions do not just work properly, but thrive.[7,8]

These basics of nutrition barely scratch the surface. Research is exploring the various avenues of how healthful nutrition is so much more than just nutrients and calories. Behaviors like sleep patterns, the gut flora, and when an individual eats can impact their mental health, physical health, and other lifestyle factors, such as quality of sleep.[9–11]

27.3.2 Whole Foods You Recognize

When thinking about changing nutrition behavior, a good first step is to take a look at the refrigerator and the pantry. Is there food in there, or food-like substances? Are there whole foods that were picked, plucked, pulled, and harvested? If there are mostly processed foods in someone's house, then there is a great deal of work to be done.

What is something that the majority of Americans have in their freezer and is the biggest contributor to sodium intake? The answer is frozen pizza. The dough comes from wheat, sauce from tomatoes, and cheese from milk. Doesn't sound too terrible, right? However, to turn it into a long-term stable frozen food, the wheat has been stripped of the nutrients, the sauce has lots of salt, fat, and sugar added, and the cheese has been processed from cow's milk. So, how does someone turn that frozen pizza into a "whole food" that is easy to prepare? Starting with the dough, most people do not have time to make their own wholewheat dough from scratch, but it is easy to purchase it. Or, someone could use a wholewheat English muffin or try a cauliflower crust. Another option is to hollow out a zucchini for a pizza base. Thinking about the sauce, the closest one can get to the whole food is slicing the tomato up, or try crushed tomatoes, or look at the nutrition label for the tomato sauce and select one with the smallest ingredient list, lowest amount of salt, and lowest amount of sugar. Lastly, the cheese can be added sparingly. A sprinkle of mozzarella and a sprinkle of a strong cheese like parmesan will deliver the flavor while limiting the extra calories and saturated fat that cheese adds. One can also use plant-based cheeses to keep the pizza plant based.

A good start is to recommend that people evaluate their food buying patterns. Think about how they can change their purchases and migrate them toward the original source of the food (see Table 27.1).

Thinking about the progression of these foods, from most processed on the left to least processed on the right, it is easy to notice that what is removed is the "extra" that's not needed. So with the "juice," when one moves to 100% juice, one loses the added sugar, and when one moves to whole fruit, one loses the concentrated source of natural sugar and adds fiber, vitamins, and minerals. The other thing that happens when one moves from left to right on this chart is that food preparation tends to increase. If food preparation is a hurdle, pick and choose where to make the changes. There are some convenience foods that still maintain the whole food and its nutrient composition. Examples include ready to microwave brown rice, canned beans (rinse to decrease sodium), plain frozen veggies, plain frozen fruit, baby carrots, cherry tomatoes, pre-sliced grilled chicken, and individual frozen pieces of fish. These items take only slightly longer to prepare than popping a frozen meal into the microwave.

When there is a patient or client who does like to cook, a provider can encourage them to purchase a Community Supported Agriculture (CSA) share or go to a farmer's market. Some simple exercises for patients can include trying a new vegetable (kohlrabi, jicama, celery root, golden beets, arugula, eggplant, and so many more choices); look

TABLE 27.1
Sample Progression toward Whole Foods

Current example	Step toward	Whole food
"Juice" or soda	100% Juice	Piece of fruit
Box cereal	Low-sugar wholewheat cereal	Oatmeal or quinoa
Frozen chicken wings	Low-ingredient whole meat chicken tender	Homemade breaded chicken breast
Frozen stir fry veggies	Frozen stir fry veggies no sauce packet	Raw sliced veggies
Hydrogenated nut butters	Natural nut butters	Raw nuts
Ramen style noodles	Rice noodles with soy sauce	Rice or wholewheat noodles with veggies and edamame

up recipes for the new items. This can be fun and exciting for patients.

27.3.2.1 Portion Control

Probably one of the most important things to stress with patients who are moving from a Standard American Diet (SAD) to a whole-food plant predominant one is portion control. Once people are enjoying a whole-food plant-based pattern of eating, portion control is less of an issue, because the fiber in plants like whole grains, vegetables, and fruits is satisfying and satiating. For those making small changes and reducing their amount of fast foods and processed foods, as well as simple carbohydrates and red meats, portion is key. A portion of meat is a deck of cards. Most restaurants supply at least four times that portion.

As the message of balance and moderation is not complicated, it does allow some wiggle room both for treats and for increasing nutrient-dense intake. The challenging part about portion control is that our baseline is all out of whack. Many think and have the perception that a foot long sub, a bag of chips, and 20 oz of soda is a normal lunch. The reality is, for most people, half of that sub, a piece of fruit, and water is the correct portion. No one has the exact same calorie and nutrition needs. To evaluate and provide a close estimate of a patient's calorie needs, a dietitian should be consulted. However, there are many guides to offer a patient to keep portion sizes appropriate. Some helpful tips for portion control include:

- Size of the plate—This matters! People tend to fill the plate. Choose a dessert plate rather than a dinner plate for meals.
- Divide the plate—Half of the plate should be filled with vegetables and/or fruits, a quarter with healthy protein, mostly plants, and a quarter with whole grains.
- Measure—Use measuring cups/spoons for a week. See how much you are actually serving yourself. Can you decrease it by one tablespoon? A quarter of a cup? After a week, you will have an idea of what serving sizes look like on your plates and in your bowls, etc.
- Serve and put away—Serve yourself the appropriate portion, and put the rest back into the pantry. You will be less likely to serve yourself seconds when it is not in front of you.
- Pre-portioned items—Purchase items already portioned (fruit cups, yogurts, string cheese) so you can grab and go!
- Eat at the table—Turn off the screens and pay attention to what you are eating, who you are eating with, and how you are feeling.
- Cook!—When you are in charge (vs. eating out), you know what the ingredients are, and you know how much you've served yourself. Tips for this will follow later in the chapter.
- Split it!—When you do eat out, ask the server to package half the entrée before bringing it to the table, or split an entrée with your friend.

27.3.2.2 Nutrients for Health

When one embarks on changing one's behavior related to nutrition in a more healthful direction, there are some nutrients that can help. Most Americans are juggling not only their weight but also the comorbidities that accompany obesity, as more than one-third of U.S. adults are obese.[12] The bottom line when thinking about healthful eating, modifying behaviors to increase health, or taking small steps in that direction is that the food has to taste good. Processed foods do this largely by adding salt, fat, and sugar.[10] There are ways to make food not only taste good without this formula but also provide some potentially beneficial influence on those obesity-specific comorbidities.

One of the obvious ways to improve the healthful qualities as well as add flavor and nutrient composition to a dish is to remove or drastically reduce the salt added and replace with herbs and spices. Basil, oregano, and rosemary are all wonderful spices that can jazz up a dish. A paste can be made with herbs and olive oil that can be used as a spread instead of butter, margarine, or mayonnaise. Turmeric has been shown to have anti-inflammatory effects, and a pinch can be added to egg white scramble, roasted veggies, rice, and soup, and blended into a smoothie.[13–15] Cinnamon is a wonderful addition to warm cereal, added to smoothies, and added to baking, and has been shown to have antioxidant properties as well as wound healing properties.[16] More studies are needed on these spices' effects in humans, as often, these spices are eaten in small quantities.[17] This leads back to the moderation and balance message, that no one item is the answer. No one item is going to be the quick fix for a strong, healthy body. The only way is to work toward a diet of balanced fruits, vegetables, plant proteins, complex carbohydrates, also called whole grains, a variety of colorful herbs and spices for additional flavor, and hydration.

27.3.2.3 Cultural Sensitivity and Nutrition

Health is not simply the biochemical state of an absence of disease or illness, but also embodies quality of life, including meaningfulness, joy, connection with others, and well-being. Health also includes a person's goals and circumstances as well as cultural values, traditions, and practice.[18,19] Similarly, eating foods does not only provide the nutrient chemicals and energy to sustain life and promote therapeutic efficacies at a biochemical level; food intake encompasses and entails emotional, social, and cultural relevance as well. What, why, and how individuals, families, and groups eat are developed and determined by cultural and religious traditions, social status, preferences, power, and more.[20]

Today, there exists a plethora of cultures and people with different eating habits, steps in food preparation, and identities in food. Eating is an intimate act one chooses, performs, and practices based on various factors (e.g. beliefs,

attitudes, needs, preferences, traditions, circumstances, environment) to sustain, promote, and celebrate life. The food a person chooses to eat reflects their identity. That is, the food choices an individual makes may reveal their social class, educational background, knowledge of food, as well as health and fitness goals. For instance, the person eating a low-fat and high-protein diet has different physique goals or preferences than the person eating a vegan diet or fast food diet. While these people may have different fitness goals or understanding of what foods are healthy and nutritious, there may be other health and cultural disparities present. These individuals, for example, may have access to different food items due to living in a health desert or due to their own financial burdens. Similarly, food is linked with power. In general, the cost of purchasing or acquiring healthy and safe foods (e.g. organic plant-based foods) is expensive, and those eating less food or unhealthy foods may have less power and be of lower socioeconomic status. Making sure that people understand that frozen vegetables and fruits or even canned vegetables and fruits (which must be rinsed) are better alternatives to fast food is essential. There are nutrients in these frozen and canned vegetables and fruits. The cost may be the same as a fast food meal. They are both cheaper, but one option offers vitamins, minerals, and antioxidants. This is an important part of education.

Another area to address is gender. Gender disparities in cooking also exist in food preparation. The traditional gender role of the female counterpart preparing and serving meals is a historically common practice. Reality TV cooking and chef shows also have popularized the art of cooking, adding prestige to the profession, which has also shaped the perceptions behind cooking. Cultural traditions additionally shape methods of cooking, what foods a person consumes, as well as how they eat. This may include family recipes passed through generations, weekly family dinners, eating a turkey for Thanksgiving in the United States, a kosher diet observed by many in the Jewish community, going to a restaurant for a meal to celebrate a special occasion, and more. Also, the foods consumed by individuals are those considered edible by a culture. Escargot is a well-known French delicacy uncommonly found on menus in American restaurants. Further, sushi has become quite popular in the Western world, but raw fish has not always been a staple of the American diet. Understanding a person's culture give you a new lens into their dietary patterns.

Furthermore, eating plays a role in relationship dynamics. Food is fundamental to culture and serves to potentiate social relationships. People dine together as a family, going out on a date for romantic pursuits, grabbing coffee to become better acquainted, or invite friends and neighbors to break bread together. These experiences promote closeness among diners as well as the sharing of cultural practices around food and nutrition. Moreover, people choose food based on their personal taste preferences. However, those foods deemed tastier are not always healthy and nutritious, so individuals selecting foods according to their taste preferences may be at an increased risk for disease. In French culture, the hedonistic value of food is held in high regard. Interestingly, French consumers rank foods displaying nutritional information more negatively and anticipate these foods to be less enjoyable to eat as well.[21] This portrays the concern that emphasizing healthy food choices may result in a utilitarian view of food as a necessity over the pleasure and comfort of food. This could make food enjoyment incongruent with health practices of eating nutritious foods.

There exists a tension between the science of food for health and how people relate to food physically, culturally, socially, and sensually.[19] According to the 2016 Food and Health Survey on Americans' food choices, taste continues to have the greatest impact on the decision to buy foods and beverages, followed by price, healthfulness, convenience, and sustainability for a decade between 2006 and 2016. Also, it has been shown that scientific understanding and use of the nutrition facts label can prompt food purchases and choices.[22] For example, a person with hypertension attempting to lower their sodium levels may opt for sodium-free or low-sodium food options. Diabetics may opt for sugar-free or sugar replacements to maintain lower blood sugars. However, the frequency of use of nutritional labels in choosing food was in general low among low-income women in Women Infants and Children food program (WIC) or other risky populations. While the use of food labels has increased in recent years, from 32% in 2004 to 52% in 2008, consumers still make their dietary decisions through various determinants of food choices including biological, psychosocial, cultural, economic, and environmental factors.[23]

In past decades, healthcare professionals have focused on and endorsed the importance of nutritional intake when promoting healthful diets and lifestyles for their patients. Meantime, the advent of genome sequencing has resulted in personalized medicine based on a person's genotype.[24] This includes the field of nutrigenomics, which encompasses the epigenetic effects of food or how nutrients trigger changes in genome expression.[25] Thus, one's genotype could be used to determine a unique diet regimen for optimal health, disease prevention, and therapy. Further, studies have shown that individuals have reported dietary recommendations based on genetics to be more understandable and useful compared with general dietary advice from their primary care providers (PCPs).[26] This novel field may be useful to improve patient compliance with provider recommendations and subsequently, health maintenance. However, despite the intrigue of nutrigenomics, the relationship of a person's environment and culture with their diet cannot be forgotten by PCPs. Providers need to inquire about the intricacies of patients' eating habits, schedule, and lifestyle to help counsel them on best lifestyle practices.[27] This also includes not just how food is prepared as a basic, but also finances for food budgets, troubles with mastication, swallowing, digestion, allergies or food intolerances, and dietary needs and preferences.

It remains clear that food is ultimately inseparable as both a biological necessity and a cultural conduit; cultural differences in diet and eating impart different disease outcomes in patients. For instance, minorities have an increased risk of obesity and comorbidities compared with Caucasians.[15] Weight loss interventions are less effective in these groups as well.[27] Cultures that consume higher amounts of processed foods and animal products have increased incidence of hyperlipidemia as well.[6] This indicates that the role of culture in food consumption needs to be addressed for effective weight management for minority patients. A focus solely on nutrition prevents a holistic approach to food that encompasses cultural sensitivity and considerations. Personalized nutrition with a holistic regard for cultural competencies includes providers well versed in the culture and language of their patients, family-oriented interventions, instructive materials in their native language, and social support within their cultural community.[18,25,27] Encompassing these individualities optimizes personalized nutrition as a tool for a healthy diet. Thus, a holistic, culturally sensitive, and individualized health approach may reinforce the effectiveness of personalized nutrition in the primary care setting.

27.3.2.4 Effective Counseling Techniques for the Nutritional Prescription

The coaching mindset is the art and heart of behavior change. It is a co-creative process that engages the patient in their own healing by illuminating a self-directed path. In this model, the patient is the expert, and the coach is the guide. This patient-centered way of engaging with clients is a fundamental shift from the current model of care, where the clinician dictates and directs. The coaching model is a theory-based practice that emphasizes collaboration and facilitation of the client's desire for change. Emerging studies show that behavior changes are enhanced when this self-directed partnership approach is utilized.

The coach–client relationship is a dynamic force that is pivotal to the change process. This relationship is built on trust, mutual respect, and partnership. At the core of this relationship is a deep understanding that clients have the ability to emerge their own answers and meaning. The pace and path toward wellness are created by the client and facilitated by the coach. It's a shift away from advising to illuminating. As listed in Table 27.2, there are *five main domains* to consider when moving from the Expert Approach to the Coach Approach.[28] "Focusing on 5 specific domains of communication enables practitioners to successfully switch from the expert approach to the coach approach when they are counseling on lifestyle medicine issues. The five domains include sharing knowledge, listening, asking questions, addressing problems, and taking responsibility."[2,27,28]

The first is *Sharing Knowledge*. The coach asks permission before launching into a lecture about a topic. The client can choose how and when information is distributed. This puts the locus of control back on the client and fosters participation. The second domain is *Active Listening.*

TABLE 27.2
Frates' Five Specific Domains of Communication for Coaching[28]

1. Sharing Knowledge
2. Listening
3. Asking Questions
4. Addressing Problems
5. Taking Responsibility

Source: Frates, E.P. and Bonnet, J., *Am. J. Lifestyle Med.*, U.S. National Library of Medicine, 2016, September. https://pubmed.ncbi.nlm.nih.gov/30202286/.

The coach listens without an agenda. It's a mindful state of listening that creates empathy and fluidness for the client. The third domain is *Asking Questions.* Open-ended, profound questions emerge from the active state of mindful listening. These deeper questions asked by the coach provoke insight and self-awareness in the client. The fourth domain is *Addressing Problems.* Problems and blocks are viewed as opportunities for growth. The focus is on the learning and not the problem. Solutions are discussed in partnership with the client, and the client makes the final call on which path to choose. The fifth domain is *Taking Responsibility.* Client participation is essential to successful behavior change. Goals and agreements are created based on the client's agenda, thus fostering follow through and self-responsibility.

Fostering self-awareness and insight is pivotal to the change process. The coach strives to assist clients in discovering their own answers by cultivating more meaningful questions. The coach moves away from interpreting and imposing meaning to asking questions such as: *"What does that mean to you?"*, *"What would that look like for you?"*, *"What did you mean by that?"* These types of exploratory open-ended questions assist the client in developing the self-awareness and insights necessary to make permanent changes in behavior.

27.3.2.5 Frates' Five-Step Model for Behavior Change

The five-step model for behavior change and motivation is a framework for successful coaching encounters.[29] This model was originally described in 2011 and has been easily adopted by healthcare providers of all types. It is currently being taught in medical schools to help future clinicians gain confidence and comfort in counseling patients about adopting and sustaining healthy lifestyles. Figure 27.1 describes the process.

This process is also described in the Introduction to Behavior Change chapter of this textbook. It is important and an essential foundational model for counseling on nutrition, exercise, stress resilience, substance use, sleep, social connections, and other behaviors associated with health.



FIGURE 27.1 The Five-Step Cycle of Collaboration. (From Frates, E.P., et al., ***Am. J. Phys. Med. Rehabil.***, U.S. National Library of Medicine, 2011, December. https://pubmed.ncbi.nlm.nih.gov/22019966/)

This model demonstrates five steps to follow when counseling patients on behavior change. It is a cycle that begins and ends with empathy. The following three paragraphs are reprinted with permission from the *Lifestyle Medicine Handbook* 2nd Edition:

The first[t] step is to *Be Empathetic*. There are two key components to empathy: *listening with intention* and *accurately reflecting* back narrative. Empathy helps to foster a connection between patient and provider. The second step is *Align Motivation*. This is based on Miller and Rollick's book *Motivation Interviewing* (*MI*). MI is a goal-oriented style of motivating that focuses on the *language of change*. The communication with MI is designed to strengthen personal motivation for a specific goal by eliciting and exploring the person's reasons for change in an environment of acceptance and compassion. The core MI skills are *OARS*. *O: open-ended questions* which allow the client to go deeper into exploring and expressing feelings and desires for change. "What makes you want to change your diet now?" *Affirmations*, finding the positives, the strengths, or as Miller and Rollick like to call it, *change talk*, and acknowledging it to enhance motivation. Change talk invites the client to give their own reasons for changing. Questions that evoke change talk are things like *"what would your life be like if you were eating less fast food daily?" "How would losing 10 lb enhance your current situation?" or "I heard you mentioned you wanted to give up gluten—what makes you say that?" R: Reflective listening*, which is demonstrating understanding by repeating or paraphrasing what you hear. *S: Summarizing* or reflecting back main points to establish rapport, connection, and facilitate the co-creation of client centered goals.

The third step in the five-step model for behavior change and motivation is *Building confidence* by identifying core strengths. The coach explores a client's core strengths by asking open-ended questions about past success and having the client identify which strengths they used and how these strengths could be applied to their current health goals. The fourth step is co-creating SMART goals with the client. SMART goals are *S*pecific, *M*easurable, *A*ction oriented, *R*ealistic and *T*ime sensitive. SMART goals take a large goal such as, *"I want to lose weight",* and break it down into smaller measurable chunks. *"How much weight? What is the first step towards doing this? When will you start this new behavior?"* are the kinds of questions used by the coach to facilitate the creation of SMART goals by the client? The fifth step is *Set Accountability*. The coach and client mutually decided on the best method of tracking and the frequency of communication and appointments. Having a very specific tracking system motivates and enhances behavior change. With the evolution of technology, it has become very convenient to measure and track in the moment. This immediate feedback keeps clients engaged with their goals and enhances behavior change. Frequent follow-up appointments allow the client to celebrate successes and explore blocks to setbacks.

For behavior change to be positive and permanent, the client's participation in the change process is required. This essential truth is shifting the landscape of medicine and health. This tried and true coaching model of collaboration and co-creation of client-center goals in an environment of empathy and compassion has the potential to transform health and facilitates deeper engagement with life.

27.3.2.6 Nutrition Counseling and Education in the Group Medical Visit Model

Nutrition counseling in the medical model acts as a perfect fusion in the patient-centered medical home for empowering the patient. In 2005, a review of the daily clinical responsibilities and demands placed on physicians estimated that it would require primary care physicians 18 hours a day to deliver evidence-based preventive and chronic disease management care.[27] Additionally, estimates vary; there is a nutrition related reason for at least 25% of all visits to primary care providers.[30] Medical students and residents receive, on average, 19.6 hours of nutrition education during their training.[31] Additionally, only 20% (3.9 hours) of the contact hours is formally nutrition science and application. The rest of the education focuses on integrated curriculum, clinical practice, biochemistry, physiology, and biochemistry.[29] American physicians are deficient in nutrition education.[32] A model for primary care clinics to empower patients to help intervene in their chronic health conditions through changing modifiable lifestyle factors has emerged. It is the group or shared medical visits, where the clinician and the nutritionist or health education specialist educate and provide a clinical evaluation experience to help address the many issues of chronic illness.[33] The fusion of nutrition counseling and

education with the clinician in primary care is the future of healthcare delivery for chronic conditions.[34]

27.3.2.7 Nutrition and the Group (Shared) Medical Visits: Application to the Primary Care Clinic

In the patient-centered medical home model of clinics in the United States, educators are being used alone or in conjunction with the clinician to allow more complete lifestyle education in nutrition to modulate chronic disease. The five major modifiable lifestyle factors include diet and nutrition, sleep, exercise and movement, thoughts and emotions, and relationships.

Maintenance of health and improvement in chronic illness are modulated by addressing these modifiable factors. This is a reimbursable model that has been used successfully in a wide range of clinical settings. Nutrition is key in the management of most chronic conditions, and group visits are an effective strategy to help encourage and empower patients to eat more nutritious foods on a regular basis.

When compared with the one-on-one session with clinicians, the group medical visit model has shown efficacy by improving tracked outcomes measures of compliance, biomarkers, follow-up, and lasting changes so that patients can meet more nutrition benchmarks.

There are many different structures to the shared medical visit session. Different monographs are available to help the clinician and clinic institute programs.[35,36]The main focus of the groups is to improve access, educate, and promote behavioral change. When a form of medical visits were incorporated into patient care in the VA, the focus was on diabetes self-management education using nurses or health coaching and also in psychotherapy and patient peer-to-peer support groups. Outcomes, time to treatment change, empowerment of the patient, and the satisfaction with their care improved. Nutrition is a key component of managing diabetes.

27.3.2.8 Using the COACH Approach™ and Group Visits in Therapeutic Programs for Chronic Disease with a Focus on Nutrition

There is an art and science to running group visits.[37] Joseph Pratt, MD was one of the first physicians to use group visits early in the 20th century, and he used them with tuberculosis patients at Mass General Hospital to improve education and treatment.[38] This model has been used to improve treatment in diabetes, metabolic syndrome, hypertension, cardiac disease, asthma, arthritis, chronic pain, and chronic headaches, to help manage stress and sleep disorders, and in the geriatric and the obstetric population.[33] A Cochrane collaboration systemic review in 2005 reviewed group-based training for self-management strategies in people with Type 2 diabetes mellitus, and it showed improvement in biomarkers: improved decreased hemoglobin A1C at 6, 12, and 24 months, lower average fasting glucose at 1 year, improved weight loss at 1 year, lower systolic blood pressure at 6 months, decreased diabetic prescription use, and improved diabetic knowledge at 1 year.

The health benefits of groups for the medically ill included decreased symptoms, improved compliance and adaptation to illness, and decreased use of emergency room visits and inpatient admissions. Blood pressure, blood glucose levels, and access to care improved. And most importantly, there was behavioral change. The benefits of this type of education and visit for the patient, clinic staff, nutrition educator or counselor, and provider are many. (See Table 27.3.)

27.3.2.8.1 Experience and Modeling

From the physicians' perspective, there is increased face-to-face time with patients. It is a more efficient patient education model than one-on-one office visits, and it allows increased integration of lifestyle change. There are a few models that have been recorded in the literature: the Scott model, which has an interdisciplinary team coordinating the group together, and the Noffsinger model, which has the physician leading the group. There are many variations.[39–42] The model needs to adjust to the location, physical plant, clinic and education personnel, and the client base. All group medical visits are local, with their own characteristics.

27.3.2.9 What Is the Focus of the Group Medical Visit?

There is a marked variety of focal points for the group medical visit. It can focus and concentrate on test results, general system issues, disease process, or a healthy process. As an example, at a primary care clinic in Ashland, Oregon, they have been using nutritionists, registered dieticians, physician assistants, nurse practitioners, and physicians for group medical visits. There are ten visits per month with three main topics: functional nutrition trimester by trimester obstetric care (healthy process), a cardiometabolic syndrome series (disease condition process), and test reviews of carotid intimal medial thickness results, or advanced

TABLE 27.3
Benefits of the Shared Medical Visit

1. Enhanced patient care experience with more education and empowerment
2. Improved patient satisfaction with the care they receive
3. Improved clinician efficiency and job do-ability
4. Improved morale and job satisfaction of the clinical and non-clinical support staff
5. Enhanced access to care for the patients
6. Physician ability to increase panel size and reopen closed practices to new patients
7. Cost effectiveness of care improved
8. Improved quality and safety of medical care delivered to patients
9. Helps providers avoid "burnout"

Adapted from [39–42]

lipids or inflammatory panels. Nutrition and its effects on lifestyle, health, and chronic illness is incorporated into all the groups.

The format and implementation are straightforward (Table 27.3), and the benefits previously outlined in Table 27.2 continue. The results have improved nutrition education, biomarkers, and therapeutic lifestyle changes. The programs have increased the frequency of delegated nutrition education and nutritionist evaluation visits for all the chronic conditions frequently seen in the clinic (Table 27.4).

The topics or focus of the groups can range from review of underlying general issues (inflammation) to specific laboratory or imaging related to a chronic process (lipids, advanced lipids, or carotid ultrasound-carotid intima media thickness). The groups can be diagnosis specific (hypertension, high cholesterol, rheumatoid arthritis), or they can form a series about the same topic (pain, cardiometabolic syndrome) (Table 27.4)

The introduction of the nutrition educator, nutritionist, nutrition counselor, or health education specialist into the primary care clinic is essential for the patient-centered medical home, the primary care clinician, and the desire for improved health and chronic disease outcome. It is important to evaluate your clinic population, demographic, level of desire, and the extent of using this tool.[43] But at the end of the day, this addition empowers all involved, generating hope and expectation because of the positive changes that occur.[44] This is a reimbursable process that is geared to the strength of all members of the clinic and health caring team with positive results.

27.3.2.10 Practical Culinary Skills to Ease Behavioral Change

In clinical encounters, whether they be in groups or in one-on-one settings, it is important to share basic culinary skills with patients whenever possible. Empowering patients to cook at home can help them save money, lower

TABLE 27.4
Examples of Topics for the Group Medical Visit and Nutrition Intervention Possibilities

Topic or Focus	Nutrition Education/Modifiable Lifestyle Factor
Test specific: Lipids, or advanced lipids, coagulation—INR, blood sugars …	Foods and diet changes that improve lipids and blood sugars, or affect coagulation. The addition of herbs/spices that impact the process underlying the abnormalities in the laboratory (co-decided by the clinician and the nutritionists)
Imaging or procedure specific: Carotid intima media thickness, colonoscopy	Ways to impact inflammation and plaque. Helping people understand root cause of the inflammation and how to keep your vessels healthyWays to help restore the bowel flora balance with food and fermented foods and how to help your bowel be healthy
Process specific: Inflammation, detoxification, malabsorption, autoimmunity, one-carbon metabolism, or methylation	Discuss/inform the role of macronutrients, micronutrients, and food choice and preparation that improves:-Inflammation (EFA, fermented foods, limiting simple carbohydrates, adequacy of antioxidant rich foods)-Detoxification or biotransformation (adequacy of color rich vegetables rich in antioxidants, minerals, vitamins for phase 1 biotransformation and adequacy of protein and sulfur amino acid containing foods for phase 2 biotransformation)-Malabsorption: discuss timing, volume, combination of foods and preparation that influences absorption. The effect of over the counter medications on absorption-Autoimmunity or allergies: foods and nutrients that help balance immunity; foods rich in vitamins D and A, and the minerals zinc and iron-One-carbon metabolism can focus on the interplay of adequacy of B vitamins, essential fatty acids, and mineral rich foods that form the foundation of adequate one-carbon metabolism balance in a person with any of the chronic illnesses associated with an imbalanced one-carbon metabolism common in primary care
Condition specific: Cardiometabolic syndrome or any of its components: hyperglycemia, hyperlipidemia, hypertension, high body fatObesityArthritisAsthmaChronic Obstructive Pulmonary Disease	A single class or a series of four or more, which helps provide a consistent group membersDetermine the many aspects of food, diet, nutrition, and lifestyle that are focused on during the session or series. All the examples of condition-specific chronic illnesses can be improved by changing the diet in a person-specific fashion
Modifiable lifestyle components: sleep, movement and exercise, emotions—stress, relationship with yourself, others, and food, diet and nutrition	All the modifiable lifestyle factors are influenced by food choice and lifestyle balance. Sleep and exercise or movements are more successful with adjustment of diet and food choice. Emotions are affected by caffeine and alcohol intake, which change nutrient requirements. Relationships with food and others are affected by the habits of food choice and consumption patterns. Disordered eating influences all chronic disease conditions
Specialty specific: Promoting healthy balanceExample:Obstetric group medical visits: preconception, first, second, third trimester, followed by lactation and introduction of foods to the newborn and infant	Each of the different stages of pregnancy can have different foods and nutrients emphasized. This is a very empowering opportunity for clinician, nutritionist, and patient alike, impacting pregnancy outcome and transgenerational health (Stone)

EFA, essential fatty acids.

their consumption of processed foods, manage their weight, reduce their intake of sodium, increase their intake of potassium, and increase their intake of vitamins, minerals, antioxidants, and other anti-inflammatory agents in a whole-food plant-based eating pattern.

The following is a list of tips and tricks to empower providers and patients to do more cooking at home.

Basic Tools and Kitchen Set Up

The pantry of a healthy kitchen should include good vinegars, spices, fresh herbs, olive oil, and other healthy oils. No-salt or reduced-salt canned products, real food salt substitutes, and assorted whole grains are also suggested. When using salt, use it as a finisher, preferably a flake sea salt (fleur de sel), so you do not have to use as much. Basic culinary skills include how to hold a knife and sharpen it and proper cooking of vegetables.

Cooking techniques include braising, roasting, grilling, steaming, and sautéing.

Braising is searing (usually meat) in some form of fat, corn oil, or olive oil, then simmering at a low temperature in a small amount of liquid or stock. Submerge the protein halfway in a covered vessel. The cooking liquid is reduced throughout the cooking process and is used as a base for the sauce for the item. Roasting is cooking by dry heat, such as an oven, convection oven, or open fire. Grilling is cooking food items by a radiant heat source below the food item. The equipment can be gas, electric, charcoal, or wood. Steaming is cooking an item with a vapor bath created by boiling water or stock. Sautéing is cooking in a small amount of fat quickly in a sauté pan on the stove top or range.

Useful ratios are given in the following subsections.

Stocks and Sauces

Vegetable Stock Basic Formula—Yield: 1 Gallon

- Assorted non-starchy vegetables: 3 lbs. to 5 quarts water, bring to a boil, and simmer for one hour. (Do not use broccoli and asparagus.)

Tomato Sauce—Yield: 1 Gallon

- 1 fl. oz. of olive oil
- 3 tbsp. of fresh minced garlic
- 2 oz. of fresh basil or 1 oz. dried basil
- 13 lbs. of fresh tomatoes or 6 quarts of w/ canned liquids
- Salt and black pepper as needed

Basic Vinaigrette

- 1.5 quarts of oil (favorite extra virgin olive oil)
- 16 fl. oz. of vinegar (whatever vinegar you prefer)
- 1 tsp. of Dijon mustard (aids in emulsifying process)
- Salt, pepper, other seasonings such as fresh herbs

1. Combine the vinegar and desired seasonings.
2. Slowly whisk in all oil until an emulsification is formed. (If too thick, slowly add cold water to adjust.)
3. Serve immediately or store up to seven days.

Note: a blender or hand mixer can also be used, using the same steps and ingredients.

Grains

Method—combine with 1 part rice (rinse, drain well before cooking)

- Par-boiled or Carolina rice—basic formula (by volume)
- Stock, seasoned 1.75 or 2 parts
- Jasmine rice: Rinse, drain well, use 1.5 parts water or stock
- Brown rice basic formula (by volume): Stock, seasoned 2.25 or 2.5 parts
- Wild rice basic formula (by volume): Stock, seasoned 3 parts
- Risotto (by volume): Stock, seasoned 3 parts. Add risotto in three stages
- Cous Cous (by volume): Stock 1.25–1.5 parts

1. Coat grains with olive oil.
2. Pour hot stock over grains, cover, let sit five minutes.
3. Fork through to separate grains.

- Firm polenta or farina grits (by volume): Stock 5 parts; polenta or grits 1 part

1. Add 0.5 part more stock for softer polenta or grits.

- Hominy grits (by weight) to hold shape: Stock 4 parts; hominy grits 1 part

Pasta Dough Basic Formula

- Durum Flour 0.5 lb.
- Semolina Flour 0.5 lb.
- Eggs, whole 4 ea.
- Oil 1–2 tbsp.
- Water 1–2 tbsp.
- Salt pinch

Healthy Substitutions

- 1 whole egg = 2 egg whites
- 1 cup of heavy cream = 1 cup of evaporated milk
- 1 cup of mayonnaise = 0.5 cup of mayonnaise and 0.5 cup of low-fat yogurt
- 1 cup of sour cream = 1 cup of low-fat yogurt plus 2 tbsp. buttermilk or fresh lemon juice

Meal/Menu Planning

1. Map out a menu weekly, before grocery shopping.
2. Try to incorporate local CSA/Farmers markets if accessible by location or monetarily feasible.
3. Use these incomplete protein combinations as substitutes for animal proteins: grains and legumes, lentils and brown rice, wholewheat pasta and beans, tortillas and beans, tofu and brown rice, hummus and wholewheat pita. These can be used for snacks, sides, or entrées.

Some guidelines for developing principles of healthy cooking should include sourcing and selecting nutrient-dense ingredients; always incorporating a variety of plant-based ingredients into every meal; and trying to always make your own stocks, sauces, and vinaigrette dressings. Following these guidelines allows you to control all ingredients that you consume.

Easy Recipes for the Hesitant Cook / Tips

1. Incorporate under-30-minute meals that are healthy and good for you.
2. Cooking in batches allows you to have enough for another meal.
3. Learn how to cook with alternate ingredients that are healthy yet have lots of flavor.
4. Experiment with different spices, seasonings, and herbs.
5. The use of "good" condiments that add flavor and not salt or sugar is important.

In conclusion, more and more doctors are using the kitchen as the first defense for someone to become healthier. Many doctors are starting with this remedy rather than medication. Dr. Walter Willet and Dr. David Eisenberg, both members of the Harvard School of Public Health, have been bridging the gap between schools of medicine and the culinary profession to create awareness for the younger up-and-coming doctors to be more aware of the correlation between medicine and healthy eating.

Culinary Resources

Creditable cooking websites and cookbooks:

- *Techniques of Healthy Cooking* by The Culinary Institute of America (CIA) February 4, 2013.
- *The Professional Chef* by The Culinary Institute of America (CIA) September 13, 2011.
- *Cooking for Special Diets* by Katherine Polenz and The Culinary Institute of America (CIA), March 10, 2014.
- www.mass.gov/massgrown is an example for the state of Massachusetts.

I would assume that all U.S. states have these resources on their State websites.

- www.eatingwell.com
- www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/

27.4 SUMMARY

Food plays a significant role in everyone's lives, and different practices and behaviors of eating psychology can be bound to different cultures. The nutrition prescription and using behavioral techniques to guide patients to adopt and sustain nutritious and delicious eating patterns require education for the patient and the provider. Learning about the kitchen, cooking, cultural norms, family values, motivation, obstacles to change, strategies around obstacles, patients' strengths, and the power of plants; recognizing whole foods; knowing about healthy portions; and using the COACH Approach ™ allow clinicians to successfully counsel patients on adopting and sustaining healthy nutritional practices throughout their lives. Nutritional counseling can be done one on one or in group visits. The important factors are to educate both provider and patient on the basics of a healthy diet that is focused on whole foods and is predominantly plant based. Behavioral approaches in enhancing nutrition practices are crucial for all groups in order to mitigate the nutrition gap and enhance health promotion.

Once people understand the guidelines for healthy eating, then coaching them to create SMART goals and keep on track with vegetables, fruits, whole grains, nuts, seeds, legumes, and other healthy sources of protein is the key to maintaining a healthy eating pattern for a lifetime. Using psychology and evidence-based approaches from a practitioner and patient perspective creates self-efficacy, which is critical for long-lasting behavior changes. As chronic disease is on the rise, nutritional needs must be met as a therapeutic lifestyle intervention. Through updating health professionals on evidence-based nutrition practices and the evolving Dietary Guidelines, dietary misinformation will be mitigated, and health promotion will be enhanced.

CLINICAL APPLICATIONS

- Optimal nutrition intervention is the cornerstone of an effective lifestyle medicine prescription.
- By taking into consideration the various cultural factors involved in nutritional practices, the clinician will be able to better design a lifestyle medicine program that patients will find easier to adhere to.
- Implementation of effective health coaching can promote patient compliance with dietary change.
- One way to provide efficient, cost-effective nutritional counseling is through group medical visits.
- Dietary excellence first starts in the kitchen. Therefore, a working knowledge of basic culinary skills is key to building healthy lifestyle habits.

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28 Behavioral Approaches to Manage Stress

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KEY POINTS

- The stress response and the relaxation response are innate protective and adaptive responses that initiate physiological and biochemical reactions in the body. The stress response can become harmful with prolonged exposure, but the relaxation response can help reverse the effects of allostatic load.
- Building resilience, practicing Mind–Body Therapies (MBTs), and making positive behavioral modifications can all help counteract the stress response, elicit the benefits of the relaxation response, and improve coping with perceived stress.
- Teaching patients to implement MBTs can help improve their adaptation to stress and is an essential treatment option for patients of all ages and health states.

28.1 THE STRESS RESPONSE AND RELAXATION RESPONSES

Stress is defined as "the non-specific response of the body to any demand for change."[1] Stress can be acute or chronic. The stress response is the physiological response, through activation of changes from the molecular to the behavioral domains.[2] A person's perception of stress is influenced by their genetic predispositions, life experiences, and environmental factors.[2] Over time, the brain initiates a cascade of both physiological and behavioral responses, leading to an increase in allostatic load (Figure 28.1).[3]

This is characterized by a cascade of immune, endocrine, and neural mediators, leading to systemic effects on organ systems.[4, 5] Chronic activation of the stress response is related to numerous chronic diseases and diminished quality of life. These non-communicable diseases (NCDs) are further fueled by damaging health behaviors under chronic stress. NCDs represent the most important global health challenge of the 21st century in terms of disease burden and mortality.[6] Stress is modifiable and is a desirable target for health interventions.

The relaxation response is a wakeful hypometabolic physiologic state that can be voluntarily elicited by many mind–body practices and counteracts the negative effects of the stress response. Figure 28.2 summarizes the physiological correlates of both the stress and relaxation response processes.[5]

28.1.1 Physiological Responses

The stress response is characterized by increased oxygen utilization, increased glucose uptake, and increased respiratory rate.[5] Through activation of the body's sympathetic nervous system, there is bronchodilation and vasoconstriction, leading to increased cardiac output, blood pressure, heart rate, and total peripheral resistance.[3,5,7–11] Oxygen-rich blood is shunted to essential organs[3,5,7–11] by the vascular system.

The relaxation response is characterized by predominance of the parasympathetic nervous system, resulting in decreased respiratory rate, oxygen consumption, and carbon dioxide elimination.[3,5,7–11] In addition, there is a reduction in cardiac output, with lower heart rates and blood pressure, as well as increased heart rate variability.[10,12–16]

28.1.2 Neurohormonal Pathways

The stress response is characterized by a cascade of biochemical changes, which are characterized by two pathways—the sympatho-adreno-medullary axis (SAM) and the hypothalamic-pituitary-adrenal axis (HPA).[3,5,7, 17] The SAM axis is rapid-acting, causing the adrenal medulla to distribute the powerful catecholamines epinephrine and norepinephrine, which activate the "fight or flight" response. This in turn, triggers the organ systems to respond by increasing heart rate, respiratory rate, oxygen consumption, and blood pressure.[3,5,7,17] In the other pathway, the anterior pituitary gland secretes adrenocorticotropic hormone (ACTH). This signals the adrenal cortex to release the hormone cortisol. The flow of cortisol initiates glucose production in the liver, elevating the body's glucose levels, which is necessary to yield adenosine triphosphate (ATP)[3,5,7,17] for utilization by cells.[16] The stress response also triggers the immune system to release pro-inflammatory cytokines, including interleukin (IL)-1 and tumor necrosis factor (TNF)-α.

Chronic stress is significantly associated with higher oxidative stress, lower telomerase activity, and shorter

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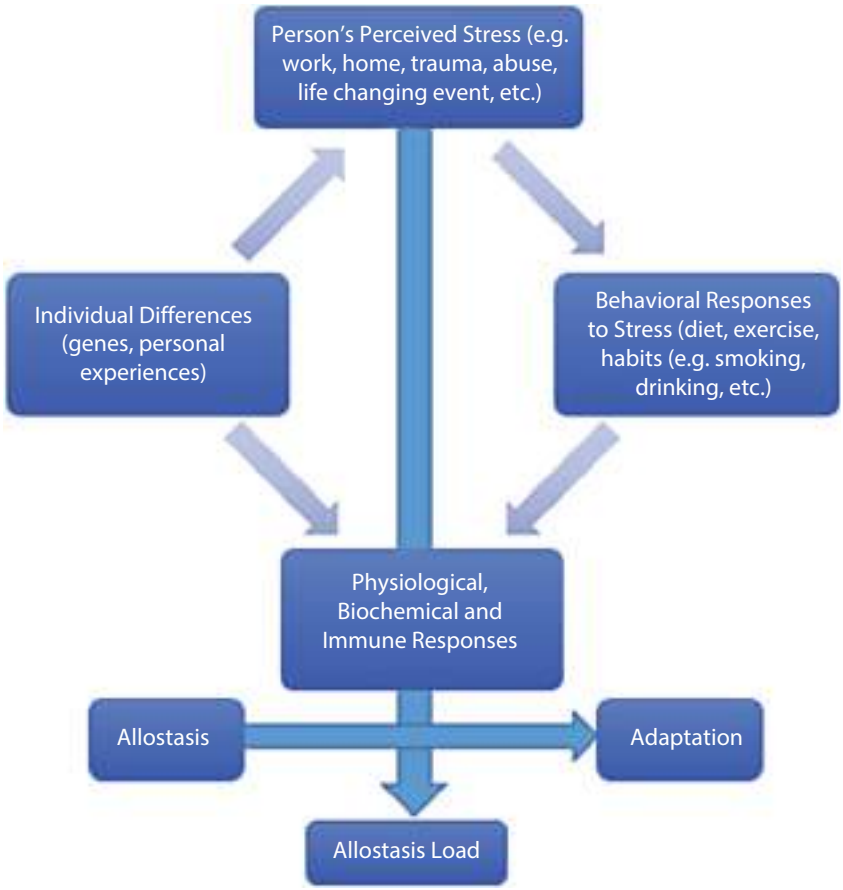


FIGURE 28.1 Moving from allostasis to allostatic load. (Adapted from McEwen, B.S., ***N. Engl. J. Med***., 338(3), 171–179, 1998.)

telomere length, which are known determinants of cell senescence and longevity. Telomere shortening is a risk factor for numerous diseases and may be a general biomarker of aging. Recent research points to the crucial roles of telomeres and telomerase in cellular aging and potentially in disease.[18]

The relaxation response elicits HPA changes, impacting the release of cortisol from the adrenal cortex.[13,20–24] It also increases nitric oxide in the vasculature.[4,22] Nitric oxide is an important biomarker that plays a role in vasodilatation and decreasing blood pressure.[4,5] The relaxation response also has immune benefits, showing an increase in lymphocyte[25] and natural killer cell activity and proliferation,[26–28] and an increase in nitric oxide[5,29] and serum IgA levels.[30] Elicitation of the relaxation response has demonstrated changes in the expression of more than 1500 genes.[4]

28.2 BUILDING RESILIENCE

Resilience is a dynamic trait that reflects an individual's ability to cultivate adaptive behaviors, thereby counteracting the negative effects of stress and returning to a state of well-being.[31,32]

Resilience is built by decreasing the stress response, promoting the relaxation response, and fostering growth enhancement. This model is summarized in Figure 28.3.

Mind–body therapies (MBTs) are essential in decreasing the stress response and activating the relaxation response. MBTs include practices from different cultural traditions. They are believed to share a common physiology as described by the relaxation response. MBTs have been shown to produce measurable reductions in levels of perceived stress,[33–47] increase positive emotions, and decrease levels of anxiety and depression.[15,22,48–58]

Table 28.1 summarizes research using MBTs in disease treatment. Helping build resilience through growth enhancement is another essential component to managing chronic stress.

The effects of stress are relative to individual experience and perception. Therefore, when patients are helped to develop stress awareness, this personal awareness allows an individual to better identify the negative effect of stress and antidote it with positive coping strategies, positive perspectives, and positive behaviors. Evidence suggests that higher positivity longitudinally predicts trait resilience[60] and is in turn associated with a sixfold decreased risk of depressive symptoms[61] and reduced stress.[62] Effective coping, alongside the regular practice of elicitation of the relaxation response, leads to more resilience.

As patients become secure in their awareness of the stress response, MBT practice, and positive coping strategies, recognition is important. Growth enhancement

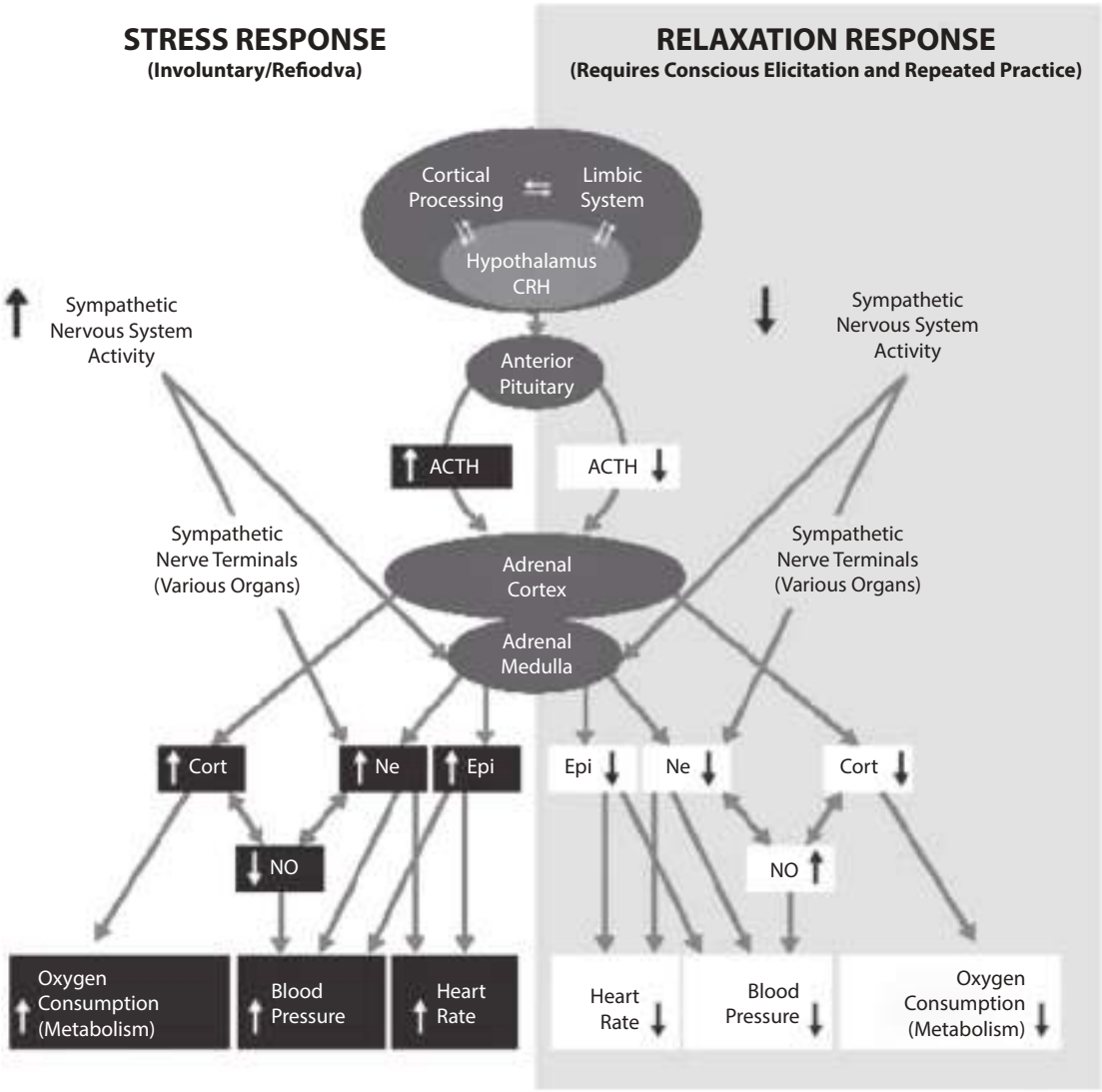


FIGURE 28.2 Comparative impact of the acute stress and relaxation responses: central and peripheral nervous system activities. (From Dusek, J.A. and Benson, H., ***Minn. Med.***, 92(5), 47, 2009.)

should be praised and reinforced by providers. This builds resilience.[33]

28.3 MIND–BODY THERAPIES

MBTs are found across many cultures (Figure 28.4)[17] Clinicians can provide prescriptions for these MBTs. Patients should be encouraged to explore different MBTs to determine which practice(s) they are comfortable with. The patients should also be encouraged to develop a regular practice. Figure 28.5 gives a general overview of tips to help patients develop a regular practice.

28.3.1 Meditation

Herbert Benson originally coined the term *relaxation response* and advised that it can be invoked by two steps:[1] repetition of a word, sound, phrase, or movement, and[2] disregarding other thoughts when they come during the practice. Meditation has been practiced for millennia across many cultures. It has been shown to have health benefits, including decreased blood pressure,[63,64] improved sleep,[62] and reduced anxiety and stress.[66–69]

28.3.1.1 Breath Awareness

Breath awareness is a single-pointed focus meditation. It is the practice of maintaining focused awareness of the breath. This is one of the easiest and most widely used meditation practices. This is exemplified in Figure 28.6.

28.3.1.2 Body Scan

The body scan is a great tool to notice any areas of tension, tightness, and discomfort within the physical body. Chronic pain patients noticed significant reduction in pain with a ten-minute body scan intervention.[73] Progressive muscle relaxation is another tool to help identify the difference

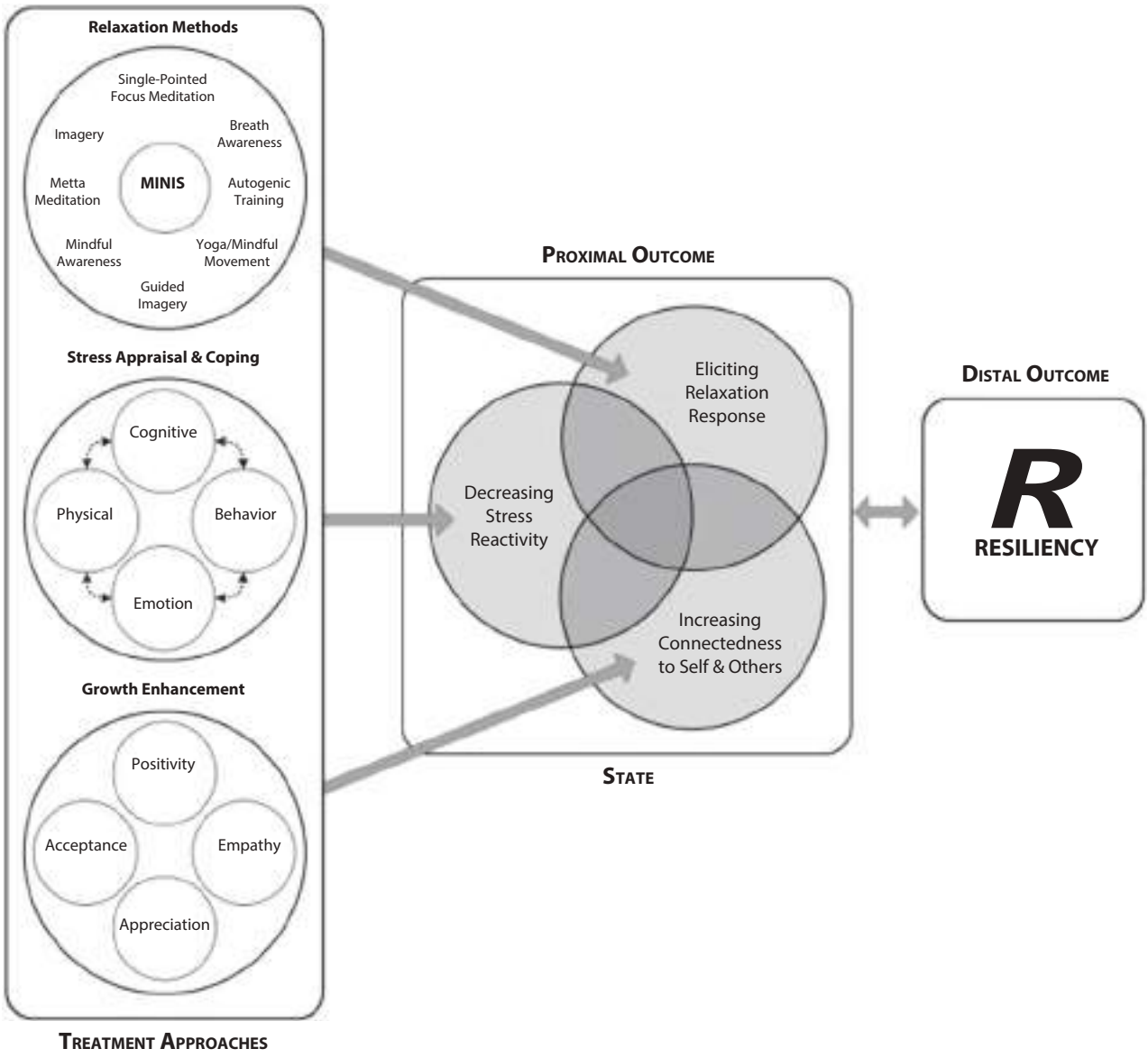


FIGURE 28.3 The relaxation response: the Relaxation Response Resiliency Program (3RP).

between tension and relaxation throughout the body. These practice techniques are described in Figures 28.7 and 28.8.

28.3.1.3 Guided Imagery

This MBT allows the use of imagination. Patients who use this while having surgery have shown higher pain tolerance, less pain and pain medication use, as well as less anxiety and lower heart rates.[72] The patient participating in imagery can sustain focus on an experience but change it in their imagination to reflect a more positive perspective or experience. The patient's own imagination can be a stress management tool by transforming negative memories and mental images[74] through visualizing growth in personal and/or social domains.[75] Imagery can reframe emotional responses to visual depictions of stress, help overcome negative memories of the past and stressful situations in the present, and prepare for anticipated stressful events in the future. A memory can be revised to reflect a more pleasant experience, which deactivates the stress response related to the experience. Figure 28.9 provides a script for guided imagery.

28.3.1.4 Contemplation and Prayer

Another way to elicit the relaxation response is contemplation and prayer. The major health benefits associated with prayer are increased sensation of relaxation and feelings of peace.[76] Many patients may resonate more with the idea of prayer, as it has been practiced throughout almost every religious tradition. There is sustained focus on an intention or positive outcome, and it requires stillness and attention on the intention. Figure 28.10 provides an example activity to guide patients through this practice.

TABLE 28.1
Conditions Treated with Mind–Body Therapies

Health Condition	Types of Practice	Intervention Effects	Research Quotation
Hypertension	YogaMeditation	The mindfulness group had lower clinically measured systolic blood pressure (SBP), 24-h SBP, at-rest SBP, and diastolic BP values.[8]	Ponte Márquez PH, Feliu-Soler A, Solé-Villa MJ, et al. Benefits of mindfulness meditation in reducing blood pressure and stress in patients with arterial hypertension. *Journal of Human Hypertension* 2019; 33(3): 237–247. doi:10.1038/s41371-018-0130-6
Surgical Pain	Qigong	Improvements were observed at 12 weeks in physical well-being and emotional well-being in BCS	Osypiuk K, Ligibel J, Giobbie-Hurder A, et al. Qigong Mind–Body Exercise as a Biopsychosocial Therapy for Persistent Post-Surgical Pain in Breast Cancer: A Pilot Study. *Integr. Cancer Ther*. 2020; 19: 1534735419893766. doi:10.1177/1534735419893766
Insomnia	Yoga	Effective treatment of insomnia	Khalsa SBS, Goldstein MR. Treatment of chronic primary sleep onset insomnia with Kundalini yoga: a randomized controlled trial with active sleep hygiene comparison. *Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2021; 17(9): 1841–1852. doi:10.5664/jcsm.9320
Irritable Bowel Syndrome	Acupuncture	Acupuncture and osteopathic medicine may be beneficial for overall IBS symptoms	Amsallem F, Sanchez S, Armoiry X, Mion F. Effectiveness of Non-Pharmacological Interventions for Irritable Bowel Syndrome: A Systematic Review. *Evidence-based Complementary & Alternative Medicine (eCAM)* November 2021: 1–10. doi:10.1155/2021/4404185
Lower Back Pain	YogaMBSRTai Chi	Practice moderately associated with alleviation of pain	Morone et al. 2016. A mind–body program for older adults with chronic low back pain: A randomized clinical trial[146].
Anxiety	MBSR	Mindfulness-based stress reduction could decrease anxiety and depression symptoms	Samira Masumian, Shahrbanoo Ghahari, Zeinab Bahram Beigi, Ali Asghar Asgharnejadfarid, Hooman Yaghmaeezadeh. The Effectiveness of Mindfulness-based Stress Reduction (MBSR) in Reducing of Depression, Anxiety and Quality of Life in Women with Generalized Anxiety Disorder. *Journal of Research in Medical and Dental Science* 2019; 7(1): 71–76. Accessed April 17, 2022

28.3.1.5 Loving Kindness

Loving-kindness meditation is a practice that helps bring more peace into the mindset and life of the individual. Patients who use this technique showed more positive emotions, decreased depression, more social supports, and decreased symptoms.[77] The practice allows individuals to bring more compassion, empathy, and kindness into their daily lives. By teaching the individual to sit in quiet stillness and send out feelings of love, kindness, compassion, and well-being toward others, it deactivates the stress response. When done toward themselves and others, it promotes positive emotions, which increases a sense of personal well-being and overall compassion for others.

28.3.2 Movement

Yoga and tai chi are two modalities that are highly associated with well-being, reduced perceived stress, increased physical fitness, and many positive health outcomes.[75–79] There are some safety concerns for practicing yoga and tai chi, but these are minimized when taught by a certified instructor.[80,81] As with all movement-based practices, it is advised that women who are pregnant, and people with certain medical conditions, such as high blood pressure, glaucoma, and sciatica, should modify or avoid certain postures, especially when starting a yoga or tai chi routine.

28.3.2.1 Yoga

Yoga is a moving meditation, coupling the breath with various body postures, that elicits the relaxation response. Evidence has shown it may be particularly helpful for those suffering from back pain, migraine, mental health concerns, and some gastrointestinal and cardiovascular conditions.[79] Yoga may help alleviate symptom intensity and severity directly through physical movement as well as indirectly through psychological mechanisms.[72] There are many styles of yoga, ranging from low-intensity restorative and Hatha practices to high-intensity vinyasa or ashtanga, each with its benefits and limitations.[85,86] It is important to review the differences between styles to make a recommendation best suited for the patient's health status and treatment goals.

28.3.2.2 Tai Chi

Tai chi is another moving meditation that connects controlled movements of the body with the breathing of the practitioner. It is a Chinese martial art that focuses on the balance of contrasting movements to create physical and

TABLE 1. Example Techniques for Eliciting the Relaxation Response

Technique	Concept	Mechanism
Breath awareness	Shift from shallow breathing to abdominal breathing. Draw air deep into lungs using even breath.	Improve ability of respiratory system to produce energy from oxygen and remove waste.
Self-hypnosis	Narrow consciousness without completely losing awareness, to allow suspension of disbelief and experience of thoughts and images as real.	Facilitates both focused, intense mental activity and state of relaxation simultaneously.
Guided imagery	Use imagination to refocus mind on positive, healing images.	Negative thoughts influence feelings and behavior, and exacerbate physical symptoms. Thoughts become reality (i.e.. you are what you think you are). Therefore, use imagination to reduce subjective stress and to treat physical symptoms.
Autogenic training	Use verbal commands that suggest bodily warmth and heaviness in limbs.	Word phrases suggest relaxation to the unconscious mind, which manifests the desired responses in the body. Aims to reverse "flight or flight" response during physical or emotional stress by promoting relaxation of the voluntary arm and leg muscles, inducing peripheral vasodilation, and normalizing cardiac activity.
Progressive muscle relaxation	Alternately tense and relax different muscle groups, to better distinguish between these two states.	Based on premise that the body responds to anxiety-provoking phenomena with muscle tension that increases subjective anxiety. Muscle relaxation reduces physiologic tension and, therefore, blocks the subjective anxious response.
Transcendental meditation	Engage in attempting to anchor attention nonjudgmentally on a silent mantra.	Negative emotion cannot persist when focusing on something other than the target of the emotion. Habitual thought patterns lose influence when brought to conscious awareness. Present focus reduces emotional extremes. Meditation also slows sympathetic nervous system activity.
Mindful awareness	Observation or attention to phenomena in the moment nonjudgmentally as they enter awareness	Strong emotions become manageable by focusing on sensations rather than the content of emotional thoughts.
Yoga	Movement meditation correlated with the breath.	Yoga is a comprehensive system of practices for physical and psychological health and well-being, and incorporates multiple techniques including physical postures/exercises, breathing exercises, and meditation/concentration techniques. As an integrative discipline, yoga takes advantage of the simultaneous application of its component techniques, all of which contribute to eliciting the relaxation response.

FIGURE 28.4 Example techniques for eliciting the relaxation response.

mental harmony. Like yoga, there are many styles of tai chi that differ slightly in technique and methodology, but all may help to manage pain and arthritis, mental health, cardiovascular disease, and neurological conditions.[78, 79] Individuals with Parkinson's disease, fibromyalgia, rheumatoid arthritis, and osteoarthritis may benefit from practicing tai chi, as it been shown to ease symptom severity and disease-specific pain, and increase balance, stability, and overall quality of life.[87–92] Reports indicate long-term efficacy of tai chi, with benefits persisting at three years' follow-up.[93]. Though it is well suited for all ages, the low-impact, slow-paced qualities of tai chi make it an attractive option for elderly patients (Figure 28.11).

28.3.3 Gratitude

Gratitude is also shown to build resilience. It is the practice of showing appreciation for the present moment, people, experiences, and opportunities in our lives. When a patient is stressed, the foundation of appreciation is lost, and thoughts can become ruminating, worrisome, and negative.[94–96]

Gratitude has many physiological benefits, including a decreased heart rate.[94] Gratitude practice has also shown changes in the brain, including those associated with emotion self-regulation and self-motivation.[97] Another study found that those who practiced gratitude had decreases in symptoms of anxiety and depression, with effects lasting three months beyond the interventions.[98] Expressing gratitude has been shown to reduce levels of perceived stress, anger, and burnout,[50,94–96,99–108] and increase feelings of well-being[95] and happiness. Practicing gratitude has been associated with an overall sense of gratefulness for loved ones, life, and social supports,[100,108] as well as leading to a more positive affect,[109] positive reframing, acceptance, humor, and better coping.[102]

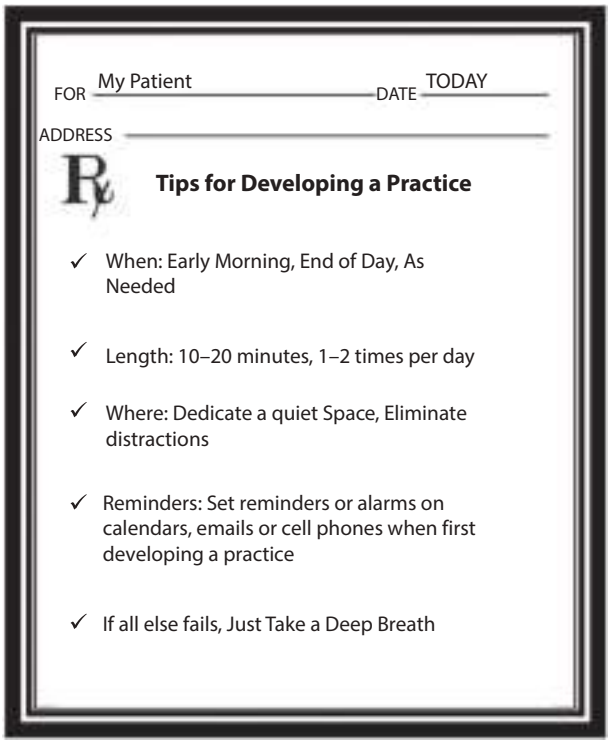


FIGURE 28.5 Tips for developing a meditation practice.

28.3.3.1 Practicing Gratitude

People who express gratitude regularly are more likely to respond to stressors with appreciation instead of negative emotions. It helps build a more positive perspective in those who have a regular practice.[94–96] Some clinicians are using gratitude as a part of treatment for anxiety, depression, and anger.[99–103,105–107,110]

Building a practice of gratitude requires expressing appreciation consistently and intentionally. The practice can be done through journaling, writing letters, talking to family and friends, and even sharing on social media. The more specific one is regarding the appreciation, the easier it is to practice. See Figure 28.12 for tips to develop a practice of gratitude.

28.3.4 Building a Positive Perspective

Building a positive perspective is a critical process in the management of stress. By building a positive perspective, individuals may better manage stress in the moment and subsequently withstand stress in the long term by using positive coping strategies and enhancing resilience.

Barbara Fredrickson (2004) developed the broaden-and-build theory of positive emotions.[111] Positive emotions are essential for optimal functioning, including building resilience, improving attention, fostering creativity, disengaging persistent negativity, improving interpersonal relationships, becoming more resourceful, increasing overall well-being, and ultimately, allowing the person to move beyond survival and into a state of thriving. Positivity also helps with emotional regulation and the ability to be more adaptive when coping with negativity and stress.[112]

Humor is essential to building a positive perspective, helping to combat and manage stress. Laughter and humor are some of the most commonly used and easily accessible self-care practices.[113] Individuals with a high sense of humor report less anxiety, view stimuli as less stressful, and are more likely to use cognitive reappraisal and problem-solving coping strategies.[114] Humor catalyzes the process of appreciation and acceptance, especially self-enhancing (laughing at oneself or making light of stress) and affiliative (making light of relatable experiences with others) humor. It is important to understand both your own and the patient's style of humor. Encourage adaptive humor and reframe any maladaptive humor, such as self-defeating and aggressive/sarcastic styles.

28.3.5 Adaptive Coping Strategies

Patients who experience stress often reach for maladaptive coping strategies that may be harmful to them. Helping patients develop more adaptive patterns will also help them secure high trait resilience, measured by self-efficacy, optimism, humor, and coherence (Table 28.2). Adaptive copers have longer, happier, and less stressful lives.[115] An important component of developing more positive and beneficial coping strategies involves cognitively reframing the patient's response to stress. Cognitive reappraisal is an adaptive strategy that aims to regulate emotions in times of stress by adjusting thought, interpretations, and responses to the stimuli.[117] It is a tool to help edit negative thoughts to shift thinking from a stress reaction to adaptive coping (Table 28.2 gives a few examples of positive coping traits, and Table 28.3 gives adaptive and maladaptive examples of problem-focused and emotion-focused coping strategies for managing stress). Using reappraisal has positive biological and physiological outcomes as well. Patients who practice cognitive reappraisal and change their perception of negative events can reduce stress by reframing psychological and physiological responses elicited by the stress response.[119]

28.3.5.1 Teaching Patients to Change Their Mind

Cognitive reappraisal is a mechanism of change used many in psychotherapeutic interventions, including cognitive-behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), Stress Management and Resiliency Training (SMART), and mindfulness-based cognitive therapy (MBCT). Healthcare providers can introduce cognitive reappraisal skills to patients, and the patients can use these in their daily life. Patients who use cognitive reappraisal skills report improvements in well-being, reduced stress, and improved health outcomes.[120]

The first step in using cognitive reappraisal is thinking of a situation or experience the patient deems "stressful." Then, help them identify the emotions that they feel related to the stressor. Every negative emotion is linked to an underlying belief that the patient feels is true. For example,

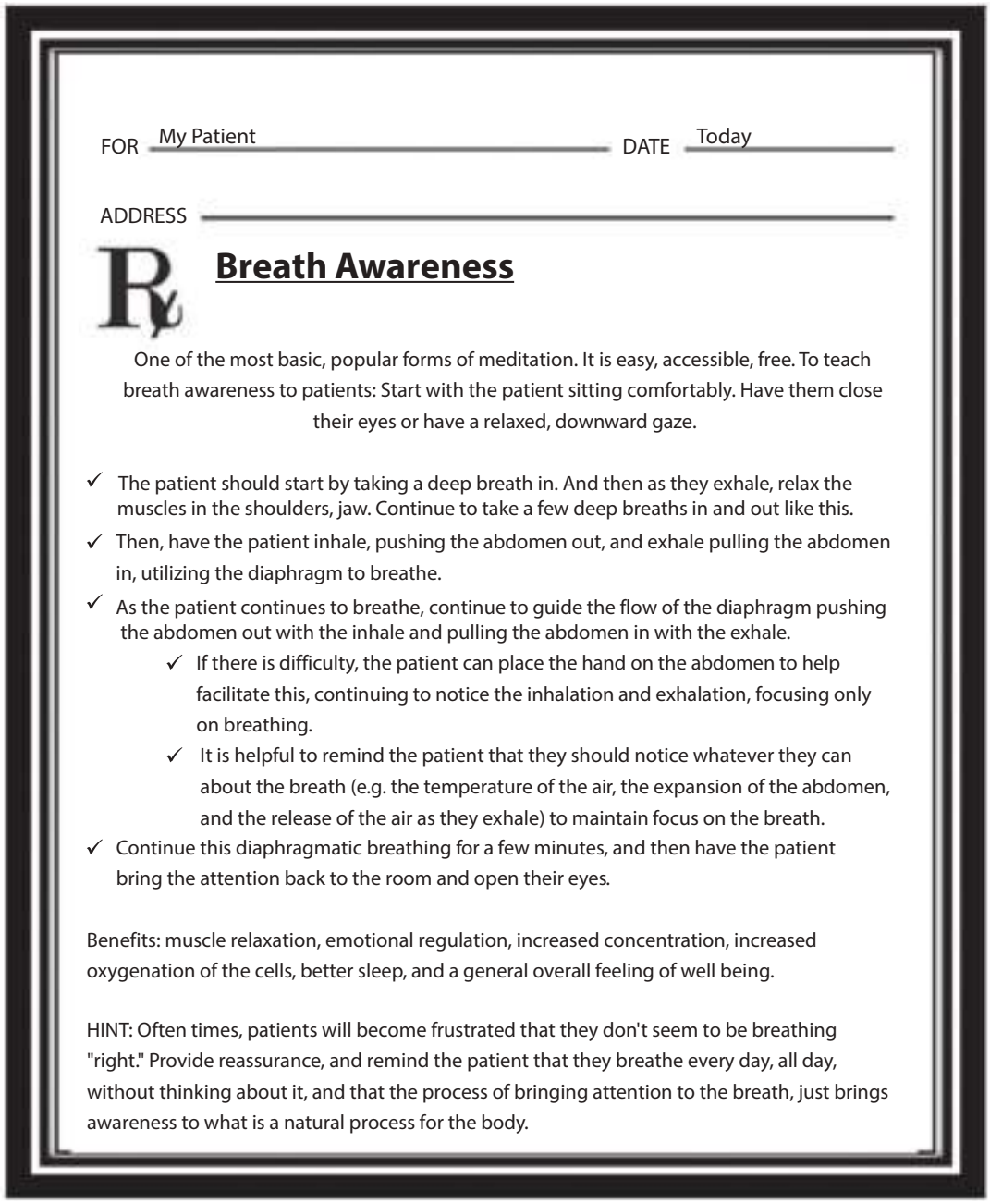


FIGURE 28.6 Tips for developing breath awareness.

the underlying belief of anxiety is "I am not safe, I am not in control." Once the emotions and underlying beliefs are identified, a reappraisal of the stressor can begin by recognizing the maladaptive, negative emotions and beliefs, and working to antidote them with positive emotion. An example could be helping a patient feel acceptance or forgiveness or surrender to the stressor. This helps them establish positive emotions with the stressor and in turn, reinforces the positive underlying belief of that emotion, releasing the negative emotion and thought patterns related to the belief. This allows the patient to move forward, reframing their thoughts to be more positive, beneficial, or motivational. Understanding this basic structure can help providers to clearly explain this process to patients and ensure its benefit (examples provided in Table 28.4). It is important to educate patients that changes take time and practicing these skills regularly will help them develop resilience over time. Tips to prescribe cognitive reappraisal to your patients can be found in Figure 28.13.

28.3.6 Other Lifestyle Modifications

Adjusting lifestyle behavior is the most basic method of making positive, lasting changes in stress levels. Healthy choices in nutrition, exercise, sleep, and habits can not only help to manage stress but also prevent and/or ease symptoms

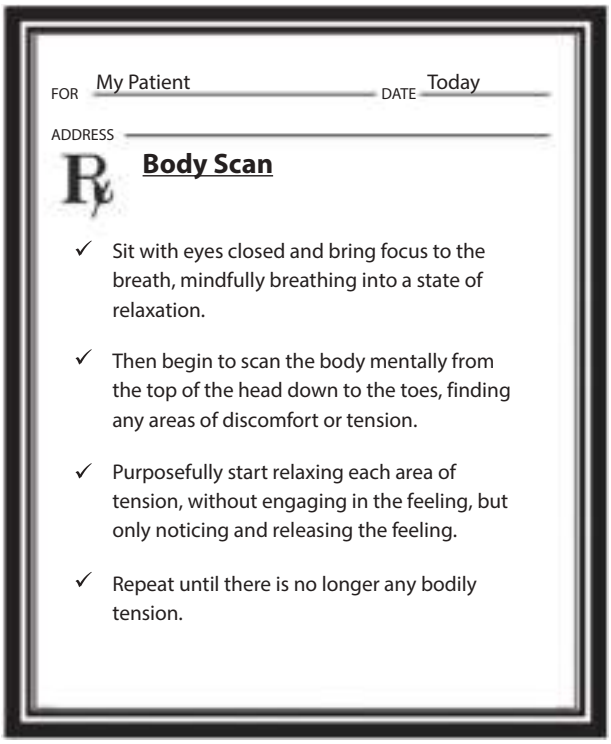


FIGURE 28.7 Tips for doing a body scan.

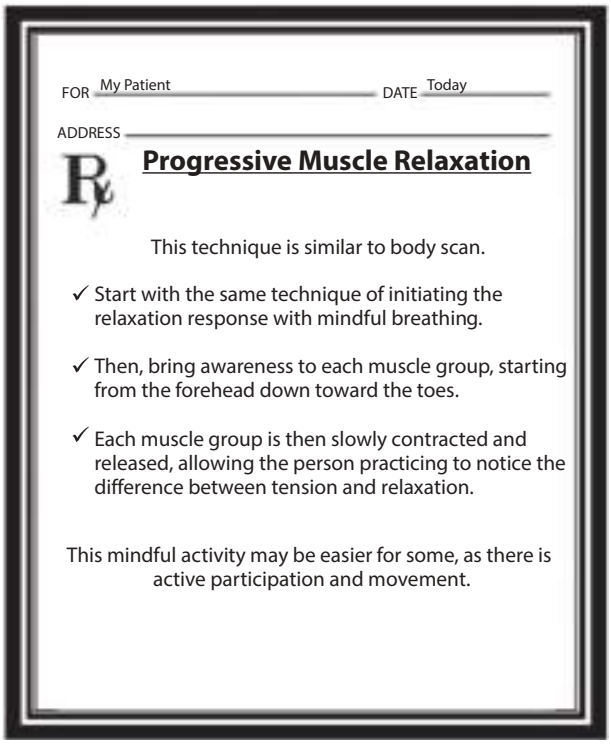


FIGURE 28.8 Tips for doing progressive muscle relaxation.

of chronic diseases.[121] These modifications are discussed in depth in other chapters of this book, but it is important to recognize that perceived stress can affect a patient's lifestyle choices. Personalized lifestyle changes can be prescribed as individualized self-care tools, as in Figure 28.14.

28.3.6.1 Nutrition and Stress

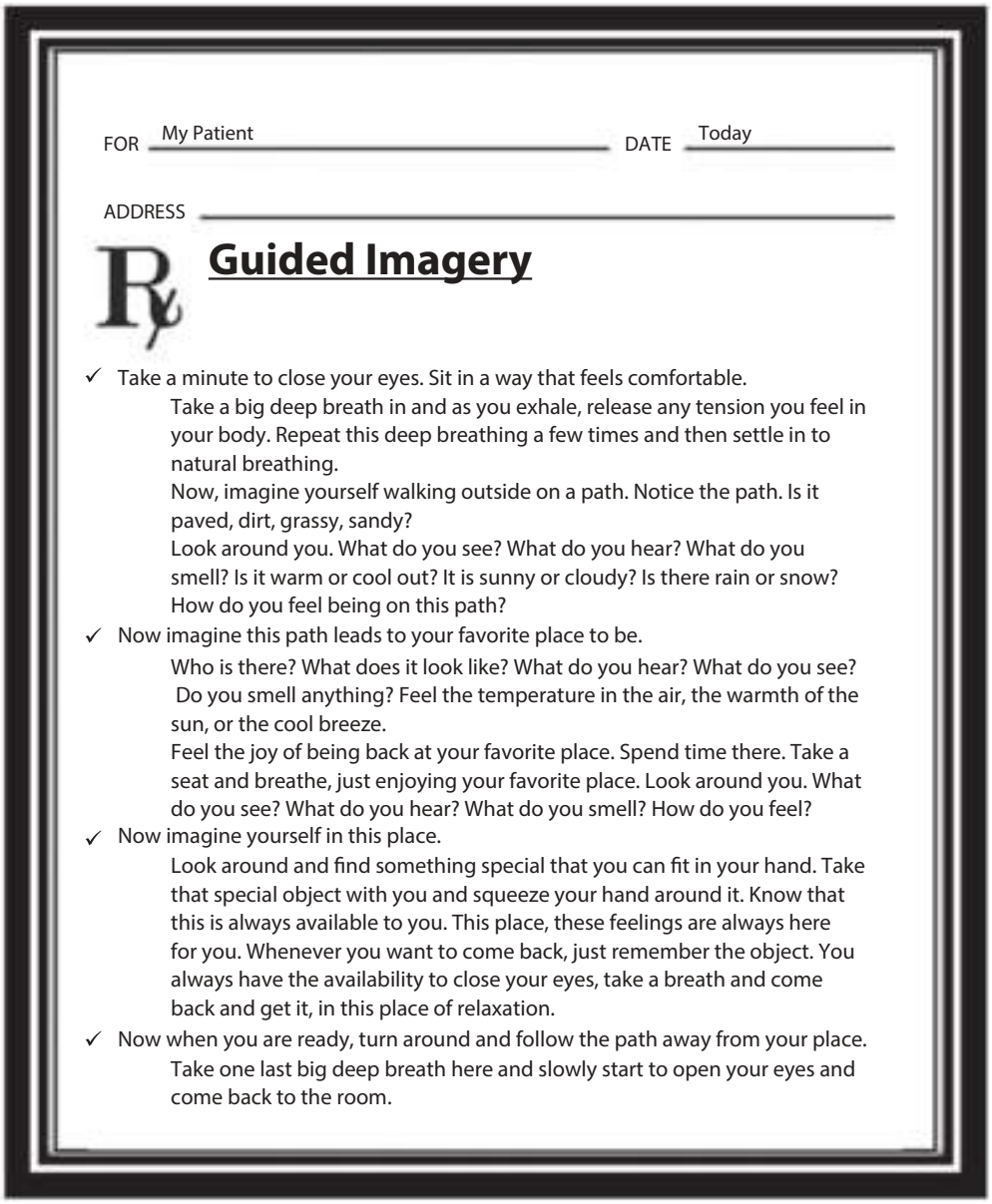
Proper nutrition is an important pillar of well-being; however, stressful stimuli can cause healthy eating habits to crumble. Stress impacts eating behaviors at physiological and neurobiological levels to such an extent that it can trigger the body's reward system to seek foods containing large amounts of sugar and fat, mirroring the response of an addiction.[122] This reward-seeking behavior is accompanied by potentially harmful alterations in glucose metabolism, insulin sensitivity, and other hormones related to energy balance.[123] Eating mindfully can ease the stress-related effects on eating behaviors. To eat mindfully is to fully engage the senses in the preparation and consumption of a meal or snack.[124] Taking the time to fully enjoy a meal reduces impulsive eating, increases enjoyment of food, and is related to preference for healthier food choices, especially for stressed individuals.[125,126] Figure 28.15 provides an example of prescribing mindful eating.

28.3.6.2 Sleep and Stress

Sleep is often sacrificed when schedules become overwhelming. Yet, this creates a harmful cycle: lack of sleep may contribute to a rise in stress, while a rise in stress can affect sleep. Stress may alter sleep patterns by increasing or decreasing the number of hours a person sleeps or feels that they need, resulting in negative consequences for cognitive and physical functioning. Sleep disturbance and deprivation are associated with inflammation, increased levels of cortisol, metabolic disruptions, and all-cause mortality.[127,128] Practicing good sleep hygiene promotes getting the necessary amount of sleep for mental and physical restoration. Sleep deprivation may lead to mood abnormalities, decreased cognitive functioning, weight gain, suppressed immune system, and exacerbation of pre-existing conditions.[129,130] According to the Centers for Disease Control and Prevention (CDC), adults are encouraged to sleep at least 7 hours, while teens need 8–10, and school-aged children need 9–12 hours per night. Toddlers and infants required the most, at 11–16 hours per 24-hour period.[131,132] Working with your patient to establish a consistent sleep schedule will improve the quality of their sleep and subsequent health.[130,128] See Sleep Tips (Figure 28.16).

28.4 THE ROLE OF TECHNOLOGY IN STRESS MANAGEMENT

Technology can be a great tool to help patients elicit the relaxation response. There are many smartphone applications, online websites, computer programs, audio recordings, and videos that can help patients develop a practice. Self-guided, online, asynchronous computer courses showed a significant decrease in stress and anxiety, as well as increasing cognitive attention.[57] Researchers are studying mobile apps and video conferencing for the treatment of stress, anxiety and depression,[42,57,133,134] and chronic pain.[135] Virtual reality programs are also being utilized as an educational


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℞ **Guided Imagery**

✓ Take a minute to close your eyes. Sit in a way that feels comfortable.
Take a big deep breath in and as you exhale, release any tension you feel in your body. Repeat this deep breathing a few times and then settle in to natural breathing.
Now, imagine yourself walking outside on a path. Notice the path. Is it paved, dirt, grassy, sandy?
Look around you. What do you see? What do you hear? What do you smell? Is it warm or cool out? It is sunny or cloudy? Is there rain or snow? How do you feel being on this path?

✓ Now imagine this path leads to your favorite place to be.
Who is there? What does it look like? What do you hear? What do you see? Do you smell anything? Feel the temperature in the air, the warmth of the sun, or the cool breeze.
Feel the joy of being back at your favorite place. Spend time there. Take a seat and breathe, just enjoying your favorite place. Look around you. What do you see? What do you hear? What do you smell? How do you feel?

✓ Now imagine yourself in this place.
Look around and find something special that you can fit in your hand. Take that special object with you and squeeze your hand around it. Know that this is always available to you. This place, these feelings are always here for you. Whenever you want to come back, just remember the object. You always have the availability to close your eyes, take a breath and come back and get it, in this place of relaxation.

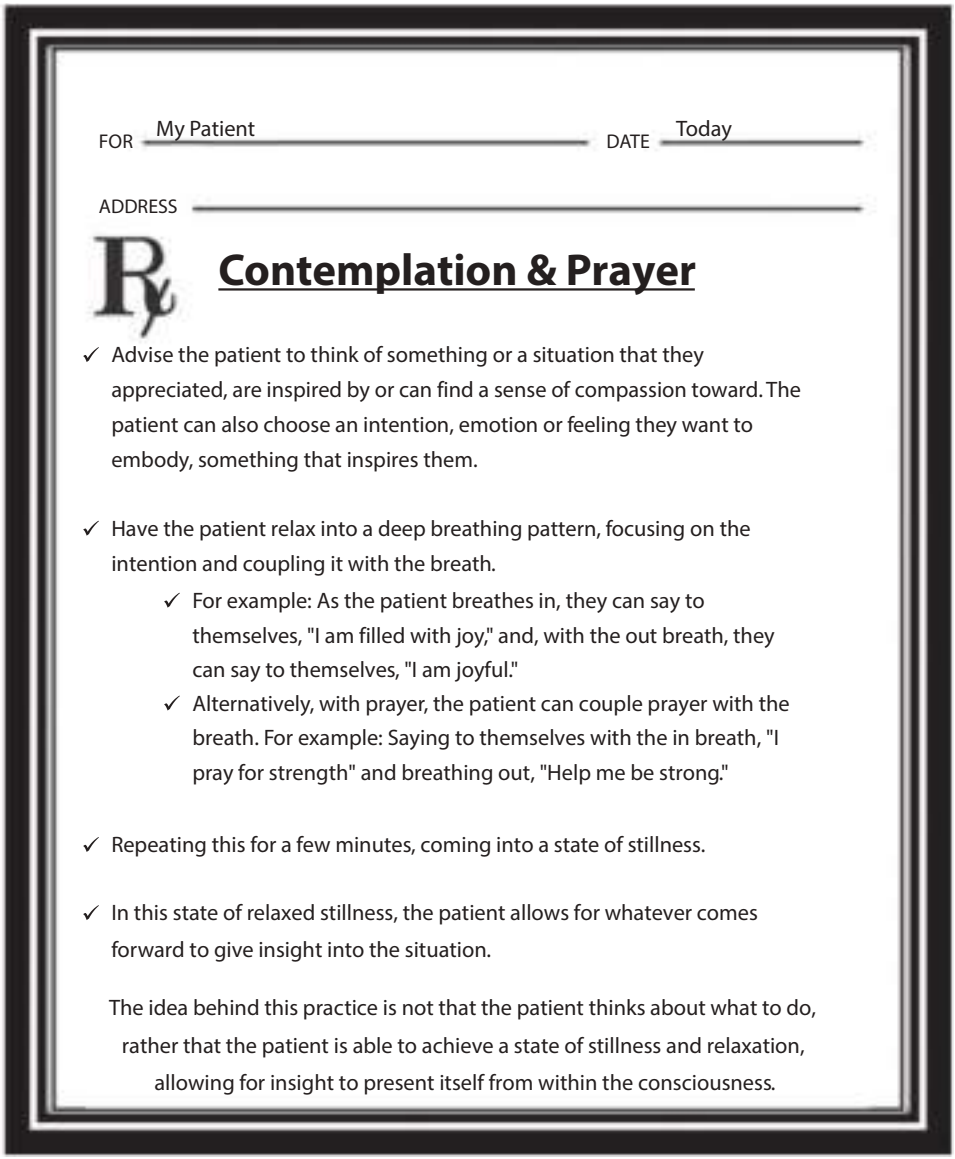
✓ Now when you are ready, turn around and follow the path away from your place.
Take one last big deep breath here and slowly start to open your eyes and come back to the room.

FIGURE 28.9 Tips for doing guided imagery.

TABLE 28.2
Protective Positive Coping Traits for Stress Management

Positive Coping Traits for Stress Management	
Self-efficacy	Confidence that one can do what is required to cope and that one's efforts will work
Optimism	Having positive expectations about the future
Humor	Being able to laugh at oneself or situations in a good-natured, light-hearted way
Coherence	Having a general orientation that sees life as meaningful and manageable

tool to elicit the relaxation response. These programs have a significant psychological benefit of lowered depression, anxiety, and perceived stress, as well as changes in physiologic markers.[55] A systematic review found considerable backing for the usefulness of online and virtual delivery of MBTs in decreasing perceived stress.[136] In addition, subjects responded positively, and with significant benefit, to an e-mail based gratitude intervention on increasing sleep


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℞ **Contemplation & Prayer**

- ✓ Advise the patient to think of something or a situation that they appreciated, are inspired by or can find a sense of compassion toward. The patient can also choose an intention, emotion or feeling they want to embody, something that inspires them.
- ✓ Have the patient relax into a deep breathing pattern, focusing on the intention and coupling it with the breath.
  - ✓ For example: As the patient breathes in, they can say to themselves, "I am filled with joy," and, with the out breath, they can say to themselves, "I am joyful."
  - ✓ Alternatively, with prayer, the patient can couple prayer with the breath. For example: Saying to themselves with the in breath, "I pray for strength" and breathing out, "Help me be strong."
- ✓ Repeating this for a few minutes, coming into a state of stillness.
- ✓ In this state of relaxed stillness, the patient allows for whatever comes forward to give insight into the situation.

The idea behind this practice is not that the patient thinks about what to do, rather that the patient is able to achieve a state of stillness and relaxation, allowing for insight to present itself from within the consciousness.

FIGURE 28.10 Tips for doing contemplation and prayer.

TABLE 28.3
Problem-focused and Emotion-focused Coping Strategies for Managing Stress

	Problem-focused Coping	Emotion-focused Coping
Aim	Action taken to reduce or remove stressor	Action taken to reduce distress caused by stressor
Example	A company is beginning a round of layoffs in the department	
Adaptive Use	Individual starts to save money and refine resume	Individual uses relaxation techniques such as meditation to reduce stress
Maladaptive Use	Individual uses substances to remove the reality of possibly losing a job	Individual denies or mentally blocks the possibility that they will lose their job

Source: Adapted from Carver, C.S. and Connor-Smith, J., *Annu. Rev. Psychol.*, 61, 679–704, 2010.

and decreasing sleep worry.[137] These resources are both practical and appealing to patients and clinicians, as they are often convenient to use and widely available, and still show significant effects on stress reduction. Another important role of technology-based interventions is that they allow increased touch points between providers and patients.

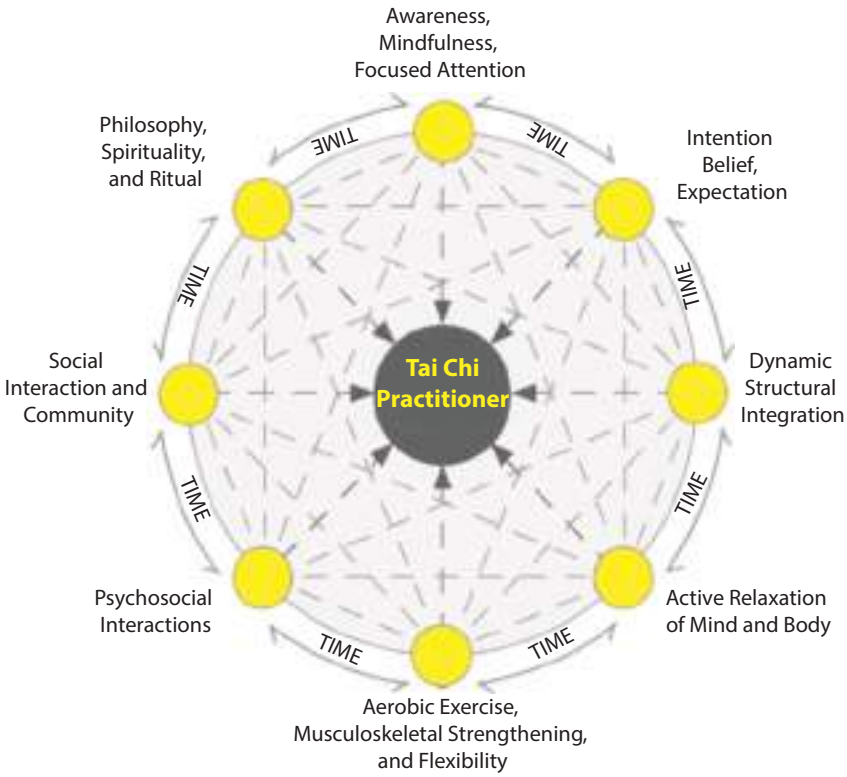


FIGURE 28.11 Tai chi as a multicomponent system.

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℞ **Tips for Practicing Gratitude**

- ✓ Be consistent: Choose a time that works for your schedule, but do it everyday
- ✓ Mix It Up: Employ different ways to express gratitude
- ✓ Be Specific: What exactly are you thankful For
- ✓ Involve Others: Share your appreciation with loved ones & strangers

FIGURE 28.12 Tips for gratitude practice.

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℞ **Cognitive Reappraisal**

- ✓ Identify stressor/stressful situation.
- ✓ Identify emotions felt related to that stressor.
- ✓ Identify underlying belief related to that emotion.
- ✓ Find positive emotion to reframe stressor.
- ✓ Reinforce underlying belief related to positive emotion.
- ✓ Reframe thoughts about stressor with new, positive, adaptive thoughts.

FIGURE 28.13 Cognitive reappraisal.



FIGURE 28.14 Tips for self-care.

28.5 SUMMARY

MBTs are beneficial on a physiological, biochemical, and immune response level to patients, and have many positive psychological and behavioral outcomes. There are many health benefits, both preventive and managerial in nature. Prescribing MBTs can become a useful tool in routine practice. Utilizing the techniques described in this chapter, building resilience, and unleashing the mind's capacity to affect health, is an essential treatment option for patients of all ages and health states. The more MBTs are integrated into practice as the standard of treatment and prevention, the more acceptable they will become, and the more positive impact there will be on our patients' health. This will also lead to more research, further confirming the benefits of MBM and paving the way for discoveries about the interconnectedness of the mind, brain, and body.

CLINICAL APPLICATIONS

- Mind–body medicine and many MBTs are beneficial to patients on a physiological, biochemical, psychological, and behavioral level.

TABLE 28.4
Reappraising Negative Automatic Thoughts

Identifying Negative Thoughts		Building an Adaptive Response	
Negative Emotion	Cognitive Distortion	Adaptive Feeling	Cognitive Reappraisal
Anger	My circumstances are unfair or unjust	Tolerance, Clarity, and Sacrifice	I allow what is and make compromises
Hopelessness	Nothing will help me, I am a lost cause	Power and Perseverance	I can have a positive influence
Sadness	I am experiencing a loss in my life	Appreciation and Detachment	I cherish and value what I have or will work with what is
Guilt	I am not living up to my own morals	Newness and Process	I value potential for growth and change, one step at a time
Shame	I've done something wrong or at risk of being found out	Courage and Choice	How can I act in the face of fear to fix the problem and prevent it for next time?
Resentment	They don't deserve my forgiveness	Forgiveness and Compassion	Focus on healing my own suffering and understanding others, not blaming them

Source: Adapted from the Stress Management and Resiliency Training: Resilience Relaxation Response (SMART-3RP, 10) coping log.

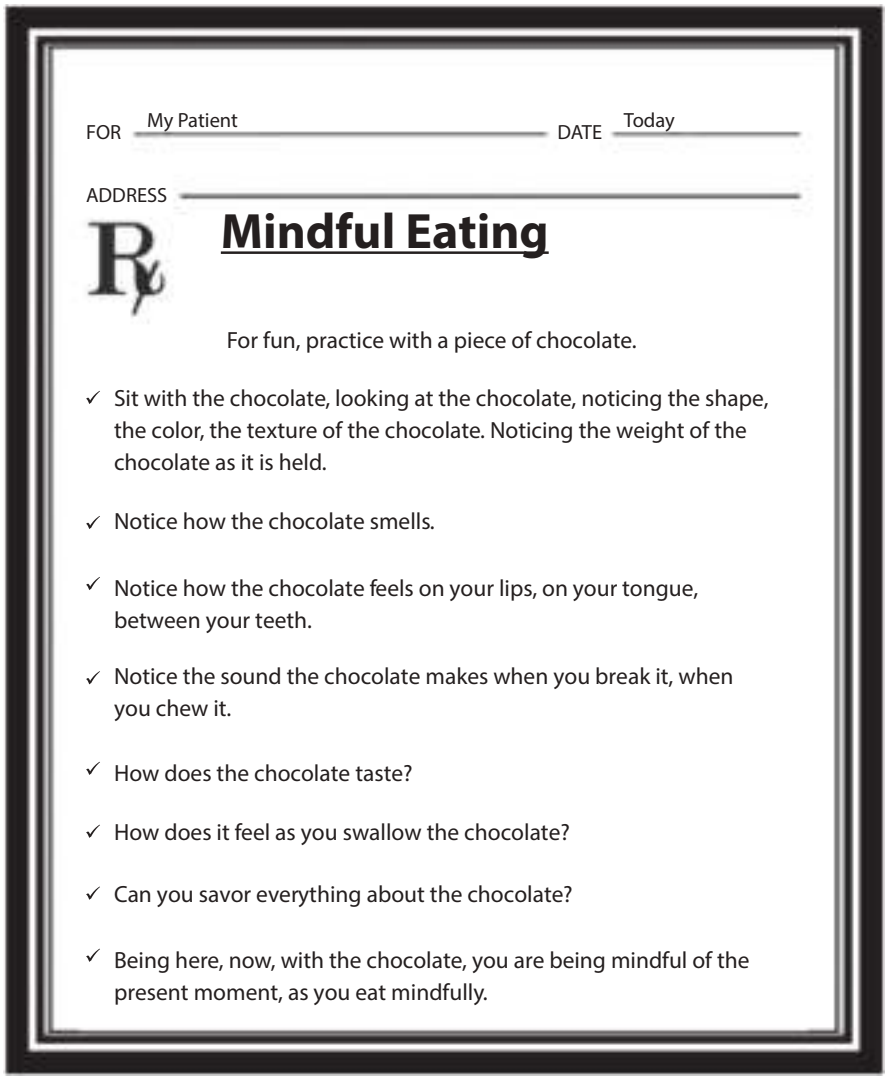


FIGURE 28.15 Tips for mindful eating.

What Does Sleeping Do?

Restorative sleep supports your body's natural healing in many ways including:

- Healthy metabolism
- Normal appetite drives
- Flushes inflammation from the brain
- Regulates the immune system

5 hours of sleep is considered core sleep and allows us to function reasonably well. A nice efficiency for those of us who can't always get a good night's sleep. However, to reap the full benefit of sleep, getting all the sleep you need often, let's your body and brain recharge by clearing out the day's accumulated by-products of stress and rebuild new resources. You feel more tolerant, more stress-hardy, more alert, more engaged, have better memory and general sense of positivity and well-being. With a good night's sleep your brain and body are more equipped to handle stress.

Sleep requirements vary from person to person varying from 7 to 9 hours. Waking refreshed is a good sign you've gotten what your body requires.

Normal sleep onset typically occurs within 20 minutes, and even if you waken during the night, you can easily resume sleep without missing your daily requirements



Positive Sleep Thoughts

- My sleep will improve as I learn these new techniques.
- Even with little sleep, I make it through the day just fine.
- Since I had poor sleep, I'll be easy on myself and aim for a little self-nurturance.
- My performance will still be fine, even if I just get core sleep.
- Like most people, I'm probably getting more sleep than I think.
- My daytime function is not just affected by my sleep.
- My daytime function is due in part to my negative, stress-related thoughts.
- Sleeping 6-7 hours per night is associated with the longest life expectance.
- I'm more likely to fall asleep as my body temperature falls throughout the night.
- My functioning will improve during the day as my body temperature rises.
- It is normal to initially feel alert if I awaken at the beginning or end of a dream - drowsiness will soon follow if I keep my mind quiet.
- These techniques have worked for others, they'll work for me.
- Lack of sleep increases my body's sleep drive, so I'll sleep much deeper next time.
- Meditation can counter some of what my body missed out on from lack of sleep.
- If I exercise today, it'll help me sleep tonight.



Adapted from
Say Goodnight to Insomnia
by Greg Jacobs, PhD



Sleep tips from the
Benson-Henry Institute
for Mind Body Medicine
at Massachusetts General Hospital

www.bensonhenryinstitute.org

FIGURE 28.16 Sleep hygiene tips.

- Providers should use the tools provided in this chapter as prescriptive for wellness promotion, disease prevention, and illness management by prescribing MBTs as routine practice.
- Prescribing these essential skills to patients, as well as developing a powerful self-practice, has the potential to increase positive interactions and interpersonal provider–patient relationships as well as to provide protective and adaptive resilience in everyone.

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29 Health Coaching and Behavior Change

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KEY POINTS

- Despite awareness that lifestyle behaviors—such as a nutritional diet and regular exercise—play a critically important role in achieving health, individuals struggle to achieve these things on their own. Supporting clients in this effort is not consistently done by any other healthcare provider than a health coach.
- Information alone does not readily result in significant or sustainable health behavior changes. People need reliable support, encouragement, empowerment, and accountability—which health and wellness coaches can provide.
- An individual's beliefs and perspectives about their health challenges and capacity to heal impact their quality of life and clinical course. Health and wellness coaching (HWC) can be a path to more empowered and positive beliefs.

29.1 INTRODUCTION

Stories. They may be our sanctuaries or our prisons—providing hope and guidance or fostering despair. We have the power to choose whether we are author, editor, or witness to these narratives. While the choice is ours, most of us need companionship along the way to create healthy and productive lives, especially when our health and well-being are threatened or disrupted. Health and wellness coaches provide the opportunity and support for individuals to actively choose—and change—their health narratives.

Our contemporary healthcare system is built around diagnosis—what is wrong and how to "fix" it or minimize the suffering. Care is prescriptive, diagnosis-driven, and often depersonalizing. Prevention is a secondary process, screening for asymptomatic existing problems. As healthcare consumers, we receive expert advice and therapeutic procedures, are prescribed pharmaceuticals, and are informed of statistical prognoses. If fortunate, we may receive education about the illness or intervention, or have help navigating the complexities of the disease-care system. However, true prevention through supporting positive health habits—such as eating well, not smoking, exercising, managing stress, cultivating positive relationships, or having quality sleep—is rarely part of our financed medical system. This is true even though such practices are responsible for at least 40% of our health outcomes, and research shows that sustaining four primary health behaviors—not using tobacco, being physically active, moderating alcohol intake, and consuming five servings a day of fruit and vegetables—predicts a fourfold difference in total mortality.[1,2] Patient-centered care endeavors to empower the individual and acknowledge the importance of the relationship between patient and provider. These relationships, however, are filtered through reductionistic frameworks within systems that allow neither time nor reimbursement for counseling for positive lifestyle change. This situation creates stories of disempowered, injured, or ill persons being told what to do and when to do it, while only rarely being engaged on why and how they may achieve these changes given their own unique life circumstances, values, and beliefs.

Health and wellness coaches partner with clients to help them recognize their own narratives of illness and healing; reveal beliefs and choose those they wish to change; reinforce their engagement and empowerment; identify their values and priorities; chart their plan for lifestyle changes within reasonable time frames; recognize resources and address barriers; set, track, and attain self-selected goals; and establish accountability and social support. They hold the vision of the wholeness within an individual—especially when the patients are unable to see it for themselves. While all healthcare providers would ideally provide some of these services, it does not routinely occur. Even in integrative practices aligned with a holistic model of healing, practitioners are the experts being sought for advice, information, or intervention rather than supporting the patient as the expert in their own life. Indeed, the health and wellness coach has been the "missing provider" from our healthcare system. The recognition of that need, and the training and employment of health and wellness coaches to fill this gap, increases our likelihood of success in improving overall health through individuals achieving sustainable lifestyle changes and creating new narratives for well-being.

29.2 HEALTH AND WELLNESS COACHING (HWC)—AS A FIELD AND A PROFESSION

Given the growing burden of chronic disease, the importance of adopting a Lifestyle Medicine approach to health and wellness has been well established elsewhere in this book. The largest malleable factor in the development and course of many chronic illnesses is lifestyle. In the 1990s, despite the recognition of the importance of personal and

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TABLE 29.1
Health Coaching is Not Counseling or Therapy

Counseling in Medicine	Health Coaching
Medical model	Learning/Development Model
Diagnosable illness in paradigm of pathology	Desirable goals and achievement in paradigm of possibility
Focus on fixing a problem	Focus on optimal performance
Professional as expert	Coach as non-judgmental partner supporting exploration of health priorities
"Why" questions with present/past focus	"How" questions with present/future focus
Restore client's level of functioning	Move to optimal behavior

TABLE 29.2

Element	% of those studies with adequate detail to code
Patient centered (Institute of Medicine 2001)	86% of 228 trials partially or completely aligned
Patient-determined goals	71% of 217 trials
Self-discovery	63% of 188 trials
Accountability	81% of 159 trials
Content education	91% of 233 trials
Relationship-based	78% of 154 trials

Full-text articles (284 total articles) were identified for the quantitative synthesis to define the key aspects of HWC, as operationalized in the literature. Six particular definitional elements were evaluated using all articles that provided adequate detail to code for each key element, of which 11 to 23% did not.

community health behavior choices, the medical system was still not successfully impacting most individuals' behavior choices.[1] Early efforts in disease and case management, patient education, and other population-based interventions showed some benefit in utilization reduction and medication compliance.[3] As established decades earlier, successfully making positive lifestyle changes requires self-efficacy (Bandura)—an individual's confidence in successfully engaging in specific behaviors. However, self-efficacy was still not readily addressed in mainstream medical care. Multiple educational initiatives were implemented both in public health forums and within physicians' practices, yet the prevalence statistics in health areas that are most significantly impacted by lifestyle choices—diabetes, obesity, and heart disease—continued to worsen. The only negative health behavior among Americans that has diminished has been smoking.[4] A comprehensive approach to tobacco usage, combining public health policies (e.g.. no smoking in restaurants), innovative treatment approaches, and increased awareness of smoking hazards, led to this success. It seems readily apparent that while having accurate information about health behaviors is critical, knowledge alone does not change behaviors. Indeed, in the field of management, it had been established that knowledge alone does not lead to action, but that attitudes, subjective norms, and perceived behavioral control were major determinants of behavior change.[5] These thoughts had not yet been extrapolated to shifting health behaviors.

29.2.1 Theoretical Platform and Historical Underpinnings

The roots of health and wellness coaching (HWC) pull heavily from different branches of psychology, beginning a century ago with Adler and Jung. Adler described our need to achieve personal goals that have value for society and how these goals stem from the unique creative power of an individual (even if unconscious). He further noted that adults use planning to create their future, emphasizing how individuals, when encouraged, feel capable and appreciated, and act in connected and cooperative ways.[6] Similarly, Jung proposed that individuals continued learning throughout life as they moved toward living authentically and "on purpose." He emphasized choosing the values by which they live rather than reflexively conforming to social norms.[7] Mid-century theorists supplemented these core tenets with important findings on how humans find personal meaning on top of meeting basic needs by striving toward self-actualization.[8,9] Humanistic psychology enhanced the study of motivation by emphasizing the role of interpersonal connectedness and sense of purpose.[10] More recent work further articulates the underpinnings of HWC through self-determination theory and self-concordance theory.[11–13] In these theories, individuals strive toward goal attainment when perceiving their goals as aligned with their core values rather than external forces. Later, developmental psychologists added a constructivist element and discerned the precedents for "vital engagement" in one's life.[14,15] Taken together, these theorists consider individuals as *lifelong learners whose individual values and sense of purpose facilitate their potential for positive change.* HWC is founded on the framework that humans strive toward self-actualization, have strong intrinsic resources, and best access their ability for positive change in a safe, confidential alliance wherein they are treated with deep respect and unconditional positive regard.

Paralleling this evolution in psychology, the social phenomenon of wholeness was reemerging in healthcare

through the holistic and complementary medicine, and well-being movements. While HWC and integrative HWC share the theoretical and applied grounding in change theory, behavioral health principles, and techniques for coaching practice, integrative HWC is informed by holistic and complementary healthcare. Apart from the following description of its evolution, and occasional differentiation in research studies, for the purposes of this chapter, we will use the term HWC to be inclusive of all health and wellness coaching practice, recognizing that integrative HWC has a deeper commitment to a mind/body/spirit perspectives and awareness of a broader range of available integrative healthcare practitioners and therapeutic approaches. Leaders in HWC and integrative HWC have joined together to advance the commonality of minimal standards setting for knowledge, skills competency, and educational requirements, acknowledging that integrative HWC requires an additional level of skill and training above this minimum.

The first U.S. holistic retreat center was created by Evarts Loomis, MD, in 1958, bringing the perspective of whole-person healing through the application of lifestyle modification, including nutrition, exercise, mind/body practices, and time in nature. In the 1970s, Dr. Loomis went on to be a co-founder of the American Holistic Medical Association. The emerging human potential movement, cultivating wellness and personal transformation, laid the groundwork for coaching in the personal development area. Tim Gallwey brought the Inner Game approach to coaching, emphasizing the process of how to get out of your own way to let your best emerge.[16] John Travis, MD, self-published *The Wellness Inventory*, launching the wellness movement and introducing the illness–wellness continuum, expanding our horizons beyond a treatment paradigm (Figure 29.1).[17]

In the 1980s, Thomas Leonard began life coaching as a practice, working to codify, popularize, and globalize the discipline of coaching outside the sporting world.[18]

Anthony Grant's work in coaching psychology advanced the legitimacy of life coaching as a platform for applying positive psychology for enhanced mental health, quality of life, and goal attainment.[19] William Miller introduced motivational interviewing (MI) for use with problem drinkers.[20] As a style of communication, it laid a foundation for HWC that deeply respected the autonomy of the individual.[21] MI is now highly evidence-based and used with multiple health issues to assess clients' present motivation to change behaviors that are inconsistent with personal values or goals.[22] In 1982, the Transtheoretical Model (TTM) was initially proposed and then further developed collaboratively by an international group of researchers, theorists, and therapists to provide a more comprehensive model of intentional change than was currently in use for the treatment of addictive behaviors.[23] Popularized in *Changing for Good*, the model posits that individuals undertaking an intentional change go non-linearly through particular stages in considering, approaching, enacting, and maintaining change. The model has continued to evolve, and as of 2016, in *Changing to Thrive*, it provides increased focus on working with individuals who are not yet ready to prepare or take action and are in need of change in a health-related area.[24]

In the 1990s, companies, beginning with IBM, began taking "coaching from being a personal development vehicle for individuals to a way of developing people in business."[25] Thomas Leonard in 1995 started the nonprofit International Coach Federation (ICF), which began to define coaching competencies and offer standardized coach credentials. By 1999, ICF implemented coach training standards and began to accredit individual life coach training programs (https://coachingfederation.org/).

29.2.2 Coaching versus Therapy

A significant proportion of patients/clients in healthcare and community health settings are also dealing with mental health conditions, including depression, anxiety, and addiction.[26] The theoretical framework described earlier has been further augmented with myriad techniques derived from over five decades of outcomes data in psychotherapy and the development of brief solution-focused therapies.[27–29] These techniques enable providers, especially coaches, to focus not on pathology but on behavior change. National standards in mental health literacy for health and wellness coaches have not yet been established but are an important gap to fill in the future. While there are important areas of overlap between HWC and psychotherapy, there are critical distinctions. One is that health and wellness coaches do not diagnose or treat, and they focus not on the diagnosis but on a goal. HWC doesn't seek to provide direction but to create a safe opportunity that allows clients to discover their own insights.[30] Clarity on HWC scope-of-practice is important. At times, individuals experiencing a psychiatric disorder,

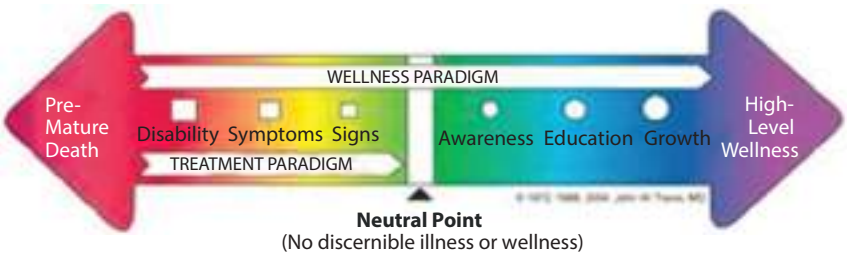


FIGURE 29.1 Illness–wellness continuum.

for example, a major depressive disorder or severe anxiety, may seek HWC as their treatment. Health and wellness coaches should be trained to know how and when to refer these individuals for appropriate treatment with licensed mental health professionals. HWC can be a safe portal into needed mental health services for some individuals who are avoiding needed therapy because of fears or misperceptions. In many situations, a client may benefit from receiving therapy and coaching at the same time—with therapy working at elucidating past events leading to current dysfunction and HWC focusing on present and future goal achievement and mind/body skill acquisition for improved self-regulation. Clients with active addictions or eating disorders are also likely to require connection to a licensed mental health provider, although HWC may sometimes work synergistically.

29.2.3 Coaching versus Health Education and Case Management

All educational approaches focus on conveying information or the teaching of skills. While health and wellness coaches do at times provide information or resources, education is never their dominant function. A "coaching approach" to teaching occurs through "elicit, provide, elicit," a technique from MI that involves exploring the client's current knowledge or understanding, asking for permission to share, offering information, and then asking how clients understood or may apply it.[31] The second philosophical difference arises from the goal setting process. The HWC agenda, always, is client-driven—not dictated by the goals or priorities of the disease management company, insurer, employer, or healthcare provider—and confirms the "clients' values, sense of purpose and personal vision for their lives."[32]

29.2.4 Standardizing the Field of Health and Wellness Coaching (HWC)

In 2008, it became clear to leaders in this field that growing numbers in four domains had created a climate of confusion and erratic quality:

(1) Widely diverse practitioners self-identifying as health and/or wellness coaches
(2) Organizations professing to offer health and/or wellness coaching as a service line
(3) HWC training programs varying widely in approach, content, skills training, format, assessment, and length
(4) Research studies with unclear or inconsistent interventions, all titled HWC

(See Section 29.4, "Evaluation and Research in Health and Wellness Coaching," for more details.)

In order to nurture the professional advancement of HWC, national standards for terms and minimal criteria for basic education needed to be established. Clear definitions and standards were also needed in order to create a consistent basis for rigorous and meaningful evaluation studies. Therefore, in 2010, the National Consortium for Credentialing Health and Wellness Coaching (NCCHWC) was born out of a national summit that brought together over 70 stakeholders from widely diverse fields of healthcare (grant support generously provided by the Institute for Integrative Health; https://tiih.org/). Those stakeholders represented professional associations in health promotion, coaching psychology, nursing, and medicine; researchers, experienced coaches, and subject matter experts; and commercial training organizations and experienced university educators in the field. With nonprofit 501(c)(3) status gained in 2013, the NCCHWC's goal was to professionalize the expanding field of HWC with an evidence-informed foundation.

Wolever, Simmons, Sforzo et al. (2013) systematically reviewed the English and Spanish HWC literature through January 2013, using the international guidelines established by PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses).[30] The Pico-derived primary research question was: *"How are interventions described as health or wellness coaching defined and operationalized in the peer-reviewed medical literature?"* Specifically, the review sought to clarify what approaches, practices, strategies, and methodologies constitute HWC in the peer-reviewed literature. A standardized definition of HWC would allow a more rigorous evaluation of HWC. In addition, the professional skills needed to appropriately train HWC could be better identified.

Overall, the literature described HWC as:

> A relationship-based (78%) process that is fully or partially patient-centered (86% of articles), included patient-determined goals (71%), incorporated self-discovery and active learning processes (63%) (vs. more passive receipt of advice), encouraged accountability for behaviors (86%), and provided some type of education to patients along with using coaching processes (91%).

The summative results of the first six years of NCCHWC work were published in 2015[33] and proposed this working definition of HWC:

> Health and Wellness Coaches are professionals from diverse backgrounds and education who work with individuals and groups in a client-centered process to facilitate and empower the client to achieve self-determined goals related to health and wellness. Successful coaching takes place when coaches apply clearly defined knowledge and skills so that clients mobilize internal strengths and external resources for sustainable change.[33]

In 2016, the NCCHWC moved into a formal collaboration with the National Board of Medical Examiners (NBME), in 2017 evolving into a 501(c)(6), the ICHWC—the International Consortium for Health and Wellness Coaching (www.ICHWC.org). This continuing work has

resulted in exacting processes for approval of educational programs and national board certification of individual coaches. In 2018, ICHWC was renamed the National Board for Health and Wellness Coaching (NBHWC) and became a nonprofit affiliate of the NBME.

29.2.5 Health and Wellness Coach Training and Education

Historically, formal training in life and executive coaching began with ICF in the mid-1990s. As of 2020, more than 30,000 coaches held one of the ICF coach credentials: Associate Certified Coach, Professional Certified Coach, and Master Certified Coach. ICF has accredited more than ~500 coach training programs worldwide (at least 125 hours of coaching competency training) (ICF website, accessed 8 June, 2022). The ICF core competencies and ethical guidelines are widely applied and respected as the foundation for professional coaching in leadership, business, and life.[34] ICF standards are mostly focused on the executive and business domains, not on health and wellness coaching.

In the 1990s, pioneering, self-identified health, wellness, and integrative health coaches began practicing. The first independent HWC training and certification program launched in 2002, and the first academic program in 2005. A best practice, collaborative process by NCCHWC from 2010 to 2016, including a Job Task Analysis and national validation survey, led to national training and educational standards to support coaches in acquiring the requisite knowledge and skills.[35] Program standards include synchronous training and mentoring in health and wellness coaching competencies confirmed by a pass/fail assessment of practical skills. By 2022, more than 110 diverse U.S. programs had been approved by the NBHWC, having met the most recent national standards from 2018. Coach graduates of NBHWC-approved training programs are eligible to sit for the national board certification for HWC, an exam of applied coaching knowledge launched nationally in September 2017 and offered triennially as of 2023. As of the time of this writing, there are ~7,400 national board-certified health and wellness coaches.[36]

This examination and process were developed jointly by NBHWC and NBME, the latter of which has implemented physician-credentialing examinations since 1915. The training and education of health and wellness coaches is supported by ten textbooks authored by thought leaders on coaching competencies, MI, and TTM, plus a growing, peer-reviewed literature base. In 2018, national HWC training and education program standards advanced to require a minimum of 60 hours of training in coaching competencies (40 hours must be synchronous, interactive training) and 15 hours of healthy lifestyle education, plus mentor coach feedback on a minimum of three full coaching sessions, and a pass/fail evaluation of a coach's demonstrated practical skills.

Health and wellness coach training and education programs approved by NBHWC are currently diverse in setting, structure, and cost, including academic non-degree; academic degree (at bachelor's degree, graduate certificate, and master's levels); private sector; government (e.g., U.S. Department of Veterans Affairs); and internal programs of large organizations, which include employee benefits vendors, wellness vendors, health systems, and health plans. Some programs have a strong integrative health focus, and others emphasize subspecialties such as nurse coaching.[37–39] Program fees vary widely from approximately $3,000 for a private sector training program to over $50,000 for the cost of a master's degree.

Currently, those from both non-clinical and licensed clinical backgrounds are eligible to become NBC-HWC. Future studies on the impact of a coach's background and training on the effectiveness of coaching may lead to further refinement of standards for the education of health and wellness coaches.

29.3 HEALTH AND WELLNESS COACHING—BEST PRACTICES IN CLINICAL AREAS OF INNOVATION

29.3.1 Health and Wellness Coaching in the Healthcare Setting

While HWC began most often as an adjunct service, often separated from the primary care team, a newer role for HWC is its integration into the healthcare delivery system, with settings including: worksite wellness centers, recreation facilities, employee health programs, community centers, and educational environments, and it is being offered for special populations like the homeless and other underserved populations.[40–46] This relatively new integration into the healthcare delivery system increases the potential for innovative HWC to become an impactful systemic change agent for health promotion and well-being optimization.

It has been well demonstrated that physician counseling for health behaviors can help patients implement positive lifestyle changes.[47] Therefore, one potential strategy to enhance HWC's impact is to integrate HWC into a patient's routine medical care. For example, in one study, nearly 1,000 patients (average body mass index [BMI] 34.5) were referred to a telephonic health coaching program by their healthcare provider for assistance with weight management. The participants receiving HWC demonstrated a 1-unit reduction in their BMI over 12 months, compared with the approximately 19,000 control patients who remained weight stable.[48] Studies have documented benefits of wellness coaching for self-care behaviors among primary care patients with prediabetes and for increasing physical activity level and improving dietary habits in breast cancer survivors.[49,50] Similarly, a recent randomized, controlled trial of patients in Air Force primary care evaluated the impact

of coaching for those with elevated risk for heart disease and/or diabetes. They found that those who received health coaching were 3.6 times more likely to exercise at recommended levels by the end of coaching, and this effect was sustained 6 months after the conclusion of the coaching.[51] Finally, Mayo Clinic researchers recently found that an eight-week health coaching home-based rehabilitation program for patients with chronic obstructive pulmonary disease (COPD) improved the patients' self-management abilities.[52]

Another setting for HWC is within a worksite wellness center. It has been well documented that stress, prevalent in the workplace, is associated with negative health behaviors and increased presence of health conditions in employees.[41] A survey of 676 healthcare employees found that the relationship between a high stress level and negative health behaviors remained consistent over five years.[52] Participation in a 12-week HWC program improved the quality of life, reduced the perceived stress level, was associated with weight loss, and improved the health behaviors of healthcare employees.[41,53]

The systematic transformation to a Whole Health approach to care by the Veteran's administration is a radical action by the largest healthcare system in the United States, and has HWC as a critical component of this new initiative.[54] A mixed-method pilot study of HWC for veterans in this new model found significant improvements in mental health, stress, and perceived health competence.[55] Growing evidence supports that having a HWC as a member of the healthcare team or wellness team can enhance behavioral and health outcomes.

29.3.2 Visit Structures and Delivery Methods

The optimal choice of structure and method for a HWC visit varies. In terms of the content of HWC interventions, MI and goal setting appear to be consistent components of the HWC interventions.[56] Contextually, in Wolever et al.'s (2013) systematic review of health coaching literature, it was noted that:

> 78% of articles indicated that the coaching occurs in the context of a consistent, ongoing relationship with a human coach who is trained in specific behavior change, communication, and motivational skills.[30]

The needs for direct connection and safe relationship both appear to be requisite for HWC, as it is defined here; therefore, synchronous, voice-to-voice connection (either in person or virtually) with a consistent provider appears optimal for effective coaching. While asynchronous interventions with healthcare providers are utilized in other areas, these have been predominantly for the purposes of education, not coaching.[57] New virtual interventions (sometimes mistakenly called coaching) are continually being explored, but their impacts on lasting behavior change are not well established at this time.[58] While single sessions with any particular health and wellness coach may have some benefit, such an intervention has been minimally examined.[59] Industry and academia continue to rapidly create novel digital interventions and refer to them as "coaching" whether or not they involve human interactions and/or evidence-based coaching methodology.

As noted, synchronous health coaching sessions can be offered in person (most studied), telephonically, or online (least studied). The format, length, frequency, and method of delivery vary widely.[60] The number, frequency, and length of HWC sessions, and the duration of engagement, are not standardized for practice or research. The typical coaching "dose" was explored in the Wolever et al. review (2013), although published studies at the time did not typically report length of session (75%), number of sessions (52%), and duration of a series of sessions (64%).[30] Where data did exist, the average duration of a coaching session was 36 minutes (ranging from 5 minutes to 2.5 hours); the average number of sessions was 10.1 (median of 6 sessions with a range of 1–90 sessions); and the average contact hours reported were 6.2 hours (median of 3 hours, with a range of 15 minutes to 135 hours). Similarly, HWC program duration for clients was quite varied. For example, 23% of the interventions were 5 weeks to 3 months; 25% were 3.5 to 6 months; and 22% were 10 to 12.5 months. More recent dosing based on HWC literature recommends initial programming of 12 sessions for a duration of 40 minutes over a period of 7–8 months.[61] Clearly, more needs to be learned about what format of delivery, length, number of sessions, and time frames of session are most effective for which outcomes in which patients.

One approach to help guide decision-making about the method of delivery for HWC is to examine the participants' own perspectives on their experience. Clark and colleagues conducted a qualitative study aimed at understanding the perspectives of employees who had completed a three-month wellness coaching program.[62] Twenty-seven worksite participants reported appreciating the personal connection with their wellness coach, and being surprised by the impact of the professional relationship they developed with their coach. They rated humor, non-judgmental communications, and evocation as being positive aspects of wellness coaching. While enjoying collaborative decision-making, they found being accountable to their wellness coach motivating. The participants felt more confident in their abilities, were able to reprioritize their wellness goals, and had a broader definition of wellness.

Similar findings were noted in a qualitative study of adult coaching participants who sought integrative HWC to address a chronic health condition. Taken together, participants described their coaching experience as "engagement in transformative change."[63] Participants also noted that mindfulness enhanced "the coaching relationship as well as promoted their engagement, competence, and autonomy in self-determined goal attainment." Participants defined their

lived experiences with integrative HWC as "whole-person engagement" in "a journey … to address a health concern and surprisingly discovered a 'new me.'"

Group coaching has been used successfully in business and leadership for some time, while individual coaching has historically been more common in HWC.[64,65] Nonetheless, group HWC is rapidly expanding, since it increases access and decreases costs.[66] Its effectiveness, however, still needs to be empirically demonstrated. In 2020, a task force initiated through the NBHWC identified core group health coaching competencies, which were validated through a national survey in 2021. Competency and training recommendations from that work will be published soon (Wolever et al. pending) and also made available through the www.NBHWC.org website.

29.3.3 Employment of Health and Wellness Coaches

In the corporate wellness sector, employers typically pay for coaching as part of a broader offering of health services, intending to control rising healthcare costs as well as improve productivity and presenteeism. Many vendors offer HWC by phone or videoconferencing at low or no cost to individual employees.[67] Health and wellness coaches who offer private practice services are predominantly working fee-for-service, and often also offer other services such as yoga, mindfulness training, energy work, personal training, cooking/nutritional instruction, and therapy (from licensed mental health providers) (Figure 29.2).

For the last several years, NBHWC has been advocating for reimbursement of coaching services within U.S. healthcare. In 2019, the U.S. Department of Veterans Affairs (VA) and NBHWC successfully applied for the creation of Current Procedural Terminology (CPT) tracking codes (Category III) for health and well-being coaching services.[68] CPT codes provide doctors and healthcare professionals with a uniform language for coding medical services and procedures to streamline reporting and increase accuracy and efficiency. NBHWC also completed a legal review supporting the use of Medicare CPT codes by HWC, including annual wellness visits, obesity counseling, chronic care management, and remote physiological monitoring services.[69] In April 2021, a taxonomy code was approved for HWC, allowing HWC to become credentialed providers with public and private payers.[70] Reimbursement of the NBC-HWC's is not mandatory with Category III CPT coaching codes, or with other existing reimbursement codes that relate to prevention, wellness, and engagement in healthy lifestyles. However, efforts to evolve these to Category I CPT codes are actively underway, and U.S. healthcare organizations are beginning to use the coaching and other CPT codes with variable reimbursement. NBHWC has documented over a million visits between 2015 and 2020 with these codes. HWC is solidly on the path to becoming an everyday healthcare intervention.

29.4 EVALUATION AND RESEARCH IN HEALTH AND WELLNESS COACHING

29.4.1 Current Evidence Base

Research from Europe, Australia, and the United States has converged to clearly demonstrate that HWC is an

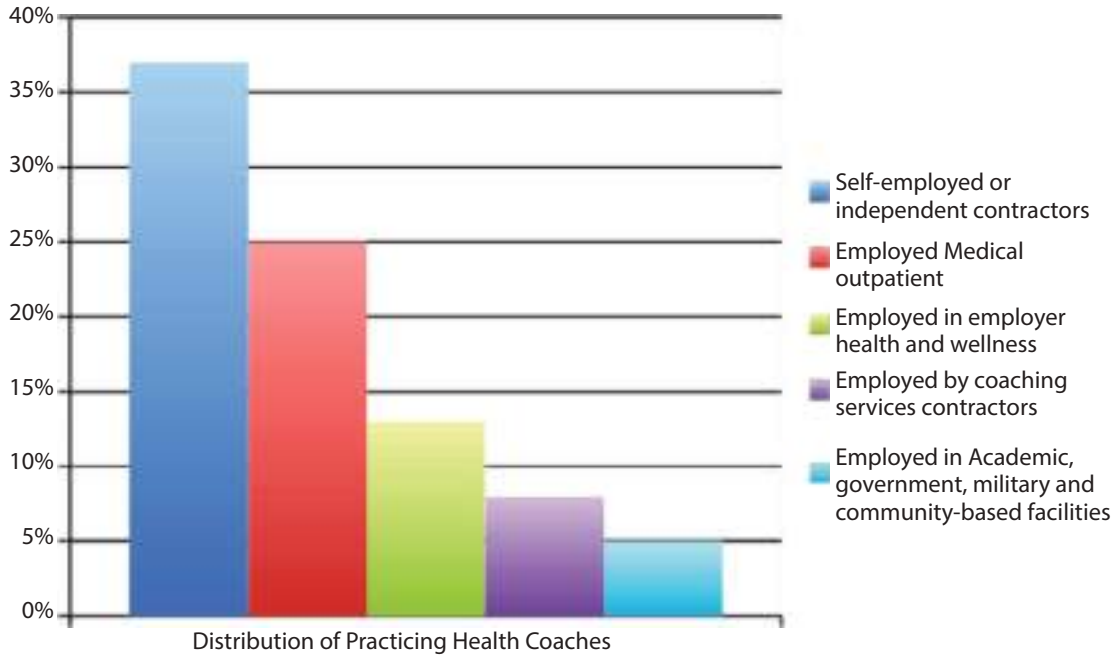


FIGURE 29.2 2014 survey of practicing health and wellness coaches.

effective approach for many health behaviors that can lead to positive outcomes for many health conditions. The first review of the HWC literature was published in 2003 in Australia.[71] Since that time, over a dozen reviews of the HWC literature have been published worldwide.[30,56,60,72–77] The HWC literature as a whole is quite consistent in demonstrating improvements in patient self-efficacy, psychological measures, and quality of life. In addition, systematic reviews and meta-analyses show change in both self-management behaviors and relevant physiological indicators; for example, type 2 diabetes and cardiovascular risk.[78,79] There continue to be equivocal findings, however, when inclusion rules are loosely defined (i.e., any study described as "health coaching" without attention to the actual methods employed). For example, recent meta-analytic studies for overweight or obesity showed HWC to produce negligible findings, but the report has these methodological problems.[43,80]

To manage this major issue, the HWC literature has been organized into a compendium using the only empirically established definition of HWC.[30,56,76] As of 2019, the literature evaluating better-defined HWC includes 231 data-based and peer-reviewed studies, with 108 being randomized designs; 58 studies address obesity and 44 address diabetes.[76] More than 50 of these investigate HWC's effects on well-being and risk reduction (employee wellness, hypertension, cholesterol). Ten studies address cancer-related challenges, while other conditions (e.g., fibromyalgia, multiple sclerosis) are addressed to a lesser extent.

Of the compendium studies examining obesity, more than 80% reported improvements in BMI or body weight after HWC. This is a robust success rate for weight loss studies reporting outcomes between six months and two years. Of the compendium studies examining diabetes, more than 80% reported improvements in A1C (a measure of long-term blood glucose control and the primary outcome for most diabetes studies). A variety of other important variables, such as diabetic self-care, body weight, and medication adherence, also improved in many of these HWC studies.

Almost 90% of the compendium studies examining wellness reported improvement in a key behavioral variable (e.g., exercise or nutritional behaviors), and many studies showed improvement in important biometric outcomes (e.g., blood pressure, cholesterol, body weight, anxiety).

In the area of cancer, about 67% of compendium studies show favorable outcomes in a population where positive outcomes are difficult to achieve. These outcomes are often psychological (e.g., stress, anxiety) but also behavioral (e.g., exercise habits). HWC can improve quality of life for cancer patients and survivors with regular access to a coach.

HWC has also been used to successfully treat aspects of other debilitating conditions, such as MS, fibromyalgia, COPD, and renal disease. While much of the research on these conditions is preliminary, it is promising.

29.5 HEALTH AND WELLNESS COACHING—PRACTICAL NUTS AND BOLTS

29.5.1 Coaches Need Coaching

It is widely accepted across all domains of professional coaching—including executive or leadership, life, and health and wellness coaching—that competent coaches regularly employ their own coaches to support their personal and professional growth. It is also similarly valuable for other healthcare providers to receive HWC for their personal health and well-being so that they "walk the wellness walk" and are better able to refer patients to coaches and support patient engagement in HWC. Walking the coaching walk enables coaches to engage in a similar process as their clients and more fully engage in lifelong learning and growth.

During professional training and education programs, health and wellness coaches are typically working with fellow students or professional coaches on their own well-being goals. In fact, emerging evidence suggests that the HWC training process itself may be seminal to improving or even optimizing the health and well-being of the trainee.[81] As an example, in the University of Minnesota's graduate programs in Integrative Health and Well-Being Coaching, all students receive three hours a semester of HWC provided by an outside professional coach who is not otherwise involved in their education (www.csh.umn.edu/education/master-arts-degree-integrative-health-and-well-being-coaching).

29.5.2 Referral to Health and Wellness Coaches

HWC calls clients to develop new health behaviors, a new positive lifestyle, or even, and sometimes most importantly, to transform underlying cognitive and belief structures. Hence, the U.S. national standards include the competency of assisting clients in assessing whether they are ready to effectively engage in a HWC program, developing and sustaining new healthy habits of mind and body. While physician referrals are rarely required for HWC, and since validated instruments to assess suitability for coaching don't yet exist, healthcare providers are best positioned to recognize patients best suited to the HWC process. The absolute best way for any healthcare provider to understand and refer to HWC is to receive HWC themselves, even if they do only an isolated session.

29.5.3 Hiring Health and Wellness Coaches

To date, there is no research that compares the effectiveness of HWC based upon coaches' educational and/or

professional backgrounds. Hence, common sense principles and evaluation of an individual's demonstrated skills are critical in employing health and wellness coaches. Ideally, a health and wellness coach has completed a reputable accredited professional program that provides skills training and integrated application of coaching-related theories, and that requires demonstration of adequate coaching skills. The health and wellness coach should demonstrate knowledge of HWC competencies, excellent communication skills, curiosity, compassion, and empathy; and should model their own commitment to optimizing their personal health and well-being. Hiring of NBC-HWCs is strongly recommended.

Healthcare organizations recruiting health and wellness coaches often look for a combination of a credible coaching credential with other health credentials. Nurses are often desired, as they bring considerable clinical and patient management experience and understanding of healthcare system issues, including scopes of practice and Health Insurance Portability and Accountability Act (HIPAA). This is true of physician assistants, nurse practitioners, and physicians as well, although more costly. Some may seek health and wellness coaches who are also dietitians or exercise physiologists, who can contribute healthy lifestyle expertise under reimbursement protocols. Health and wellness coaches with formal mental health licensure may perform dual roles—delivering therapy services as well as coaching, provided they clearly articulate which role they are using with a client.

29.5.4 Assimilation of Health and Wellness Coaches

A challenge for health and wellness coaches in many organizations is that the culture and leadership practices in a particular setting may not align with key coaching principles—such as fostering autonomy, intrinsic motivation, compassion, mindfulness, strengths, self-awareness, and an open, creative, and collaborative change process. Consequently, health and wellness coaches may feel isolated and unsupported by their teams and leaders. Ideally, health and wellness coaches have supervisors who have a deep understanding of coaching and teams that are well informed on the nature of HWC. Fortunately, there is an emerging interest in developing coaching cultures within organizations such that all leaders and team members learn basic coaching and communication skills. This will enhance the acceptance and support of professional coaches and their effectiveness in their roles.

29.5.5 Protecting Client/Patient Privacy

A successful HWC engagement depends upon trust (i.e., the health and wellness coach is benevolent, authentic, honest, and competent), privacy, and confidentiality. It is important for health and wellness coaches to follow established practices to protect the privacy and confidentiality of client/patient information, including following HIPAA requirements for technology security and sharing of patient/client information with other providers. It's vital that clients are informed of practices that protect their privacy and require their permission for sharing of personal information.

29.6 HEALTH COACHING IN THE FUTURE OF HEALTHCARE—A VISION OF HOPE

An existing body of outcome studies suggests that the key levers for achieving healthy change include *the therapeutic alliance*, *the client's active participation*, *the client's perception of the issues*, *the client's guided generation of the solution*, *and the client's use of resources.* HWC, as defined by the NBHWC, embodies these aspects of a supportive and creative relationship to elicit positive lifestyle change. The health and wellness coach is effective in supporting the competence of the patient by eliciting intrinsic motivation based on the personal values and strengths of the individual and by inviting active participation and empowerment through specific communication techniques.[82] The client's perceptions of the issue and generation of the solution are explored in the context of the client's values. An emphasis on strengths and continued learning allows the health and wellness coach to support the clients' own vision of their best selves. Borrowing from positive psychology and other strength-based approaches, the health and wellness coach also trains clients both to recognize how they are continuing to learn and to see the impact of their own positive behavior in bringing about their vision.[82, 83] This process applies key lessons from health psychology on the importance of tracking behaviors.[84] Effective self-management interventions that are central to care of chronic disease are then provided using particular education techniques that align with how adults best learn.[85–90] Finally, the health and wellness coach plays a key role in helping the client to develop support networks and resources that access the client's community and healthcare system.

It is time for us to call in a new vision of health and healthcare in America. Health coaching can play a pivotal role in the creation of this new narrative. Innovative models that partner education for self-efficacy with health and wellness coaching, like the PACT program for chronic pain, leverage our healthcare dollars and improve outcomes. Health and wellness coaches can provide critical skills to our evolving interprofessional healthcare teams that place the client, or patient, at the center of their own care.[91] As noted previously, the VA healthcare system has been implementing early initiatives along this line, bringing in a holistic philosophy of care, empowering the patient in their own

care, and actively employing coaching techniques with patients.[92,93]

This new narrative will very much emerge from the dreams, the pioneering initiatives, and the intentions we generate today. In systems theory, the most unstable systems are those most able to be suddenly and powerfully changed. Transformation arises through chaos, which is an accurate descriptor of our current system of medical care in the United States. HWC has the potential, right now, to change our stories of health and well-being, individually and as a system. HWC can be a transformative agent, helping to create a system of care—nationally, if not globally—that empowers individuals in their efforts not just to survive or recover from disease, but to create and sustain holistic health and optimal well-being.

CLINICAL APPLICATIONS

Consider connecting patients to individual or group HWC, especially in the following situations. A patient:

- Receives a new diagnosis of any illness for which lifestyle behaviors contribute significantly, either to the cause or to the course of that illness. This could include anything from cardiac disease and diabetes to cancer.
- Is living with a chronic disease and would functionally do better if able to make improvements in habits around eating, exercise, sleep, stress management, medication utilization, relationships, or perspectives on their challenges.
- Wants to improve their overall health and well-being, and decrease risks for future disease or disabilities. They are asking for help in making real change.

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Part V

Lifestyle Medicine Approaches to Dysglycemia



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30 Overview: Dysglycemia-Based Chronic Disease—Exposing Lifestyle Medicine Targets

Michael A. Via, MD and Jeffrey I. Mechanick, MD

KEY POINTS

1. Disease manifestations of insulin resistance are highly prevalent in modern populations.
2. A classification system for dysglycemia-based chronic disease includes disease progression and severity, and allows the clinician to appropriately gauge risk to make recommendations.
3. Lifestyle recommendations are central to the treatment plan at all stages, and should include optimizing nutrition, physical activity, sleep hygiene, and behavior.

30.1 INTRODUCTION

Glucose is the main currency for human energy homeostasis. Dysregulation of glucose metabolism, or dysglycemia, encompasses pathophysiological events that yield chronic non-communicable diseases. The extremely high prevalence of dysglycemia gives rise to high economic cost, reduced life expectancy, and through multiple potential complications, reduced quality of life.[1] Many diseases, such as type 2 diabetes (T2D) or polycystic ovary syndrome (PCOS), result from dysglycemia. Collectively, when specific mechanistic drivers produce a specific pathophysiological state and clinical phenotype that persist for more than three months, a "driver-based chronic disease" ensues. In the case of dysglycemia as the driver, this state is dysglycemia-based chronic disease (DBCD), which is pragmatically modeled according to four distinct, sequential stages in the natural history. The impetus for developing this model was criticism that diagnoses of insulin resistance syndrome or prediabetes were not cost-effective (in the context of providing pharmacological intervention, such as metformin); the response to this was to consider these states not in isolation but rather, in the context of a natural progression of dysglycemic states amenable to early prevention of vascular complications.[1] The major advantage of this new construct is that early and sustainable prevention targets are codified. In other words, the targets are clearer, easy to identify, and actionable through specific prevention modalities to reduce morbidity and mortality attributable to dysglycemia.

30.2 DEFINITION AND CLINICAL MANIFESTATIONS

The pathophysiology of insulin resistance and downstream effects that upset pancreatic β-cell function create a dysglycemic state.[1] Early signs of DBCD include abnormal adiposity (e.g., elevated body mass index [BMI], waist circumference [WC], ectopic fat, and measurable adipokine changes), insulin resistance (e.g., euglycemia, hyperinsulinemia, and abnormal homeostatic model assessment [HOMA]), and eventually with a β-cell defect, mild hyperglycemia (prediabetes; e.g., impaired fasting glucose and/or glucose tolerance).[2] Moreover, patients who develop hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol, and/or hypertension meet one of several published criteria for the metabolic syndrome (MetS).[3–5] In contrast to the static cluster of pathological states comprising MetS, configuring other driver-based chronic diseases (adiposity-based [ABCD], hypertension-based [HBCD], and lipid-based [LBCD] chronic disease) into a comprehensive cardiometabolic-based chronic disease (CMBCD) represents a dynamic model also amenable to early/sustainable preventive care.[6,7] Further progression of insulin resistance and β-cell defects leads to T2D. Other conditions directly associated with insulin resistance include PCOS, gestational diabetes mellitus (GDM), obstructive sleep apnea (OSA), and hepatosteatosis. Additionally, patients with insulin resistance are at increased risk for cardiovascular disease (CVD) and cancer, the top two causes of mortality worldwide.[8,9] These clinical manifestations of DBCD can greatly impact the lives of patients with disease-specific effects, disease state interactions, and increased mortality.

Another common feature among dysglycemic states is scientific controversy over the definition of disease. For example, there are six validated definitions of MetS[9] and three definitions of PCOS.[10] In fact, the definition of prediabetes can vary by published study and clinical practice.[1] In general, prediabetes is present when serum levels of glucose are elevated while the patient is fasting, postprandial, or after oral glucose challenge, but not high enough to be classified as T2D. Many authors divide prediabetes into two categories: impaired glucose tolerance and impaired fasting glucose, based on glucose tolerance testing and fasting

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glucose levels, respectively. Additionally, hemoglobin A1c (A1C) levels above normal (≥5.7%) but below 6.5% may be considered as prediabetes. Using this definition based on A1C, patients diagnosed with prediabetes demonstrate an approximate 70–74% lifetime risk for the development of frank T2D.[11] Additionally, a 10–30% increased risk of CVD is reported in patients with prediabetes,[12] and the risk for many common types of cancer is 30–50% higher than in the general population.[9] While it should be noted that the variance of definitions of prediabetes can affect the observed risk levels, these risks remain elevated regardless of the specific definition of prediabetes.[12] The association of CVD with prediabetes changes the context of prediabetes from just a predisease state defined by diabetes risk to a specific cardiometabolic risk descriptor. For instance, there is an average 20% increased risk for cardiovascular events in patients with prediabetes than in those without prediabetes.[13] In a cohort study of almost 7000 patients, the risk for development of heart failure over five years was 7.8% among those with prediabetes (and 12% for patients with T2D), compared with only 0.78% for patients with euglycemia.[14] Published trials demonstrate beneficial effects of lifestyle and weight loss strategies to mitigate the cardiovascular risk increase in this prediabetes population, further supporting the role of the DBCD framework for early preventive measures.[15]

More important than dividing patients into the binary "haves" and "have-nots" with respect to T2D risk for complications, the continuum of risk represented in the DBCD framework should guide an appropriate clinical response, viewed as an intervention to prevent disease progression. Successful examples of this practice are incorporated into current guidelines for hyperlipidemia and hypertension management.[16] Hepatosteatosis and OSA are also graded in a similar fashion by disease severity.[17,18] The high risk for CMBCD among patients with DBCD necessitates intervention, mainly through identification and implementation of opportune healthy lifestyle practices, with guideline-directed pharmacological and procedural interventions as indicated. Accordingly, a four-stage system based on the natural history has been proposed for DBCD classification to enhance precision, clarity, target exposure, and successful outcomes with preventive care (Figure 30.1).[1]

Stage 1 is risk (conferred by primary drivers of genetics, environment, and behavior), stage 2 is predisease (or prediabetes), stage 3 is disease (or T2D), and stage 4 is complications. It should be made very clear that DBCD is not a competing term with T2D. Rather, T2D is interpreted as stage 3 DBCD and part of a spectrum that mandates preventive care. Similarly, prediabetes is interpreted as stage 2 DBCD and likewise, mandates prevention of this pathophysiological state at high risk for not only T2D but CVD as

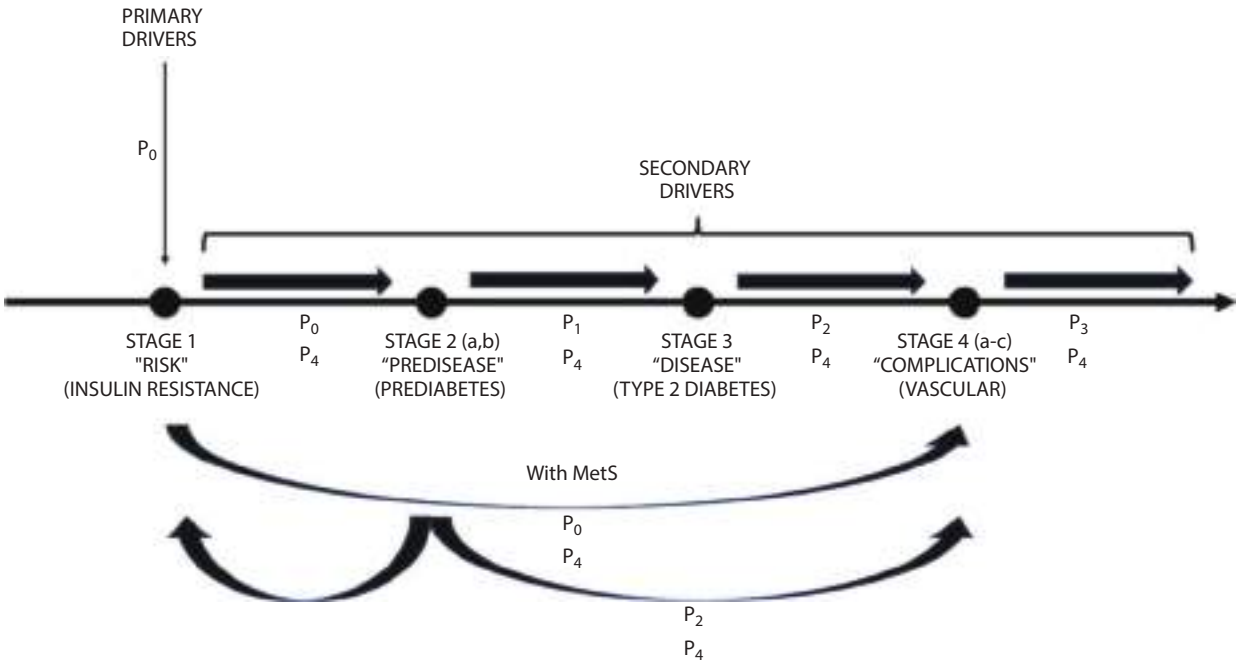


FIGURE 30.1 The dysglycemia-based chronic disease model. In this four-stage model, primary drivers are genetic, epigenetic, environmental, and behavioral factors, and secondary drivers are abnormal adiposity, systemic inflammation, disrupted control of energy homeostasis, vascular endothelium, cardiomyocyte pathophysiology, and pancreatic islet cell function. DBCD stage 2 prediabetes is subclassified into 2a (lower A1C) and 2b (higher A1C), and DBCD stage 4 complications are subclassified into 4a (mild), 4b (moderate), and 4c (severe). DBCD stage 1 (insulin resistance) can leapfrog to CVD in the setting of MetS (with/without prediabetes or T2D). DBCD stage 2 (prediabetes) can regress to normoglycemia, remain as prediabetes, directly/stepwise progress to T2D, or leapfrog to vascular complications (especially CVD) without developing T2D. Prevention modalities ($P_{0–4}$) are mapped to DBCD stages, drivers, and pathophysiological targets, and then modified based on SDOH and other ethno-cultural factors, to facilitate early intervention. (Adapted from Mechanick, J.I., et al., ***Endocr. Pract***., 24(11), 995–1011, 2018).

well.[13,19] Each of the DBCD stages is managed with a specific form of prevention (Table 30.1), modified by individualized social determinants of health (SDOH) (Table 30.2).

Several comments deserve special mention at this point to add clarity to the DBCD model. First, this model principally applies to T2D and not type 1 diabetes or other types of diabetes (gestational, atypical, mitochondrial, pancreatogenous, etc.), though the progression of DBCD from stage 3 to stage 4 is relevant to all diabetes types. Second, the implementation of lifestyle medicine at all DBCD stages potentially reduces the need for pharmacological and procedural interventions, accentuating the need for quaternary prevention (the avoidance of overmedicalization). Third, there are overlapping uses of prevention modalities for any given DBCD stage (e.g., even though primary prevention is most important for stage 2 prediabetes, primordial and quaternary prevention should also be applied, secondary prevention is needed if there is already some CVD even without T2D, and tertiary prevention is needed for comorbidities and other diseases, if they exist). Fourth and last, all recommendations are subjected to modification based on ethno-cultural and other individual factors. Hence, the DBCD model is fluid and complex, requiring further study and validation. Nevertheless, there is sufficient DBCD structure now to demonstrate the critical role of lifestyle medicine in the management of patients with dysglycemia.

30.3 STAGE 1: INSULIN RESISTANCE

Stage 1 DBCD is classified as "risk" or insulin resistance and is managed with primordial prevention. Patients with insulin resistance demonstrate normal glucose levels but elevations in serum insulin. Oftentimes, patients in this "risk" stage are overlooked, as a normal glucose is falsely

TABLE 30.1
Types of Prevention

Type	Scale	Description	Stage of DBCD
Primordial	Population	Prevention of risk	**1**
Primary	Individual	Prevention of disease	**2**
Secondary	Individual	Prevention of complications	2,3
Tertiary	Individual	Prevention of suffering/mortality	**4**
Quaternary	Population Individual	Prevention of overmedicalization	1–4

Primary and secondary prevention are both applied to prediabetes, since stage 2 DBCD can either sequentially progress to stage 3 DBCD (T2D) or leapfrog to stage 4 (complications); stage 2 DBCD can also revert to stage 1 DBCD with euglycemia with implementation of primary prevention. Quaternary prevention is ethically sound practice of medicine and exemplified through the routine use of properly implemented structured lifestyle medicine at all stages of DBCD to reduce the need for more risky/costly pharmacotherapy/procedures.

TABLE 30.2
Social Determinants of Health

Determinant	Description
Childhood Development	Allostatic stress and abnormal adiposity
Crime	Allostatic stress and decreased perceived safety
Culture	Nonphysical human factors that aggregate in a specific population/ethnicity
Discrimination/Oppression	Structural conflict
Disparities in Access to Quality Healthcare	Correlates with ethno-cultural and socio-economic factors
Education	Correlates with health literacy and access to care
Employment	Correlates with socio-economic factors
Food Insecurity	Leads to unhealthy dietary patterns
Housing/Amenities	Structural deterioration
Income/Poverty	Correlates with access to care
Religion/Spirituality (R/S)	In certain cultures, decreased R/S is associated with increased chronic disease risk
Work Conditions	Unhealthy lifestyle in many workplaces

Social determinants of health are non-biological drivers of chronic disease phenotypes that require prompt detection and remediation at both population and individual scales.

reassuring, and routine measurements of serum insulin and glucose tolerance testing are impractical. Moreover, insulin resistance is so highly prevalent now. with unhealthy lifestyles and abnormal adiposity,[20,21] that it may be reasonable to approach every patient with a case-finding strategy as though there is already some degree of insulin resistance present. Early lifestyle interventions may yield the most effective and sustainable results, notwithstanding infrastructural and socio-economic challenges with implementation (e.g., affordability, lack of reimbursement, inadequate training, too few lifestyle medicine centers, etc.). The presence of risk factors for insulin resistance, including a family history of T2D, *in utero* exposure to GDM, a personal history of GDM, PCOS, weight gain with abnormal adiposity, or hypertension should strengthen the need for a lifestyle intervention.[1] Many patients with insulin resistance also meet criteria for MetS and increased CVD risk,[5] which can aid in the recognition of insulin resistance without measurement of insulin levels.

The high prevalence of insulin resistance represents opportunities for public health measures. Policies targeting modifiable primary drivers of DBCD (behavior and some environmental factors; genetics are not modifiable) have been implemented with varying degrees of success.[22] Examples include taxes on sugar-containing beverages; construction of bicycle lanes, hiking trails, and other outdoor spaces that encourage physical activity; posted nutritional contents of menu items in restaurants and proper nutritional labeling on foods; and general informational campaigns to educate the public on healthy lifestyle choices.[1] Clearly, more work is needed on a societal level as part of primordial prevention in a diabetogenic environment, particularly for young children and women of reproductive age. For individual patients, healthy lifestyle choices at this stage can mitigate risk at stage 1 DBCD and by inference, all subsequent stages of DBCD. In the future, stage 1 DBCD may be more easily detected not only with commercially validated, accessible, and affordable biochemical testing but with molecular profiling as well (e.g., genomics, epigenomics, transcriptomics, and metabolomics).

30.4 STAGE 2: PREDIABETES

Stage 2 DBCD is classified as "predisease" or prediabetes and is managed with primary (to prevent progression to DBCD stage 3—T2D) and secondary (to prevent progression of early/asymptomatic CVD in CMBCD stage 3 to later/symptomatic CVD in CMBCD stage 4, even without T2D) prevention. Presently, there is no standard definition of prediabetes. However, the demonstrable increase in glycemia as well as the increase in cardiometabolic and cancer risks supports recognition and preventive interventions at this stage.[1,15] Besides the risk of regression of prediabetes to normoglycemia, there is a high risk for advancement of prediabetes to T2D as well as to microvascular, atherosclerotic, and heart failure complications, constituting a basis for structured lifestyle modification.[1,13,19]

Prediabetes may be subdivided into DBCD stage 2a: lower risk—fasting glucose of 110 mg/dL or lower, or A1c of 6.0% or lower; and DBCD stage 2b: higher risk—fasting glucose above 110 mg/dL, or A1c higher than 6.0%.[23] In the future, there may be additional diagnostic criteria for prediabetes based on continuous glucose monitoring data, especially regarding postprandial excursions and glycemic variability.[24] In addition, many of the current diagnostic criteria may need adjustment for different ethno-cultural populations based on biological determinants and SDOH, similar to that seen for BMI and WC for abnormal adiposity.[25] Primary and secondary prevention tactics consist of intensive lifestyle change and when needed, pharmacotherapy, especially for stage 2b.[1] Patients who demonstrate higher levels of insulin resistance markers are at increased risk for progression to DBCD stages 3 and 4.[26]

30.5 STAGE 3: TYPE 2 DIABETES

Stage 3 DBCD is classified as "disease" or T2D and is managed with secondary prevention. Frank T2D is diagnosed by fasting plasma glucose of 126 mg/dL or higher, two non-fasting "casual" glucose levels of 200 mg/dL or higher (not in a stressed state), or A1C of 6.5% or higher. Similarly to stage 2, the diagnostic criteria for T2D may be refined with continuous glucose monitoring data and various biological determinants and SDOH that vary with different ethno-cultural populations.[25,27] This stage represents a threshold for higher cardiometabolic risk than stage 2 DBCD and justifies pharmacological therapy in many patients or bariatric/metabolic surgery in highly selected patients. However, an intensive lifestyle intervention should be applied in all patients with T2D; this has been shown to reduce multiple risks, including cardiovascular and microvascular outcomes, and has the potential to greatly modify the trajectory of this chronic condition, including obviating the need for pharmacotherapy or procedures.[28] There are several definitions (validated and unvalidated) authored by different professional medical societies on diabetes reversal, remission, and even cure, many of which have been studied in the context of lifestyle medicine interventions. These include partial remission (A1C 5.7% to 6.4%) and complete remission (A1C <5.7%) applicable at least three months after cessation of glucose-lowering medications.[29,30]

30.6 STAGE 4: TYPE 2 DIABETES WITH VASCULAR COMPLICATIONS

Stage 4 DBCD is classified as "complications" (typically, macrovascular from insulin resistance and microvascular from hyperglycemia) and is managed with tertiary prevention. Complications arise in patients with advanced T2D not only from the many mechanisms of metabolic disruption but also from the length of time these derangements were at play causing tissue damage.[31] Severe microvascular disease (e.g., nephropathy, neuropathy, and retinopathy) and

macrovascular (e.g., atherosclerosis of coronary, carotid/cerebral, and peripheral arteries, as well as aorta and other large vessels) disease represent two of the most significant complications of DBCD and the defining feature of stage 4 DBCD. Patients with atherosclerotic CVD can develop heart failure (along with cardiac microvascular disease), myocardial infarction, and dysrhythmias (with/without stroke). Cerebrovascular disease can lead to stroke and/or cognitive dysfunction.[31] Peripheral vascular disease may manifest as ischemic ulcers or amputations. Interestingly, diabetes may have a protective role in patients with aortic aneurysm, possibly through increased vascular stiffness generated by enhanced protein glycation in patients with diabetes, which may prevent aneurysm formation.[32] Patients with advanced renal disease may require hemodialysis, which further disrupts metabolic efficiency. Chronic kidney disease, especially with microalbuminuria, can be a risk itself for CVD.[33] The development of peripheral and autonomic neuropathy in patients with T2D is also associated with increased cardiovascular risk.[34] The wide range in type and severity of complications in stage 4 DBCD supports subclassifications into stage 4a DBCD—mild; 4b DBCD—moderate; and 4c DBCD—severe disease, with specific interventional implications.[1]

While medical and possibly surgical treatments are required for nearly all types and severities of complications in stage 4 DBCD, lifestyle intervention must still be applied to mitigate various pathogenic mechanisms and improve quality of life metrics.[1,35] The management strategy in patients with stage 4 DBCD is centered on psychosocial, behavioral, and economic targets to prevent clinical suffering, further progression of complications, and mortality. The clinician–patient relationship should be driven by patient-directed goals of care with an emphasis on minimizing iatrogenic adverse effects of therapies.[1]

30.7 PREVALENCE

Dysglycemia-based chronic disease is highly prevalent in current populations, both in the United States and worldwide. Prevalence rates of each stage and associated conditions are given in Table 30.3. In cross-sectional studies, nearly 75% of the U.S. population demonstrate the presence of insulin resistance (stage 1 DBCD), and over 10% have T2D (stage 3 DBCD).[36,37] With such staggering numbers, the need for widespread lifestyle modification becomes resolutely clear.

30.8 PATHOPHYSIOLOGY

The molecular mechanisms of DBCD are grounded in genetic, epigenetic, environmental, and behavioral factors that constitute primary drivers. The multigene hypothesis suggests that patients with genetic predisposition faced with modern environmental conditions are at high risk. However, genome-wide studies demonstrate that just about 2–3% of the heritability for DBCD may be explained by genes.[38] The vast majority of DBCD risk is carried by environmental factors that alter molecular, cellular, tissue, and organ levels of function, as well as altering lifestyle behaviors.[39–41] Once primary drivers instigate DBCD stage 1, further stage progression is impelled by secondary drivers:

TABLE 30.3
Prevalence by Stage of DBCD and Associated Conditions

	Prevalence	
	U.S.	Worldwide
DBCD Stage 1: Insulin Resistance	74.5%	50–60%
DBCD Stage 2: Prediabetes	28–35%	30–45%
DBCD Stage 3: Type 2 Diabetes	10.5%	7.2%
DBCD Stage 4: Type 2 Diabetes with Complications	6.0%	1–2%
The Metabolic Syndrome (National Cholesterol Education Program criteria)	35.0%	20–40%
Obesity	42.4%	10.9%
Hypertension	45.4%	17.1%
Hepatosteatosis	24.1%	24.5%
Obstructive Sleep Apnea—Moderate to Severe (men)	25.0%	4.0%
Obstructive Sleep Apnea—Moderate to Severe (women)	9.0%	2.0%
Polycystic Ovary Syndrome (among women of reproductive age; Rotterdam Criteria)	6–21%	6–21%
Gestational Diabetes (among pregnant women)	7.0%	10.3%

See Lizneva et al. 2010,[10] Gonzalez-Rivas et al. 2021,[20] Martinez et al. 2017,[21] Tamayo et al. 2014,[36] Writing Group Members et al. 2016, [37], International Diabetes Federation,[64], CDC[120], World Health Organization 2021,[121] Younossi et al. 2016,[122] and Khattak et al.[123]

Abbreviations: CVD—cardiovascular disease; DBCD—dysglycemia-based chronic disease; MetS—metabolic syndrome; P_0—primordial prevention; P_1—primary prevention; P_2—secondary prevention; P_3—tertiary prevention; SDOH—social determinants of health; T2D—type 2 diabetes.

abnormal adiposity and insulin resistance, systemic inflammation, disrupted control of energy homeostasis, vascular endothelium, cardiomyocyte pathophysiology, and pancreatic islet cell function. With the exception of genetics (non-modifiable), it is these rudimentary pathophysiological events that map to specific lifestyle medicine actions and specific prevention modalities.

30.8.1 Primary Drivers

30.8.1.1 Genetics

Genome-wide association studies (GWAS) have identified over 400 genes that confer risk for insulin resistance, obesity, and T2D.[42] Several large GWAS studies have evaluated approximately 27 million gene variants to yield these findings.[41,43] The genes identified influence processes that affect fasting glucose, insulin activity, and hemoglobin glycosylation, among other metabolic pathways. However, risk modeling using genetic scores based on GWAS data is rather disappointing. Gene-based models are less predictive for the development of T2D than simple anthropomorphic measures, such as BMI.[42] Presently, the utility of genetics in DBCD risk mapping is unclear, though there may be value in identifying targets for personalized medicine.[42] While genetic predisposition contributes to the development of DBCD, the rapid rise in prevalence of all stages of DBCD suggests that other factors hold greater influence.[42]

30.8.1.2 Epigenetics

Epigenetic processes include heritable, non-translational modification of genes and gene expression that are influenced by environmental conditions. Some examples include DNA modification by methylation, acetylation, or phosphorylation; or histone modification by acetylation or ubiquitination.[44] These processes influence gene expression over generations. A landmark study demonstrates that specific DNA methylation sites, as well as an overall increase in DNA methylation variance, are present among patients with obesity, suggesting the importance of epigenetic mechanisms in DBCD development.[45] Genome-wide methylation studies demonstrate that approximately 18% of the individual variance in BMI of an individual patient can be explained by DNA methylation.[46] Other epigenetic processes, such as histone acetylation affecting pancreatic β-cell function, are being identified as risks for DBCD and cardiometabolic disease.[44] Lifestyle interventions, such as increased physical activity and dietary pattern, can beneficially affect DNA methylation.[44] It is also likely that lifestyle interventions can affect other epigenetic mechanisms that underlie DBCD.[44]

30.8.1.3 Environment, Behavior, and Lifestyles

The concept of environmental factors encompasses all influences on physiology outside those conferred by genetics. This primary driver represents the lion's share of risk for DBCD.[1,47] Behavioral factors result from the interplay between genetics and environment. In turn, modern lifestyles result from the aggregated effects of the three primary drivers: genetics, environment, and behavior. Lifestyles have evolved through industrialization and information age technologies and form the final common pathway to DBCD stage 1.[1,48] Sedentary behavior, food choice and availability, reduced sleep duration, stress, and alcohol consumption are among the most influential lifestyle choices and behaviors conferring cardiometabolic risk.[47] Various SDOH, including food and housing security, daily work schedules and conditions, culture, and crime, among others, also influence risk in vulnerable populations (Table 30.2).[49]

30.8.2 Secondary Drivers

30.8.2.1 Abnormal Adiposity and Insulin Resistance

Insulin resistance, the central concept driving DBCD, encompasses systemic metabolic dysfunction that affects a wide range of biochemical and hormonal regulatory pathways within metabolically active tissues. Increased adiposity, in both volume and distribution (abdominal, especially visceral adipose tissue), drives systemic inflammation and leads to changes in levels of circulating adipokines, such as leptin, omentin, resistin, visfatin, and adiponectin. Network analyses of adipokines and associated proteins are highly suggestive of dysfunctional adipose signaling in the development and progression of DBCD.[50,51]

In additional to signaling, visceral adipose tissue processes energy pathways inefficiently, leading to reduced uptake and increased circulation of free fatty acids (FFA).[6] The resultant excess FFA in circulation may be ectopically taken up by tissues that do not ordinarily store so much fat, such as skeletal muscle, cardiac muscle and surrounding tissue (epi- and pericardium), liver, kidney, bone marrow, vasculature, and pancreas, contributing to further insulin resistance.[6] Abdominal obesity, assessed by WC, correlates more closely with insulin resistance and with cardiovascular risk than BMI.[1] Epicardial adipose tissue is associated with atherosclerosis, vascular inflammation, and arterial stiffness. Together, these specific mechanisms induced by dysfunctional and excessive adipose tissue are described as adiposity-based chronic disease (ABCD),[52] which serves as a key metabolic driver of DBCD.

30.8.2.2 Systemic Inflammation

Systemic inflammation is another hallmark feature of DBCD and is associated with abnormal adiposity. Immune cells, including macrophages, T cells, and neutrophils, are recruited to adipose depots and are highly active, as demonstrated by increased expression of cytokine/chemokine receptors, as well as CDC11c and β2 integrin, in macrophages.[53] Additionally, direct cell–cell contact among TH1 cells and adipocytes contributes to immune activation and reduces the generation of brown adipose tissue.[53] Tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-10 levels are increased.[53] Systemic inflammation is also driven

by generalized endoplasmic reticulum stress, leading to protein misfolding,[54] and by reduced clearance of advanced glycated end-products.[55] The various aspects of systemic inflammation, including cytokines, chemokines, plasminogen activator inhibitor-1, sialic acid, and fibrinogen, affect insulin production, pancreatic β-cell function, and target tissue insulin sensitivity, all contributing to DBCD.[56]

30.8.2.3 Disrupted Control of Energy Homeostasis

Another aspect of DBCD is central metabolic dysregulation. Many regulatory pathways are affected in DBCD. Among these, resistance to leptin, a hormone released by adipocytes that promotes satiety and influences hypothalamic metabolic regulation and insulin resistance, is common.[57] Leptin resistance results in elevated leptin levels, which confer a three- to fourfold increase in risk of cardiovascular events[58] as well as an approximately 30% increased risk in mortality among patients with known atherosclerotic disease.[59]

Adiponectin is the most abundant adipokine hormone produced by adipocytes, and its activity contributes to cardiometabolic risk.[60] GWAS have identified polymorphisms of the adiponectin gene as risks for T2D.[61] In patients with abdominal obesity, reduced circulating adiponectin levels are associated with insulin resistance through diminished adiponectin receptor activation in skeletal muscle and hepatocytes.[62] An animal model study of adiponectin infusion demonstrates reduced hepatic gluconeogenesis, suggesting that low levels of adiponectin promote hepatic glucose synthesis.[63] Diminished adiponectin activity also impairs insulin release by pancreatic β-cells and is associated with β-cell apoptosis.[64] Within adipocytes themselves, reduced adiponectin activity leads to reduced peroxisome proliferator-activated receptor-α activity, which promotes glucose and fatty acid uptake.[60] These effects of reduced adiponectin serve to drive DBCD progression.

Other disruptions in energy metabolism include improper hepatic glucose release during meals, which is partly due to a reduction in the levels and activity of incretin hormones, such as glucagon-like peptide 1 (GLP1) and 2 (GLP2).[6] The diminished satiety regulation that is consequent to low GLP1 and GLP2, as well as reduced leptin activity and changes in many other adipokine signals, leads to greater caloric intake.[6]

The gastrointestinal (GI) microflora speciation and activity are also affected by insulin resistance and obesity within the host.[65] An increased ratio of Bacteroidetes to Firmicute bacteria and a reduced GI bacterial diversity, which are observed among patients following Western dietary patterns, are associated with insulin resistance and cardiometabolic risk.[60] These changes drive DBCD through microflora–host signaling, disruption of circadian cycles, and excessive appetite stimulation through ghrelin release.[65] In some studies, altered microflora are associated with dietary preferences for diminished fruit and vegetable intake, choices detrimental to DBCD and cardiometabolic risk.[66]

30.8.2.4 Vascular Endothelium

Within the vascular endothelium, insulin resistance directly leads to reduced lipoprotein lipase and endothelial nitric oxide (NO) synthase activities, as well as increased endothelin-1 secretion, giving rise to increased oxidative free radical species production.[67] Vascular lipoprotein lipase activity is mediated by insulin and diminished in states of insulin resistance.[68] This results in hypertriglyceridemia (a component of MetS), which is independently associated with cardiometabolic risk.[68] Also, NO synthase is influenced by insulin activity. In states of insulin resistance, reduced NO production leads to vasoconstriction and is associated with hypertension, another driver of cardiometabolic risk.[69] Activity of the renin angiotensin pathway is also increased in insulin resistance, raising the risk of hypertension even further.[70] Other activities of the vascular endothelium affected by insulin resistance include increased expression of E-selectin and vascular cell adhesion molecule-1, which leads to macrophage recruitment and increased activation of inflammatory pathways.[71]

30.8.2.5 Cardiomyocyte Pathophysiology

Impaired energy metabolism and contractility of cardiomyocytes and reduced capillary recruitment within skeletal muscle are observed in DBCD. Cardiomyocyte metabolism shifts from balanced utilization of both fatty acids and glucose as energy substrate to a reliance on fatty acid oxidation.[72] This leads to increased reactive oxygen species and is associated with increased intracellular lipid storage within cardiomyocytes, resulting in myocardial lipotoxicity (impaired function associated with accumulation of lipid).[72] Animal models of insulin resistance demonstrate reduced cardiac contractility with this change in substrate utilization that is demonstrated prior to the development of hyperglycemia.[72] Left ventricular hypertrophy and cardiac fibrosis result from cardiac insulin resistance, hyperlipidemia, systemic inflammation, increased activity of the renin angiotensin pathway, cardiac microvascular disease, and reduced NO synthesis.[73] These effects contribute to diastolic dysfunction, which is commonly observed in T2D. Voltage gated ion channel activity within cardiomyocytes is also diminished, which may be associated with the observed increased cardiac arrhythmia risk, reduced electrocardiogram activity, and increased rate of T-wave inversions seen in patients with T2D.[74]

30.8.2.6 Pancreatic Islet Function

In the setting of insulin resistance, pancreatic β-cells produce increased amounts of insulin to meet demand; however, dysfunction develops in the timing and amount of insulin produced.[75] Lipotoxicity to β-cells, which results from excess circulating FFA in DBCD, is suggested by pre-clinical models as a potential mechanism for dysfunction.[76] Glucotoxicity, which occurs during hyperglycemia as patients progress to stage 2/3 DBCD, reduces the expression of genes needed to maintain β-cell differentiation and function.[77] Amyloid deposition within pancreatic islets,

replacing functional β-cells, is also observed as DBCD progresses and likely contributes to diminished β-cell activity.[78] Another mechanism seen in animal models of T2D involves macrophage infiltration within pancreatic islets, which may also reduce β-cell activity.[79]

These factors and possibly others contribute to pancreatic β-cell apoptosis and quiescence to nonfunctional cells within the pancreatic islets in response to systemic insulin resistance. The continued loss of β-cell activity drives the progression of stage 1 to stage 2/3 DBCD when hyperglycemia develops/worsens.[75] Pancreatic α-cells are also affected in the evolution of DBCD, possibly through diminished GLP1 and GLP2 activity, leading to untimely glucagon secretion that stimulates inappropriate hepatic glucose release.

30.9 LIFESTYLE TARGETS

A healthy lifestyle is paramount at all stages of DBCD. Modern living affords many instances and conveniences that threaten metabolic health. Recognition and implementation of healthy lifestyle choices should be considered among all patients with DBCD, who represent a large portion of current populations. Change is often difficult to implement, but making sustained steps in definable aspects of lifestyle can optimize clinical outcomes.[1] The DBCD model serves as a tool to clearly expose specific lifestyle targets at specific timepoints in the natural history of dysglycemia. The strategy is to intervene as early as possible, with an implementation tactic that is sustainable over the lifespan, to achieve significant clinical benefits.

30.9.1 Dietary Choice

Dietary patterns represent perhaps the most obvious lifestyle aspect worth addressing. In general, a healthy dietary pattern is recommended, with an emphasis on sustainability.[80] This will require clinical agility in assessments of food preferences, barriers to change, logistics of daily activities, as well as cultural and other personal considerations.[81] Both dietary content as well as timing of food consumption should be reviewed. In general, dietary patterns with a high content of fruits, vegetables, legumes, and nuts provide high amounts of fiber, are low in sodium, impart a beneficial influence on GI microflora, reduce systemic inflammation, and can reduce the risk of DBCD stage progression as well as promote regression to improved states of glucose metabolism.[1] Avoidance of detrimental dietary components such as simple sugars, *trans*-fats, and calorie-dense foods is also beneficial in DBCD.[2]

30.9.2 Physical Activity

Another common target is physical activity and exercise, which should be incorporated into daily routines. However, the amount and type of exercise remain controversial, with the sustainability of regular physical activity among the most important considerations. Direct incorporation, such as modifying a regular commute, or dedicating a specific time for exercise represent achievable targets for lifestyle intervention in most patients. On the basis of many clinical studies and published guidelines, at least 150 minutes of physical activity divided over 5–7 days per week is a reasonable suggested minimum.[1,6,52] Both cardiovascular exercise, which promotes reduction of visceral adipose accumulation and reduced insulin resistance, and strength training, which provides the benefit of increased muscle mass and reduced myocyte adipose content, should be considered.[82] Exercise also improves glucose metabolism through non-insulin-induced glucose utilization, improving hyperglycemia and potentially reducing glucotoxicity.[83]

30.9.3 Sleep Hygiene

Sleep is a defining feature of circadian rhythmicity and affects the metabolic function of the hypothalamus, liver, pancreas, adipose tissue, and skeletal muscle, among other tissues. Disrupted sleep promotes insulin resistance and impairs pancreatic β-cell function.[84,85] As a lifestyle choice, the amount and quality of sleep has been declining. In 1960, adults spent an average of nine hours sleeping per night compared with seven hours currently.[86] In children, the average sleep time has reduced by one hour per night over this same interval.[87] The quality of sleep has also deteriorated: insomnia, defined as waking at night at least three times per week, is reported among 25–35% of adults.[88]

Cross-sectional studies demonstrate a close association between reduced sleep time and weight gain.[89] In a randomized trial, adults who sustained sleep restriction for only five days demonstrated increased calorie consumption and weight gain.[90,91] Food preferences are also affected by sleep.[92] A 52% increase in consumption of sweets and desserts was reported in one crossover trial of sleep deprivation.[92] An elevation in ghrelin levels and a reduction in leptin levels are observed in people who are sleep deprived, which may affect dietary choice and consumption.[93] Both the quality and the amount of sleep are important potential targets for the prevention and treatment of DBCD.[84,86] Conversely, improvements in dietary patterns and increased physical activity can increase the total time and quality of sleep.[94]

Disordered sleep is associated with weight gain and worsened insulin resistance through disruption of circadian rhythmicity.[86] Among the most common sleep disorders, OSA is highly prevalent in adults with DBCD, especially in men (Table 30.3), and among patients with more advanced stages of DBCD. For example, a 60% prevalence of OSA is reported in patients with MetS.[95,96] In patients with T2D and obesity, 75% to 85% demonstrate OSA to any degree, and 50–55% have moderate to severe OSA.[97] OSA represents a common risk in DBCD that is often overlooked and underdiagnosed.[95]

Interventional treatment of OSA includes continuous positive airway pressure (CPAP) devices, which reduce

the cardiovascular risk and improve symptoms of headache and daytime drowsiness. In patients with moderate to severe OSA, cardiometabolic improvements, mainly in blood pressure and lipid profile, are also noted with CPAP use. In one series, 13% of patients with OSA and MetS no longer met criteria for MetS after three months of CPAP therapy.[96] Additionally, an intensive lifestyle modification that promotes weight loss can also improve the severity of OSA and confer improvement in sleep hygiene.[98]

30.9.4 Environmental Lighting

The mammalian circadian clock is generated by a pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus with involvement of specific genes and a molecular mechanism that has been elucidated over the past few decades.[99] In humans, the endogenous circadian rhythm is longer than 24 hours and must be entrained daily by environmental cues, mainly light.[99] Other organ systems have separate clocks. These include the gastrointestinal tract clock set by food intake, the musculoskeletal clock set by food intake and physical activity, the adipose clock synchronized to the SCN clock and modified by food intake, and the pancreatic clock, which is influenced by light/dark cycles through SCN signaling.[100] The basic circadian clock function is generated by expression of positive arm genes (CLOCK, PAS2, BMAL1), which induces subsequent expression of negative arm genes (PER1, PER2, PER3, CRY1, CRY2).[101] In turn, the negative arm genes inhibit the transcription of positive arm genes, generating a negative feedback loop that cycles daily.[101]

Under the influence and synchronization of several clocks located in different organs and tissues, glucose tolerance varies by time of day. For instance, glucose tolerance is approximately 15–20% higher in the morning than in the evening.[102] Pancreatic β-cell activity also demonstrates a diurnal pattern, demonstrated by glucose clamping studies.[100] This pattern is disrupted by circadian misalignment protocol studies after mixed meal testing in patients without diabetes, in which light and dark cycles are inverted over one week, with a consequent 27% reduction of first phase insulin secretion, a 14% increase in late phase insulin secretion, and a 1.6% increase in glucose levels.[102]

By entraining the SCN clock, light exposure emerges as one of the many modifiable primary environmental factors that contribute to ABCD and DBCD risk. Observational studies of light exposure during the night reveal a 1.89 odds ratio (OR) for obesity that increases by light exposure level.[100] A randomized trial of healthy subjects demonstrates increased postprandial insulin and glucose levels with exposure to bright light at night.[103] The quality of light also affects insulin resistance. Randomized trials of blue light, which mimics the light produced by screen devices (e.g., smartphones, tablets, and computers), demonstrate increased association with insulin resistance among healthy individuals.[100] In sum, the timing and quality of light exposure as part of a modern lifestyle, as well as timing of other factors that influence circadian rhythm, such as food intake and physical activity, are potential targets in the prevention of development and progression of DBCD.

30.9.5 Stress Reduction

Chronic stress impacts multiple systemic functions. In the case of DBCD, states of chronic stress activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to increased cortisol and catecholamine levels, and consequent worsened insulin resistance.[104] Glucagon levels are also elevated, and leptin resistance is observed, which may drive intake of calorie-dense food.[105] Additionally, consumption of palatable calorie-dense food may trigger endogenous opioid release, stimulating reward pathways and reinforcing poor food choice in response to chronic stress.[105] Stress, which may be psychological or non-psychological (such as systemic inflammation) in nature, is associated with increased cardiometabolic risk.[106] The INTERHEART study showed an OR of 1.55 (1.4–1.6 95% confidence interval [CI]) for cardiovascular events with high chronic stress, as well as significant ($p < 0.01$) OR for presence of T2D (2.6 in men, 4.2 in women), abdominal obesity (2.2 in both sexes), and reduced physical activity (0.48 in both sexes).[106] Sleep is also commonly disrupted by stress.[106] Methods for stress reduction can help to reverse these trends and should be included among lifestyle interventions for DBCD.[107,108]

30.9.6 Alcohol Intake

Alcohol intake is always a controversial topic, especially in the context of healthy lifestyle. Abstinence of alcohol is commonly promoted for health, including cardiometabolic health.[109] A meta-analysis of global health data suggests that any alcohol consumption is associated with increased risk.[110] However, other studies may suggest that moderate alcohol consumption may also promote favorable cardiometabolic risk.[111] Analysis of moderate alcohol consumption, especially when in the form of wine, demonstrates improvement in insulin resistance, as well as reduction in cholesterol levels and reduction in systemic inflammation.[112] At excessive levels, alcohol intake is associated with increased cardiometabolic risk, including higher rates of MetS, hypertension, and abdominal adiposity, as well as other general risks.[111,113] Another concern with alcohol consumption in patients with DBCD is the theoretical risk of accelerated hepatosteatosis.[114] It is currently unclear whether moderate alcohol consumption exacerbates this condition. In one small study, moderate alcohol consumption was not associated with increased hepatosteatosis among patients with obesity,[115] but more study is needed.

30.9.7 Endocrine Disruptors

Many chemicals with various industrial uses demonstrate biological properties that affect hormone signaling.

Common products that contain currently known endocrine disrupting compounds (EDCs) include plastic containers, toys, cosmetics, perfumes, paints, flame retardants, packaging material, insecticides, and fungicides, among many other sources. Most commonly, these EDCs affect reproductive and metabolic pathways.[116] A large number of EDCs have been associated with the development of DBCD. Among the most studied is bisphenol A, which is associated with weight gain and obesity as well as affecting adipokine signaling, which contributes to insulin resistance.[117,118] Additionally, bisphenol A blocks calcium and potassium channels of pancreatic β-cells, decreasing insulin release.[116] Similarly, the persistent organic pollutant tetrachloro-dibenzo-dioxin diminishes glucose entry into β-cells, also blunting insulin release.[116] Exposure to polychlorinated biphenyl compounds or organochlorine pesticide mixtures leads to reduced insulin activity in skeletal muscle and adipose tissue.[116]

Central control of metabolism within the hypothalamus may also be affected by EDCs. The flame retardant tetrabromobisphenol A reduces melanocortin-4 receptor activity within the arcuate nucleus, which leads to reduced thermogenesis and increased calorie consumption.[119] Many other EDCs can affect regulation of energy metabolism, leading to DBCD. As novel industrial chemicals are regularly introduced, continual study is needed. Implementation of methods to reduce EDC exposure to humans represents a form of primordial prevention and another underutilized lifestyle intervention in patients with DBCD.

30.10 CONCLUSIONS AND CONSIDERATIONS

DBCD spans the non-communicable conditions of insulin resistance, prediabetes, T2D, and vascular consequences, as well as the associated conditions of PCOS, OSA, GDM, hepatosteatosis, and hypertension, and presents a great societal disease burden. The extraordinarily high prevalence of DBCD stages 1 and 2, with potential for progression and complications, makes these early conditions prime targets for lifestyle medicine. Lifestyle interventions in the later DBCD stages 3 and 4 also yield significant benefits in complication rates and quality of life. Approaches should address multiple aspects of lifestyle, such as dietary pattern, exercise and physical activity, sleep hygiene and circadian rhythms, stress reduction, alcohol moderation or abstinence, and minimizing exposure to EDCs. Modern culture often promotes unhealthy choices in each of these areas, and this trend is progressing, leading to even more pressure for new paradigms of care for chronic metabolic diseases, such as the DBCD model. A successful program in lifestyle medicine should implement healthful choices and objectives for each stage of DBCD to maximally impact metabolic health of individuals and society as a whole.

SUMMARY OF CLINICAL APPLICATIONS AND TARGETS IN DBCD[1,7,52,86,99,107,109]

Dietary Pattern	High content of fruits, vegetables, legumes, nuts, providing high amounts of fiber and low in sodium
Physical Activity	At least 150 minutes over 5–7 days per week
Sleep Duration	At least seven hours nightly
Sleep Quality	Screen for disorders of sleep, especially OSA
Environmental Lighting	Bright lighting in the mornings and dim lighting in the evenings
Stress Reduction	Methods to reduce and minimize stressors
Alcohol Consumption	Abstinence or minimal intake
Endocrine Disruptors	Avoidance and minimization of exposure, where possible

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31 Context: Impact of Dysglycemia and Lifestyle Medicine on Cardiometabolic-Based Chronic Disease

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KEY POINTS

- Patients with dysglycemia are at high risk for cardiovascular disease.
- The cardiometabolic-based chronic disease model exposes opportunities for early and sustainable prevention of cardiovascular disease in patients with dysglycemia.
- Genetics, environment, and behavior are primary drivers, and dysglycemia is an important secondary/metabolic driver of cardiometabolic-based chronic disease.
- Cardiometabolic disease endpoints include coronary heart disease, heart failure, and atrial fibrillation.

31.1 INTRODUCTION

Dysglycemia-based chronic disease (DBCD) exerts a large impact on cardiometabolic-based chronic disease (CMBCD) development and progression in terms of measurable cardiovascular disease (CVD) endpoints. Importantly, DBCD is largely driven by abnormal adiposity, inflammation, and subsequent insulin resistance. In this chapter, the context of dysglycemia is emphasized, namely, the prevention of CVD. Specifically, the impact of lifestyle on abnormal adiposity and the impact of dysglycemia, as well as other metabolic factors, on CVD using the CMBCD model will be discussed.

CVD includes a wide spectrum of disorders affecting the heart and blood vessels, clustered into atherosclerosis and coronary heart disease (CHD; coronary artery disease [CAD] plus cardiac microvascular disease), heart failure (HF), and atrial fibrillation (AF). CVD is the leading cause of death in the world, and despite overall decreases in mortality rates, total CVD-related deaths appear to be increasing again due to population growth, aging, obesity, and type 2 diabetes (T2D) prevalence trajectories.[1–3] Additionally, increased CVD mortality trends are noted in the low- and middle-income socioeconomic and educational strata, as well as certain ethnocultural populations with unhealthy lifestyles, due to less access to effective preventive strategies.[4,5] Notwithstanding these population disparities, it is imperative that healthcare systems effectively promote lifestyle and risk factor modifications to prevent CVD for all people.

CVD is often first recognized when patients present with significant symptoms such as angina, acute coronary syndrome (ACS), stroke, HF, and claudication (as a manifestation of peripheral arterial disease [PAD]). These conditions often manifest after prolonged exposure to modifiable CVD risk factors, including dyslipidemia, T2D, smoking, hypertension, and obesity (conventionally defined as a body mass index [BMI] ≥30 kg/m^2 [≥25 kg/m^2 for Asians]).[6,7] The advent of statins as a low-density lipoprotein cholesterol (LDL-C) lowering therapy led to significant CVD risk reduction on a population level,[8] and high potency statins have been shown to lower CVD risk by 44%.[9] However, despite reduction in LDL-C, residual CVD risk remains, largely due to other unaddressed metabolic factors such as insulin resistance.[10] Given the burden of CVD borne by populations and individual patients, more effective prevention strategies are needed. Therefore, it is important to recognize CVD as a chronic disease process with opportunities for primordial, primary, secondary, and tertiary prevention that can lead to mitigation of end-stage CVD events, particularly advanced CHD and advanced HF requiring advanced therapies or transplantation.

31.2 WHAT IS CARDIOMETABOLIC-BASED CHRONIC DISEASE?

Cardiometabolic-based chronic disease describes a model for the identification and optimization of early risk factors for CHD, HF, and AF for delivery of sustainable preventive care.[11] The postulated architecture of this model begins with primary drivers (genetics, environment, and behavior) that establish a particular lifestyle and an array of secondary or metabolic drivers (abnormal adiposity, dysglycemia, hypertension, dyslipidemia, and residual risk factors, all associated with the metabolic syndrome [MetS]). The central abnormality in CMBCD is insulin resistance, occupying a locus where abnormal adiposity (adiposity-based chronic disease [ABCD]) and dysglycemia (DBCD) intersect. Even though any of the metabolic

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drivers can individually lead to CVD, a common scenario is the aggregate effect of these metabolic drivers, in varying levels of contribution and timing on the development and progression of CVD.

CMBCD can be divided into four stages: stage 1, risk; stage 2, predisease; stage 3, disease; and stage 4, complications. Stage 1 describes how primary and secondary drivers confer CVD risk. Stage 2 describes how the risk factors result in the predisease phenotype, such as the development of subclinical atherosclerosis. Stage 3 describes the presence of CMBCD as an early disease without symptoms: for example, diastolic dysfunction and signs of HF but without significant symptoms. Stage 4 describes symptomatic manifestations such as macrovascular CVD events (anginal coronary disease and myocardial infarction [MI] potentially requiring intervention). For clarity, several conventional terms can be interpreted within terms of the ABCD/DBCD/CMBCD models: "overweight" is ABCD stage 2; "obesity" is ABCD stage 3; "insulin resistance" is DBCD stage 1; "prediabetes" is DBCD stage 2; and "T2D" is DBCD stage 3. Also, the ABCD, DBCD, and CMBCD models all fall within a larger paradigm of "driver-based chronic disease," principally based on the causal relationships of key mechanistic drivers with chronic disease.[11]

31.3 PRIMARY DRIVERS OF CMBCD RISK

31.3.1 Genetics

The risk of developing CMBCD is driven by a complex interplay among genetics, environment, and behavior. Although it is known that family history plays a significant role in the development of CMBCD and CVD events, it has been difficult to pinpoint monogenic etiologies. Rather, CVD is inherited through a complex polygenic pattern resulting in variable phenotypic expression.[12] Although monogenic variants can still result in high-risk phenotypic conditions such as familial hypercholesterolemia, CAD is driven largely by single-nucleotide polymorphisms. Consequently, polygenic risk scores have been developed for CAD prediction, but most of these risk scores are suited to research and not routine clinical practice.[13] Furthermore, there is variability in the polygenic risk score based on ethnicity, limiting a generalized approach. For instance, certain polygenic risk scores have been developed and validated in European Caucasian populations and therefore may underestimate the risk in populations descended from African, South Asian, and Hispanic ancestries.[14–16]

In addition to genetic variants, gene regulatory networks play a significant role in the phenotypic expression of these variants and explaining the heritability of CAD.[17] Epigenetic regulation provides a logical explanation for how environment interacts with genes to create a specific phenotype. For example, epigenetic modifications arising *in utero* with maternal gestational diabetes may confer an insulin resistance phenotype in the offspring, which persists into adulthood, potentially leading to T2D, obesity, and CVD.[18,19] Additionally, newborns born to women with obesity tend to have thicker interventricular septa and reduced cardiac function as measured by global strain, strain rate, and tissue Doppler velocities compared with newborns born to women of normal weight.[20] As advances in genomics research continue to occur, it is expected that validated polygenic risk scores will be available for clinical application in CMBCD risk.

31.3.2 Environment, Behavior, and Lifestyles

Environment, which includes both the nonphysical (e.g., cultural) and the physical (e.g., built or human-made) environment, can significantly influence the risk of developing CMBCD and its progression. Particularly, socioeconomic strata, decreased access to quality healthcare, low education and literacy levels, air and noise pollution, and poor quality of drinking water are all associated with increased risk of CVD.[21] Exposure to persistent air pollution, particularly in urban environments, has been shown to be associated with increased CVD risk.[22,23] Increased exposure to fine particulate matter has also been shown to be associated with T2D. In a longitudinal cohort study of 1,729,108 participants, Bowe et al. found that increased exposure to fine particulate matter was associated with increased incident cases of and mortality from. Additionally, the burden of T2D was skewed more heavily toward low-income and lower-to-middle-income countries.[24]

A low socioeconomic stratum, particularly the lowest quartile, confers significant risk for the development of CMBCD. In a longitudinal cross-sectional analysis of CVD mortality trends from 1980 to 2014, lower literacy levels, poverty rates, and violent crime rates accounted for 60% of the variance in the CV mortality trajectory among 3,133 U.S. counties.[25] Additionally, individuals from these backgrounds have lower access to and utilization of preventive resources. These individuals are less likely to receive counseling, have annual checkups, participate in exercise, and receive smoking cessation counseling compared with high-income adults.[26] Additionally, low socioeconomic status is significantly associated with the incidence of T2D.[27] These factors combine to impel significant progression of CMBCD from stage 1 to eventually, stage 4.

Once genetics and environment have initialized physiological events leading to abnormal adiposity, insulin resistance, and CMBCD, individual behaviors can modulate this progression and expose opportunities for intervention. As an example, in at-risk patients with unhealthy dietary patterns, instituting healthy eating patterns can lower BMI, waist-to-height ratio, and waist circumference, resulting in lower CMBCD risk.[28] Lifestyle interventions in children, particularly through effective nutrition counseling and messaging, can potentially lead to increased knowledge and health literacy that can be sustained in the future.[29]. However, similar interventions in adults from low socioeconomic status were not found to be as sustainable, suggesting

that primordial prevention through promotion of healthy lifestyle habits needs to begin at an earlier age.[30]

Together, genetics, environment, and behavior play a significant role in classifying individuals as being in stage 1 of CMBCD, namely, exhibiting a lifestyle that is at risk for abnormal adiposity, insulin resistance, and downstream consequences of insulin resistance, including CVD. Although genomics continues to be an area of fascination for prediction of risk, this branch of study provides little utility for intervention. On the other hand, environmental stressors and behavioral factors continue to confer risk in people, especially those from low socioeconomic strata with poor health literacy. Policies geared toward intervening and supporting the lifestyles of these populations by addressing unhealthy aspects of the built environment and behavior may decrease the risk associated with the development and progression of CMBCD.

31.4 SECONDARY/METABOLIC DRIVERS OF CMBCD RISK

31.4.1 Adiposity-Based Chronic Disease

Once primary drivers and a resultant unhealthy lifestyle orchestrate physiological events that induce abnormal adiposity, insulin resistance ensues. In this fashion, ABCD is an early and critical secondary and metabolic driver of CMBCD. In addition, ABCD is a more scientifically accurate, actionable, and less stigmatized diagnostic term than obesity (which is more narrowly defined as ABCD stage 3), and was developed by the American Association of Clinical Endocrinologists (AACE) to describe the complex progressive disease that develops from abnormalities not only in the (increased) amount of adiposity, but also in the distribution and function of adiposity.[31]

Adipose tissue is made up of adipocytes, fibroblasts, vascular cells, lymphocytes, and macrophages. Excess caloric intake promotes recruitment of adipocyte precursors and resultant adipocyte hyperplasia. However, the hyperplastic response becomes impaired with aging, insulin resistance, and other disease states as well as with chronic overeating. This results in adipocyte hypertrophy and adipose tissue dysfunction.[32]

Abnormal adiposity has historically been viewed as excessive weight gain with abnormally increased BMI. However, the use of just weight gain and abnormally increased BMI to describe pathological adiposity has led to confusion, paradoxes, and therapeutic failures, since not all patients with obesity are insulin resistant, and individuals without obesity may still harbor an insulin resistant state despite not being obese. In fact, only about 11% of the individual variability in insulin sensitivity can be explained by differences in BMI.[33] Additionally, if weight gain occurs on an insulin resistant background, then asymmetric adipose tissue accumulation is favored, particularly in the intra-abdominal area. Furthermore, this adipose tissue can induce inflammation with influx of macrophages and abnormalities in circulating adipokines. Further weight gain can worsen insulin resistance and intensify inflammation, oxidative stress, and glucose intolerance.[33]

Abnormal distribution of adiposity is now understood as an intermediary step between excess calorie consumption (unhealthy lifestyle from primary drivers) and inflammation, leading to insulin resistance and CVD. Increased gluteofemoral subcutaneous adipose tissue is associated with entrapment of free fatty acids, which decreases ectopic free fatty acid uptake and therefore, exerts significant cardioprotective effects.[34,35] Conversely, increased adipose tissue accumulation in the intra-abdominal area is associated with increases in free fatty acid uptake in ectopic areas (liver, skeletal muscle, pericardium, epicardium, intestines, kidney, and pancreas) and therefore contributes to increased CVD risk.[33] Additionally, the presence of dysfunctional adipose tissue reflects inadequate accommodation of free fatty acids as fuel storage and therefore, more free fatty acids available to adversely affect the vasculature.[36]

Adipocytes release adipokines, which are regulatory peptides that produce a state of interconnectedness among the immune, endocrine-metabolic, and CV systems through autocrine/paracrine effects in adipose tissue and endocrine effects among multiple remote organs.[37] Within this network, the two most studied are adiponectin and leptin. Leptin acts in the hypothalamus to suppress appetite and food intake, increase energy expenditure, and regulate body weight.[38] Simply put, elevated levels of leptin signal satiety, whereas decreased levels signal hunger.

Abnormal adiposity also produces changes in adipokine signatures and consequent interactions with satiety centers in the hypothalamus, affecting eating behaviors. These changes promote increased caloric intake and therefore, maintenance of excess adipose tissue mass. In one study of 50 overweight/obese patients, despite persistent caloric restriction induced weight loss at one year, leptin levels remained decreased, as well as other maladaptive responses in satiety hormones, providing an explanation for the difficulty in maintaining weight loss with dietary changes.[39]

Additionally, ABCD can lead to hyperglycemia in the setting of insulin resistance by compromising the compensatory insulin secretion rate. In a murine model, obesity leads to increased macrophages in the pancreas, resulting in β-cell dysfunction and hyperglycemia. However, evidence of direct signaling from adipose tissue to β-cells is lacking. Other potential mechanisms linking abnormal adiposity with β-cell dysfunction include abnormal autophagy, apoptosis via IL-1β-FasL pathways, lipotoxicity, and others.[11] Adiposity is directly associated with inflammation; patients with ABCD stage 3 preferentially accumulate fat in the intra-abdominal compartment containing increased macrophages, which produce tumor necrosis factor (TNF)-α, IL-6, and MCP-1. In multiple studies of obese mice, white adipose tissue has been found to upregulate the transcription of inflammatory and macrophage-related genes.[40,41] Furthermore, this upregulation was found to precede a

dramatic increase in circulating insulin level, indicative of developing insulin resistance.[40]

In short, ABCD is a significant metabolic driver of inflammation, insulin resistance, hyperglycemia, and CMBCD, as once accumulation of dysfunctional adipose tissue occurs, there are multiple biological mechanisms in place to further ectopic fat distribution (Figure 31.1).

31.4.2 Dysglycemia-Based Chronic Disease

Dysglycemia refers to abnormal glucose physiology and comprises insulin resistance, prediabetes, and T2D. Similarly to CMBCD, DBCD refers to a framework with implications for intervention to prevent the progression from insulin resistance to β-cell defects causing hyperglycemia (mild/early = prediabetes; more severe/late = T2D) and vascular complications (macrovascular from insulin resistance; microvascular from hyperglycemia).[42] More specifically, insulin resistance leads to CVD, specifically CHD and HF, through direct effects on glucose homeostasis, alterations in lipids and lipoproteins, inflammation, vascular endothelium, and cardiac metabolism (Figure 31.2).

31.5 PATHOPHYSIOLOGY OF DBCD IN THE PROGRESSION OF CMBCD

Glucose homeostasis occurs as insulin is secreted by the pancreatic β-cells via glucose sensing and metabolism-–secretion coupling, and then insulin promotes glucose uptake in skeletal muscle, hepatocytes, and other tissues to maintain a euglycemic state. However, once insulin resistance occurs as a result of abnormal adiposity, inflammation, and/or genetic predispositions, pancreatic β-cells have to compensate and increase insulin secretion. Over time, as insulin resistance progresses, insulin secretion becomes insufficient, and hyperglycemia (fasting and/or postprandial, depending on primary and secondary drivers) ensues.[42] Hyperglycemia leads to the formation of advanced glycation end-products (AGE), which can generate reactive oxygen species, thereby increasing oxidative stress on the artery wall. Additionally, hyperglycemia enhances monocyte adhesion to endothelial cells by activation of nuclear factor kappa beta (NF-κβ).[43]

Insulin plays a role in the regulation of lipid metabolism; it promotes storage of triglycerides and inhibits lipolysis in adipose tissue.[43] Insulin also reduces hepatic very low-density lipoprotein (VLDL) production due to its effect on reducing the availability of free fatty acids.[43] Furthermore, insulin also reduces apolipoprotein B production and is a potent activator of lipoprotein lipase, promoting the catabolism of triglyceride-rich lipoproteins. Insulin also increases low-density lipoprotein (LDL) receptor expression on the surface of hepatocytes, increasing LDL clearance from the plasma.[44]

Given insulin's significant role in lipid metabolism, insulin resistance leads to increased plasma triglycerides, reduced high-density lipoprotein (HDL) cholesterol, increased hepatic VLDL production, and increased LDL particle concentration without necessarily a change in LDL-C levels.[43] The high levels of VLDL are due to increased hepatic production coupled with reduced lipoprotein lipase activity and catabolism of VLDL.[43] The high levels of VLDL combined with the actions of cholesteryl ester transfer protein (CETP) and hepatic lipase lead to increases in small dense LDL particle generation. This is because CETP works to transfer triglycerides to HDL and LDL in exchange for cholesterol esters to VLDL and chylomicrons. The triglyceride-rich LDL is a substrate for hepatic lipase, which works to generate small dense LDL particles,[45] which are known to be proatherogenic and associated with increased risk of atherosclerotic CVD.[46]

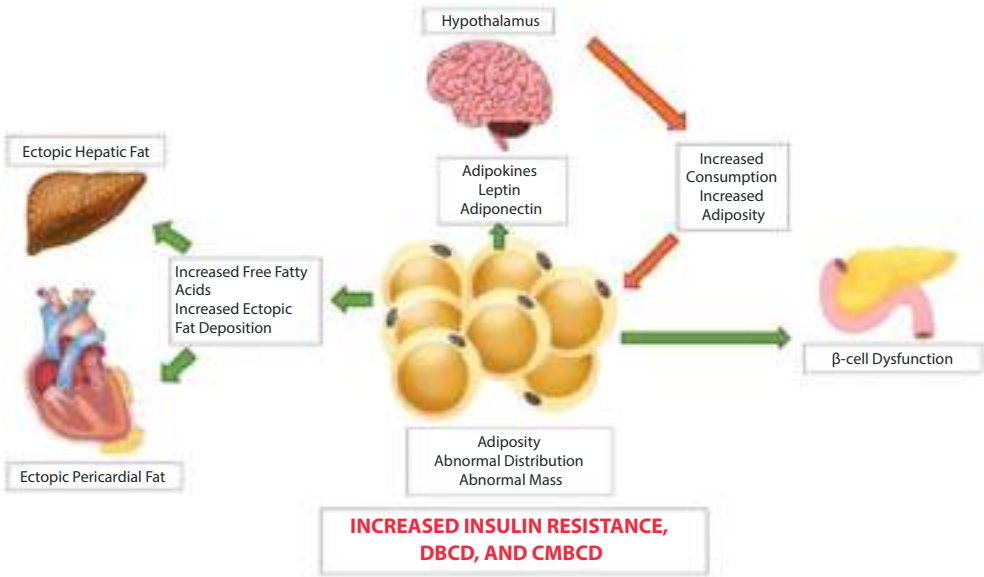


FIGURE 31.1 Mechanistic drivers of insulin resistance due to abnormal adiposity. CMBCD = cardiometabolic-based chronic disease; DBCD = dysglycemia-based chronic disease.

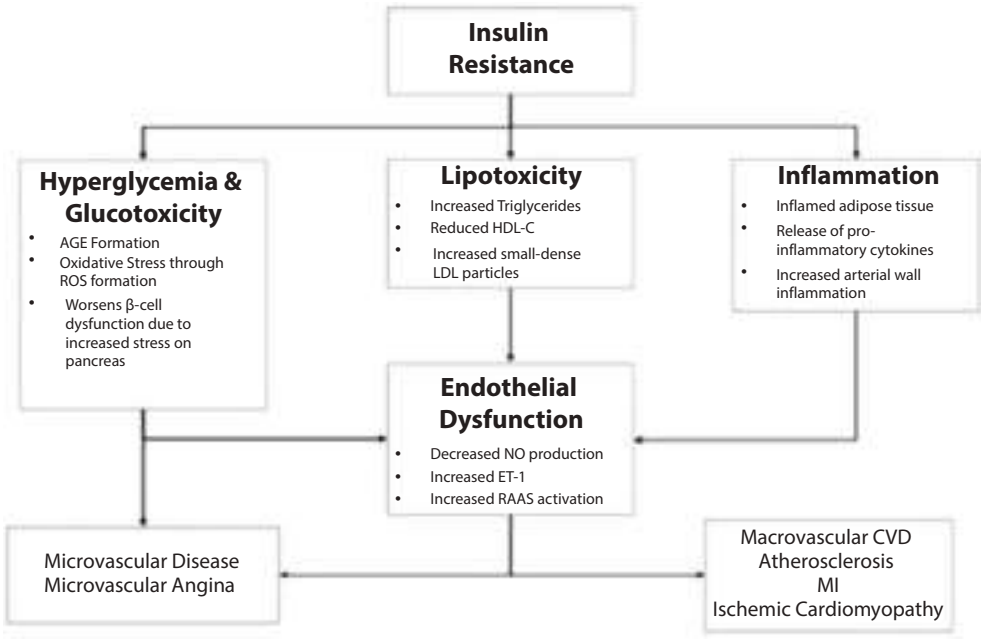


FIGURE 31.2 Mechanistic drivers of microvascular and macrovascular disease due to insulin resistance. AGE = advanced glycation end-products; CVD = cardiovascular disease; ET-1 = endothelin-1; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NO = nitric oxide; RAAS = renin-angiotensin-aldosterone system; ROS = reactive oxygen species.

Insulin resistance also leads to inflammation, which compounds the effects of dyslipidemia and hyperglycemia, specifically, inflammation of adipose tissue. This leads to the release of proinflammatory cytokines and subsequent oxidation of triglyceride-rich lipoproteins. Also, the hyperglycemic state promotes glycation of small dense LDL. These lipoprotein particles are rendered proinflammatory and induce an immune response causing macrophage activation and vascular wall inflammation, resulting in coronary plaque genesis and progression.[47,48]

Insulin resistance also has direct effects on the vascular endothelium, leading to vascular smooth muscle progression and coronary artery stenoses. Insulin signaling regulates endothelial nitric oxide synthase activity and production of the vasodilator nitric oxide. With the development of insulin resistance, the ability to produce nitric oxide is inhibited, causing increased vasoconstriction. Additionally, hyperinsulinemia in the insulin resistant state leads to increased endothelin-1 production via the mitogen-activated protein kinase (MAPK) signaling pathway, yielding further vasoconstriction and promotion of vascular smooth muscle cell proliferation.[49] Additionally, insulin resistance has been linked to increased signaling in the renin-angiotensin-aldosterone system (RAAS), leading to impaired vascular relaxation and increased production of reactive oxygen species.[50] Furthermore, this contributes to increased incidence of hypertension and progression of CMBCD in patients with insulin resistance.

Insulin resistance also affects the myocardium. With enhanced lipolysis and increased availability of free fatty acids, there is increased ectopic lipid accumulation, resulting in myocardial lipotoxicity. Intracellular inflammatory factors, mitochondrial dysfunction, and oxidative stress impair insulin signaling and lead to activation of NF-κβ-mediated pathways that enhance myocyte inflammation.[51] The myocardium preferentially relies on free fatty acids for fuel. With ischemia, the heart switches to glucose for fuel. However, in the insulin resistant state, the ability to utilize glucose as a substrate for fuel for the myocyte is impaired, and when combined with endothelial dysfunction, increased activation of the RAAS, and increased inflammation and oxidative stress, structural dysfunction can result, typically ischemic cardiomyopathy with a reduced ejection fraction.

Alternatively, HF can manifest with preserved ejection fraction. Repeated cellular injury and abnormalities in contractile proteins in the setting of diabetes and insulin resistance can lead to cardiac tissue interstitial fibrosis and therefore, cardiac stiffness. Cardiac stiffness impairs the myocardial relaxation during diastole. The result is HF with preserved ejection fraction (HFpEF) accompanied by left atrial dilation and increased left ventricular (LV) mass. Left atrial dilation often leads to AF and therefore, worsens HFpEF.[52] Table 31.1 summarizes the pathophysiological effects of adiposity and dysglycemia on CVD.

31.6 THE PROGRESSION FROM INSULIN RESISTANCE TO CVD

Insulin resistance is a consequence of abnormal adiposity, particularly ABCD stage 2 (overweight) and stage 3 (obesity). Insulin resistance also represents the DBCD

TABLE 31.1
Key Effects of Adiposity and Dysglycemia on CVD

Effect	Coronary Heart Disease	Heart Failure	Atrial Fibrillation
ABCD	↑ Prevalence↑ CAC progression	↑ HFpEF	↑ Prevalence↑ Peri/epicardial adipose tissue
DBCD	↑ Platelet reactivity↑ Risk of MI↓ Myocardial perfusion	↑ ECV↑ HFpEF↑ Microvascular disease↑ Diastolic dysfunction↑ Cardiac lipotoxicity↓ Myocardial performance	↑ Prevalence
MetS	↑ Prevalence↑ Coronary plaques↓ Prognosis after first ACS	↑ Prevalence	↑ Prevalence

ABCD = adiposity-based chronic disease; ACS = acute coronary syndrome; CAC = coronary artery calcium; DBCD = dysglycemia-based chronic disease; ECV = extracellular volume; HFpEF = heart failure with preserved ejection fraction; MetS = metabolic syndrome; MI = myocardial infarction.
Source: adapted from Mechanick, J.I., et al., *Journal of the American College of Cardiology*, 75(5), 525–538, 2020.

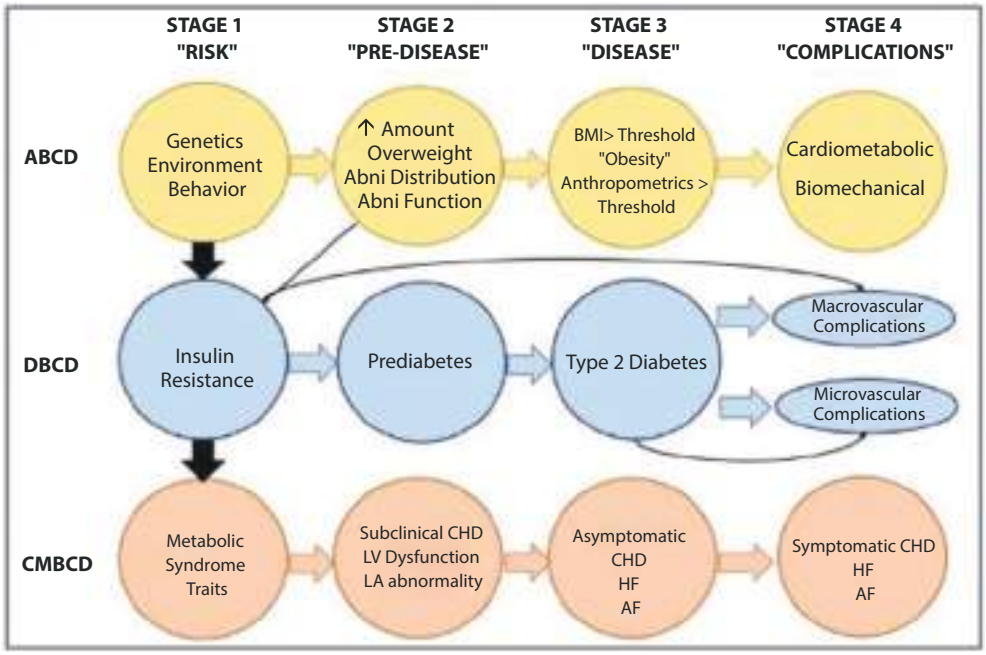


FIGURE 31.3 The driver-based models of chronic disease.The black arrows indicate the relationships between the different metabolic drivers and CMBCD. DBCD impels CMBCD. ABCD = adiposity-based chronic disease; AF = atrial fibrillation; BMI = body mass index; CHD = coronary heart disease; CMBCD = cardiometabolic-based chronic disease; DBCD = dysglycemia-based chronic disease; HF = heart failure; LA = left atrium; LV = left ventricle. (Adapted from Mechanick, J.I., et al., ***Journal of the American College of Cardiology***, 75(5), 525–538, 2020.)

stage 1 and can impel progression to DBCD stage 2 (prediabetes), stage 3 (T2D), and stage 4 (vascular complications) through various pathophysiological pathways. Furthermore, each stage of ABCD and DBCD can lead to progression of CMBCD alone or in combination with other metabolic drivers (i.e., the interactive array of MetS traits). As CMBCD progresses, asymptomatic phenotypes deteriorate into symptomatic phenotypes, which then often require urgent intervention. Figure 31.3 displays the imputation of the ABCD and DBCD models into CMBCD risk and progression.

The intent of building and implementing these driver-based chronic disease models in the cardiometabolic space is to identify early targets for prevention of severe DBCD, CVD complications, and events. Early targets are preferred over later targets when possible. Early targets include unhealthy lifestyles, abnormal adiposity, and insulin resistance, and are primarily managed with intensive lifestyle change. Later targets are addressed with coronary revascularization for CAD via coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), advanced therapies such as left ventricular assist devices or transplantation for advanced ischemic cardiomyopathy leading to ventricular arrhythmias, and pharmacotherapy/electrophysiological ablations for AF. Compared with lifestyle interventions to address early targets, addressing these

later events is riskier and more costly. It is important to note that there is an evidence-based role for the addition of judicious pharmacotherapy with lifestyle change when addressing early targets, such as insulin resistance. The most recent iteration of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for primary prevention recommends the initiation of anti-glycemic therapies once the hemoglobin A1c (A1C) is greater than 6.5%.[53] However, it is well known that insulin resistance begins at A1C levels below 6.5%, and the lifetime risk of insulin resistance progressing to T2D is 70–74%.[54,55] Furthermore, insulin resistance and prediabetes are independently associated with increased risk of atherosclerotic CVD and increased CVD morbidity and mortality despite the lack of progression to T2D.[56,57]

31.7 PROGRESSION FROM HYPERGLYCEMIA TO CMBCD

In DBCD stages 3 and 4, hyperglycemia with a backdrop of insulin resistance is highly impactful on the prevalence of CHD. Through direct effects of hyperglycemia and hyperinsulinemia, the coronary vasculature has progressive plaque development that leads to atherosclerotic CVD. Progressive plaque development leads to the CMBCD stage, and particularly CHD. Patients with advanced T2D present with stable angina and are at increased risk for MI. Stable angina is a result of progressive vascular smooth muscle proliferation, leading to fibrous plaque formation, and eventually, the stenoses progress to cause symptoms of exertional angina. The increased risk for MI is due to significant atherosclerotic plaque burden, and plaque confers risk for ACS due to rupture. Additionally, patients with diabetes tend to have more aggressive atherosclerosis, more diffuse coronary lesions, smaller coronary vessels, and more extensive disease. For this reason, T2D is associated with a two- to four-fold increased mortality from heart disease.[58]

Additionally, the presence of T2D significantly affects revascularization strategies for patients with CHD, and this should be considered an additional impetus to prevent the progression of insulin resistance to T2D. Due to the increased risk of repeat revascularization, patients with T2D tend to experience a higher mortality rate.[59] Multiple clinical trials have led to the conclusion that patients with T2D and multivessel disease, defined as the presence of obstructive CAD in at least two vessels, should undergo revascularization with CABG to improve mortality.[60,61] Additionally, patients with T2D requiring revascularization often present with ischemic cardiomyopathy, as the insulin resistant state drives lipotoxicity, inflammation, and fibrosis in the myocardium. Revascularization of ischemic cardiomyopathy has shown mortality benefits over the long term, but in the short term, there is significant upfront risk of morbidity and mortality.[62] Overall, the impact of DBCD stages 3 and 4 on CVD is well defined and is significantly linked to cardiovascular morbidity and mortality.

31.8 DIFFERENTIATING THE RELATIONSHIPS BETWEEN TYPE 1 AND TYPE 2 DIABETES AND CMBCD

The focus of the DBCD model is on the prevention of progression of insulin resistance to T2D. However, type 1 diabetes mellitus (T1D) has a significant impact on CMBCD, albeit different from that of T2D. The central pathophysiological abnormality causing hyperglycemia in T1D is the absence of insulin production, typically due to autoimmune destruction of β-cells, whereas in T2D, it is insulin resistance and a subsequent β-cell defect. Since the insulin deficiency and resultant hyperglycemia are generally earlier in patients with T1D compared with T2D, it is not surprising that these patients with T1D have an almost threefold higher mortality than the general population, driven mainly by premature atherosclerotic disease.[63,64]

Hyperglycemia due to T1D results in significant downstream effects from an early age. Increased glucose in the bloodstream results in protein glycation, and early-stage protein glycation products undergo complex reactions, such as oxidation, dehydration, and condensation to form AGEs. These AGEs are not easily metabolized and tend to accumulate more in those with a history of inadequate glucose control. Additionally, these AGEs accelerate the progression of vascular disorders.[65] In one study of 105 Japanese patients with T1D, there was increased presence of skin AGEs in patients with T1D compared with healthy control patients, indicative of early presence of AGEs in skin vasculature.[66] Given the predilection of AGEs for the microvasculature, patients with T1D tend to present with microvascular dysfunction in various arterial beds, particularly diabetic nephropathy, which can further contribute to CMBCD and CVD risk.[63] The findings of the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) Study revealed that intensive treatment to achieve strict glucose control versus conventional therapy resulted in significant benefits regarding CVD risk.[67,68]

Due to the presence of hyperglycemia, patients with T1D are more likely to present with atherosclerotic microvascular complications, including chronic kidney disease (CKD), PAD, and microvascular dysfunction in the heart. These microvascular complications result in angina that is not treatable by epicardial coronary interventions. Additionally, the microvascular angiopathy can lead to diastolic dysfunction and HFpEF, and when coupled with CKD, these patients often have chronic chest discomfort and shortness of breath.

The cardiovascular manifestations of T1D are different from those of T2D due to their varying pathophysiological mechanisms. Because T2D is due to insulin resistance, hyperglycemia and its consequences may take years to manifest, as the pancreas is initially capable of secreting more insulin to overcome the resistance. Therefore, as

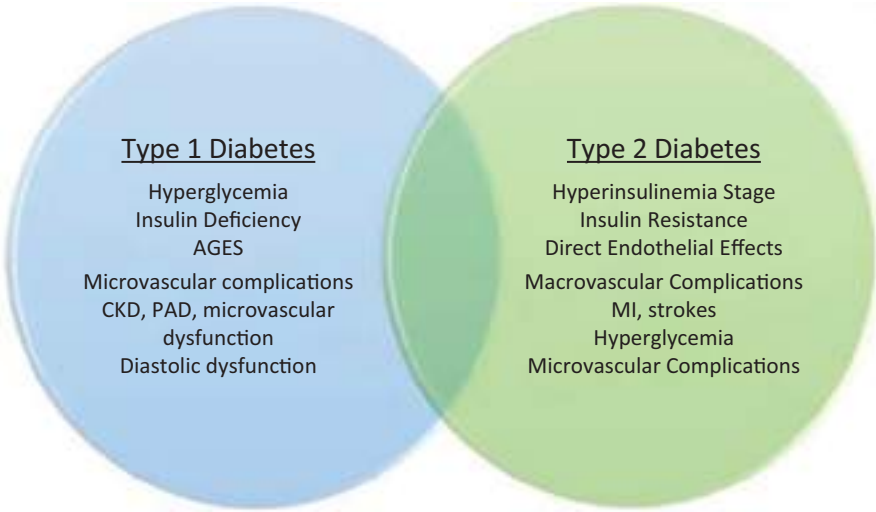


FIGURE 31.4 Type 1 versus Type 2 diabetes with regard to cardiovascular manifestations. AGEs.= advanced glycation end-products; CKD = chronic kidney disease; MI = myocardial infarction; PAD = peripheral artery disease.

TABLE 31.2
Cardiometabolic-Based Chronic Disease Prevention Types, Targets, and Features

Primordial	Primary	Secondary	Tertiary	Quaternary
Targets: • Environment • Behavior • CMBCD Stage 1	Targets: • Insulin resistance • Subclinical atherosclerosis • CMBCD Stage 2	Targets: • T2D • Coronary artery disease • CMBCD Stage 3	Targets: • Ischemic CHD • HFpEF • CMBCD Stage 4	Ethical behavior: • Avoid over-medicalization • Avoid action if in doubt • Judicious use of pharmacotherapy
Interventions: • Screening • Lifestyle education • Behavioral programs • Nutrition education • Aerobic physical activity • Progressive resistance training	Interventions (Primordial prevention plus): • Body imaging • Weight-loss medications • Metformin • Statins	Interventions (Primary prevention plus): • Diagnostic testing • Risk stratification • SGLT2i/GLP1ra • Other pharmacology	Interventions (Secondary prevention plus): • Cardiac catheterization/PCI • Surgical procedures • ↑ Cost • ↑ Iatrogenesis	

CHD = coronary heart disease; CMBCD = cardiometabolic-based chronic disease; GLP1ra = glucagon-like peptide 1 receptor agonist; HFpEF = heart failure with preserved ejection fraction; PCI = percutaneous coronary intervention; SGLT2i = sodium-glucose cotransporter-2 inhibitors; T2D = type 2 diabetes.

Source: Adapted from Mechanick, J.I., et al., *Journal of the American College of Cardiology*, 75(5), 539–555, 2020.

it takes time for the hyperglycemia to develop, the CVD manifestations in patients with T2D are more due to the direct effects of increased insulin resistance on the endothelium, including increased inflammation, oxidative stress, and vasoconstriction, which if left uncontrolled, can lead to macrovascular complications in the epicardial vessels. However, as DBCD progresses in the patient with T2D toward significant hyperglycemia, microvascular complications result as they do in patients with T1D. Figure 31.4 delineates the differences in the cardiovascular manifestations between patients with T1D and T2D.

31.9 CMBCD IDENTIFICATION OF DYSGLYCEMIA TARGETS FOR LIFESTYLE INTERVENTION

The CMBCD model is designed to identify targets for intervention prior to the onset of significant CVD, and even before significant T2D and insulin resistance. The specific prevention modality that can be implemented depends on the particular DBCD/CMBCD stage-dependent target. Prevention modalities are primordial, primary, secondary, tertiary, and quaternary (Table 31.2).

31.10 PRIMORDIAL PREVENTION OF DYSGLYCEMIA RISK AND PREDIABETES IN CMBCD STAGE 1 USING LIFESTYLE MEDICINE

Primordial prevention targets stage 1 of driver-based chronic disease models. The targets are primary drivers that modify behavior and environment to prevent the development of MetS traits. In ABCD, the goal is to prevent the accumulation of dysfunctional adipose tissue. In DBCD, the goal is to prevent insulin resistance. In CMBCD, the goal is to prevent MetS traits or the initiation of any secondary/metabolic driver of CVD. Primordial prevention is therefore implemented using lifestyle medicine interventions, e.g., adopting a healthy lifestyle, preventing abnormal weight gain, promoting healthy dietary habits, and encouraging regular aerobic exercise.[69] Additionally, government policies at the local and national levels are typically needed to promote healthy lifestyles, especially for underserved populations.

31.11 PRIMARY PREVENTION OF T2D IN CMBCD STAGE 2 USING LIFESTYLE MEDICINE

Primary prevention targets stage 2 of driver-based chronic disease models. For ABCD, the target is to focus on detection and reduction of abnormal adipose tissue through exercise and resistance training. For DBCD, the focus is prediabetes and preventing the progression to T2D. In ABCD stage 2, control of adiposity with weight loss and healthy lifestyles will help prevent DBCD stages 2 and 3. Both ABCD and DBCD stage 2 contribute to the definition of CMBCD stage 2, which is defined as subclinical atherosclerotic disease, HF, or electrical disease, typically detected with specialized cardiac testing. Interventions for both ABCD and DBCD stage 2 involve lifestyle interventions but can also include guideline-directed pharmacology; metformin is historically the favored agent for primary prevention of T2D.[31,42] However, one may consider other medications that are associated with weight loss and glycemic control, as well as cardio- and renal protection (e.g., sodium-glucose cotransport-2 inhibitors or glucagon-like peptide-1 receptor agonists), in ABCD/DBCD stage 2.[69]

31.12 SECONDARY PREVENTION OF T2D COMPLICATIONS IN CMBCD STAGE 3 USING LIFESTYLE MEDICINE

Secondary prevention targets stage 3 of driver-based chronic disease models. ABCD stage 3 refers to obesity, which is strictly defined by BMI only; DBCD stage 3 refers to T2D, which is strictly defined by glucose or A1C levels only; and CMBCD stage 3 refers to atherosclerotic CAD/CHD (and other atherosclerosis of other arterial beds) without symptoms, cardiac dysfunction without symptoms, specifically diastolic dysfunction, and AF without symptoms. At this stage, the goal is to modify the cardiovascular risk factors and prevent CVD events, such as worsening HF or ischemic CHD requiring revascularization, and prevent strokes and myocardial infarctions. Treatment of stage 3 ABCD/DBCD stage 3 includes lifestyle change, but for stage 3 DBCD, pharmacology is usually required. Metformin is historically first-line therapy for T2D treatment. However, glucagon-like peptide-1 receptor agonists have shown significant benefit in cardiovascular outcomes, have been particularly effective in helping with weight loss, and should be considered at this stage. given the ability to prevent progression of both ABCD and DBCD.[70,71] Sodium-glucose cotransport-2 inhibitors have also shown significant benefit in patients with CVD[72,73] and are increasingly utilized in cardiovascular clinical practice to treat patients with CHD and HF.[74] At CMBCD stage 3, cardiovascular testing may be requested to assess atherosclerotic burden with coronary computed tomography imaging. One can also consider nuclear perfusion imaging testing to assess for obstructive CAD. Of note, bariatric surgery may be considered in higher risk ABCD stage 3, as multiple studies have demonstrated that bariatric surgery not only reduces excess weight long term but also leads to reduction in T2D, HTN, and dyslipidemia.[75,76]

31.13 TERTIARY PREVENTION OF COMPLICATIONS, MORBIDITY, AND MORTALITY IN CMBCD STAGE 4 USING LIFESTYLE MEDICINE

Tertiary prevention targets stage 4 of driver-based chronic disease. At this stage, complications of adiposity and dysglycemia have occurred, including both microvascular and macrovascular complications. The patient may have developed clinical CAD, presents with symptoms of exertional angina, and requires revascularization. Alternatively, the patient has progressed from diastolic dysfunction to HF with preserved, mid-range, or reduced ejection fraction and may be hospitalized for decompensated heart failure. Or, the patient with AF develops incapacitating symptoms and is at high risk for stroke. At this stage, the goal is to manage the disease burden and symptoms and prevent recurrence of events, such as need for revascularization procedures, MI/stroke, heart failure hospitalizations, and/or electrophysiological studies, ablations, and other procedures. Preventive interventions at this stage can be costly, and future efforts should focus on reducing these costs of healthcare and the overall economic burden to the healthcare system. At this stage of CMBCD, there is also increased risk of mortality from the disease or the procedure.

31.14 QUATERNARY PREVENTION OF OVER-MEDICALIZATION IN DYSGLYCEMIA CARE IN ALL STAGES OF CMBCD

Quaternary prevention is a relatively new concept to identify patients who are at risk for over-medicalization and

to therefore prevent unnecessary testing and potentially harmful interventions. Quaternary prevention is represented by ethical behavior by the healthcare professional and is applied at all stages of ABCD, DBCD, and CMBCD. Lifestyle interventions must be prioritized at all stages of CMBCD, and when necessary, pharmacotherapy and procedures should be utilized judiciously.[77]

CLINICAL APPLICATIONS

The ABCD, DBCD, and CMBCD models have significant clinical applications, which are summarized here. Early recognition of risk factors for the development of adiposity and discussion of lifestyle interventions with patients at the initial visit are important. Additionally, these clinical visits require assessing the presence of stage 1 and stage 2 of these driver-based chronic disease models by checking height, weight, BMI, waist to hip ratio, blood pressure, A1C, and a lipid panel. An early assessment of these sometimes overlooked factors can allow prompt classification into one of the stages of the models. facilitating a lifestyle medicine care plan. In short, it is recommended that these classification systems be utilized to promote earlier identification of risk factors to prevent progression to more significant disease.

31.16 CONCLUSIONS

In the CMBCD model, the main drivers of progression of CMBCD are adiposity and dysglycemia, modeled as ABCD and DBCD, respectively. The nascence of CMBCD stage 1 begins with abnormal adiposity, defined as abnormal amount, distribution, and function of adipose tissue. ABCD drives insulin resistance and progression of hyperglycemia, leading to significant effects on the macro- and microvasculature and the structural function of the heart. The CMBCD model provides a practical guide for early intervention and prevention of progression of CMBCD to stages 3 and 4.

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32 Management: Lifestyle Medicine Approaches to Insulin Resistance, Prediabetes, Type 2 Diabetes, and Diabetes Complications

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KEY POINTS

- Given the growing prevalence of type 2 diabetes, awareness of insulin resistant and prediabetes states, and the need for early and sustainable preventive care, the dysglycemia-based chronic disease (DBCD) model was developed with a focus on reducing cardiometabolic risk and cardiovascular event rates.
- Lifestyle interventions focused on healthy dietary patterns, such as Mediterranean diets, regular physical activity, stress reduction, and sleep hygiene, and behavioral interventions utilizing mobile technology have a role in preventing the progression of type 2 diabetes.
- Large-scale lifestyle interventions, such as the Diabetes Prevention Program (DPP), which randomized subjects with impaired fasting glucose or impaired glucose tolerance to a curriculum focused on diet, physical activity, and weight loss, have shown significant benefit in reduced progression toward type 2 diabetes.
- The Look AHEAD study is the largest study assessing the benefit of an intensive lifestyle intervention in patients with type 2 diabetes and obesity; however, the intervention was not associated with a reduction in cardiovascular outcomes.
- While management of patients with uncontrolled type 2 diabetes with severe complications tends to be focused on pharmacological therapy and surgery, healthy dietary patterns, such as Mediterranean diets, and daily physical activity, in combination with the use of dietary supplements and nutraceuticals, may reduce disease progression.

32.1 INTRODUCTION

More than 34 million Americans (about 1 in 10) have diabetes, according to the National Diabetes Statistics Report for 2020 by the Centers for Disease Control and Prevention.[1] Patients with type 2 diabetes (T2D) are affected by microvascular and macrovascular (including cardiovascular [e.g., coronary heart disease, peripheral vascular disease, and cerebrovascular disease]) complications.[2] Moreover, diabetes and its complications are extremely costly, both resulting in loss in quality of life and incurring greater than $300 billion annually in healthcare expenditures, including costs of anti-hyperglycemic medications, diagnostic and therapeutic procedures, hospitalizations, and other aspects of chronic care.[1,3,4] While glycemic control and prevention of diabetes complications are crucial, there is significant value in focusing on interventions that are known to specifically delay the onset, slow the progression, and/or prevent diabetes and consequent complications altogether.

Dysglycemia is defined as any abnormality in glycemic status that is associated with disease or the potential for disease. The dysglycemia-based chronic disease (DBCD) model was created by the American Association of Clinical Endocrinology (AACE) and characterizes four distinct stages (risk, predisease, disease, and complications) that are actionable to reduce the potential impact of T2D, cardiometabolic risk, and cardiovascular events.[5] The DBCD care model prompts early intervention, emphasizes structured lifestyle change, and focuses on mitigation of progression from one stage to a subsequent worse stage, thereby lowering risk, morbidity, suffering, costs, and mortality.[6] From a pragmatic standpoint and to clarify nomenclature, prediabetes is DBCD stage 2, and T2D is DBCD stage 3.

A healthy lifestyle has been shown to reduce mortality, and numerous evidence-based, clinical practice guidelines support lifestyle medicine as an effective approach in the prevention, treatment, and reversal of chronic diseases, such as cardiovascular disease (CVD), diabetes, obesity, and cancer.[7–9] In the United States and other countries, lifestyle interventions have been shown to be extremely effective for T2D prevention in terms of cost, number of diabetes cases prevented, and quality-adjusted life years (QALYs).[10–12] For example, a clinical trial by Herman et al.[13] showed

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that lifestyle intervention was not only cost-effective in all age groups, but effectively delayed the development of T2D by approximately 11 years, compared with metformin, which delayed the development of T2D by only 3 years. Given the chronic nature of diabetes and the increased costs associated with its progression, lifestyle medicine is especially important in delaying diabetes onset. This chapter highlights various DBCD stage–specific lifestyle interventions (including dietary patterns, physical activity, stress management, sleep hygiene, behavioral changes, glucose monitoring technologies, and legislation) with a spotlight on mitigating disease progression.

32.2 DBCD STAGE 1: INSULIN RESISTANCE

32.2.1 General Concepts

Insulin resistance is the earliest stage (stage 1) of DBCD and starts at birth, involving various factors, such as molecular risk for islet-cell dysfunction and genomic/epigenomic risk.[5] The prevalence of insulin resistance ranges from 15.5% to 46.5% among adults worldwide, and approximately 40% of American adults aged 18–44 years without diabetes have insulin resistance.[14–16]

In the insulin resistant state, there is reduced biological effect for any given concentration of insulin, and this can occur physiologically or pathologically.[17] There are no commercially available molecular screening tests to detect the molecular risk for islet-cell dysfunction.[5] However, there are some quantitative estimates of insulin resistance, two of which are the euglycemic clamp test and the homeostasis assessment model for insulin resistance (HOMA-IR), which correlate well ($p < 0.0001$).[18] The "gold-standard" test is the euglycemic clamp, which is useful for smaller studies and measures stimulated insulin resistance.[17] HOMA-IR estimates basal (compared with stimulated) insulin resistance, is more appropriate for large epidemiological studies, and is a mathematical model obtained when fasting plasma glucose and fasting insulin/c-peptide concentrations are available.[17]

32.2.2 Drivers

32.2.2.1 Family History of T2D

Family history (FHx) of T2D is associated with increased risk for insulin resistance in various populations of different ages and ethnicities.[19–22] In a cross-sectional analysis by Anderwald et al.[19] (N = 1,048 healthy European adults), a positive FHx of T2D is associated with insulin resistance using the hyperinsulinemic clamp test. Specifically, the M-value was lower in those patients with a FHx of T2D (indicating a greater degree of insulin resistance) when compared with patients without a FHx of T2D or patients with a FHx of CVD alone ($p < 0.02$).[19] Another study by Zhu et al.[20] found that Chinese patients with a positive FHx of diabetes benefit more from lifestyle interventions than those without a positive FHx, irrespective of age, baseline body mass index (BMI), waist circumference, sex, and weight change.

32.2.2.2 Abnormal Adiposity

Abnormal adiposity results from the net effect of primary drivers (genetics, environment, and behavior), which determine one's lifestyle, healthy or unhealthy.[23] Adiposity-based chronic disease (ABCD) also consists of four stages (risk, predisease, disease, and complications) but incorporates abnormal distribution and function of fat in addition to abnormally high amounts.[23] ABCD, along with DBCD and hypertension- and dyslipidemia-based chronic disease, is a secondary, or metabolic, driver of cardiometabolic-based chronic disease (CMBCD). In these frameworks, overweight is ABCD stage 2, and obesity is ABCD stage 3 (Figure 32.1).[23]

ABCD in general, and obesity in particular, leads to insulin resistance and hyperinsulinemia through impaired insulin signaling, but inversely, insulin resistance can lead to obesity through various mechanisms studied in both rodents and humans.[24] These relationships between obesity and insulin resistance are seen across all ethno-cultural populations and across a full range of body weights.[24] The risk for T2D and insulin resistance rises as body fat content increases.[24] Moreover, central/visceral (intra-abdominal) fat depots are more strongly linked to insulin resistance than peripheral fat depots.[25] In a cross-sectional study in Lebanon of 286 subjects (134 males, mean age 43.7 years), a higher proportion of men with obesity were insulin resistant (42.9%) compared with not insulin resistant (18.3%, $p > 0.001$) and had higher body fat, waist circumference, and glucose and insulin levels.[16]

32.2.2.3 Stress

Chronic stress has been recognized as an independent risk factor for insulin resistance, especially given the effects of increased cortisol levels on blood glucose levels and fat accumulation.[26] Recent studies have also looked at the role of acute stress in insulin resistance: Li et al.[27] conducted glucose/insulin tolerance tests in mice exposed to an acute psychological stressor (foot shock and behavioral escape test). Mice exposed to the foot shocks had abnormal glycemic responses when compared with normal mice, implicating a hepatic mechanism.[27] Yan et al.[26] measured the degree of insulin resistance by HOMA-IR and job-related psychosocial stress (via the Copenhagen Psychosocial Questionnaire) in 766 Chinese workers. There was a significant association with insulin resistance with respect to specific scales on the questionnaire, and cortisol was positively correlated with HOMA-IR and found to be an independent positive predictor for HOMA-IR ($p < 0.05$).[26]

32.2.2.4 Sleep Hygiene

The quality and quantity of sleep affect insulin resistance and therefore, both T2D and obesity. To start, obstructive sleep apnea (OSA) is found in 71% of people with diabetes and characterized by intermittent hypoxia and sleep

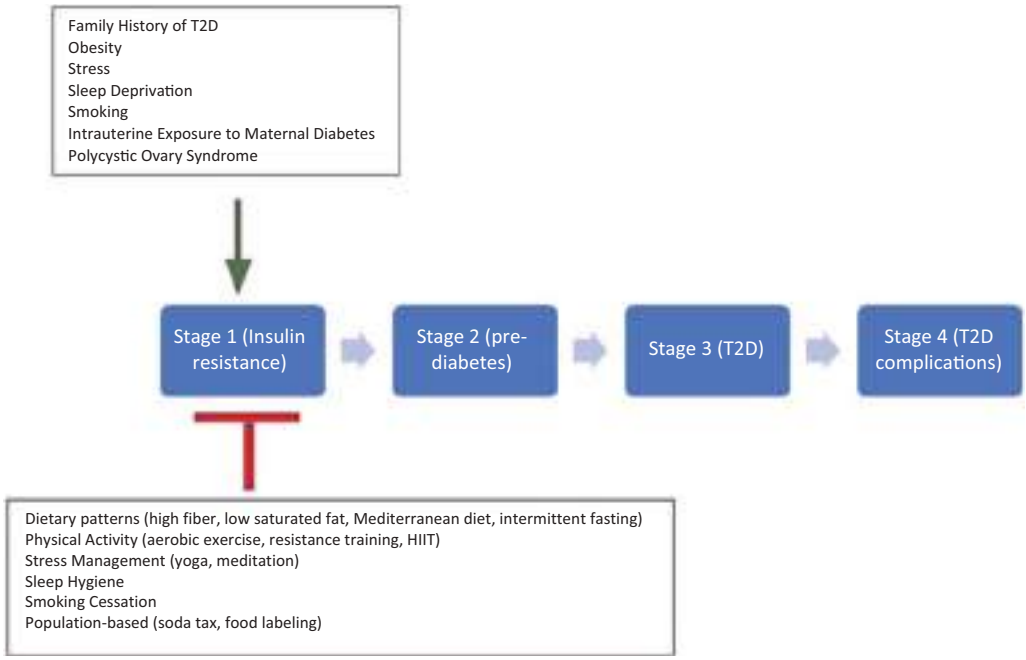


FIGURE 32.1 Factors contributing to insulin resistance and lifestyle interventions proposed to delay progression. Green arrow represents mechanistic drivers; red bar represents mitigation by lifestyle interventions. T2D = type 2 diabetes.

fragmentation, both of which have been shown to be associated with glucose intolerance.[28] Intermittent hypoxia has been studied in murine models of OSA and shown to lead to glucose intolerance and impaired insulin secretion.[29] In humans, intermittent hypoxia in healthy volunteers decreased insulin sensitivity.[30] Also, sleep fragmentation in healthy volunteers who were frequently awakened from sleep showed decreased morning insulin sensitivity and increased morning cortisol levels, with the degree of disruption of sleep correlating with the degree of blunting of insulin sensitivity.[31,32] There are also several cross-sectional studies showing a strong association between OSA and insulin resistance.[28] For example, a study by McArdle et al.[33] of 21 men with OSA, matched with 21 men without OSA, showed that insulin resistance (measured by HOMA) was higher in those with OSA ($p = 0.02$).

Interestingly, there are a number of studies that look at sleep deprivation over time and its effects on insulin resistance in healthy adults. A study by Donga et al.[34] looked at partial sleep deprivation during only a single night in nine healthy subjects and showed that there was increased insulin resistance (assessed via hyperinsulinemic euglycemic clamp) and endogenous glucose production when individuals had four hours of sleep compared with when individuals had about eight hours of sleep ($p = 0.017$). Subsequently, Buxton et al.[35] looked at sleep restriction for one week in 20 healthy mean with five hours of sleep for seven nights (normally, subjects slept for around ten hours). This study showed that insulin sensitivity was reduced on average by 20% after sleep restriction for one week ($p = 0.001$) when assessed by the intravenous glucose tolerance test and by 11% when assessed by the clamp method.[35] Lastly, chronic sleep loss affects diabetes and obesity risk.[36] Loss of sleep affects appetite, in part, by causing decreased levels of leptin and increased levels of ghrelin.[36] Together, these changes resulting from sleep deprivation correlate with increased hunger and appetite and lead to overeating and weight gain.[36]

32.2.2.5 Smoking

Tobacco smoking is associated with insulin resistance. There is a dose-dependent relationship between the quantity of cigarettes smoked per day and the degree of insulin resistance observed.[37] Smoking directly increases risk for insulin resistance via hormone activation as well as indirectly via effects that increase abdominal adiposity.[38]

32.2.2.6 Intrauterine Exposure to Maternal Diabetes

Another important risk factor and genetic component of insulin resistance is intrauterine exposure to maternal diabetes (type 1, type 2, or gestational [GDM]). Pregnancy is an insulin resistant state, and insulin resistance increases as pregnancy advances to ensure adequate carbohydrate supply for the fetus.[39] A number of factors, including maternal hormones (e.g., estrogen, progesterone, and human placental lactogen), increases in cortisol, and changes in other cytokines mediate the decline in insulin sensitivity during pregnancy.[39,40] Factors such as genetics and epigenetics, obesity, unhealthy dietary patterns, and physical inactivity can increase insulin resistance in pregnancy and have implications for both the mother and the offspring, in the short term and the long term.[41,42] For example, up to 30% of women of reproductive age are obese, and the prevalence of women starting pregnancy with a BMI of 30 kg/m^2 or greater has

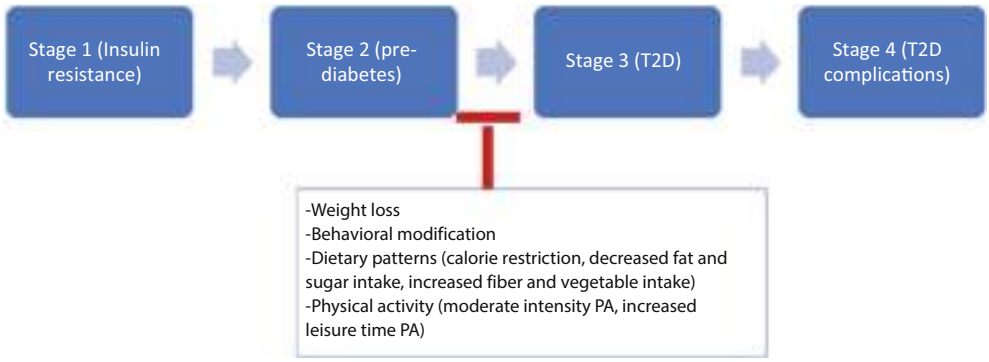


FIGURE 32.2 Diabetes-based chronic disease stages and lifestyle interventions proposed to delay progression. Red bar represents mitigation by lifestyle interventions. T2D = Type 2 diabetes, PA = physical activity.

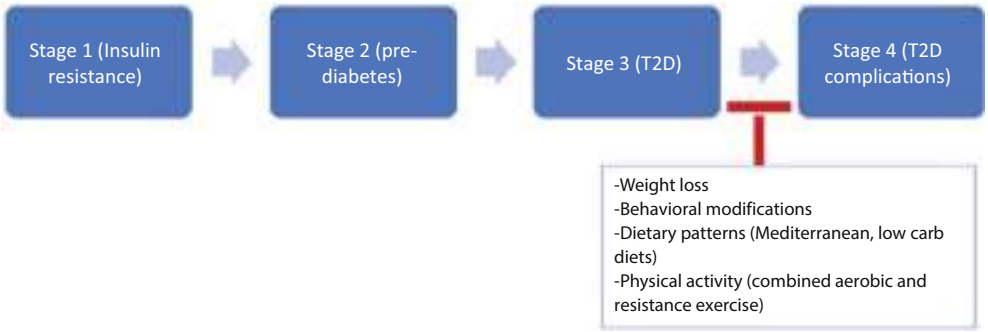


FIGURE 32.3 Diabetes-based chronic disease stages and lifestyle interventions proposed to delay progression. Red bar represents mitigation by lifestyle interventions. T2D = Type 2 diabetes.

steadily increased.[42,43] Maternal overweight and obesity are associated with a higher risk of GDM.[43] Moreover, *in utero* exposure to higher levels of glucose, such as in the offspring of mothers with GDM, was associated with impaired glucose intolerance (10.6% of children affected compared with 5% of children of mothers who did not have GDM) and increased adiposity at 10–14 years of age.[42]

32.2.2.7 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) affects as many as 6–12% of women of reproductive age in the United States; women with PCOS are often insulin resistant and therefore, at higher risk to develop prediabetes and T2D.[44] According to the Centers for Disease Control (CDC), more than half of women with PCOS develop T2D by the age of 40 years.[44] PCOS is familial, and women with a FHx of PCOS or T2D are more likely to develop PCOS.[44] Bacha et al.[45] studied the ontogeny of PCOS and insulin resistance *in utero* and early childhood and found that hyperinsulinemic traits can be detectable as early as two months of age in daughters of PCOS women. Specifically, intrauterine testosterone excess and gestational hyperglycemia may contribute to early differentiation of PCOS, but fetal testosterone exposure needs to be clarified.[45] Focusing on early childhood markers for hyperinsulinemia and adiposity, along with ovarian and adrenal endocrine abnormalities, even before the diagnosis of PCOS may be beneficial, as it would allow lifestyle intervention during childhood and adolescence, and possibly prevent familial genetic predisposition to PCOS from manifesting as a phenotype in adulthood. This, in turn, would decrease both insulin resistance and the incidence of T2D.

32.2.3 Lifestyle Interventions to Mitigate Progression of Insulin Resistance to Later DBCD Stages

32.2.3.1 Dietary Patterns

Dietary interventions focus on reducing body weight and abnormal adiposity (while sparing muscle tissue), as well as nurturing a healthy metabolism.[46] Diets high in certain types of fiber promote improved post-prandial glucose and insulin responses, with oat fiber and guar gum being the most beneficial types of dietary fiber for insulin resistance.[46] A double-blind placebo-controlled trial by Landin et al.[47] tested the effectiveness of guar gum on insulin sensitivity in 25 healthy, non-obese men. The study involved 10 grams of guar gum or placebo three times daily for six weeks, and this intervention was effective in decreasing fasting blood glucose ($p < 0.001$) and improving insulin sensitivity ($p < 0.01$, via the euglycemic clamp technique; Figures 32.2 and 32.3).[47]

The type of fat consumed is also important. Patients at higher risk of diabetes should specifically focus on a diet lower in saturated fats and higher in monounsaturated fats

(MUFAs) and polyunsaturated fats (PUFAs).[48–50] A meta-analysis by Imamura et al.[48] concluded that the most favorable effects on glycemic status and insulin resistance were seen when carbohydrates, saturated fats, and even MUFAs were replaced with PUFAs. In particular, the study concluded that each 5% energy of increased MUFAs or PUFAs improved hemoglobin A1c (A1C) by approximately 0.1%, which in turn predicts a potential reduction in the incidence of T2D by as much as 22%.[48]

Jurado-Ruiz et al.[51] found that high-fat EVOO diets significantly improved insulin sensitivity and glucose tolerance in mice with diet induced diabetes. Similar results were also seen in MUFA-rich diets in humans, where ingestion of a virgin olive oil–based breakfast improved HOMA-IR, postprandial glucose, and insulin concentrations when compared with a carbohydrate rich diet.[49] On the other hand, there is no consensus on the ideal carbohydrate content for diets in the prevention of insulin resistance. While a diet low in carbohydrates improves fasting blood sugars and facilitates weight loss (adipose tissue and lean body mass), loss of muscle tissue is not ideal for improving insulin resistance.[46]

The ATTICA study in Greece involved 1,485 participants without diabetes at baseline and determined the incidence of diabetes over ten years. In participants who were non-adherent to a Mediterranean diet (measured by Trichopoulou's Mediterranean diet score), the incidence of diabetes was 21%, compared with an 8% incidence in those with intermediate adherence and a 5% incidence in those with high adherence to the diet ($p < 0.001$).[52] Mediterranean diets refer to several dietary patterns observed in multiple regions on the Mediterranean Sea. These dietary patterns involve higher plant protein and lower animal protein consumption when compared with Western diets, and this difference is worth noting because of the different amino acid content. For example, branched-chain amino acids, such as leucine, isoleucine, and valine, are 20–40% lower in Mediterranean diets when compared with Western diets, and these branched-chain amino acids have been found to modulate insulin sensitivity.[53,54] Reducing dietary intake of branched-chain amino acids can improve glucose tolerance and body composition.[55]

Liang et al.[56] studied insulin resistant rats and compared treatment with intermittent fasting (every other day) to treatment with metformin (and no intermittent fasting) or no intervention at all (all insulin resistant rats were fed a high fat diet). HOMA-IR induced by a high fat diet was found to be significantly decreased by intermittent fasting therapy in mice when compared with the control group ($p < 0.05$), and these results were comparable to those of the metformin group, showing that intermittent fasting significantly improves insulin sensitivity.[56] Furthermore, time-restricted eating (TRE), which is a form of the intermittent fasting dietary pattern that restricts eating to a period of four to ten hours a day, has shown improvement in glycemic control in animal and human studies. Specifically, Chung et al.[57] studied TRE in obese mice that had access to a high fat diet for only eight hours compared with obese mice that were fed a high fat diet *ad libitum* and found that HOMA-IR was significantly reduced in the TRE mice.[57] Moreover, in a recent review by Cienfuegos et al.[58] on TRE in humans, fasting insulin was reduced with improvement in insulin sensitivity in subjects with prediabetes and obesity. Subsequent randomized controlled clinical trials (RCTs) of TRE in patients with T2D and obesity have shown improvement in blood glucose and insulin sensitivity.[59,60]

32.2.3.2 Physical Activity

A review on exercise training and insulin resistance by Keshel et al.[61] concluded that significant improvements in insulin sensitivity are seen with weight reduction, but exercise-induced weight loss allows more sustained improvements in weight and glucose metabolism. This is largely because dietary weight loss may lower fat tissue but will not influence muscle metabolism as exercise training will do.

Studies have suggested that both aerobic exercise and resistance training are important in weight loss and in the prevention of insulin resistance.[61] A meta-analysis by Jelleyman et al.[62] saw that study participants with or at risk for T2D had greater reductions in fasting glucose ($p < 0.001$) with high-intensity interval training (HIIT) when compared with controls (i.e., without other interventions, such as diet restriction or resistance training). Another study by Hwang et al.[63] compared HIIT with moderate-intensity continuous training in healthy older adults (mean age 65 years) and observed that insulin resistance (via HOMA-IR) decreased in HIIT by 26% ($p = 0.016$) but not with moderate-intensity continuous training.

A study by McAuley et al.[64] looked at 79 men and women with insulin resistance (determined by the euglycemic insulin clamp) and randomized them to either a control lifestyle intervention, a modest lifestyle intervention (based on current diet and lifestyle recommendations, <11% saturated fat, 50% carbohydrates, and 30 min activity/5 days a week) and a more intensive lifestyle intervention (lower fat and higher fiber, <6% from saturated fat, 55% carbohydrates with >35 grams fiber/day, and at least 20 minutes daily reaching 80–90% of age-predicted maximum heart rate). This study showed a significant improvement in insulin sensitivity (23% increase, $p = 0.006$) in the intensive group when compared with the modest group (9% increase but not statistically significant), suggesting the need for more intensive interventions, which include more fiber and higher-intensity training.[64]

Lifestyle interventions can also help prevent early insulin resistance, such as that seen in adolescents and children. In the PANIC study, Lakka et al.[65] showed that a two-year dietary and physical activity intervention over six time points in 504 normal weight children (ages six to nine years) attenuated the increase in insulin resistance when compared with a control group.[65] After these interventions, HOMA-IR increased by 0.18 units less over a span of two years in the intervention group when compared with the

control group (p = 0.023).[65] The findings support that prevention of insulin resistance, and T2D by extension, should begin in childhood in the general pediatric population. This is a powerful example of primordial prevention—a population-based intervention design to decrease risk (e.g., DBCD stage 1) of chronic disease.

32.2.3.3 Mobile Technology

In the modern world, many technologies have taken advantage of the smartphone platform for mobile health, specifically for weight loss and diabetes prevention. A pilot study by Michaelides et al.[66] concentrated on the effectiveness of Noom™, which delivers structured curricula with human coaches, in 54 patients with prediabetes, ages 18–75 years, with A1C values ranging from 5.7% to 6.4%. Weight loss and BMI were significant at 16 and 24 weeks ($p < 0.001$). However, this study did not measure A1C levels or other markers for insulin resistance as main endpoints.

32.2.3.4 Stress Management

Meditation and yoga assist with stress management and the prevention of insulin resistance. A RCT by Paul-Labrador et al.[67] looked at the efficacy of transcendental meditation (TM) compared with health education in 84 subjects with coronary heart disease (only ~15–20% of these patients had a previous diagnosis of diabetes). The study found the TM group to have beneficial changes in insulin resistance (p = 0.01) compared with the health education group.[67] A second, more recent study by Sinha et al.[68] looked at the effect of meditation on blood glucose, A1C, and insulin levels in patients with coronary artery disease. After six months of meditation (in person twice a week and also at home for a minimum of five times a week), fasting blood glucose, postprandial blood glucose, and A1C levels all significantly improved in the meditation group when compared with the control group.[68] These results show that meditation and yoga can improve insulin resistance in patients with and without diabetes.

32.2.3.5 Sleep Hygiene

In patients with habitual sleep restriction, studies suggest that sleep extension may have a beneficial impact on insulin sensitivity. Leproult et al.[69] studied glucose metabolism in 16 adults (healthy and not obese) with chronic sleep restriction during a six-week period. Subjects were instructed to increase sleep by just one hour per day, which successfully improved fasting insulin sensitivity (p = 0.002).[69] Another recent study by So-ngern et al.[70] investigated the potential benefits of a two-week sleep extension on glucose metabolism with a crossover study involving 21 participants. All subjects reported sleeping 6 hours or less nightly (average of 318.7 minutes), and after a 2-week period of sleep extension, there was improved glucose metabolism (measured by HOMA-IR) in the eight subjects who were able to sleep more than 6 hours a night (average of 396 minutes).[70] It has been recently suggested in some studies that longer sleep duration in children is associated with lower levels of insulin resistance (by HOMA-IR), though properly conducted studies are lacking.[71]

32.2.3.6 Smoking Cessation

Several studies have shown the beneficial effects of smoking intervention on improving insulin sensitivity. One such study of 40 male, non-obese smokers used the euglycemic hyperinsulinemic clamp technique to show that in spite of a modest increase in body weight in 17 subjects who successfully quit smoking over eight weeks, the degree of insulin sensitivity increased significantly (by an average of 11%) following smoking cessation, while it remained completely unchanged in the control group of 23 patients (p = 0.0095).[72] Another study by Kim et al.[73] analyzed the correlation between length of time since smoking cessation and markers of insulin resistance (HOMA-IR) in 164 former Korean male smokers and compared them with 104 never smokers. There was a statistically significant negative correlation with the length of time since smoking cessation (p = 0.009); that is, the length of time was an independent predictor of HOMA-IR (p = 0.039).[73] Clearly, smoking reduction or cessation is an important intervention for those at risk for insulin resistance or already identified as insulin resistant.

32.2.3.7 Maternal Health

A recent study by Most et al.[74] suggests that women with obesity should not consume additional energy in pregnancy; rather, fetal development can be supported by maternal fat mass, commensurate with a daily calorie deficit of about 100 kcal. Moreover, recent studies all suggest that weight targets should be individualized based on pre-pregnancy BMI in women with obesity, and both dietary and physical activity interventions for weight loss in the preconception period can reduce the risk of excessive weight gain in pregnancy.[42]

The low glycemic index diet (LGID), where at least 50% of daily calories consists of high fiber carbohydrate, was shown to be most effective in improving insulin sensitivity in women with GDM. The effectiveness of the LGID was demonstrated in several studies, including a RCT by Hernandez et al.[75] where 12 pregnant women with overweight or obesity and GDM at 31 weeks were assigned to a LGID (high fiber) versus a low-carbohydrate/high-fat diet. The results showed that with the LGID, fasting glucose levels improved significantly (p = 0.03), along with insulin resistance (p = 0.005), with less need for insulin therapy.[75]

Clinical studies have overwhelmingly concluded that diet and exercise interventions should start preconception, as limited success has been seen when these lifestyle interventions are implemented late, when mothers are already overweight or have GDM.[76] Moreover, due to poor adherence to some strategies, such as targeting 150 minutes/week of moderate-intensity exercise during pregnancy, which is too time consuming, there have been some more practical diet–exercise strategies, such as TRE (a daily eating window of ten hours or less) and high-intensity intermittent exercise (HIT) two or three times weekly (a more time

efficient intervention). Initial studies suggest that supervised HIT in the first trimester of pregnancy reduces the incidence of GDM twofold among women who are overweight or obese.[77]

Lastly, few studies exist regarding the benefits of wearable technology, such as continuous glucose monitoring (CGM) devices, during pregnancy in preventing insulin resistance. In patients with type 1 diabetes on insulin pumps during pregnancy, CGMs are accurate and affordable, suggesting that such technology might be useful in the future for detecting and managing early DBCD stages.[78]

32.2.3.8 Population-Based Interventions

Several lifestyle-based diabetes prevention programs have shown that incorporating education and community-based peer support (in addition to diet and exercise) is both successful and cost-effective in individuals who are at high risk for developing diabetes.[10,11,65] In looking at population-based interventions, a systematic review by Zhou et al.[10] showed that implementing a population-wide tax on sugar-sweetened beverages is an important and cost-saving population-based policy approach to prevent T2D globally. With respect to a soda tax, Maa[79] found that consuming one sugar-sweetened beverage (SSB) a day can increase the risk of developing T2D by 26%. A cross-sectional study by Lana et al.[80] conducted in 7,842 individuals in Spain looked at the relationship of habitual SSBs to insulin resistance and found that an increase of one serving of SSB per day resulted in higher concentrations of insulin, leptin, and HOMA-IR (1.9%, $p = 0.04$) in women with normal weight and in men (HOMA-IR > 3%, $p = 0.021$). Moreover, a longitudinal analysis of the effects of a tax on SSBs implemented in Mexico shows that three years after implementation, there was a 4.7 percentage point increase in the probability of being non-consumers of soft drinks, and the probability of being a medium or high level consumer of soft drinks decreased by 6.8 and 6.1 percentage points, respectively.[81] Taken together, these studies affirm that a SSB tax is cost-effective and can decrease the risk of insulin resistance.

The U.S. Food and Drug Administration under the Obama Administration in 2016 advocated for an "added sugar" label to allow consumers to make more informed choices about healthy eating, but unfortunately, the implementation of this label was placed on hold by the Trump Administration in 2017. Nevertheless, there is research regarding food labeling and effects on insulin resistance from other countries. A study by Han et al. [82] studied the relationship between food labeling and HOMA-IR in adults without diabetes in South Korea after nutrition labeling became mandatory in 1995. Of the 2,931 participants surveyed, 24.8% indicated that they checked nutrition labeling and actively used the labels. Moreover, checking nutrition labels was inversely associated with HOMA-IR scores ($p = 0.0164$), with the association being more significant in people with obesity or in those who paid attention to their health.[82]

A meta-analysis by Afshin et al.[83] attempted to look at the prospective impact of food pricing on dietary consumption and concluded that the use of subsidies (i.e., a 10% decrease in the price of healthy foods) increased the consumption of fruits and vegetables by 14%. Additionally, changes in the price of fruits and vegetables reduced BMI by -0.04 kg/m^2 per 10% price decrease.[83] However, despite the positive effects of individual policies and behavioral economics on BMI and dysglycemia, the failure of current legislative actions to effect pervasive and durable change is likely due to the lack of a true cultural transformation to healthy living.[84] This will likely require a large number of legislative acts and a critical mass effect where populations find increased value in being healthy.[84]

32.3 DBCD STAGE 2: PREDIABETES

32.3.1 General Concepts

Prediabetes is considered a "predisease" state that results from insulin resistance (normoglycemia) and an consequent early β-cell defect with eventual mild hyperglycemia, and leads to DBCD progression with worsening hyperglycemia (T2D), diabetes complications (especially CVD), and in some, even regression to normoglycemia.[5] According to the American Diabetes Association (ADA), prediabetes can be defined by any one of the following: impaired fasting glucose (100–125 mg/dL), impaired glucose tolerance (plasma glucose of 140–199 mg/dL two hours after 75 g oral glucose load), or A1C of 5.7 to 6.4%.[85] The World Health Organization defines prediabetes as either impaired fasting glucose (110–125 mg/dL) or impaired glucose tolerance (plasma glucose of 140–200 mg/dL two hours after 75 g oral glucose load) but does not consider A1C in its diagnostic criteria.[86] From 2013 to 2016, the CDC estimated that 34.5% of all U.S. adults over the age of 18 had prediabetes.[87] Given the variability in definitions for prediabetes and variability across populations, it is difficult to estimate how many patients who meet criteria for prediabetes will develop T2D during their lifetimes, though according to the ADA, this is estimated at 70%.[88]

32.3.2 Lifestyle Interventions to Mitigate Progression of Prediabetes to Later DBCD Stages

32.3.2.1 Dietary Patterns and Physical Activity

In the United States, one of the largest RCTs looking at the effect of lifestyle interventions on the progression to T2D in at-risk individuals was conducted in the late 1990s and early 2000s by the Diabetes Prevention Program Research Group (DPPRG).[89] In this study, 3,234 people without T2D but with elevated fasting blood glucose levels or elevated blood glucose after a two-hour oral glucose tolerance test were randomized into one of three trial arms: 1) standard lifestyle recommendations plus 850 mg metformin twice

per day, 2) standard lifestyle recommendations plus placebo pill twice per day, or 3) intensive lifestyle recommendations with a 16-lesson curriculum that encouraged weight loss and moderate-intensity physical activity. After a follow-up period of about three years, the cumulative incidence of T2D was 28.9% in the standard lifestyle recommendations plus placebo group, 21.7% in the standard lifestyle recommendations plus metformin group, and 14.4% in the intensive lifestyle recommendations group. After the initial three-year follow-up period, the DPPRG continued to follow this original cohort of patients over ten years and noted that the incidence of T2DM was decreased by 18% and 34% in the original metformin and intensive lifestyle therapy groups, respectively, when compared with placebo.[90] Further studies looking at the independent effect of physical activity on diabetes prevention in this cohort have shown that over a 12-year follow-up, there was a 6% decrease in T2DM incidence for every six metabolic equivalents of task (METs) per week for all treatment groups combined.[91]

Other studies have investigated the effect of lifestyle interventions on the progression of prediabetes to T2D in non-U.S. populations. One such study conducted in Da Qing, China randomized 577 participants with impaired glucose tolerance and a mean BMI 25.7 kg/m^2 to one of four groups: dietary interventions, physical activity interventions, diet plus physical activity interventions, and control, which were then combined after the initial six year intervention period.[92] At the end of their 30-year follow-up period, they found that the median delay in onset of T2DM was 3.96 years for the intervention group, and the number needed to treat (NNT) with lifestyle interventions to prevent one case of T2DM over 30 years was 10 (95% confident interval [CI] 7 to 23). In a follow-up trial by Gong et al.,[93] the original Da Qing Diabetes Prevention Outcomes study participants were followed for an additional 20-year period after the initial 6-year intervention and monitored for the development of microvascular complications of T2D. In this study, the incidence of severe retinopathy was 47% lower in the original intervention group, but when adjusted for the delay in onset of T2D in the intervention group, the incidence of severe retinopathy between the two groups was similar, suggesting that the delayed onset of T2D is what led to this decrease in retinopathy incidence.[93] Unfortunately, there were no differences in incidence of severe nephropathy or neuropathy during this follow-up period, a finding which the authors felt may have been explained by overall low rates and relatively short duration of T2D in both groups.[93]

A similar large RCT was conducted in Finland, in which 522 middle aged individuals with overweight and impaired glucose tolerance were randomized to either a control group (received annual information on general diet and exercise) or an intervention group where they were encouraged to lose 5% body weight, engage in physical activity, and reduce fat intake.[94] After initial mean follow-up of 3.2 years, it was found that the risk of progression to T2D was reduced by 58% in the intervention group, and after 6 years, the absolute risk reduction was 15% for the intervention group.[95]

A 2006 study in India randomized 531 patients with impaired glucose tolerance to one of four intervention arms: control, lifestyle interventions, twice-daily metformin, and lifestyle measures plus twice-daily metformin.[96] After a median follow-up period of 30 months, the researchers found that compared with controls, there was a relative risk reduction in progression to T2D of 28.5% in the lifestyle intervention group, 26.4% in the metformin group, and 28.2% in the lifestyle plus metformin group.[96] The results of the U.S., Da Qing, Finnish, and Indian trials are summarized in Table 32.1.

32.3.2.2 Mobile Technology

A 2013 trial in India addressed whether SMS-text messaging encouraging lifestyle change could be effective in preventing the onset of T2D in 537 men aged 35–55 years with impaired glucose tolerance.[97] After a mean follow-up of 20.2 months, the researchers found that the absolute risk reduction for development of T2D as measured by oral glucose tolerance test was 9% in the intervention group, and the NNT to prevent 1 case of T2D was 11.

A similar, larger study was conducted in both India and the United Kingdom, including men and women and the use of A1C determinations.[98] However, after a mean two-year follow-up period, there were no significant differences in the incidence of T2D between the intervention and control groups (22.7% and 21% control and intervention, respectively; hazard ratio [HR] 0.89, 95% CI 0.74–1.07, p = 0.22).

32.3.2.3 Sleep Hygiene

Disordered sleep, specifically OSA, has been suggested as an independent risk factor for insulin resistance.[99,100] A RCT showed that treatment of OSA with continuous positive airway pressure (CPAP) for eight hours nightly for two weeks could improve insulin sensitivity in individuals with prediabetes.[101] Additionally, sleep apnea has been shown in observational trials to be associated with an increased risk of development of clinical T2D; this risk is attenuated by consistent use of CPAP.[102]

32.4 DBCD STAGE 3: TYPE 2 DIABETES

32.4.1 General Concepts

In 2019, it was estimated that there are 37.3 million people in the United States living with diabetes, amounting to 11.3% of the total population, and 14.7% of adults over the age of 18 and 29.2% of adults over the age of 65 have diabetes.[87] Worldwide, 2019 estimates show that 493 million people are living with diabetes, and that number is projected to reach 700 million by 2045.[103] Independently of other risk factors, diabetes incurs a twofold increased risk of CVD.[104] Given the widespread prevalence of T2D and its associated morbidity, improved management of this condition is of great clinical and research concern. Though pharmacologic treatments are part of the mainstay of treatment for T2D, lifestyle therapies and treatments remain

TABLE 32.1
Summary of Diabetes Prevention Trials

Trial	Lifestyle intervention	Follow-up period	Results
United States Diabetes Prevention Program[90]	• Individual and group educational sessions • Low-calorie, low-fat diet • Moderate PA for 150 min/week • Goal weight loss of 7%	10 years	34% lower incidence of T2D in lifestyle intervention group compared with control, median delay in onset of T2D of 4 years
Da Qing Diabetes Prevention Outcomes Study[92]	• Dietary changes (increased vegetable intake, decreased sugar and alcohol intake) • PA (increased leisure-time PA) • Only recommended decreased caloric intake to overweight and obese participants	30 years	Median delay in onset of T2D of 3.96 years in intervention group, NNT = 10
Finnish Diabetes Prevention Study[95]	• Individual and group sessions • Dietary recommendations to: reduce total fat to <30% and saturated fats to <10% of total caloric intake, increase fiber intake • PA of at least 30 min moderate intensity per day • Goal weight loss 5% or greater	6 years	Absolute risk reduction in T2D of 15% in intervention group
Indian Diabetes Prevention Programme[96]	• Monthly phone calls and biannual personal sessions • Dietary advice focused on: reduction in intake of total calories, refined carbohydrates, fats, and sugars, and increased intake of fiber	30 months	Relative risk reduction in T2D incidence of 28.5% in lifestyle intervention compared with control, NNT over 30 months = 6.4

NNT = number needed to treat; PA = physical activity; T2D = type 2 diabetes.

critical for successful outcomes. AACE recommends lifestyle therapies as standard of care for management of T2D and prevention of its associated adverse outcomes.[105] The ADA considers lifestyle medicine to be part of standard of care to improve glycemic control and clinical outcomes in patients with diabetes.[106]

32.4.2 Lifestyle Interventions to Mitigate Progression of T2D to Diabetes Complications

32.4.2.1 Dietary Patterns

One of the most important aspects of lifestyle intervention for the management of T2D is weight loss through dietary changes and increased physical activity—the focus of the Look AHEAD trial (Table 32.2).[107]

In this large multicenter trial, 5,145 people with overweight or obesity between the ages of 45 and 75 years old with a diagnosis of T2D were randomized to either an intensive lifestyle program aimed at promoting weight loss of 7% or more through decreased caloric intake and increased physical activity, or a control group that received diabetes support and education. This study's intervention period was terminated early due to futility after a median follow-up period of 9.6 years. While there was significantly greater weight loss in the intervention group compared with the control group at the study's end (6.0% loss from baseline vs. 3.5%), there was no significant difference in primary outcome: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina (1.83 and 1.92 events per 100 person years). Notably, at the end of the follow-up period, the HgbA1c in the intervention group was significantly (0.22%) lower than in the control group. However, low-density lipoprotein cholesterol (LDL-C) levels were 1.6 mg/dL lower in the control group, and the use of statins was higher in the control group, as was the use of antihypertensive medications and insulin. The authors concluded that the lack of difference in outcome rates may have been explained by the increased use of statins in the control group, or that the degree of weight loss in the intervention group may not have been large enough. To address the latter, a *post-hoc* analysis [108] found that participants in the intensive lifestyle group who lost at least 10% of their bodyweight had a 20% lower risk of the primary outcome compared with the control group. Even though this trial showed no difference in cardiovascular outcomes between intensive lifestyle interventions and control, the fact that there was an improvement in HgbA1c in the intervention group suggests that it would be worthwhile for future research to revisit this question, especially given that the differing rates of statin use may have affected results. Additionally, *post-hoc* analyses of renal outcomes of the Look AHEAD trial found that the incidence of very-high-risk chronic kidney disease (CKD) was 31% lower in the intensive lifestyle intervention group.[109]

Mediterranean diets are associated with lower A1C levels in T2D.[110] A large meta-analysis in 2015, including nine randomized controlled trials on Mediterranean style diets (N = 1,178 participants), found improvements in measures

TABLE 32.2
Summary of the Look AHEAD Trial

Population	Intervention	Control	Outcomes
5,145 individuals with overweight or obesity between ages 45 and 75 with a diagnosis of T2D	Aimed to promote weight loss of 7% or more through dietary plan with individual caloric goals and 30% total calories from fat and 15% from protein, plus 175 min/week of moderate-intensity PA, plus individual counseling and coaching	Three group sessions per year covering topics related to nutrition, exercise, and living with diabetes	• Significantly greater weight loss in intervention group (6.0% loss from baseline vs. 3.5%) • A1C 0.22% lower in intervention group • LDL-C 1.6 mg/dL lower in control group • Higher use of statins and antihypertensive meds in control • No differences in cardiovascular outcomes (composite of death from CVD, nonfatal MI, nonfatal stroke, hospitalization for angina) with 1.83 and 1.92 events per 100 person years in intervention and control, respectively

A1C = hemoglobin A1c; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PA = physical activity; T2D = type 2 diabetes.
See Wing et al. [107]

of glycemic control and CVD risk in T2D.[111] Huo et al.[111] found that Mediterranean style diets were associated with a 0.30% mean greater decrease in A1C, a 0.29 kg/m^2 greater reduction in BMI, and a 0.14 mmol/L greater decrease in total cholesterol compared with controls. There is also evidence from the PREDIMED trial that a Mediterranean diet is associated with reduced incidence of myocardial infarction, stroke, or death from cardiovascular causes.[112] In this study, 7,447 middle aged men and women from Spain with high cardiovascular risk (but no history of known CVD) were randomized to one of three diets: Mediterranean with EVOO, Mediterranean with nuts, or control diet with advice to reduce dietary fat intake.[112] Subgroup analysis showed that in participants with T2D at baseline, there was a 29% decreased risk of major cardiovascular event in the combined Mediterranean diet groups compared with controls (HR 0.71, 95% CI 0.51–0.98).

In a randomized controlled trial comparing isocaloric low-carbohydrate, high–unsaturated fat diets (14% carbohydrate, 28% protein, 58% fat, of which <10% was saturated fats) versus high-carbohydrate, low-fat diets (53% carbohydrate, 17% protein, 30% fat, of which <10% was saturated fats) over a two year period in adults with T2D, both groups achieved equivalent mean weight losses of 6.6 to 6.8 kg and reductions in A1C of 0.6% and 0.9%, respectively.[113] However, the low-carbohydrate group achieved a statistically greater reduction in diabetes medication use.[113]

In another large meta-analysis, the effects of a low-carbohydrate (less than 26% of total calories from carbohydrate) and very low-carbohydrate (less than 10% of total calories from carbohydrates, enough to induce ketosis) diet on various outcomes in patients with T2D were examined.[114] This study found that low-carb and very low-carb diets were associated with a mean 0.23% greater reduction in A1C at one year compared with controls.[114]

32.4.2.2 Physical Activity

Aerobic and resistance training exercise reduce A1C levels, as supported by a study of 250 previously sedentary individuals 39–70 years of age with A1C levels of 6.6% to 9.9% at baseline, randomized to aerobic training, resistance training, combined exercise training, or control. [115] After six months, there was a decrease in A1C levels in all three exercise groups. This study demonstrates that both aerobic and resistance training exercise can improve glycemic control in T2D and that combined exercise programs are even more beneficial. Subsequent *post-hoc* analysis showed a dose-dependent response with every 20% increase in adherence to the three assigned sessions per week, though this was only significant in the aerobic and combined exercise groups.[116] Additionally, an Italian study found that a 12-month combined aerobic and resistance exercise program with supervised sessions of 150 min/week plus exercise counseling was associated with a 0.30% greater decrease in A1C compared with exercise counseling alone in adults who were previously sedentary, overweight or obese, with T2DM and metabolic syndrome (MetS).[117]

In a randomized study by Balducci et al.,[118] participants with T2D received exercise counseling or 150 min/week of supervised aerobic and resistance training, the intensity of which was adjusted throughout the study to meet 55–70% of VO_{2max} and 60–80% of maximum resistance repetition maximums.[118] At the end of the 12-month intervention, improvements in cardiopulmonary fitness as measured by VO_{2max} and strength were associated with improvements in A1C, high-density lipoprotein cholesterol (HDL-C), and high sensitivity C reactive protein (hs-CRP), independently of weight loss, suggesting a reduction in overall CVD risk.[118] Though these results are promising, the highly regulated design of the exercise intervention and the impracticality of quantifying measures of physical fitness in the clinical

setting limit the generalizability of these results to a real-world patient setting.

32.4.2.3 Mobile Technology

The first of the mobile apps to be approved by the Food and Drug Administration (FDA), BlueStar, was designed to improve self-monitoring of blood glucose, encourage lifestyle modification, and assist with medication titration.[119] A randomized controlled trial of the app versus standard of care to improve A1C in 223 individuals with poorly controlled T2D (A1C ≥8.0%) took place in Canada and found that after three months, there was no statistically significant difference in A1C.[120] However, there was low overall usage of the app in this trial, and there may not have been a long enough follow-up period to produce reductions in A1C levels.[120]

An additional study in Germany randomized 2,441 individuals with T2D to either standard of care or a telemedicine-based lifestyle management program, though ultimately, only 115 individuals whom baseline and three-month follow-up data was available were included in the analysis.[121] There was a statistically significant reduction in A1C in the intervention group (7.05% to 6.58%, $p < 0.05$) but not in the control group (6.89% to 6.95%, $p = 0.465$).[121] In another study conducted in New Zealand, the effects of a nine-month text message–based intervention on A1C reductions in poorly controlled type 1 and type 2 diabetes were examined. There was a 4.23 mmol/mol greater decrease in A1C in the intervention compared with control groups at the end of nine months.[122]

32.5 DBCD STAGE 4: COMPLICATIONS

32.5.1 General Concepts

Stage 4 of the DBCD model is represented by those with diabetes who have progressed to having vascular complications and therefore, are at greatest risk for morbidity and mortality.[5] It is felt that dysglycemia and insulin resistance can contribute to the formation of reactive oxygen species (ROS), which in combination with oxidative stress, inflammation, mitochondrial dysfunction, formation of advanced glycated end-products (AGE), and neurohumoral mechanisms, lead to dysfunction of the endothelium and atherothrombosis.[123,124] Other components of MetS, including dyslipidemia, hypertension, and obesity, as well as age, sex, duration of diabetes, and genetic factors, contribute to the development of microvascular complications.[125]

It is well known that CVD is the leading cause of morbidity and mortality in those with diabetes, who have two to five times greater risk of heart disease.[126] The CDC reports that in 2018, approximately 1.87 million hospital admissions were attributable to heart disease in the setting of diabetes, with a smaller proportion attributed to amputation and other diabetes complications.[127] In terms of microvascular disease, between 2009 and 2014, the estimated prevalence of diabetic kidney disease was 26.2%,[128] and data from 1980 to 2008 estimate that 34.6% of individuals worldwide with diabetes had some form of diabetic retinopathy.[129] Estimates of diabetic neuropathy prevalence are more difficult to ascertain, given variability in the definition across studies, but diabetes has been estimated to be the cause of distal polyneuropathies in up to 50% of cases.[130,131]

Intensive glucose control emphasizing pharmacotherapy and/or surgical intervention is the standard of care to help patients with complications from uncontrolled T2D.[132] While lifestyle interventions may not play a central role in the management of severe complications, changes in lifestyle may help improve cardiometabolic risk factors and morbidity.

32.5.2 Lifestyle Interventions to Mitigate Development of Further Morbidity and Prevent Mortality from Diabetes Complications

32.5.2.1 Macrovascular Disease: Dietary Patterns and Physical Activity

Most clinical research looking at dietary patterns in diabetes populations has focused on Mediterranean diets, which are rich in alpha-linolenic acid, a plant based omega 3 PUFA found in many seeds and oils, and suggested to be cardioprotective.[133] The Mediterranean dietary pattern has been shown to reduce the risk of T2D, reduce metabolic markers, and lower cardiovascular events and mortality.[134] However there have only been a few studies involving subjects with established coronary heart disease (CHD) and specifically focused on subjects with T2D. The Lyon Heart Study examined whether a Mediterranean diet could reduce the risk of recurrent myocardial infarction and included a subset of patients with T2D.[133] Between 1988 and 1992, 605 participants from France were recruited and randomized to a Mediterranean diet or a more prudent Western diet with appropriate counseling. After a mean of 27 months, the group randomized to the Mediterranean diet had significantly fewer events, with the primary endpoint being death from cardiovascular causes or nonfatal myocardial infarction.[133] In another smaller study, 101 participants with established heart disease were assigned to an education program for one year or written advice only on the Mediterranean diet. After one year, there was no significant improvement in inflammatory markers or fasting insulin.[135] Both of these studies included a small proportion (<10%) of subjects with T2D.

Other diets, including the low-carbohydrate diet, have also been shown to improve glucose homeostasis, reduce diabetes risk, and improve weight loss, but have not been fully tested for secondary prevention of heart disease in diabetes populations.[136] The DASH (Dietary Approaches to Stop Hypertension) eating pattern focuses on low-fat foods, whole grains, and a variety of fruits, vegetables, and nuts, with limited sweets, and has been shown to be helpful in controlling hypertension and reducing insulin resistance,

hyperlipidemia, and obesity.[137] While suggestive of benefit in populations with diabetes and heart disease, there is some concern about the recommended carbohydrate intake in the DASH diet being excessive, so more studies are needed.

Dietary supplements and nutraceuticals with proven benefit > risk play a growing role for patients wanting to reduce cardiometabolic risk factors[138]. Vitamins C, D, and E have been tested in animal models and show some benefit in terms of assisting with cardiac vascular remodeling.[139] Preclinical data with carnitine, which plays a role in fatty acid transfer within mitochondria, amino acids, ribose, and flavonoids may also assist in ischemia-reperfusion injury.[139] Supplementation with coenzyme Q10, essential for cellular energy production, in combination with selenium was given over four years to 443 elderly patients in Sweden, of whom 21% had T2D and a similar percentage had heart disease. The treatment group with T2D was noted to have significantly reduced cardiovascular mortality (HR: 0.51; 95%CI 0.36–0.74; p = 0.0003) over ten years compared with placebo, and there was a trend toward reduced cardiovascular mortality in those with ischemic heart disease (p = 0.071).[140] Supplementation with omega 3 PUFAs has also been promising, given preclinical data suggesting benefit in ischemia-reperfusion and clinical studies indicating a role in cardiac prevention.[139] In a randomized placebo-controlled double-blinded study of 90 subjects with both T2D and heart disease, supplementation was provided with 1,000 mg fish oil or 1,000 mg flax-seed oil or placebo for 12 weeks. Those treated with fish oil or flax-seed oil had significant reductions in serum insulin levels, total nitrate, and total antioxidant capacity; this suggested that flax-seed oil can be a vegetarian/vegan alternative to fish oil to provide metabolic benefits.[141]

It is well known that regular physical activity is crucial and recommended in the setting of CHD prevention and treatment. While underutilized, cardiac rehabilitation programs can help patients with recovery, assist with weight loss, provide psychological benefit, and reduce cardiometabolic risk factors.[142] By meeting the guidelines of 150–300 minutes per week of moderate activity or 75–150 minutes of vigorous physical activity, cardiovascular morbidity and mortality is reduced independently of diabetes status.[143] Duration, intensity, and specifics of aerobic and resistance training should be personalized to the patient, with further research needed in this high-risk population.[142]

In the Look AHEAD study, there were changes in cardiorespiratory fitness as measured by a graded exercise test, independently associated with improvements in glucose, A1C, HDL-C, and triglycerides, in those randomized to the intensive lifestyle intervention compared with the diabetes support/education arm.[144] Of concern, in 14% of the total subjects with a CVD history, there was a non-significant increase in primary outcome of myocardial infarction, stroke, hospitalized angina or mortality, with a HR for ILI versus DSE of 1.13 (95% CI 0.90–1.41).[145] In further exploratory analysis, those with established heart disease were more often white, male, and older, with greater use of statins, anti-hypertensives, and insulin, but the treatment response heterogeneity could not be explained by changes in fitness, hypoglycemia rates, or differences in weight loss. *Post-hoc* analysis demonstrated that this effect was found to be secondary to increased rates of nonfatal myocardial infarction, which could have been driven by the physical activity component of the lifestyle intervention.[145] These results further reinforce the idea that studies looking at cardiovascular outcomes must take into account heterogeneity in treatment response based on CVD history.

32.5.2.2 Mobile Technology

Mobile technology poses an attractive approach to help patients with CHD in terms of monitoring symptoms, medication adherence, and encouraging healthy lifestyle behaviors. The CHAT-DM study randomized 502 subjects in China with T2D and heart disease to either text messaging with educational information (six per week) for six months or usual care[146]. Researchers noted a significant reduction in A1C over six months, and a reduction in fasting glucose in the intervention group, but no other differences in BMI, LDL-C, systolic blood pressure, or physical activity.[146] In the Australian Tobacco, Exercise and Diet Messages (TEXT ME) trial, 710 subjects with established heart disease, of whom 32% had T2D, were randomized to frequent lifestyle-based text messaging versus usual care for six months.[147] Those receiving the text message messages found them useful and were noted to have a significant reduction in LDL-C, systolic blood pressure, and BMI, and increase in physical activity, compared with the control group at the end of six months.[147]

32.5.3 Microvascular: Dietary Patterns and Physical Activity

There is growing interest in the role of dietary patterns, dietary supplements and nutraceuticals, and behavioral interventions in the management of diabetic microvascular disease. Traditionally, dietary management of nephropathy has emphasized restriction of protein and moderation of electrolytes and minerals, including sodium, potassium, magnesium, and phosphorus.[148] To further investigate the potential benefit of DASH or Mediterranean style dietary patterns in end stage renal disease, more than 9,000 subjects in a multinational cohort, of whom 32% had diabetes and nephropathy, were followed for almost three years for cardiovascular or all-cause mortality. Diet scores were derived from a food frequency questionnaire provided to subjects. There was no association between following a DASH or Mediterranean eating pattern and cardiovascular mortality or all-cause mortality.[149]

In a six-month behavioral intervention study, 121 patients with uncontrolled T2D and nephropathy and 49 healthy volunteers were randomized to an intensive lifestyle intervention of twice weekly phone calls for six months versus twice weekly phone calls for the first three months followed by

monthly phone calls for the second three months combined with caloric restriction and at least 300 minutes per week of moderate-intensity activity.[150] After six months, there was significant reduction in BMI and A1C in the intensive lifestyle intervention group compared with the control group, and reductions in interleukin-6 and tumor necrosis factor-α, but no change in renal function.[150] In sum, these results indicate that close supervision and frequent encouragement of lifestyle changes can reduce the progression of diabetes nephropathy.

In the setting of neuropathy, dietary interventions have focused on dietary supplements and nutraceuticals with antioxidant properties. Alpha-lipoic acid (ALA) has been tested both orally and intravenously, with short-term studies indicating benefit in reducing total symptom score and deficits.[151] In a longer randomized, double-blind, parallel-group trial, ALA was given orally over four years to 460 patients with symmetric distal diabetic polyneuropathy.[152] While there was no significant difference in the primary outcome, a composite of Neuropathy Impairment Score (NIS), neurophysiologic testing, and other markers indicated improvement in symptoms and reduction in deficits with ALA.[152] Nicotinamide riboside has also been postulated to help improve symptoms of neuropathy by directly enhancing energy metabolism in neuronal mitochondria.[153] In patients with neuropathy and vascular disease who have progressed to developing foot ulcers, zinc, vitamin D, vitamin E, and probiotics have been investigated. In a small study of 57 patients with grade 3 diabetic foot ulcers, supplementation with 250 mg daily magnesium and 400 IU vitamin E over 12 weeks helped reduce ulcer size and also reduced fasting glucose, A1C, and lipid levels.[154] In another 12-week study, 200 mg of coenzyme Q10 was provided daily to 70 patients with diabetic neuropathy, with no difference in symptoms of neuropathy, but the inflammatory marker hs-CRP was reduced in the intervention group.[155] In another RCT of 60 patients from Iran with grade 3 diabetic foot ulcers, patients received either a probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) or placebo.[156] Over 12 weeks, probiotic administration significantly lowered ulcer length and depth and was associated with lower fasting glucose, A1C, and inflammatory markers without adverse effects.[156] In a parallel study in 60 subjects with grade 3 diabetic foot ulcer, administration of zinc sulfate supplements containing 50 mg elemental zinc was associated with reduction in ulcer length and width, significant lowering of fasting glucose and A1C, and reduction in hs-CRP and markers of antioxidants over 12 weeks.[157] In another study, the combination of B12, acetyl-L carnitine, ALA, and superoxide dismutase was compared with placebo over 12 months in a group of 85 patients with diabetic neuropathy.[158] Significant differences were noted in the Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE), measurement of the vibration perception threshold (BIO), Cardiovascular Autonomic Reflex Tests (CART), measurement of nerve function, and pain (PS) and quality of life (QL) questionnaires.[158]

In the setting of neuropathy, exercise must be closely monitored due to the risk of developing foot ulcers with weight bearing exercise, and to assess for treatment induced neuropathy, which can occur acutely after the onset of glucose control in those with previously poorly controlled diabetes. In a 10-week study involving an exercise intervention with both aerobic and strengthening exercise based on the American College of Sports Medicine guidelines, 17 patients with established diabetic neuropathy and an average duration of diabetes of 12.4 years were followed. After the ten-week intervention, there was significant improvement in pain, using a visual analog scale as well as reduction in neuropathy symptoms based on the Michigan Neuropathy Screening instrument, and increase in intraepidermal nerve fiber density measured by proximal skin biopsy.[159] While short in duration and limited by the "very poor" exercise capacity measured by VO_{2max} at baseline, the results suggest the importance of both aerobic and strengthening exercises in neuropathy.[159] In a pilot study assessing the benefits of Tai chi, 20 subjects with diabetic neuropathy were given a 1-hour lesson twice weekly for 12 weeks, with noted improved balance, reduction in total symptom score, and reduced fasting glucose.[160] Overall, exercise interventions > four weeks focused on mobility, balance, proprioception, and resistance training have shown mixed benefits in patients with neuropathy, with varied outcome measures and duration making it hard to determine efficacy.[161]

In the setting of retinopathy, there have been few large-scale lifestyle/dietary interventions focused on patients with established retinopathy. Lutein, found in dark leafy vegetables and egg yolk, has been felt to be helpful in diabetes retinopathy and other diseases of the retina, such as age-related macular degeneration, due to its anti-inflammatory and antioxidant function.[162] Similarly, vitamins including B-complex, vitamin C, vitamin D, folate, and N-acetyl cysteine can help protect the retina by improving blood vessel elasticity, improving neuron function, and improving vision.[163] The PREDIMED study, one of the largest prospective studies assessing the benefit of a Mediterranean diet in patients with T2D, found that a Mediterranean diet supplemented with EVOO reduced the incidence of diabetes retinopathy, but did not include those with pre-existing retinopathy.[164]

32.6 CONCLUSION

Diabetes mellitus is a growing worldwide problem with significant morbidity and mortality that not only affects individual patients living with the disease but also places a significant burden on healthcare systems. While there are many medical therapies that can be used to improve management of diabetes and reduce the risk of its complications, as with many chronic diseases, safe and effective prevention strategies remain of critical importance throughout the various stages of DBCD.[5] Lifestyle interventions, such as

TABLE 32.3
Summary of Management Strategies for DBCD

DBCD Stage	Pathophysiological Target	Strategy
1	Insulin resistance	Diet—increased fiber, increased MUFA and PUFA Exercise—aerobic and resistance training Sleep hygiene Smoking cessation
2	Prediabetes	Intensive lifestyle modification Weight loss Behavioral counseling and support Sleep apnea-treatment
3	T2D	Diet—Mediterranean and low carbohydrate Weight loss Exercise-aerobic and resistance training Behavioral counseling and support
4	T2D with complications	Diet—Mediterranean Behavioral counseling and support Supplements and nutraceuticals

T2D—Type 2 diabetes.

improvements in nutrition, physical activity, and sleep, are of key importance in the mitigation of DBCD progression (Table 32.3). Currently, most research regarding the role of lifestyle interventions in T2D prevention when applied to the DBCD model pertains to stages 1 (insulin resistance) and 2 (prediabetes). There are promising data that specific dietary patterns such as the Mediterranean diet and low-carb diets can improve measures of glycemic control in patients with T2DM or reduce cardiovascular events. There is limited research on the role of lifestyle interventions for management of T2DM complications, as more research focuses on the role of various pharmaceutical interventions for T2D management. Overall, it is clear that lifestyle interventions play an important role in management throughout the DBCD paradigm, though this is a growing area of research, and further studies are needed to better quantify the magnitude of impact these interventions provide in preventive medicine.

DISCLOSURES

JM received honoraria from Abbott Nutrition and serves on advisory boards for Aveta.Life, L-Nutra, and Twin Health.

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33 Implementation: Lifestyle Medicine Tactics to Optimize Dysglycemia Care

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KEY POINTS

- DBCD is a care model centered on early and sustainable preventive actions to retard or even eliminate dysglycemia progression and consequences, mitigating disease burden, cost, and related suffering.
- Tactics implemented to reduce DBCD burden should be patient-centered and consider ethnocultural factors, SDOH, and biopsychosocial factors, with the additional requirement of being sustainable over time.
- Lifestyle interventions to reduce DBCD burden have been widely investigated, showing improvement of care. The use of a multidisciplinary approach, specialized institutions for lifestyle interventions, and wearable technologies have been shown to improve T2D prevention and care.
- Lifestyle interventions can be done at community or national levels, targeting hundreds of thousands of individuals at risk.

ABBREVIATIONS

- A1C—Hemoglobin A1c
- ABCD—Adiposity-based chronic disease
- BMI—Body mass index
- CMBCD—Cardiometabolic-based chronic disease
- DBCD—Dysglycemia based chronic disease
- DPP—Diabetes Prevention Program
- HCP—Healthcare professional
- LMC—Lifestyle Medicine Centers
- LMCSL—Lifestyle Medicine Clinical Service Lines
- MNT—Medical nutrition therapy
- NDPP—National Diabetes Prevention Program
- SDOH—Social determinants of health
- T2D—Type 2 diabetes
- tCMBCD—Transcultural cardiometabolic-based chronic disease model
- tDNA—Transcultural Diabetes Nutrition Algorithm

33.1 WHY ARE LIFESTYLE MEDICINE TACTICS NECESSARY TO MANAGE DYSGLYCEMIA?

There are several key mechanistic metabolic drivers for cardiovascular disease (CVD) that constitute cardiometabolic risk: abnormal adiposity, dysglycemia, hypertension, dyslipidemia, and other residual risks (inflammation, thrombosis, etc.). Unfortunately, the prevalence of overweight/obesity and type 2 diabetes (T2D) has increased in the Americas from 1980 to 2014.[1] Since 1990, the number of disability-adjusted life years (DALYs) for diabetes increased by 1.68% per year in the United States, reaching 4.01% of total DALYs in 2019.[2] In addition, T2D is associated with increased severity of coronavirus disease 2019 (COVID-19)[3] and is a component of COVID-related cardiometabolic syndrome.[4]

"Dysglycemia" is a term that encompasses the progressive impairment of glucose regulation, spanning from early insulin resistance, to beta-cell dysfunction with mild hyperglycemia (prediabetes), to more severe hyperglycemia (T2D), to macro- and microvascular complications. This disease progression model has been termed "dysglycemia based chronic disease" (DBCD) and is intended to simplify the biological continuum of this cardiometabolic driver into a comprehensible and actionable format for preventive interventions.[5] Many patients with DBCD harbor other cardiometabolic risk factors, so management must be comprehensive in nature and not just glycemia centric. Moreover, at the earliest pathogenic step, DBCD arises from a complex interaction of biological and social determinants, or primary drivers, consisting of genetic, environmental, and behavioral factors.[6]

Lifestyle medicine is the non-pharmacological and non-procedural management of chronic disease.[7] It is estimated that more than 80% of chronic conditions could be avoided by the implementation of lifestyle recommendations.[8] Type 2 diabetes is intimately associated with lifestyles and specifically, food behaviors, with abnormal adiposity and dietary risks as the two most important risk factors.[9] Lifestyle impacts not only the development of cardiometabolic risk factors but also their prognoses.[8,10] For example, in a systematic review including 128 studies, behavior-based interventions with or without weight loss, medications were more effective at reducing excess weight

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and the risk of developing T2D than control conditions, and besides, weight-loss medications were associated with higher rates of harm.[11]

The weight of evidence and body of knowledge that guide lifestyle strategies to prevent DBCD development and progression are considerable. However, ideas and intent, workflows and business plans cannot directly heal. This requires action—actualization of plans. Strategy refers to long-term deliverables and what needs to happen. Tactics refer to shorter-term actions and how they are implemented. The difficulties in translating knowledge to action are referred to as practice gaps. There is an urgent need to close practice gaps in lifestyle medicine, especially in the management of DBCD. Specifically, this requires the implementation of concrete, easily understood tactical steps that focus on lifestyle modifications, including healthy nutrition, physical activity, stress management, behavior modification, sleep hygiene, and tobacco/alcohol cessation, adapted to various social determinants of health, ethnocultural factors, patient-centered approaches, and economic barriers to confer a reasonable degree of sustainability.[12] In this chapter, a set of distinct tactics are presented.

33.2 TACTIC 1: TO CONSTRUCT NEW DYSGLYCEMIA CHRONIC DISEASE MODELS

Lifestyle medicine recommendations need to be formulated and interpreted in a chronic care model that is comprehensive, robust, and predictive of relevant events. Current models of cardiometabolic risk that are body mass index (BMI) centric,[13] gluco-centric,[6,14] or metabolic syndrome (MetS) centric[15,16] have demonstrated pitfalls when applied to complex, real-world clinical scenarios (e.g., obesity paradoxes,[17] CVD mortality with tight glycemic control,[18,19] and unclear pragmatic use of a static cluster of MetS traits.[16]

The cardiometabolic-based chronic disease (CMBCD) model was designed to address these pitfalls and also optimize early and sustainable cardiometabolic preventive care that mitigates CVD risk, primarily focusing on structured lifestyle changes.[20,21] The tCMBCD comprises three dimensions: stages, drivers, and social determinants of health (SDOH). In the first dimension, the four stages are mapped to specific prevention modalities: stage 1 (Risk ↦ Primordial prevention of risk development and progression), stage 2 (Predisease ↦ Primary prevention of disease), stage 3 (Disease ↦ Secondary prevention of complications), and stage 4 (Complications ↦ Tertiary prevention of suffering and mortality); each stage is also subject to quaternary prevention (the avoidance of overmedicalization and unethical behavior).[6,21,22] In the second dimension, individual metabolic drivers are considered as progressing and interacting along these four stages. These metabolic drivers are regarded as adiposity-based chronic disease (ABCD), dysglycemia-based chronic disease (DBCD), hypertension-based chronic disease (HBCD), and lipid-based chronic disease (LBCD), with residual factors recognized in the overall CMBCD model. In the third dimension, each stage × driver cell is populated with SDOH that confer precision to preventive actions. When cardiometabolic risk is interpreted in terms of transcultural factors, as part of SDOH, the result is a transcultural CMBCD model (tCMBCD).[6, 22] The tCMBCD components are being validated in populations of diverse cultures and ethnicities in the United States, Iran, Brazil, and Romania; ABCD and DBCD validations and specific transcultural adaptations in Czech Republic; and ABCD validations in Venezuela.[23–26]

The DBCD model is understood in the context of the larger tCMBCD model and constitutes a new way to approach diabetes prevention and management. This model focused on the pathophysiology, natural history, and clinical impact of dysglycemia, and was originally designed to address pragmatic questions of whether insulin resistance and prediabetes should be treated.[20] The DBCD model answers this question by exposing these early stages as opportunities for preventive care, primarily with lifestyle medicine. Further studies have characterized DBCD in more complex ways: for example, by depicting prediabetes progressing directly to T2D or leapfrogging to vascular complications, or even regressing to normoglycemia; or interacting with abnormal adiposity, hypertension, and dyslipidemia at the level of inflammation. Similarly to the CMBCD template, DBCD stages map to specific preventive care modalities (Figure 33.1). In stage 1, "Risk," the insulin resistance state with normoglycemic levels but also increased risk for macrovascular complications, maps to primordial preventive strategies (i.e., community/school education) and also primary/secondary prevention strategies in the setting of accelerated atherosclerosis.[27] In stage 2, "Prediabetes," mild hyperglycemia, which increases the risk for microvascular complications (around 10% of subjects with prediabetes already present hyperglycemia-related complications,[28] and about 70% progress to T2D during their life),[27] maps to primary preventive strategies (i.e., those modeled by the National Diabetes Prevention Program are recommended).[29,30] In stage 3, T2D, in which sustained hyperglycemia severely increases the development of complications, maps to secondary preventive strategies (i.e., modeled by the Look AHEAD Program) that should be applied to prevent the progression to complications.[31] In stage 4, Complications, where microvascular and/or macrovascular events are present, tertiary preventive care with greater participation of pharmacotherapy is available to improve quality of life, decrease suffering, and avoid future events and mortality.

33.3 TACTIC 2: TO CREATE LIFESTYLE MEDICINE CENTERS AND CLINICAL SERVICE LINES FOR DYSGLYCEMIA

Guideline-directed, evidence-based lifestyle medicine recommendations are best implemented when the

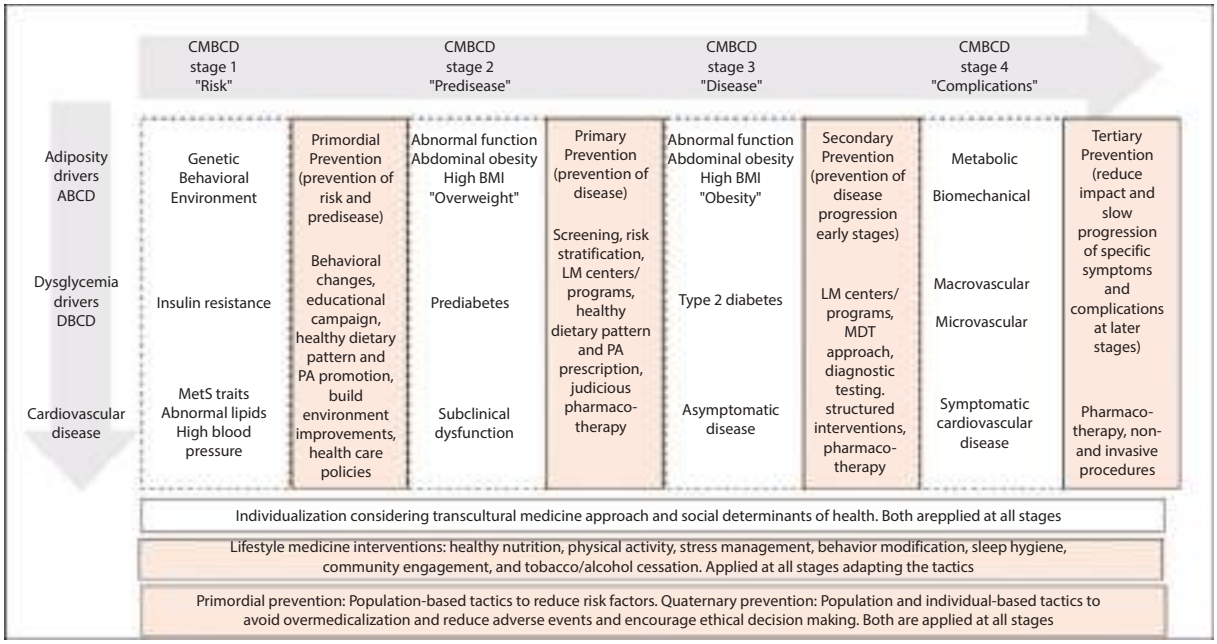


FIGURE 33.1 The transcultural cardiometabolic-based chronic disease model and prevention strategies. (Adapted from Mechanick, J.I., et al., ***Journal of the American College of Cardiology***, 75(5), 525–38, 2020)

infrastructure for service delivery is optimized, such as in Lifestyle Medicine Centers (LMC) and Lifestyle Medicine Clinical Service Lines (LMCSL).[32] A diligent literature search (MEDLINE database) was conducted to detect transcultural LMC/LMSLs that implement successful and evidence-based lifestyle medicine protocols addressing diabetes prevention and management in the United States, with results published in peer-reviewed journals in English up to July 2021. In addition, diabetes centers reported in Google Maps with the terms "diabetes," "lifestyle," AND "center" were reviewed and vetted in terms of peer-reviewed journal publications; these references were then reviewed with respect to evidence-based lifestyle medicine interventions or protocols for the prevention and treatment of diabetes. Results in the form of specific LMC/LMCSLs were curated according to different operational and performance aspects. Of the 3,172 results in MEDLINE and 56 centers located in the United States via Google Maps, 3 reports published as book chapters describing components of the implementation were found[33–35] (other centers were added as informative examples) (Table 33.1).

All of the LMC/LMCSLs included interventions to treat T2D that involved healthy eating and physical activity. Other lifestyle medicine services, such as sleep hygiene, stress reduction, behavioral science, tobacco cessation, alcohol moderation, and community engagement, were provided by more specialized centers. The staff of most institutions included endocrinologists, diabetes educators, and nurse practitioners, although other centers employed different medical specialists (i.e., cardiologists), exercise physiologists, nutritionists, dietitians, health coaches, and social workers. Aspects related to the transculturalization of care were reported by a few centers. For instance, Lifedoc Health[36] routinely considered cultural competency during the screening and intervention processes for Latino/Hispanic and African American populations; roughly 90% of their staff were bilingual and provided patients with nutrition meal plans and food exchange lists specific to culture and country; the Marie-Josée and Henry R. Kravis Center for Clinical Cardiovascular Health[33] included transculturalization of care as a lecture topic of their medical education program for healthcare professionals (HCPs) and staff; the Joslin Diabetes Center[37] offers two multicultural clinics, a Latino Clinic and an Asian American Clinic; and the Northwestern Medicine Center[38] offers educational materials in Spanish. Many of the centers offer more than one program that adapts to the needs of the patients and focuses on specific goals, including the utilization of telemedicine strategies and the focus on diabetes education. Research activities are also an important part of some of these centers, especially the university-affiliated institutions. Participation in clinical trials is widely reported by the biggest centers that conduct several research activities, such as the Joslin Diabetes Center,[37] Northwest Medicine Center,[38] Mayo Clinic,[39] Diabetes Center at Tufts Medical Center,[40] Boston Medical Center,[41] and LifeDoc Health.[36]

33.4 TACTIC 3: TO TRANSLATE DYSGLYCEMIA EVIDENCE INTO WHITE PAPERS IN PROFESSIONAL MEDICAL SOCIETIES

Lifestyle medicine is explicitly included in many, but not all, clinical practice guidelines (CPG) developed by scientific societies and health institutions worldwide promoting a multidisciplinary/comprehensive approach to DBCD

TABLE 33.1
Lifestyle Recommendations in Clinical Practice Guidelines

CPG (Region–Country)	AACE/ACE (United States)[42,43]	ADA (United States)[44]	ESC/EASD (Europe)[45]	Diabetes Canada Clinical Practice Guidelines Expert Committee (Canada)[46]	IDF (World)[47,48]	ACC/AHA[105]
Prevention or delay of T2D	Patients with prediabetes should modify their lifestyle by having a reduced-calorie healthy meal plan, physical activity, and behavioral interventions.	Patients with prediabetes should have intensive lifestyle behavior change to achieve 7% loss of initial body weight and increase moderate-intensity physical activity to at least 150 min/week.	Lifestyle intervention is recommended to delay or prevent the progression of pre-DM states, such as IGT to T2D.	In individuals with prediabetes, a structured program of healthy behavioral interventions is recommended that includes moderate weight loss and regular physical activity.	Lifestyle modification with physical activity and/or healthy diet can delay or prevent the onset of T2D.	Patients with prediabetes should lose 5% to 10% of initial weight with intensive lifestyle interventions. This is recommended in adults with obesity to reduce caloric intake by ≥500 kcal/day from baseline, limiting women to 1,200 to 1,500 kcal/day and men to 1,500 to 1,800 kcal/day.
MNT	Individualized MNT by a trained nutritionist in all patients with diabetes/prediabetes. Patients with overweight should restrict their caloric intake with the initial goal of reducing body weight by at least 5% to 10%.	MNT should be used to promote and support healthful eating patterns, address individual nutrition needs, maintain the pleasure of eating, and provide practical tools.	Nutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Among people at high CV risk (49% had diabetes), a Mediterranean diet supplemented with olive oil or nuts is recommended. There is no ideal percentage of calories from carbohydrate, protein, and fat for people with diabetes.	Patients should receive nutrition counseling by a registered dietitian. Nutrition education may be delivered in either a small group or a one-on one setting. The macronutrient distribution as a percentage of total energy can range from 45% to 60% carbohydrate, 15% to 20% protein, and 20% to 35% fat.	Multidisciplinary, patient-centered, and well-coordinated approaches.	A plant-based and Mediterranean diet is recommended, along with increased fruit, nut, vegetable, legume, and lean vegetable or animal protein (preferably fish) intake.
DSME	People with DM should receive DSME at the time of DM diagnosis and subsequently as appropriate. This includes MNT, physical activity, avoidance of tobacco products, and adequate sleep.	All people with diabetes should participate in DSME and receive support needed to facilitate the knowledge, decision making, and skill mastery necessary for diabetes self-care.	Group-based structured education programs are recommended in patients with diabetes, to improve knowledge, glycemic control, disease management, and patient empowerment.	DSME that incorporates cognitive-behavioral educational interventions, such as problem solving, goal setting, self-monitoring of health parameters, dietary modifications, and physical activity, should be implemented for all able individuals with diabetes.	Provide ongoing self-management support, taking account of culture, ethnicity, psychosocial, and disability issues.	N/R

(*Continued*)

TABLE 33.1 (CONTINUED)
Lifestyle Recommendations in Clinical Practice Guidelines

CPG (Region–Country)	AACE/ACE (United States)[42,43]	ADA (United States)[44]	ESC/EASD (Europe)[45]	Diabetes Canada Clinical Practice Guidelines Expert Committee (Canada)[46]	IDF (World)[47,48]	ACC/AHA[105]
Physical activity	At least ≥150 minutes per week of moderate-intensity activity, such as brisk walking (e.g., 15- to 20-minute miles) and strength training.	Children with diabetes or prediabetes should perform at least 60 min of physical activity/day. Adults with diabetes should perform at least 150 min/week of moderate-intensity aerobic physical activity, as well as reduce sedentary time.	Moderate-to-vigorous physical activity, combination of aerobic and resistance exercise, for ≥150 min/week is recommended.	150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise, to improve glycemic control. Interval training, resistance exercise at least twice a week, should also be practiced.	At least between 3 and five days a week, for a minimum of 30–45 minutes/day.	At least 150 minutes per week of moderate-intensity aerobic physical activity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity).
Psychosocial Assessment and Care	Behavioral support from family and friends. Obesity and diabetes are associated with high rates of anxiety and depression, psychosocial interventions should be performed routinely.	A collaborative patient-centered approach is recommended with the goal of optimizing health outcomes and health-related quality of life. Psychological screening and follow up assessment for symptoms of diabetes distress, depression, anxiety, and cognitive capacities should be performed. Older adults (>65 years) must be considered for evaluation of cognitive impairment and depression.		Motivational interventions, coping skills, self-efficacy enhancement, stress management, and family interventions are all helpful. An expert in mental health and/or psychosocial issues should provide intervention when required.	Teams can include community health workers and peer supporters trained to meet the physical and psychosocial needs of the person with diabetes.	Environmental and psychosocial factors, including depression, stress, self-efficacy, and social support, should be evaluated to improve achievement of glycemic control and adherence to treatment.

CV: cardiovascular, DM: diabetes mellitus, DSME: diabetes self-management education, IGT: impaired glucose tolerance, MNT: medical nutrition therapy, T2D: type 2 diabetes, N/R: not reported.
Source: Adapted from Nieto-Martínez, R., et al., *Endocrinology and Metabolism Clinics of North America*, 45(4), 967–1009, 2016.

care. The various approaches to lifestyle medicine in dysglycemia care by CPG development teams of the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE),[42,43] the American Diabetes Association (ADA),[44] the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD),[45] Diabetes Canada Clinical Practice Guidelines Expert Committee,[46] and International Diabetes Federation[47,48] are compared (Table 33.2).

In 2020, a consensus statement published by the AACE/ACE[42] on the comprehensive T2D management algorithm, emphasized the importance of lifestyle optimization and loss of excess weight in patients with ABCD and DBCD. This is reflected by the top hierarchical ranking of lifestyle prescriptions that include reduced-calorie healthy meal plans, physical activity, and behavioral interventions.[42] Of note, most CPGs on dysglycemia recommend lifestyle modifications (focused on weight loss) starting with the prediabetes (DBCD stage 2) to delay the progression to T2D and complications, with the bulk of the document devoted to diabetes (DBCD stage 3 and other types of diabetes). Most CPGs encourage individualized medical nutrition therapy (MNT) and multidisciplinary team approaches, physical activity, recognition and interventions directed to behavioral and psychological factors, and the prevention and management of complications (DBCD stage 4), such as CVD, nephropathy, retinopathy, and neuropathy.

The American College of Lifestyle Medicine (ACLM)[49] and the Institute of Lifestyle Medicine were created in 2004 and 2007, respectively, to promote medical education, lifestyle training programs, public advocacy, and the formation of Lifestyle Medicine Centers to protocolize evidence-based lifestyle interventions in research and clinical settings. In 2015, the Lifestyle Medicine Global Alliance (LMGA)[50] started as an initiative of the ACLM to increase the communication among lifestyle medicine professional organizations in the world, representing different regions (Africa, Asia, Australasia, Europe, Latin America, and South Pacific) and countries (Albania, Brazil, Canada, China, India, Iran, Israel, Italy, Japan, Korea, Lithuania, Philippines, Poland, Portugal, Romania, the United Kingdom, and the United States).[51]

33.5 TACTIC 4: TO CULTURALLY ADAPT WHITE PAPERS FOR PRECISION DYSGLYCEMIA CARE

Beyond scientific meetings and continuing medical education, it is recommended that professional medical societies, institutions, and other organizations deepen their contribution to dysglycemia care by advancing the transcultural adaptations of lifestyle medicine recommendations for DBCD in their specific countries. In the United States between 2017 and 2020, diabetes prevalence rates varied according to ethnicity (non-Hispanic white [13.6%], Hispanic [15.5%], non-Hispanic Asian [16.7%], and non-Hispanic African American [17.4%]),[52] which can be explained in part by biological, environmental, and cultural factors. The high level of diversity in the U.S. population compromises the precision of T2D care, necessitating the use of transcultural medicine in the routine patient–provider encounter.[53,54].

Each DBCD stage is patient-centered and considers ethnocultural factors (e.g., language, beliefs, values, food security, food preferences, eating patterns and culinary practices, religion, health policies, politics, environmental exposures, alcohol and tobacco use, physical activity, behaviors, specific anthropometric and laboratory cutoffs), SDOH (e.g., socio-economic status, education, social and community context, structural racism and discrimination, housing instability, education, occupation, healthcare access, health literacy, health inequities, local healthcare practices, neighborhood, socio-economic environment, and the built environment), and biopsychosocial factors (anxiety/depression, stressful situations, allostatic load), which in aggregate modify the DBCD phenotype and response to lifestyle, pharmacological, and procedural interventions. This again argues for a formal, protocolized transcultural approach.

"Transcultural" is a term applied to gaining knowledge about how diseases are expressed and managed in different cultures, and how evidence-based clinical recommendations are adapted from a source to a target population by experts from both sources to achieve better outcomes.[5,54,55] Broadly speaking, the comprehensive transculturalization process comprises the following sequential actions: (a) capturing and curating pragmatic, relevant evidence–based recommendations from source CPG and culturally adapting to a specific target population, (b) creating derivative cutoffs and screening tools, (c) packaging recommendations and tools into easily messaged evidence-based lifestyle interventions, and (d) building Lifestyle Medicine Centers/Service Lines/Programs in source and target populations for successful implementation of these interventions. This process results in a set of individualized evidence-based recommendations for each patient (Figure 33.2).

Once material is selected for transculturalization, the required actions and resources must be identified and organized. This process involves the use of available evidence, taxonomies, and frameworks that would allow the translation of theory into practice under different settings (clinical, organizational, public health, or policy contexts).[5] Various taxonomies have been developed to adapt and replicate health interventions in a systematic way. For implementation, Proctor et al.[56] proposed a model of outcomes that involve eight different elements: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability, which help to specify processes and measures for success on multiple levels. After an intervention is implemented, it is necessary to evaluate the effectiveness of the strategy. The Reach, Effectiveness,

TABLE 33.2
Lifestyle Medicine and Diabetes Centers in the United States

Center name/Website	Scope/Target	Structure (S)/Lifestyle interventions (LSI)[a]	Resources	Transcultural factors and implementation described	Business model	Programs implemented	Clinical trials participation[b]	Strengths and challenges
Lifedoc Health https://lifedochealth.org/36	Multidisciplinary and data-driven healthcare organization committed to preventing cardiometabolic chronic conditions by increasing access to care through a multidisciplinary standardized outcome-oriented model	S: Multiple services (endocrinology, nurse practitioners, lifestyle providers, pharmacists, care coordination) working in a multidisciplinary team approachB, N, PA, SH, SR, WB	Endocrinologist, nurse practitioners, registered nurses, and exercise physiologist, lifestyle expertise leadership	Consider cultural competency of screening and interventions to Latino/Hispanic and African American populations Cultural/country-specific nutrition meal plans and exchange lists	Fee-for-service reimbursement billing to insurance, mostly Medicare/Medicaid (64%) and private (18%) 18% non-insured patients served by a through Vida plus a discount membership program (12%) or self-pay (6%) Self-sustainable. No research grant funds	Lifestyle program for CMBCD Interventions based on Diabetes Prevention Program and the Diabetes Self-Management Education and Support Program with transcultural adaptations	Liraglutide for Weight Management in Adolescents with Obesity[106] CREDENCE trial[107] ELLIPSE Trial[108]	Multidisciplinary and transcultural approach Attending underserved minorities independently of insurance status Financial self-sustainability Outcomes-based interventions and protocols Lifestyle prescriptions to all DBCD and CMBCD stages
Joslin Diabetes Center www.joslin.org/[37]	Center with multidisciplinary approach to ensure people with diabetes get the most advanced medical care, education, and aggressive prevention and management of complications	S: The center counts with Adult Clinic, Pediatric Clinic, Eye Institute and Diabetes Research and Education centersLSI: B, EP, N, PA, SR, WB	Endocrinologists, nurse practitioners, and registered nurses, dietitians, and exercise physiologists	The center offers two multicultural clinics—a Latino Clinic and Asian American Clinic	Joslin is a 501(c)(3) non-profit organization. It receives support from donors over the world by strategies as fundraising events. It works with many medical insurance companies	Why WAIT[109] DO IT (Diabetes Outpatient Intensive Treatment) Program	Diabetes Prevention Program outcomes study[110] Dairy study[111] Exercise training study[112] Look AHEAD-E[113] Meal Replacement Study[114]	N/R
Rippe Lifestyle Institute https://rippehealth.com/rippelifestyle/[115]	A leading organization performing research and communicating the ways daily lifestyle habits and practices affect health	S: The Center has relationships with various academic medical centers and teaching hospitals. Counts with Rippe Health Evaluation and Rippe Lifestyle Institute, as well as Medical Weight Management and Metabolism Clinic.LSI: B, N, PA, SR, WB	Physicians, research nurses, registered dietitians, exercise physiologists, and senior level scientists	N/R	The center has relationships with various academic medical centers and teaching hospitals that afforded access to multiple, high level, expensive technologies. Also, a private research laboratory was established.Executive Health Program billing occurs according to contracts with companies who have sent their executives The RLI does not participate with any insurance plans	Executive Health Program GE Health "Wear Red" Campaign	N/R	Current efforts with the largest self-insured healthcare organization in the State of Massachusetts are underway to develop programs that incorporate lifestyle medicine. The goal of this partnership is to improve patient outcomes and satisfaction, control expenses, and perhaps even reduce physician burnout

(*Continued*)

TABLE 33.2 (CONTINUED)
Lifestyle Medicine and Diabetes Centers in the United States

Center name/Website	Scope/Target	Structure (S)/Lifestyle interventions (LSI)[a]	Resources	Transcultural factors and implementation described	Business model	Programs implemented	Clinical trials participation[b]	Strengths and challenges
Northwestern Medicine Center www.nm.org/[38]	Specialty referral center for the treatment of obesity. The primary foundational concept in obesity care is to guide and assist patients in making healthier dietary, physical activity, and behavioral choices	S: Northwestern Medicine links Northwestern Memorial Health system and Northwestern University's Feinberg School of Medicine. The center is co-located with the Bariatric Surgery program within the Digestive Health Center of Northwestern MedicineLSI: B, N, PA, SR, WB	Medical and mental health care providers, nurses. Other disciplines may include health coaches, exercise specialists, and social workers	Educational materials for adults and children in English and Spanish.	Administrative support for the Center is shared between the University and Northwestern Medical Group. Staff salaries and productivity benchmarks are determined by their respective departments or divisions. It uses an individualized, fee-for-service model of care	N/R	The MOBILE Study[116] EMPA-KIDNEY Trial[117] Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs)[118] Transformative Research in Diabetic Nephropathy (TRIDENT)[119]	This is the only program that provides comprehensive obesity care within the Northwestern Medicine system; timely patient access and availability for new and return appointments are difficult. Despite the increased demand for services, there is a lack of physical space for growth within the Medical Center
The Marie-Josée and Henry R. Kravis Center for Clinical Cardiovascular Health www.mountsinai.org/locations/msd-east-85/kravis-heart-center[120]	The Center integrates clinical cardiology, endocrinology, and nutrition, with exercise physiology and dietetics, in a dedicated and durable high-touch/high-tech immersive environment, to optimize cardiovascular health	S: The Center is part of Mount Sinai Heart, which also houses the Cardiovascular Institute in the Mount Sinai Health SystemLSI: B, PA, SR, SH, T	Endocrinologist, cardiologist, internist, medical educators, exercise physiologists, dietitians	Transculturalization of care reported	The center was developed within a sponsoring academic health system. The objective is to develop an economic self-sustained program. Revenue streams result from services billing insurance plans and self-pay	Cardiology/Endocrinology Clinical Practice Cardiac Rehabilitation/Medical Fitness	N/R	Economic sustainability using this structure has not been possible due to the high fixed overhead costs and mandated compliance with rules and regulations. Referrals for nutrition counseling by the registered dietitian have also been targeted for improvements

(*Continued*)

TABLE 33.2 (CONTINUED)
Lifestyle Medicine and Diabetes Centers in the United States

Center name/Website	Scope/Target	Structure (S)/Lifestyle interventions (LSI)[a]	Resources	Transcultural factors and implementation described	Business model	Programs implemented	Clinical trials participation[b]	Strengths and challenges
Diabetes Center at Tufts Medical Center www.tuftsmedicalcenter.org/patient-care-services/departments-and-services/endocrinology/clinical-care-services/diabetes-clinic[40]	Understand the basis of the endocrine system through research, develop more effective treatments, and provide the highest standards of care to improve the lives of patients with endocrine disorders	S: Additional services include podiatry, vascular surgery, including the Wound Center at Tufts Medical Center, nephrology, neurology, and the New England Eye CenterLSI: B, N, PA, WB	Endocrinologists, advance care practitioners, nurses, and clinical pharmacists	N/R	Receive donations	Lifestyle Coaching Program for Diabetes and Weight Loss Telemedicine initiative Diabetes Self-Management Education group	Vitamin D and Type 2 Diabetes Study[121]	N/R
Boston Medical Center www.bmc.org/diabetes[41]	The program is designed to help patients and their primary care provider understand their conditions related to diabetes through education, medication, monitoring, nutrition and exercise recommendations	S: Offers comprehensive diabetes care in including nutrition, podiatry, ophthalmology, cardiology, and dental servicesLSI: B, N, PA, WB	Diabetes specialists, nurse practitioners, certified diabetes educators (including nurses, pharmacists, and dietitians)	N/R	As a non-profit organization, Boston Medical Center receives donations	Diabetes education program Inpatient program	PIONEER 2[122] Linagliptin Inpatient Trial[123] SWITCH PRO[124]	N/R
The Alpine Center for Diabetes, Endocrinology, and Metabolism www.thealpinecenter.com/services/diabetes[125]	The Center combines education, lifestyle design, and technology to manage symptoms and live a high quality of life	S: N/RLSI: N, PA, WB	Medical doctors	N/R		Undo Type 2 Program Beat Prediabetes Coaching LeanMD weight loss program	N/R	N/R

(*Continued*)

TABLE 33.2 (CONTINUED)
Lifestyle Medicine and Diabetes Centers in the United States

Center name/Website	Scope/Target	Structure (S)/Lifestyle interventions (LSI)[a]	Resources	Transcultural factors and implementation described	Business model	Programs implemented	Clinical trials participation[b]	Strengths and challenges
Palm Beach Diabetes and Endocrine Specialists Diabetes Center www.pbdes.com/diabetes-education/123-program/[126]	The center offers personalized treatment programs designed to promote individual patient involvement with their care, as well as customized healthy eating lifestyles and exercise training	S: The Center counts with four offices in Florida LSI: N, PA, WB	Specially trained physicians, diabetes and endocrinology specialists, nutritionists, and certified diabetes educators	N/R		Living Well with Diabetes 1-2-3 Program	N/R	N/R
Mayo Clinic Diabetes Mellitus Specialty Group[39] www.mayoclinic.org/departments-centers/diabetes-mellitus-specialty-group/overview/ovc-20392572	Diabetes Mellitus Specialty Group providers care for and treat patients with all aspects of diabetes, including insulin therapy, hypoglycemia, pregnancy, nutrition, exercise, and complication prevention	S: Mayo Clinic's Division of Endocrinology, Diabetes, Metabolism, & Nutrition is one of the largest in the world, with locations in Arizona, Florida, Minnesota, and several communities throughout the Mayo Clinic Health System (MCHS). Count with Diabetes Technology Clinic. For pregnant patients work with Maternal Foetal Medicine Specialty GroupLSI: B, N, PA, SR, WB	Top-ranked team of endocrinologists	N/R	As a non-profit organization, Mayo Clinic relies on generous, compassionate people to support the activities. Mayo Clinic works with hundreds of insurance companies	Diabetes Unit Outpatient and Inpatient Diabetes Education Program	A Study of the Genetic Links of T2D in Latino Families[127] Impact of Nutrition Education and Access to Nutritious Foods on Diabetes Control[128] The Work of Being a Patient with Diabetes: Data Collection Via a Smartphone Application[129]	N/R

[a]Lifestyle interventions (LSI): Behavior (B); Eating problems (EP); Nutrition (N); Physical Activity (PA); Stress Reduction (SR); Well-Being (WB); Sleep Hygiene (SH).
[b]Some informative examples are included, as many of these centers have participated in many clinical trials.
MDT: multidisciplinary team, SDOH: social determinants of health, SMA: share medical appointment, N/R: not reported, CMBCD: cardiometabolic-based chronic disease, DBCD: dysglycemia-based chronic disease.

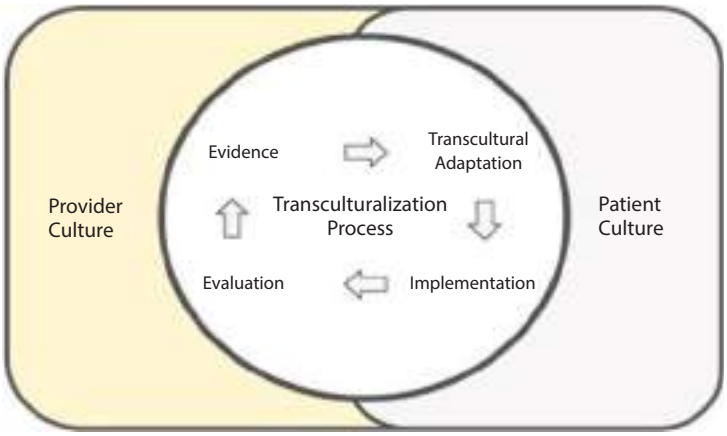


FIGURE 33.2 Transculturalization process closes the gap between the provider and patient cultures.[151]

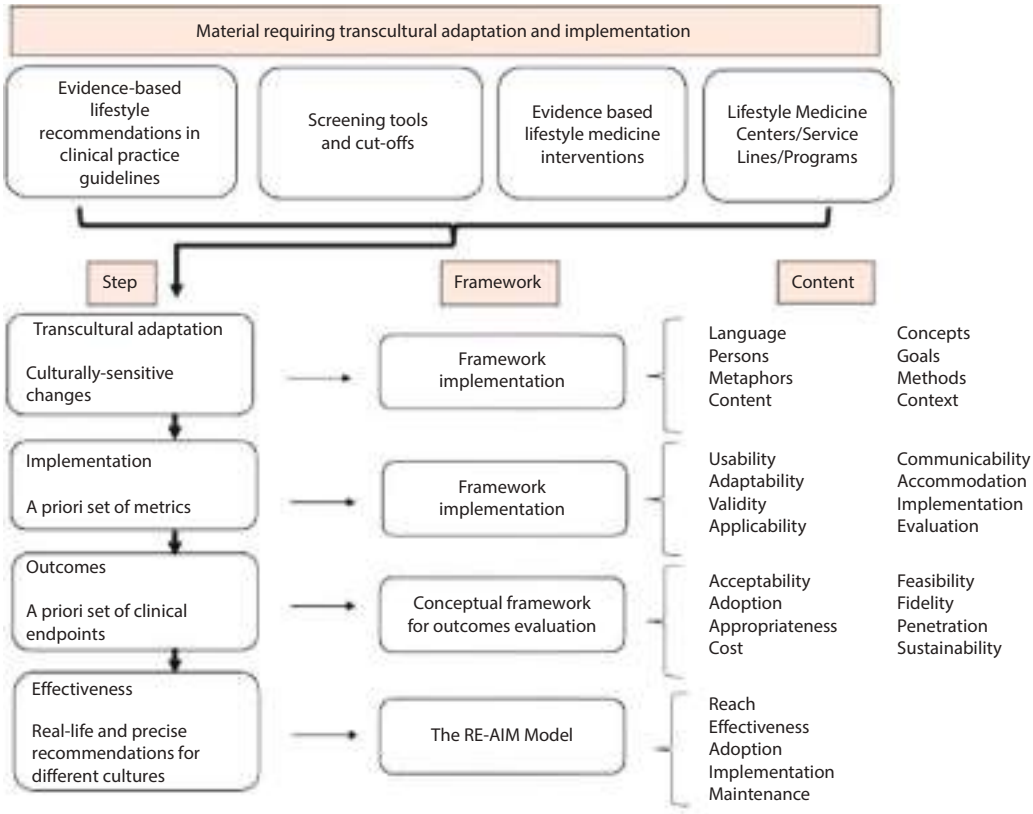


FIGURE 33.3 Stepwise approach and frameworks for transcultural adaptation and implementation of lifestyle recommendations. Ecological validity model,[67] implementation framework,[152] conceptual framework for outcomes,[82,152] and the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework. [153] (Adapted from Nieto-Martínez, R., et al., ***Endocrinology and Metabolism Clinics of North America***, 45(4), 967–1009, 2016.)

Adoption, Implementation, and Maintenance (RE-AIM) framework allows the reporting of key issues related to the implementation and external validity of health interventions.[57] The final goal of implementation is to improve patient- and population-based clinical outcomes. Challenges in the implementation process occur at individual and organizational levels (e.g., patient education, health policies) and include practical issues (e.g., cost and acceptability). A previously proposed algorithm[5] is updated in Figure 33.3.

In 2010, an international core committee of diabetes specialists and endocrinologists developed an evidence-based algorithmic template of diabetes care—the transcultural Diabetes Nutrition Algorithm (tDNA).[58] The tDNA was developed to culturally adapt the recommendations from the AACE/ACE/ADA diabetes CPGs with a focus on MNT for different settings on a global scale. This strategy provided HCPs with a validated portable tool, in electronic or printed format, that was culturally adapted and

inclusive of the best scientific evidence available in each country or region. Specifically, the tDNA was adapted to seven countries/regions (South-East Asia, Asian-India, Malaysia, Canada, Venezuela, Mexico, and Brazil)[59–65] and validated in Malaysia.[66] The steps in the tDNA transcultural adaptation process include: (a) identification of the target population, (b) identification of the clinical question, (c) identification of the appropriate source evidence base, (d) identification of experts in the source and target populations to adapt the evidence using validated frameworks (e.g., the Ecological Validity Model,[67] and (e) synthesis of the transcultural recommendations and algorithm.[68]

33.5.1 Transcultural Component 1: Lifestyle Medicine in Clinical Practice Guidelines

Transcultural factors in CPG adaptations for diabetes prevention and management[5] and HCP–patient encounters should recognize and address cultural barriers to implementing lifestyle strategies.[12] Lifestyle recommendations suggested by professional medical societies are typically implemented under different socio-economics, political settings, and cultures. The validation of CPG in many international-target settings would result in an improvement in adherence and outcomes in dysglycemia care. Every region has barriers that could preclude the implementation of certain lifestyle medicine tactics developed and recommended under ideal conditions. For example, the implementation of the DPP in other settings has shown lower effectiveness than in the original U.S. DPP trial.[5] Common barriers found in the implementation of guideline recommendations include fragmentation of the healthcare system, the need to adapt to chronic disease management, and education. These barriers can be addressed through the comprehensive transculturalization process.

One example of a transcultural adaptation of lifestyle recommendations in CPGs on dysglycemia was the initiative developed by the Brazil Society of Diabetes, which adapted American and European diabetes guidelines based on the resources and therapies available through Brazil's public health system, called the Sistema Único de Saúde.[69] Another transcultural consideration effort is represented by the Native Diabetes Wellness Program (NDWP), fostered by the Division of Diabetes Translation of the Centers for Disease Control and Prevention (CDC), which, using shared messages and other tactics, supports sustainable ecological approaches and health practices to promote traditional foods, physical activity, and social support in American Indian / Alaska Native populations.[70]

33.5.2 Transcultural Component 2: Adapting Screening Tools, Cutoffs, and Interventions

The validation of risk scores in different settings is an important step in the process of screening and implementation of prevention programs. Some screening tools are widely used across the globe despite being developed for certain populations. One of the most popular screening tools to detect T2D risk is the Finland Diabetes Risk Score (FINDRISC), which has been externally validated in many countries (e.g., the United States,[71] Venezuela,[72] Colombia,[73] Peru,[74] Uruguay[75]). Another example of culturally adapted diagnostic tools is abdominal cutoffs to detect aggregation of cardiometabolic risk factors,[28,56] as well as BMI cutoffs for identifying excess adiposity and cardiovascular risk.[76–78] The determination of ≥94 cm in men and ≥90 cm in women as cutoff points to identify people with abdominal obesity, after comparing measurements of visceral adipose tissue obtained by computerized axial tomography with abdominal circumference in participants from five Latin American countries, is another transcultural approach experience.[79] The modification of the Mediterranean pyramid using local foods and culinary techniques proposed in the Venezuelan tDNA version is also an example of transcultural adaptation.[77] New data from lifestyle clinical trials and practical experiences would allow the use of more specific interventions for each population,[55,80,81] but it is important to highlight that every adaptation should be followed by validation studies of implementability, endpoints, and effectiveness.[5,82]

33.5.3 Transcultural Component 3: Routine Use in Lifestyle Medicine Centers

Implementation strategies are used to translate evidence-based recommendations into actions within the framework of an *a priori* healthcare model (e.g., DBCD). This translation incorporates physical components, human resources, policies, and protocols that constitute a LMC/LMCSL. In a LMC/LMCSL, the implementation of new interventions should be appropriate for the target settings and population. Ideally, all DBCD interventions should be culturally sensitive, involving exercise plans and diabetes-specific nutrition.[58] More importantly, in a transculturalized LMC/LMCSL, it is necessary to adapt the nutritional strategies and physical exercise plans to the specific population (e.g., delivering menus involving foods from different countries and exercise plans adapted to preferences, customs, and routines). In a patient-centered care model, transculturation plays an even greater role; this is why the implementation and validation of ethno-culturally adapted interventions is becoming more important[54] (Table 33.2).

Diabetes oriented LMC/LMCSL guide prevention, screening, diagnosis, and treatment strategies. The services should reflect the cultural diversity of the targeted population, as well as the characteristics of the area of influence (e.g., migrating population, availability of resources, physical spaces, among others), avoiding health disparities. The main human diversity challenges facing a LMC/LMCSL are summarized in the following.[12]

(a) *Cultural competence of the staff*
- Familiarization with the target community and the appropriate evidence-based culturally adapted materials needed
- Awareness of SDOH and cultural differences
- Development of communication skills that enhance interaction with patients (e.g., motivational interviewing) by showing cultural respect and a safe environment (e.g., bilingual staff and printed/web-based materials)

(b) *Infrastructure and services*
- Separation of spaces by gender in Arab cultures
- Avoiding religious symbolisms

(c) *Information and software resources*
- Medical history to include SDOH
- Written tools (questionnaires, screening tools, scores) adapted by language with cultural customization
- Use of specific cutoff points in anthropometric and laboratory assessments by age, gender, and ethnicity (see example in Table 33.3)

(d) *Administrative and organizational elements*
- Universal healthcare and different payment models
- Decreasing inequities in access to lifestyle medicine care[83]

33.6 TACTIC 5: TO BUILD MULTIDISCIPLINARY TEAMS FOR DYSGLYCEMIA CARE

Multidisciplinary care is associated with improved outcome in dysglycemia care and involves the participation of two or more HCPs (e.g., nurses, doctors, nutritionists, dietitians, and exercise physiologists) working together with the same patient. A meta-analysis of 16 clinical trials in 2007–2017, performed in Asia, Australia, Europe, and the United States, comparing the outcomes in patients with uncontrolled T2D undergoing MDT care (with more than two different HCPs) versus usual care (provided solely by physicians), reported that the patients in the MDT group had a higher reduction of hemoglobin A1c (A1C) (median difference = −0.55%, 95% confidence interval [CI] = −0.65% to −0.45%, $p < 0.001$) and systolic blood pressure (median difference = −4.89 mmHg, 95% CI = −6.64 to −3.13 mmHg, $p < 0.001$).[84] Moreover, MDT costs and utilization were similar in the MDT group compared with usual care,[84] possibly due to redistribution of ancillary tasks (e.g., monitoring, counseling, assessing, and optimizing medications of patients), which could help to reduce patient load for physicians.[84]

A review assessing patients' and HCPs' perceptions toward MDT care in T2D found that synergistic teamwork was more efficient and expeditious.[85] Furthermore, HCPs reported that trust in the other team members was essential

TABLE 33.3
Summary of Lifestyle Medicine Tactics to Optimize Dysglycemia Care

Tactic	Description	Components
1	Chronic Disease Models	Adiposity-Based Chronic Disease
		Dysglycemia-Based Chronic Disease
		Cardiometabolic-Based Chronic Disease
2	Infrastructure	Lifestyle Medicine Center
		Lifestyle Medicine Clinical Service Line
3	White Papers	Professional Medical Society
		Scoping and Systematic Reviews
		Position Papers
		Consensus Conferences
		Clinical Practice Guidelines
4	Transculturalization	Clinical Practice Guidelines
		Screening Tools, Cutoffs, and Interventions
		Routine Use in Lifestyle Medicine Centers/Clinical Service Lines
5	Multidisciplinary Teams	Champion/Leader
		Members
		Collaborative Culture
6	Community Engagement	Projects
		Health Workers
7	Public Policy	Municipality
		State/Province
		National
8	Technology	Wearables
		Cloud-Based

to provide better care.[85] Other challenges for MDT include improving communication and addressing differences in opinion among team members. Patients expressed more satisfaction and reduced waiting times with the MDT approach, leading to improved relationships and better use of other healthcare services, such as dietitians and podiatrists.[85].

A one-year retrospective review in 2018 of 598 adults (African American 59%, Hispanic 35%, and Caucasian 6%) with a mean age of 43.8 years ± 14.0 who attended in Lifedoc Health—a multidisciplinary center for CMBCD—was performed.[83] Patients who were activated for change, with ≥ one cardiometabolic risk factor (overweight/obesity, prediabetes/diabetes, or hypertension), and treated under a MDT protocol were compared with patients who qualified for MDT but instead were treated solely by a PCP.[83] After one year of intervention, patients treated by the MDT had a greater reduction (β, 95% CI) in weight (−4.29 kg, −7.62, −0.97), BMI (−1.43 kg/m^2, −2.68, −0.18), systolic blood pressure (−2.18 mmHg, −4.09, −0.26), and diastolic blood pressure (−1.97 mmHg, −3.34, −0.60).[83] They also had 77% higher odds of reducing their initial weight by ≥5%, 83% higher odds of reducing their body mass index by ≥1 point, and 59% higher odds of reducing their diastolic blood pressure by ≥2 mmHg.[83] The number of encounters was an important factor in mediating these positive results; among those engaged with the MDT, 30.9% of their visits were for lifestyle intervention.[83]

A meta-analysis showed that T2D care provided by a MDT consisting of at least a registered nurse, registered dietician, and physician (primary care and/or specialist) (model 1), or a MDT consisting of a pharmacist and primary care physician (model 2), produced a clinically significant reduction in A1C compared with usual care (−1.00%, 95% CI −1.27, −0.73 for model 1 and −1.05%, 95% CI −1.57, −0.52 for model 2).[86] Moreover, model 2 showed a significant decrease in systolic blood pressure (−7.13 mmHg, 95% CI −11.78, −2.48).[86] In both models, the outcomes were similar independently of the setting of healthcare delivery (primary care vs. hospital outpatient clinic vs. community clinic).[86]

Reported strategies to improve HCP practices in low- and middle-income countries include the use of job aids as well as information and communication technology, the combination of training with other strategies, such as supervision or group problem solving, and financial incentives for HCPs.[87] Although those strategies alone seem to have a low to moderate effect, the combination of training with group discussions seem to have better outcomes.[87] Additionally, some studies have shown that this effect is more significant when they are combined with community support.[87]

33.7 TACTIC 6: TO ENGAGE COMMUNITY RESOURCES IN DYSGLYCEMIA CARE

Some studies have reported that the most effective educational strategies to prevent diabetes were implemented at the community level, especially when they were permanent or maintained for long periods of time.[88] This highlights the relevance of sustainability. An example of community interventions at a national level is Project IMPACT, a diabetes self-management program conducted by the American Pharmacists Association (APhA) Foundation to help patients with T2D and limited access to healthcare.[89] This project involved the participation of different HCPs in 25 communities across the United States. Some of the tactics used by Project IMPACT involved determining the patient's individualized needs by identifying knowledge deficits (low health literacy).[89] Some of the strategies included one-on-one patient visits, motivational interviewing, point-of-care testing to gain an understanding of the patient's health condition, creating a personalized plan of care, and teaching patients about insulin injection techniques and the importance of medication adherence. Patients receiving care from the MDT had a reduction of 1.2% in A1C and a decrease in other cardiovascular risk factors, such as systolic and diastolic blood pressure (8.3 mmHg and 3.5 mmHg, respectively), and low-density lipoprotein (16.6 mg/dL).[89]

A Canadian study analyzing the association between built and natural environment features (walkability and park availability) and physical activity, obesity, and diabetes prevalence found that walkable neighborhoods were associated with lower rates of diabetes (highest vs. lowest quintile odds ratio [OR] = 0.62, 95% CI: 0.45, 0.85, and OR = 0.63, 95% CI: 0.47, 0.84, respectively).[90] The results of this study support the need to increase walkable and green areas and highlights how environmental factors impact the prevalence of diabetes.[90]

In another review, community health worker (CHW) interventions for the prevention and management of chronic diseases, including patient education, referral of high-risk individuals to physicians, and provision of social support through home visits, were associated with positive outcomes for patients with diabetes in seven of ten studies included.[91] Some of these improvements were increased knowledge of T2D symptoms and prevention measures, medication adherence, and improved outcomes (e.g., fasting blood sugar, A1C, and BMI).[91] Tactics based on CHWs in preventing and treating T2D are best understood when considering the gaps in healthcare delivery. In low-resource settings with fragmented healthcare systems, CHWs can identify individuals at high risk of diabetes through non-laboratory screening tools or point-of-care capillary glucose tests, and then facilitate diabetes self-management.[91] The evidence on the combination of responsibilities, training of CHWs, and length of intervention varies significantly, but such programs have improved treatment adherence.[91] Also, CHWs can help patients to understand integrative medicine in pluralistic health environments and navigate the health system due to CHWs' intimate knowledge of the local culture and health practices.[91] Nevertheless, CHW interventions need to be transculturalized to a population's genetic, social, racial, and environmental factors to optimize effectiveness.[92]

33.8 TACTIC 7: TO PROMOTE SCALABLE PUBLIC POLICIES ON DYSGLYCEMIA RISK REDUCTION

Public policies to decrease cardiovascular risk factors have been successfully implemented in many parts of the world. An example of a national initiative to decrease the burden of T2D in the United States is the National Diabetes Prevention Program (NDPP), an evidence-based lifestyle intervention applied to prevent diabetes in hundreds of thousands of individuals at risk.[29] This program was implemented under the leadership of the CDC, based on the result of the Diabetes Prevention Program (DPP), a 27-center clinical trial that demonstrated a 58% reduction in the incidence of T2D over three years and a sustainable benefit in decreasing cardiovascular risk factors and the incidence of metabolic syndrome.[29] Over one year, the NDPP promoted weight loss using different strategies, including in-person or virtual modalities.[29] Similar strategies have been implemented in China, Finland, India, and Venezuela.[93,94]

Other examples of policy strategies to improve population health include changing the quality of the food supply (e.g., secure healthier foods in educational institutions),[95] improving transportation systems,[96] and developing awareness campaigns by public health agencies (e.g., Do I Have Prediabetes Campaign, Your Health with Joan Lunden).[69] Media campaigns, including televisions and radio broadcasts (e.g., Five Steps for Your Health),[69] are a common approach to significantly promote healthy behaviors.

It is important to increase the awareness and diagnosis of T2D and prediabetes. More than 80 million Americans are estimated to have prediabetes.[29] Increasing awareness of prediabetes has been shown to promote behavioral changes to decrease the risk of progression to T2D.[29]

Some strategies that can increase patients' and HCPs' assessment of T2D include the expansion of point-of-care devices for diabetes screening in dental offices, pharmacies, and community-based settings, and encouraging diabetes risk assessment practices among HCPs with tools such as the ADA Diabetes Risk Test and the CDC Prediabetes Test.[97] It is also important to encourage NCPs to assess associated conditions in patients with diabetes.[98] An example of this is the VIDA Project, an 18-month intervention that provided structured diabetes education, training in foot care, and an in-service for HCPs on diabetes management.[69]

33.9 TACTIC 8: TO LEVERAGE TECHNOLOGY FOR DYSGLYCEMIA MANAGEMENT

The impact of technology in healthcare systems and patient care is growing every day. The U.S. Food and Drug Administration defines mobile health as the use of mobile and wireless devices to improve health delivery and outcomes, potentially reaching thousands of people. Many strategies have been developed allowing patients to access easy-to-use technologies. The use of technology in treating chronic conditions that require lifelong control, such as diabetes, can be an important step to improve outcomes. A meta-analysis studying the results of 6 interventions and 1,001 patients determined that wearable device-based interventions for 12 months or less could result in better glycemic control in patients with T2D than the usual care.[99] Clinical trials have demonstrated a significant decrease in levels of A1C in patients benefitting from mobile health interventions. Although wearable activity trackers are effective to improve the levels of physical activity in patients with cardiometabolic conditions,[100] when these strategies are combined with other approaches, such as in-person HCP consultations, the improvement in physical activity rates has been higher.[101]

Recently, several companies are offering what are called connected diabetes care products. These are digital diabetes management systems that involve the use of smartphones and other devices with connectivity, in conjunction with remote coaching with continuous support. Such strategies are currently growing and can improve healthcare delivery care in underserved areas, where empowering the patients on their own care could significantly impact how diabetes is managed. Nevertheless, more evidence of the effectiveness of these tools is needed.[102,103] The efficacy of mobile phone apps for lifestyle modification in diabetes management comparing five types of interventions—web-based, mobile phone applications (apps), a digital versatile disc (DVD), virtual reality, or telehealth—showed a significant reduction in the mean A1C level in patients with T2D.[104] The study analyzed subgroups for the short-term (3–6 months) and long term (9–12 months), finding the overall effect on A1C significant ($p < 0.01$) in both subgroups.[104] The effect remained statistically significant ($p < 0.01$) after adjusting for publication bias.[104]

33.10 CONCLUSION

DBCD, a representation of different stages of chronic disease resulting from dysglycemia, is a pathophysiologically based care model with an actionable approach, centered on early and sustainable prevention tactics that mitigate disease burden, cost, and related suffering (Table 33.4). T2D (DBCD stage 3) is a significant cause of morbidity and mortality worldwide; therefore, there is an urgent need to create comprehensive care models and tactics that incorporate preventive actions to retard or even eliminate DBCD progression and consequences. Those tactics should consider ethnocultural factors, SDOH, and biopsychosocial factors, with the additional requirement of being sustainable over time. Lifestyle interventions are explicitly included in T2D CPGs, and some tactics can be implemented in specialized institutions (e.g., LMC/LMCSL) with a MDT approach, which has shown a significant benefit compared with usual care. Moreover, other tactics can be implemented at a community or national level, such as the DPP, a preventive care program focusing on diabetes and applied to hundreds of thousands of individuals at risk. Finally, wearable technologies have been shown to improve T2D care, presenting now as a promising strategy to promote lifestyle interventions.

TABLE 33.4
Clinical Applications

Case: African American female evaluated in a Lifestyle Medicine Center for T2D and Cardiovascular Risk Management.

Scope: This is an example that includes new cardiometabolic models, multidisciplinary teams, and transcultural approaches for screening, diagnosis, and implementation of lifestyle interventions implemented in a Lifestyle Medicine Program.

Patient presentation

A 65-year-old African American woman with obesity, hypertension, and T2D is referred to a Lifestyle Medicine Center to improve her diabetes control and reduce her cardiovascular disease risks. Since her husband passed away two years ago, she lives alone, has developed major depression, and has increased tobacco consumption significantly. Her only daughter lives in New York. She has multimorbid chronic disease, defined as the presence of two or more chronic conditions.[130]

Evidence-based theory

Evaluation and transcultural approach

CDC reports show that African American (AA) women have the highest rates of obesity and T2D compared with other race groups in the United States.[131,132] In a cross-sectional study of 4,856,326 participants, it was shown that AA adults have higher prevalence of diabetes, hypertension, and physical inactivity than Caucasian adults, and that these disparities have consistently trended upward among the AA population.[133] Additionally, AAs may have higher levels of A1C than non-Hispanic whites, but with similar fasting and post–glucose load glucose levels.[44] Due to the disproportionate burden of diabetes in these populations, it is necessary to develop and implement greater strategies that allow better disease management. An increased adherence to lifestyle interventions and medication can be achieved in African Americans with T2D by implementation of culturally targeted self-management programs in the community.[54]

Transcultural factors with social determinants must be incorporated into the evaluation of this patient and should be part of the Lifestyle Medicine Center protocol. The availability of proper information and culturally specific anthropometric and laboratory cutoffs led to higher diagnostic accuracy for risk factors and chronic diseases amenable to lifestyle medicine interventions. A critical part of the transcultural approach for different ethnicities is the formal assessment of SDOH.[54] SDOH can be captured through the Protocol for Responding to and Assessing Patient's Assets, Risk, and Experiences (PRAPARE) tool,[134] referring them to community-based resources, and ultimately, closing the loop to confirm whether the patients' needs were met.

Lifestyle and behavioral questionnaires should be applied in this patient. Mild cognitive impairment was evaluated with the Montreal Cognitive Assessment, which has demonstrated its cross-cultural applicability.[135] The Geriatric Depression Scale has been widely used in ethno-culturally diverse elderly medical patient populations (i.e., Asians, AAs, Mexican Americans) and has demonstrated good internal consistency and stability over a 15-month interval in AAs.[136] The Mini Nutritional Assessment (MNA) has also demonstrated reliability in defining the nutritional state of elderly patients[137] and has been validated in different cultures.[138–140]

Clinical practice applications

The patient was received by a diligent, compassionate, and culturally competent staff with knowledge, attitudes, and skills, and the patient perceived respect from all the personnel. The CMBCD protocol included individualized case finding and risk stratification with a detailed history focusing on modifiable cardiovascular risk factors, anthropometric assessment (e.g., weight, height, waist circumference, and % body fat using bioimpedance), physical examination, and biochemical evaluation using validated markers (e.g., A1C, C-reactive protein, and lipids).

Questionnaires were created and presented to the patient in the reception area prior to each encounter to capture this information. This patient did not complete high school. Although her house has the benefit of all necessary utilities (water, electricity, gas, etc.), housing instability (e.g., difficulty with rent or mortgage payments, overcrowding, moving frequently, and/or staying with relatives) was detected, and her daughter is planning to relocate her to a nursing home facility. Food insecurity, defined as either a limited or uncertain availability of nutritionally adequate and innocuous foods or the incapacity to acquire them by socially acceptable means,[141] in the last year was also reported. Annual income categorized her into low income/poverty status. She maintains her medical insurance but has stopped taking some of her medications because of the lack of transportation to pick them up.

Several additional specific lifestyle and behavioral questionnaires were applied in this patient. Cognition was intact by Montreal Cognitive Assessment,[135] Geriatric Depression Scale (short version 15 items) was consistent with severe depression,[136] Sleep quality score[142] reported bad sleep quality (8 points), and Sleep apnea screening (No SAS score) was negative to detect.[143] Multiple factors for malnutrition were detected: poor dentition, depression, living alone, functional status, multiple chronic diseases, and food insecurity.

(*Continued*)

TABLE 33.4 (CONTINUED)
Clinical Applications

Physical examination and laboratory

Vitamin D insufficiency is established from the point at which serum intact parathyroid hormone levels significantly rise.[144] The 25-hydroxyvitamin D threshold for insufficiency is approximately 20 ng/mL for AAs versus approximately 30 ng/mL in Caucasians.[145] Thus, in this patient, a level of 25-hydroxyvitamin D of 26 ng/mL is considered normal. If the specific eGFR cutoff point for AAs had not been considered, the patient would have been categorized with chronic kidney disease 3b with possible unnecessary therapeutic interventions. Compared with Caucasians, AA females have 13.8% lower FEV1 and 14.4% lower FVC.[146] Therefore, the use of specific ethno-culturally adjusted predictive data is recommended for routine encounters and interpretation of a host of metrics in a lifestyle medicine center.

Physical examination showed high values of BMI (31.2 kg/m^2) and body fat (37%). Fasting blood glucose was 147 mg/dl, and A1C was 7.8%, evidencing suboptimal control of diabetes. The patient reported incomplete adherence to her prescribed medication (metformin 1,000 mg and sitagliptin 50 mg combined twice daily). Chest auscultation detected expiratory wheeze, and she uses accessory muscles when short of breath. Oral exam reveals tooth loss and periodontal disease. There is no peripheral edema.

Other significant laboratory results include Hgb 9.6 g/L (low); LDL cholesterol 147 mg/dL (goal <70 mg/dL); creatinine 1.28 mg/dL (high); estimated glomerular filtration rate 50 mL/min/1.73 m^2 (chronic kidney disease 3A for African Americans);[147] and 25-hydroxyvitamin D 26 ng/mL (low for Caucasian population, but normal for African Americans). Spirometry reported a forced expiratory volume 1st second (FEV1) of 1.04 L (37% of predictive value for African Americans), forced vital capacity (FVC) of 2.03 L (61% of predictive value for African Americans), and FEV1/FVC of 51% (low; normal >80%) with both obstructive and restrictive findings. Chronic conditions diagnosed during the evaluation included chronic obstructive pulmonary disease (COPD), anemia, chronic kidney disease stage 3A due to hypertension, depression, and tobacco use disorder. Based on muscular strength and muscle mass, a sarcopenia diagnosis was also established.

Discussion and interventions

Interventions for all aspects of the lifestyle medicine evaluation must be considered.

Evidence-based physical activity prescription should be provided.

A physical rehabilitation protocol to stop and overcome sarcopenia and frailty was designed with supervised resistance training, which is demonstrated to improve muscle strength and physical performance.[148] Recommendations for older patients are available.[149] The tDNA[77] includes physical activity recommendations to start at low intensity for this patient: aerobic (slow walking, stationary cycling) for a minimum of 10 minutes to increase the pulse rate less than 40% of the maximum heart rate. The progressive resistance training program should initially involve at least three large muscle groups (e.g., quadriceps, biceps, and triceps) with two sets of ten repetitions per muscle group, performed on three nonconsecutive days per week. Flexibility and balance exercises include stretching to the point of tightness and holding the position for a few seconds on all days that aerobic or muscle-strengthening activity is performed. Balance training exercise should occur two to three times per week. The lack of transportation and living alone are barriers to physical rehabilitation, so an outpatient physiotherapist is an alternative while the patient gains autonomy in their daily tasks. Patient's preferences should always be considered. Motivations (e.g., perceived health benefits, social support, and enjoyment) and barriers (e.g., time, physical limitations, peer pressure and family responsibilities, and weather and poor neighborhood conditions) to physical activity have been identified in older African American women.[150] Dancing in groups and other modalities such as as tai-chi or yoga were preferred choices and are easy to customize based on African American cultural preferences.[150] In these patients, chair-based exercises can be an option.

MNT prescription should be provided.

Medical nutritional therapy is an important component of lifestyle medicine. This patient's preference is African American cuisine, including barbecued meats, sweet cornbread, fried chicken, and desserts. Sides include black-eyed peas, candied yams, macaroni and cheese, and stewed greens. Thus, a nutritional recommendation was made based on detailed conversations between the patient and the nutritionist. An individualized healthy eating plan was fashioned considering physiologic changes (poor dentition and less sense of taste), customs, and preferences. Cultural attitudes toward dietary supplements should be explored prior to their prescription. Parenthetically, diabetes-specific formulas should be used in cases of DBCD.

Recommendation for other lifestyle medicine components should be provided.

Screening of sleep quality prompt to sleep hygiene recommendations and sleep apnea detected. Sleep hygiene recommendations are routinely provided and should include at least seven hours of sleep. The management of depression and smoking cessation was also addressed.

Conclusion and reflection

This is an example of how complex it is to manage a patient with multimorbid chronic disease, In this patient, tertiary prevention measures should be implemented to avoid the appearance and impact of the complications associated with DBCD, although the ideal would be to have intervened beforehand to avoid these complications; now, the burden for the patient and the health system is much greater. Is it possible to cover all the details in a routine medical visit? Is it feasible for the provider to know, or have the information available, about the clinical practice guidelines and their respective transcultural adaptations to make diagnostic and treatment decisions with greater precision?

AA: African American, CMBCD: cardiometabolic-based chronic disease, CDC: Centers for Disease Control and Prevention, DBCD: dysglycemia-based chronic disease, AC1: glycated hemoglobin, MNT: medical nutrition therapy, SDOH: social determinants of health, tDNA: Transcultural Diabetes Nutrition Algorithm, T2D: type 2 diabetes.

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34 Adiposity-Based Chronic Disease

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KEY POINTS

- Adipose tissue plays an important role in the regulation and implementation of energy homeostasis.
- Dysfunction of adipose tissue and accumulation as visceral and intracellular lipid storage is associated with insulin resistance syndromes, especially type 2 diabetes and sequelae such as cardiometabolic disease.
- Use of the term "obesity" fails to identify some patients with dysfunctional adipose tissue and may overestimate risk for adverse outcomes in other patients.
- Categorization of patients based on accumulation and dysfunction of adipose tissue adds value for identification and clinical attention.
- The nature of adiposity-based chronic disease identifies an at-risk population that stands to benefit from a lifestyle intervention.

34.1 INTRODUCTION

The physiological role of intracellular fat deposition in the regulation of energy metabolism allows the classification of adiposity-based chronic disease (ABCD) as a distinct entity and diagnostic term, with opportunities for research, clinical applications, and intensive lifestyle interventions.[1] Fat deposition occurs in eutopic adipose tissue (adipocytes) with various body distributions, as well as in ectopic sites (non-adipocytes, such as myocytes and hepatocytes).[2] Depending on the deposition location, distribution, and function, intracellular fat directly and indirectly participates in energy metabolism through intermediary metabolism and hormone receptor signal transduction, producing states of inflammation, insulin resistance, abnormal food-seeking behavior, and organ dysfunction.[3] Some specific examples include impaired cardiomyocyte contractility and hepatocyte inflammation associated with intracellular ectopic lipid deposits. For the purpose of clarity and communication, the term "adiposity" refers to all sites of intracellular fat deposition, constituting a full range of healthy to unhealthy pathophysiological mechanisms. The term ABCD refers to the chronic disease state causally associated with abnormalities of adiposity (Table 34.1). This is distinguished from the term "obesity," which is currently and strictly defined as having a body mass index (BMI) greater than a defined cutoff (e.g., 30 kg/m^2 or greater for Caucasians), and is the most common descriptor used in clinical studies of patients with abnormal adiposity. The clinical diagnosis of ABCD may be supported by anthropometrics (e.g., BMI and waist circumference), body composition technologies (e.g., bioelectrical impedance and dual X-ray absorptiometry), and other imaging studies (e.g., ultrasonography, computerized tomography, magnetic resonance, and positron emission tomography),[4] as well as serum markers of adipose function, including adipokines, triglycerides, and inflammation (Table 34.2).[5,6]

Unfortunately, multiple and conflicting health messaging about the definition and the causes of obesity, best lifestyle practices, and unproven therapies only aggravates confusion within the scientific literature,[7,8] lay press,[9] and popular culture.[10,11] Abnormal adiposity poses significant and irrefutable health risks, but sustainable lifestyle interventions, though logically sound and evidence-based, are very difficult to implement. This incongruence commonly leads to therapeutic nihilism and clinical inertia on the part of both healthcare professionals (HCPs) and patients. To some degree, this follows from the widely held belief that obesity is a personal choice rather than a *bona fide* chronic disease state with hallmark biological and behavioral components.

Despite the classification of obesity as a disease a decade ago, negative personal and societal connotations remain associated with the word "obesity."[1,7,8] Moreover, limitations in the use of BMI to predict adverse risk, especially among Asian populations,[12] as well as acceptance of changing societal norms may cast doubt on the urgency and severity of risk among patients with obesity.[13] To address these concerns, the concept of ABCD emphasizes the unhealthy nature of adiposity extending well beyond simple BMI or body weight, which includes abnormal body fat distribution, anthropometrics, and adipocyte secretome patterns. Changes in production of adipokines, such as leptin, resistin, and adiponectin, as well as activation of systemic inflammatory pathways within adipose tissue are among the most notable alterations of adipocyte function.[6,14] This greater detail allows more precise therapeutic interventions, particularly structured lifestyle interventions, but also requires a more robust diagnostic coding system for reimbursement and economic incentive for ABCD tactics.[15]

On this basis, the condition of ABCD may be described in a staging system that conveys severity of risk and likelihood of progression to subsequent stages.[1] ABCD stage 1 is defined as "risk" for abnormal adiposity (amount, distribution, and/or function) and is based on primary drivers (genetics, environment, and behavior that in aggregate contribute to a person's lifestyle). ABCD stage 2 is defined

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TABLE 34.1
Defining Characteristics of ABCD

Adiposity Variable	Metric
Increased mass	Anthropometrics (e.g., weight and BMI)
	Body composition imaging (e.g., DXA)
Abnormal distribution	Anthropometrics (e.g., WC and WHR)
	Body composition imaging (e.g., DXA)
	Organ imaging (e.g., cardiac CT/MR, echocardiogram, FibroScan, and liver/kidney/pancreas ultrasound)
Abnormal function	Adipokine/cytokine levels (e.g., adiponectin and leptin)

ABCD is differentiated from "obesity" by abnormal distribution and function, as well as considering all four ABCD stages instead of just stages 3 and 4.
ABCD: adiposity-based chronic disease; BMI: body mass index; DXA: dual energy X-ray absorption; WC: waist circumference; WHR: waist-to-hip ratio; CT: computed tomography; MR: magnetic resonance.
See Lu et al.,[4] Kouli et al.,[5] and Vallance et al.[129]

TABLE 34.2
Selected Energy and Inflammation Signal Networks Affected in ABCD

Adipokines	Change in ABCD
Adiponectin	Reduced
Leptin	Elevated
Resistin	Elevated
Visfatin	Elevated
Cytokines	
Interleukin-1	Elevated
Interleukin-6	Elevated
Tumor Necrosis Factor-α	Elevated
Other Signal Molecules	
Fibroblast Growth Factor-21	Elevated
Glucagon-Like Peptide 1	Reduced
Ghrelin	Elevated
Plasminogen Activator Inhibitor-1	Elevated
Mechanistic Target of Rapamycin	Reduced

ABCD: adiposity-based chronic disease. See Kouli et al.[5]

as "predisease" and includes not only overweight (which is defined exclusively in terms of BMI) but also disease-level abnormalities in adiposity distribution and function (not yet defined). ABCD stage 3 is defined as "disease" and includes not only obesity (which is defined exclusively in terms of BMI) but also disease-level abnormalities in adiposity distribution and function (not yet defined). The condition of prediabetes, though considered as predisease, may be included within stage 3 ABCD as a measure of advanced dysmetabolic state.[1] Interestingly, as happenstance would have it, a pure BMI-based overweight (e.g., 25 kg/m^2 or greater for Caucasians) state could be considered as "overweight-based chronic disease," or "OBCD" ("obesity"—"O"—"B"—"C"—"D"). ABCD stage 4 is defined as "complications" and includes metabolic and non-metabolic (including biomechanical) adiposity-based conditions that have adverse effects on quality-adjusted life years (QALYs). This framework highlights the preventive care paradigm, wherein early detection of abnormal adiposity factors and sustainable action can mitigate or even abrogate pathophysiological progression, leading to improved individual and population health.

Several important points need to be emphasized here. First, there are distinct advantages of the ABCD framework over the conventional "obesity" framework: more accurate pathophysiology, easier recognition of antecedent preventive care intervention opportunities, and use of more precise and less stigmatizing numerical (cf. semantic) classifiers. Second, the ABCD framework is not a metabolic model of obesity, since non-metabolic drivers and complications are included (social determinants of health [SDOH], stigma and mental health, other organ system dysfunction [e.g., gastrointestinal/microbiome, neurocognitive, orthopedic/arthropathic, and cardiopulmonary], and patient-centered care). In fact, two sound and well-validated complication scoring tools—the Edmonton Obesity Staging System[16] and the Cardiometabolic Disease Staging System[17]—may be used to subclassify adiposity-related complications in ABCD stage 4.

Interventions for ABCD should be viewed as preventive (decreased risk and predisease for patients in stage 1; decreased disease and complications for patients in stage 2; decreased complications for patients in stage 3; and decreased suffering and mortality for patients in stage 4). In addition, these preventive interventions should be performed in the context of improving "health" and not just an ABCD metric or descriptor.

Until routine and validated assessments of abnormal adiposity distribution and function are available, individual clinical priorities should be based on the percentage of weight loss needed (according to evidence relating complication improvement with amounts of weight loss).[7] Intervention modalities (lifestyle, medications, and procedures) should then be identified, which are associated with the amount of weight loss needed. The first actual interventional step in ABCD management is a laser-focused behavioral intervention to activate patients for change; this intensive lifestyle intervention approach must be continued even as pharmaceutical and procedural interventions are considered and potentially delivered. Given the high prevalence rate of obesity in modern populations, which has reached 42% in the United States and 9% worldwide in 2018,[18] as well as the limited access to other therapeutic options,[19] an intensive lifestyle modification may be the only available option for the majority of patients with ABCD worldwide. Fortunately, in many people, the effective implementation of structured lifestyle change for patients with ABCD promises to decrease the need for more costly medical and surgical interventions (quaternary prevention).

34.2 CONSEQUENCES OF ABCD

The health consequences of ABCD are far-reaching and include metabolic and non-metabolic conditions (Table 34.3). Prediction of specific ABCD sequelae can be difficult. Not all patients with ABCD develop each of the associated complications. Additionally, the degree of adipose tissue accumulation may not correlate with the severity or the incidence of ABCD-associated complications, especially in conditions characterized by abnormalities in the distribution and function of adipose tissue. Some authors propose the existence of a subset of patients with "metabolically healthy" obesity (MHO), who are not at increased risk for cardiovascular disease (CVD) or type 2 diabetes (T2D) despite the presence of a BMI above 30 kg/m^2 (highlighting the problem of defining obesity by a simple arithmetical formula).[20,21] Depending on definition, this may account for 7–20% of patients with obesity in cross-sectional studies.[22] However, this phenomenon may be transient.[20] Over time, patients with MHO demonstrate conversion with increased rates of T2D, insulin resistance, and CVD.[20,23,24] These patients with MHO are also at risk for other ABCD-associated complications (Table 34.3),[25] consistently with a more complex networking model that demonstrates multiple affected pathways and emergent properties.[6]

More significantly, many ABCD-associated complications instigate adverse lifestyle choices associated with vicious cycles involving abnormal adiposity, stigma and weight bias, and unhealthy behaviors. For example, orthopedic injuries, cardiovascular atherosclerotic disease, or depression can prevent regular exercise and favor individual preference for sedentary activity.[26–28] Obstructive sleep apnea (OSA), with a prevalence observed between 35% and 96% in patients with obesity, disrupts healthy sleep hygiene.[29–31] Dysglycemia syndromes, such as T2D, polycystic ovary syndrome (PCOS), and the metabolic syndrome, affect hormonal control of energy homeostasis, which may render attempts at weight loss through lifestyle intervention more difficult.[32] In several studies, patients with T2D achieved approximately 50% of the weight loss that was sustained by patients without T2D following identical dietary and exercise protocols.[33,34] Similarly, women with PCOS demonstrate less weight loss than obesity-matched women without PCOS,[35] and high rates of relapse are noted among patients with PCOS who have initial success with weight loss.[36]

TABLE 34.3
ABCD-Related Conditions

Condition	Relative Risk[a]	Adiposity Amount	Characteristic Distribution	Abnormal Adipocyte Function	References
Metabolic					
Type 2 Diabetes	7.7	++++	++++	++++	162
Polycystic Ovary Syndrome	1.5	+	++	++	163, 164
Hepatosteatosis	1.9	++	+++	++	165, 166
Obstructive Sleep Apnea	3.6	+++	++	++	167, 168
Cardiovascular					
Hypertension	2.0	++	++	+	162, 169
Atherosclerotic Disease	1.6	++	++	+++	162, 170
Arrhythmia	1.49	+	+++	++	171, 172
Orthopedic					
Osteoarthritis	1.39	+	+	–	162, 173
Tendon Injuries	1.7	++	++	++	174, 175
Gout	2.2	++	+	+	176, 177
Gonadal Function					
Infertility (women)	1.2	+	++	++	178, 179
Hypothalamic hypogonadism (men)	1.6	++	+++	+++	180
Gastrointestinal					
Cholelithiasis	1.8	++	+	++	162, 181
Psychiatric					
Depression	2.0	++	+++	+++	182
Cancer					
Adiposity-related (esophageal, colon, pancreatic, prostate, kidney, liver, gall bladder)	1.5	++	+	+	162, 183

[a]Relative risk in stage 3 or 4 ABCD in comparison to patients without obesity.

34.3 INTENSIVE LIFESTYLE INTERVENTION

All patients with ABCD should strive for a healthy lifestyle, avoiding or minimizing modern conveniences and living practices that are detrimental to metabolic health. It may be difficult to define specific populations at risk for ABCD, though the vast differences in modern lifestyles and built environments compared with those of prior generations and even distant ancestors are suggestive that the current population would benefit from healthy lifestyle interventions.

Among the most obvious aspects is the choice of a dietary pattern. Any demonstrably healthy dietary pattern is recommended, provided a durable effect can be realized.[37] Enhanced adherence and sustainability will require motivational interviewing and behavioral assessments of food preferences, daily activities and logistics, cultural mores, tastes, religion-based rules, and other idiosyncrasies.[38,39] HCPs should exercise flexibility and poise to offer up quick alternatives for a successful trajectory when clinical progress has stalled.[40,41] A dietary pattern that is high in fruits, vegetables, nuts, and complex carbohydrates, with controlled amounts of meats and fish, and negligible amounts of processed foods and sugar-containing beverages provides the greatest benefit to patients with ABCD.[7,42] Some of the most widely studied dietary patterns with these attributes include Mediterranean diets, the New Nordic Diet, the Ornish Diet, and the Dietary Approaches to Stop Hypertension (DASH) diet, among others.[43–46] In the largest published randomized trial, patients assigned to a Mediterranean diet group had the greatest amount of weight loss, as well as reduction in T2D, reduction in cardiovascular events, and reduction in mortality, compared with those assigned to low-fat or low-carbohydrate diet groups.[43] The New Nordic Diet, the Ornish Diet, and the DASH diet, which overlap substantially with Mediterranean Diets in categorized food content, may have similar benefits. A very useful tactic to enhance adherence is to have website addresses, electronic and printed materials, and other information modalities for these dietary patterns at the ready for every patient.[40] Various wearable technologies that synchronize with smartphones and access cloud-based software can be trialed and optimized for individual patients.[47]

In addition to total body adipose content, the localized distribution and function of adipose tissue can be improved by the adoption of healthy dietary patterns. In one randomized trial, subjects assigned to a Mediterranean diet demonstrated improvement in insulin resistance by 37%, reduced inflammation by 37%, and increased adiponectin by 43% after one year, suggesting improved adipose function.[48] A population study of 5,079 individuals demonstrated reduced visceral, cardiac, and hepatic but no change in subcutaneous adipose tissue among those who followed dietary patterns that closely resembled the Mediterranean diet.[49]

Increased physical activity and exercise should also be incorporated into daily routines. Although the amount and type of exercise have not been fully settled, regular participation in physical activity is important. Many studies and organizations suggest that at least 150 minutes of physical activity divided over 5–7 days per week constitutes a reasonable minimum.[7] Although this level of physical activity may yield only modest (0–3 kg) weight loss, it generates significant improvement in metabolic health and insulin resistance, reduced risk of T2D incidence (30–60%), and improvement in hypertension cardiometabolic risk.[50] Continued regular physical activity is also associated with greater success in the maintenance of weight loss, with the greatest efficacy among patients who combined physical activity with dietary and other lifestyle changes.[50] Strength training provides the benefit of increased muscle mass, reducing myocyte adipose content, while cardiovascular exercise promotes reduction of visceral adipose accumulation.[51] Both of these endpoints are desirable in ABCD. Adipose function, assessed by adipokine production and inflammation, is also greatly enhanced through regular physical activity and exercise.[52] In addition to optimizing the choice of dietary pattern and amount of physical activity, many other individual lifestyle factors can impact the risk of ABCD (Table 34.4).[1]

TABLE 34.4
Effects of Lifestyle Intervention on Components of ABCD

Intervention (reference)	Abnormal Adipose Amount	Abnormal Adipose Distribution	Abnormal Adipose Function
Dietary Pattern[43]	Moderate	Moderate	Moderate
Physical Activity[7]	Negligible	Moderate	Moderate
Sleep Hygiene[66,67]	Strong	Moderate	Moderate
Stress Reduction[78,79,86]	Mild	Moderate	Strong
Antibiotic Use[101]	Mild	–	–
Endocrine Disruptors[184]	Moderate	Moderate	Strong
Alcohol Moderation[117,119,120]	Moderate	Negligible	Moderate
Mood[124,126]	Moderate	NA	Strong
Community Engagement[144]	Moderate	NA	Strong

Dashes indicate that sufficient data are not available.

34.4 SLEEP HYGIENE

Sleep affects metabolic regulation. As a defining feature of circadian rhythm, the amount, quality, and timing of sleep cycles affect hypothalamic function, cortisol release, thyroid function, hepatic glucose production, brown fat activation, and insulin resistance.[53] Additionally, pancreatic β-cell function is impaired in states of sleep deprivation.[54] This may reflect the responsiveness that β-cells demonstrate to melatonin secretion, which is itself diminished in disrupted circadian rhythms.[55]

In the modern era, average sleep duration has been declining. Time spent sleeping by adults has decreased from an average of 9 hours per night to 7 hours per night over the past 40 years.[56] In children, sleep time has reduced by an average of 0.75 min/night/year for the past century.[57] These trends continue to spread worldwide.[56,57] In addition to reduced sleep time, the presence of insomnia, defined as waking in the middle of the night at least three times weekly, is reported among 25–35% of adults.[58]

In children, no upper limit of healthy sleep has been identified, and a longer duration of sleep is associated with reduced amounts of adiposity, improved quality of life, and improved academic success.[59] In a meta-analysis of longitudinal trials in children, longer sleep duration was associated with reduced adiposity by an odds ratio of 1.89.[59] For every one hour of sleep duration, the annual rate of BMI increase was reduced by 0.05 kg/m^2.

In adults, between seven and nine hours of sleep is recommended nightly, and eight to ten hours of sleep is recommended in adolescents.[60,61] As with studies in children, adults exhibit increased adiposity, especially visceral adiposity, in association with shorter sleep duration.[62] In one observational trial, an increase in sleep time from less than six hours to seven or eight hours resulted in a reduction of visceral fat gain over six years of follow-up.[63]

Several randomized trials demonstrate that even short-term sleep restriction for five days causes weight gain in adults. This is attributed to increased calorie consumption (by 130%) in the sleep-deprived group compared with the control group.[64,65] In a crossover study, a 52% increase in consumption of sweets and desserts was observed during times of sleep deprivation.[66] These results may be explained by elevation in circulating ghrelin levels and reduction in leptin levels, which are observed in periods of sleep restriction.[67] Both of these hormonal markers of adipose dysfunction within ABCD would be expected to increase appetite and exacerbate insulin resistance.[54,67]

The importance of adequate sleep combined with other lifestyle interventions has also been demonstrated in a series of cross-sectional trials.[62] One observational study demonstrated an association of decreased sleep time and increased calorie consumption among obese women compared with normal-weight controls.[68] In another study, an inverse linear relationship between self-reported sleep duration and BMI was observed.[69] Data from the National Health and Nutrition Examination Survey also demonstrate a strong association between reduced sleep time and adiposity.[70] Additionally, patients with obesity demonstrate increased sleep latency and reduced percentage of time in rapid eye movement (REM) sleep.[56] A concerted effort to attain sufficient time for sleep is an important part of a healthy lifestyle, especially in the prevention and treatment of ABCD.[53,56]

Disordered sleep is disruptive to circadian rhythms and associated with weight gain.[56] OSA is highly prevalent in adults with obesity and disruptive to healthy sleep. In one longitudinal study, a 10% increase in body weight was associated with a sixfold increased risk of OSA.[71] The use of devices that provide continuous positive airway pressure (CPAP) can reduce the cardiovascular impact of OSA and improve symptoms of daytime drowsiness. Additionally, randomized trials demonstrate that the use of CPAP devices among patients with OSA improved insulin resistance by an average of 0.39 units in the homeostasis model, mainly through reduction in fasting insulin levels.[72] It remains unclear how this intervention may specifically affect adipose distribution and function in ABCD.[73] On the other hand, weight loss through intensive lifestyle modification can improve measures of OSA, simultaneously improving overall sleep hygiene synergistically with CPAP use.[74,75]

34.5 STRESS REDUCTION

The human response to chronic stress is associated with ABCD and involves hypothalamic dysfunction, increased consumption of palatable and calorie-dense foods, and reduced physical activity.[76,77] The hormonal profile in chronic stress includes elevations of cortisol, catecholamines, and insulin as part of an insulin resistant state.[77] In one cross-sectional study, chronic stress was associated with increased food cravings despite increased leptin levels, suggesting the presence of leptin resistance and adipose dysfunction in response to stress, as well as diminished adiponectin release.[78] Another study demonstrated that elevated cortisol and increased visceral fat accumulation are associated with increased stress.[79] Moreover, elevated cortisol induces visceral adipose release of inflammatory factors, including tumor necrosis factor α, interleukin(IL)-1, IL-6, and reactive oxygen species, through greater production and reduced glutathione antioxidant activity.[80]

Interventions to reduce stress are central to any healthy lifestyle. However, given the multiple stressors that are regularly present in everyday life, simple avoidance of stressful situations is often not possible. Modalities to address stress and activities to lessen pathophysiologic effects of stress may be beneficial in ABCD.[1] A lifestyle intervention of healthy dietary choices and physical activity >150 min/week itself can reduce stress and symptoms of depression.[81] Incorporation of a Mediterranean diet demonstrates a 41% reduction in the incidence of depression, a marker of reduced psychological stress.[82]

Direct techniques for stress reduction include mindfulness, cognitive-behavioral therapies (CBTs), and psychodynamic

techniques, which may be beneficial, though results are not always consistent.[83] In studies of mindfulness based stress reduction, markers of inflammation and adipokine levels in patients with obesity are observed.[84, 85] In one randomized controlled trial, women with obesity or overweight were assigned to either a mindfulness group that met once weekly to discuss stress reduction techniques and given recommendations for daily home sessions for 30–45 minutes each, or a control group that met weekly with a dietitian to review nutritional recommendations.[86] By eight weeks, depression and anxiety declined in the mindfulness group, and quality of life improved. These effects persisted at 16 weeks after the end of intervention. Additionally, fasting insulin and systolic blood pressure improved in the mindfulness group compared with controls both at the end of the trial and 16 weeks after its conclusion. Mindfulness techniques of stress reduction are promising lifestyle interventions in ABCD. This approach has also been shown to reduce binge-eating episodes in at-risk patients.[87]

Another method for stress reduction is through regular participation in low-impact exercises such as yoga. In a randomized trial of women with overweight or obesity, those assigned to the treatment group sustained a 2.4-kg weight loss and a 3.8-cm decrease in waist circumference after 12 weeks of twice-weekly 90-minute yoga classes.[88] Additionally, self-assessment measures of stress declined, while measures of quality of life and of self-esteem improved with yoga treatment. A second published randomized trial in men with overweight or obesity demonstrates reduction in weight by 2.2 kg and reduction in perceived stress score.[89] These results are similar to earlier observational studies indicating that the practice of yoga can improve stress and adipose tissue accumulation over the short term.[90]

As a lifestyle intervention, behavior therapy incorporates interventional methods to adjust a person's maladaptive behavior practices. This is particularly helpful in the approach to a patient with ABCD. Behavior modification intervention should include measures for stimulus control, use of rewards, which may be verbal, setting achievable goals and discouraging unrealistic goals, relapse prevention, and patient-driven self-correction for problems that may arise. A meta-analysis of seven trials demonstrates a significant improvement in sustainable weight loss (8.5 kg vs. 0.4 kg) when regular behavior sessions are incorporated in a comprehensive lifestyle intervention.[91]

34.6 ANTIBIOTIC USE AND THE MICROBIOME

34.6.1 Antibiotic Use by Humans

Since their discovery, antibiotics have been critical for the treatment of infectious disease of bacterial or fungal origin. Clear success has led to widespread use and overuse of antibiotics, including dubious medical practices that employ antibiotic use for conditions that may not be bacterial in origin. A 2019 survey of U.S. Medicare beneficiaries found that there were 454 prescriptions for antibiotics filled for every 1,000 patients.[92] This figure leads to concerns regarding the development of antibiotic resistance and pathological metabolic effects.

Antibiotic use can affect microflora residing within the gastrointestinal (GI) tract, serving as an exemplar of how other lifestyle changes that affect gut microbiota can indirectly lead to ABCD. Hundreds of species of bacteria and fungi are present within the colon of each individual and take part in a complex relationship between the host and other species of microflora.[93] These microbes directly affect host energy homeostasis through metabolism of sugars and fiber present in the intestinal chyme to produce short chain fatty acids that are available for utilization by the host. Approximately 5–10% of the total daily calorie consumption is obtained in this fashion.[94] Additionally, through multiple routes of signaling with the host, the GI microflora can influence the degree of insulin resistance, systemic inflammation, and metabolic rate, and may affect other health aspects of the host such as mood and cardiovascular function.[93,95,96]

Fermentation of undigestible dietary starches and fiber leads to production by the GI microflora of short chain fatty acids (SCFA), which can act as signal molecules. Through activation of the free fatty acid receptor 2 and 3 located on neuroendocrine cells of the GI tract, pancreatic β-cells, macrophages, and adipocytes, SCFA potentially affect several pathways in metabolic regulation.[97,98] Reduced SCFA activity diminishes leptin production and may contribute to ABCD, as well as to insulin resistance, through reductions in release of glucagon-like peptides 1 and 2.[99] However, it is presently unclear if SCFA levels are affected by antibiotic therapies.[98]

Still, a number of population studies have been published that associate the use of antibiotics with weight gain and obesity. This is especially evident among infants and children treated with antibiotics. In a study of children born to normal-weight mothers within the Danish National Birth Cohort, the use of any class of antibiotics in early life was associated with an increased risk of overweight by age 7 (odds ratio of 1.54).[100] A large international study demonstrates increased BMI at ages 5–8 among boys who were treated with antibiotics within the first year of life.[101] In another international cohort involving 8 medical centers located in low-resource settings, 1,954 infants followed until age 2 demonstrated significant weight gain without change in body length among those treated with one or more courses of various classes of antibiotics.[102] In this trial, penicillins, cephalosporins, macrolides, and metronidazole had the largest effects on weight gain. A recent analysis of the Irish National Longitudinal Study of Children that included longitudinal follow-up to age 5 demonstrated that four or more treatment courses with antibiotics were associated with obesity by age 5 (odds ratio 1.6; 1.1–2.3).[103] A meta-analysis of 15 trials corroborates this association of childhood antibiotic use and increased risk of obesity.[104]

Few studies have been conducted regarding the metabolic effect of antibiotics in adults. In one seven-day study, oral vancomycin significantly altered the species composition of GI microflora of subjects with obesity but did not demonstrate metabolic changes either during this trial or afterward.[105] Amoxicillin also had no discernable effect on metabolism. In another trial, 11 patients with obesity, insulin resistance, and detectable methane on breath testing were treated with neomycin and rifaximin until methane could no longer be detected, which took an average of ten days of treatment.[106] The bacterium *Methanobrevibacter smithii* is presumed responsible for methane production, and stool levels of *M. smithii* were eradicated in 8 of 11 subjects after the treatment course. In all subjects, low-density lipoprotein levels declined and insulin sensitivity by oral glucose tolerance testing improved after treatment. This trial suggests a potential cardiometabolic risk benefit from GI microflora manipulation.

Though other confounding factors within many of these reported studies may influence the results, the prudent and minimal use of antibiotics in medical practice may help prevent weight gain and influence other aspects of ABCD, especially among infants and children. Certain classes of antibiotics, such as sulfonamides, appear to have neutral effects on weight and may be preferred in appropriate clinical settings. Protocols for the active manipulation of GI microflora to generate beneficial metabolic effects require more study before firm recommendations can be made.

34.6.2 Antibiotic Use in Farming

The use of antibiotics outside the medical field may also play an indirect role in the development of ABCD and lead to sound conjecture about optimal food sourcing as part of healthy lifestyles. Widespread use of antibiotics by livestock farmers yields animals that gain weight faster and require less feed.[107] Nutrient changes within food products due to this practice have not been formally evaluated. However, changes within the livestock microbiome have been reported.[108] These observations of accelerated growth and altered microbiome are suggestive that the nutrient makeup of meat derived from antibiotic treated livestock may be altered, though further study is warranted in this field.

34.7 ENDOCRINE DISRUPTORS

Multiple classes of industrially produced chemical compounds demonstrate biological properties that affect hormone signaling. A subset of these endocrine disrupting compounds (EDC) has been shown to affect adipose tissue accumulation, distribution, and function.[109,110] In several studies, childhood exposure to bisphenol A, among the more well-studied EDC, is associated with weight gain and obesity.[111] Exposure to bisphenol A is also associated with reduced adiponectin and increased resistin gene expression,[112] as is exposure to octylphenol, another EDC.[113] Exposure to tetrabromobisphenol A, a flame retardant, reduces melancortin-4 receptor expression in the arcuate nucleus of the hypothalamus that regulates metabolism, leading to increased calorie consumption and weight gain.[114] Another exposure risk occurs as patients with ABCD successfully lose weight; lipid soluble EDC may be released into the circulation, especially from visceral adipose depots that may concentrate toxins.[115] Many other EDC can affect energy metabolism and mechanisms leading to ABCD, requiring ongoing clinical study.

34.8 ALCOHOL MODERATION

High alcohol intake is associated with adverse health outcomes, including death. In contrast, moderate alcohol consumption, especially consumption of wine, has been demonstrated to improve markers of insulin resistance, cholesterol levels, and systemic inflammation, suggesting improvement in adipose function.[116] Recently published trials continue to support the findings that moderate alcohol intake, defined as 14 drinks per week for men and 9 drinks per week for women, is associated with a lower incidence of T2D compared with non-drinkers and compared with heavy alcohol consumption in a "J-shaped" association.[117,118] In a study of 224 subjects with T2D who were assigned to receive 150 mL of either red wine, white wine, or water daily, both of the groups given wine showed reduced insulin resistance measured by fasting insulin levels, with increases in high-density lipoprotein levels in the red wine group.[119] Adipose tissue distribution is not affected by moderate alcohol intake.[120] Additionally, a recent analysis of global disease burden for non-communicable disease suggests that any level of alcohol consumption may convey cardiometabolic risk.[121]

General drawbacks of alcohol consumption include the risk of dependence and the potential for cognitive impairment, especially while operating motor vehicles or simply walking along a busy street. Another concern is the theoretical risk of accelerated hepatosteatosis when patients at high risk for non-alcoholic fatty liver disease consume alcohol regularly.[122] The DIONYSOS study appeared to support this claim; however, in this trial, an increase in steatosis was observed only in subjects with obesity who consumed more than 60 g alcohol, or four standard drinks, daily.[123] Within the trial, this group was known as the "heavy drinkers." Moderate alcohol consumption was not associated with increased hepatosteatosis in patients with obesity.

34.9 MOOD

Disorders of mood, such as depression and anxiety, have a complex relationship with weight gain and risk of ABCD. Obesity and depression often occur together in the same patient, in part due to common molecular mechanisms, including altered hypothalamic-pituitary-adrenal axis signaling, increased oxidative stress, and increased systemic inflammation.[124] In a published cohort, an increased

prevalence of depression is associated with increased leptin levels, suggesting that adipose function is affected in patients with depression.[125] The presence of depression is also associated with increased risk for the development of obesity later in life.[126–129] In the Whitehall II study, patients with increased levels of psychological stress over a ten-year period had BMI increased by 0.6 kg/m^2 and demonstrated a greater central distribution of adiposity.[130]

Patients with obesity demonstrate a poorer response to antidepressant therapy.[131–133] Additionally, many antidepressant medications induce weight gain and adiposity, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors.[134] Atypical antipsychotics, which may be applied in major depressive disorder, induce intense weight gain, insulin resistance, increased circulating leptin, and reduced adiponectin.[135] Still, the successful treatment of depression is often accompanied by significant weight loss and improvement in ABCD.[136] Moreover, weight loss in patients with ABCD has been shown to reduce depressive symptoms and improve quality of life.[137]

Aside from pharmacologic therapies, CBT can improve mood disorders and weight loss efforts. In one trial, patients with depression and obesity randomized to receive modified CBT that included aspects of healthy living had more sustainable weight loss and improved mood compared with standard CBT practices over 48 weeks of observation.[138] In another trial, CBT was associated with weight loss among adolescents with obesity and depression.[139] Multiple studies in adult patients with obesity and depression demonstrate the effectiveness of CBT in addressing both conditions.[91]

Other forms of behavior modification, including control of stimulus exposure, empowerment for self-correction of problems that arise, modification of unrealistic goals, systems for use of rewards, and relapse prevention, can be beneficial.[41] When combined with regular behavioral sessions, these strategies demonstrate an average 8.4-kg weight loss over two years.[91] Improvements in adipose function and distribution would be expected in association with weight loss; however, these effects of CBT have not been assessed.[91,139] Practically speaking, with proper training, HCPs outside the specialty of psychiatry can successfully implement CBT in the management of ABCD.[140]

34.10 COMMUNITY ENGAGEMENT

Close personal contacts and community involvement exhibit considerable influence on individual behavior patterns and on patterns of weight gain.[141] Moreover, efforts within communities to emphasize healthy lifestyle choices can reduce the impact of ABCD. Community programs that engage whole families in healthy dietary patterns, physical activity, and well-being have been shown to diminish childhood obesity.[142] These programs regularly meet as a group, create and nurture self-encouragement behaviors, and result in better health.[143] Improvements in quality of life and reductions in adiposity have been observed with these type of interventions.[143] In one randomized trial, a community-based intervention induced weight loss of 7.8%, adiponectin increases by 27%, and leptin decreases by 22% after one year, suggesting improvement in adipose function and overall decreased ABCD-related risks.[144]

Several barriers to program efficacy have been observed, including the main driver of program avoidance: parental concerns of psychosocial well-being, with little regard for other long-term sequelae of ABCD.[143] Denial or lack of recognition by parents also presents a significant barrier to program initiation. With any lifestyle intervention, care should be taken to avoid incurring body dissatisfaction, reduced self-esteem, or other effects detrimental to mental health in the target audience.[145] Programs that frame their central message as promotion of a healthy lifestyle are more successful than programs that specifically target weight loss.[146] To repeat, "health" is the preferred therapeutic target in ABCD care.

The direct involvement of families may be fundamental to this process; implementation of a five-year health and well-being intervention program through elementary schools with minimal parental involvement had no effect on adiposity.[147] In contrast, faith-based programs may represent important modes of community outreach for ABCD prevention.[148] In one randomized study involving congregations of 20 churches, a therapeutic intervention consisting of hourly weekly meetings emphasizing dietary patterns and physical activity achieved in the Diabetes Prevention Project (DPP) was compared with a control intervention that just involved general information.[149] The DPP arm showed a 2.4-kg weight loss after six months compared with a 0.4-kg weight gain by the control group. Several other observational trials of faith-based community intervention programs also show promise of improved weight reduction.[150,151]

The recognition of community engagement as a means to drive healthy behaviors has prompted the development of online virtual communities with the goal of improved health.[152] Though these have received much fanfare, results are inconsistent and depend on perceived emotional support (though levels of support can vary greatly).[152] In contract, in-person, family-oriented community engagement is a successful approach to adopting a healthy lifestyle.[150–152]

34.11 TRANSCULTURALIZATION

The cultural background of each individual has significant impact on lifestyle choices and response to medical advice. Any lifestyle directive, such as a suggested dietary pattern, should be congruent with a patient's cultural tradition to be sustainable.[153] This approach garners community support and promotes durable and successful healthy lifestyle changes. In contrast, recommended dietary patterns at odds with a patient's own culture will often incur transgressions if they are not adequately addressed.[154] In

some cases, advising a reversion to tradition may be beneficial. For example, persons of Asian descent who return to a traditional Asian diet that is rich in fruits and vegetables, green tea, beans, nuts, and spices, and is low in red meat, demonstrate improvement in insulin resistance and ABCD, and cardiovascular outcome reduction.[153,155] Patients with other backgrounds may be responsive to traditional lifestyles.

Some cultures traditionally place value on weight gain as a marker of wealth, high social standing, and overall well-being. However, the worldwide increased prevalence of adiposity has triggered responses by governments, cultural leaders, international charitable organizations, the World Health Organization, and the United Nations to address non-communicable chronic diseases, including ABCD.[156–158] Recommendations to address ABCD among various nations include the identification and education of physicians and cultural leaders within different regions who would serve as agents of change.[154] A respectful understanding of local culture can allow adaptation of lifestyle interventions to curtail ABCD and associated complications, with the potential for broad impact when implemented globally.

In addition to cultural adaptations for lifestyle medicine approaches, ethnic variation can lead to a range of ABCD phenotypes. Traditional measures of obesity, such as waist-to-hip ratio or BMI, do not capture the full risk conferred by adiposity in Eastern Asian and Indian populations.[12] As a model of cardiometabolic risk, the distribution, function, and amount of adiposity among these populations are more predictive than BMI alone.[159,160] As an example, when matched for age and BMI, Asian patients demonstrate higher circulating leptin and lower adiponectin, emphasizing the importance of adipose function rather than BMI.[161]

34.12 CONCLUSION

The growing worldwide epidemic of obesity is among the highest intervention priorities in healthcare. A number of important lifestyle factors have been identified in addition to the individualization of dietary patterns and physical activity. Unfortunately, a slow rate of success coupled with therapeutic inertia on local and national scales requires new ways to regard the problem. Moreover, a clinically meaningful lifestyle approach requires resources and dedicated clinical attention as well as disease delineation.[15]

ABCD is a new diagnostic term that incorporates not only body weight and BMI, which is all that current obesity definitions and interventions rely on, but also healthy and unhealthy distributions and secretory functions of body fat. This broader conceptualization of this metabolic problem permits a better understanding of pathophysiology, analysis of current evidence, and formulation of effective interventions. Future directions should focus on validation studies involving biological data on drivers and complications; statistical associations related to stage progression; causal relationships (linear and non-linear) among drivers (biological and social determinants of health) and complications; and interventional studies that prevent stage development and/or progression. Potential clinical applications of these studies would be the routine incorporation of not only anthropometrics but also body scanning for adipose distribution assessment and broad molecular testing to identify multiple adipokine abnormalities in order to improve health in patients with ABCD.[1]

Healthy lifestyle interventions to mitigate ABCD include individualization and adoption of healthy dietary patterns and physical activity programs. Improvements in sleep hygiene, reduction in stress, and treatment of both clinical and subclinical disorders of mood can also impact weight gain, improve adipose tissue function and distribution, and improve overall well-being among patients with ABCD. Judicious and minimal use of antibiotics, especially among infants and children, can also mitigate weight gain and possibly prevent the development of ABCD. Avoidance of EDC wherever possible, population-based improvements in food sourcing, and moderation of alcohol intake among adults may also have a role. Beyond the individual, the involvement of community and culturally–sensitive medical practices can help to redirect normative trends in clinical practice. When optimized, these important lifestyle factors can significantly reduce ABCD and its associated detrimental effects.

CLINICAL APPLICATIONS

- Identification of patients with ABCD may include waist circumference measurement, presence of conditions associated with insulin resistance, signs of insulin resistance (e.g., acanthosis nigricans, skin tags), and abnormal lipid profiles, among other measures to be determined within this relatively new classification system.
- Selection of a demonstrably healthy dietary pattern should be congruent with a patient's preferences and sustainable over the long term.
- Physical activity of at least 150 minutes per week divided over 5–7 days is recommended to mitigate the health consequences of ABCD.
- For adults, between seven and nine hours of sleep per night can reduce insulin resistance and is associated with reduced adipose accumulation.
- A comprehensive approach to lifestyle medicine for ABCD should also include methods for stress reduction, avoidance of endocrine disrupting compounds, recognition and treatment of mood disorders, and participation in active community engagement.

DISCLOSURES

MV – none
JM – Abbott nutrition: Lecturer
L-Nutra, Aveta.Life, Twin Health: Advisory Boards

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Part VI

Lifestyle Issues in the Prevention and Treatment of Cancer



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35 Exercise Oncology: The Role of Exercise across the Cancer Control Continuum

Maxime Caru, PhD and Kathryn H. Schmitz, MPH, PhD, FACSM, FTOS, FNAK

KEY POINTS

- Research continues to affirm physical activity's role in primary, secondary, and tertiary cancer prevention.
- Multiple guidelines have been released urging clinicians to prescribe physical activity to patients according to their cancer status.
- Multiple barriers often stand between patients and their ability or desire to engage in physical activity; clinicians have a duty to help and support their patients.
- There are multiple models of exercise oncology practice in common use in the United States.

35.1 GLOBAL CANCER BURDEN

35.1.1 Adults and Older Adults

There were 19.3 million new diagnoses of cancer and approximately 10 million deaths from cancer in 2020.[1] This is expected to rise to an estimated 28.4 million diagnoses per year by 2040. The most common diagnoses were female breast, followed by lung, colorectum, prostate, stomach, and liver cancers. Figure 35.1 presents the distribution of diagnoses and causes of cancer death in 2020. Cancer is presently the second leading cause of death worldwide, with expectations that it will be the leading cause of death by 2060.[2] Lung, colorectum, and liver are the most common causes of cancer death.

The variability in incidence of cancer globally largely arises from environmental and behavioral exposures rather than biology. The incidence of cancers is lower in lower income countries, but once diagnosed, mortality is higher in lower income countries.

Cancer is a disease of aging. The incidence of cancer increases with age (Figure 35.2), with estimates of 25 cases per 100,000 among people under age 20, 350 per 100,000 people among those aged 45–49, and more than 1,000 per 100,000 among those aged 60 years or more.

Further, the majority of cancer survivors are older adults as well. In 2016, it was estimated that 62% of cancer survivors were 65 or older. By 2040, it is estimated that 73% of cancer survivors will be 65 or older. When we outline the physical activity needs of those who have been diagnosed with cancer, this age distribution must be kept in mind.

35.1.2 Children, Adolescents and Young Adults

Although it could be expected that children are less likely to have chronic diseases, the fact remains that cancer is a common disease and is a leading cause of death for children, adolescents, and young adults. Children (ages 0 to 14 years) and adolescent and young adult patients (ages of 15 to 39 years) with cancer make up a unique population in oncology. Each year, almost 10,500 children receive a diagnosis of cancer, and approximately 77,000 adolescent and young adult patients are newly diagnosed each year in the United States.[3] In the last two decades, the survival rates have significantly improved, and almost 85% of children, adolescents, and young adults are living at least five years post diagnosis. A recent report from the National Cancer Institute informed that there are at least 483,000 childhood cancer survivors in the United States as of 2019.[4] As a result of their survival, cancer survivors face chronic health problems related to their cancer treatments that can be moderated with physical activity.[5,6]

35.2 PHYSICAL ACTIVITY AND CANCER PREVENTION

35.2.1 Overview

In recent years, clinicians and researchers have been working together to strengthen evidence-based medicine on the benefits of adopting a healthy lifestyle for patients living with and beyond cancer. Physical activity plays a key role in the development and regulation of multiple body systems and begins from an early age with the movement of the body in space. There are age-specific physical activity guidelines for healthy people to help prevent and manage chronic diseases, in addition to providing a myriad of other physical and mental health benefits.[7]

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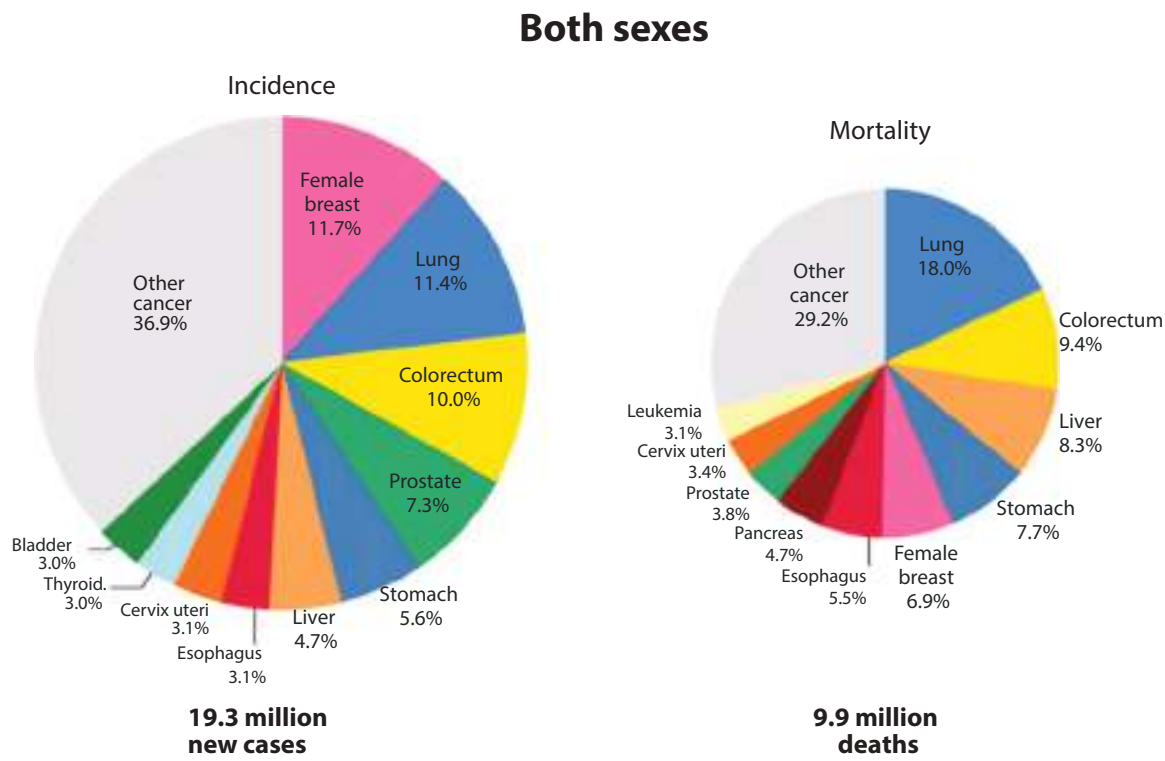


FIGURE 35.1 Incidence and mortality from cancer, worldwide, 2020. (From Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. ***CA: a cancer journal for clinicians***, 71(3), 209–249. Reproduced by permission of John Wiley and Sons.)

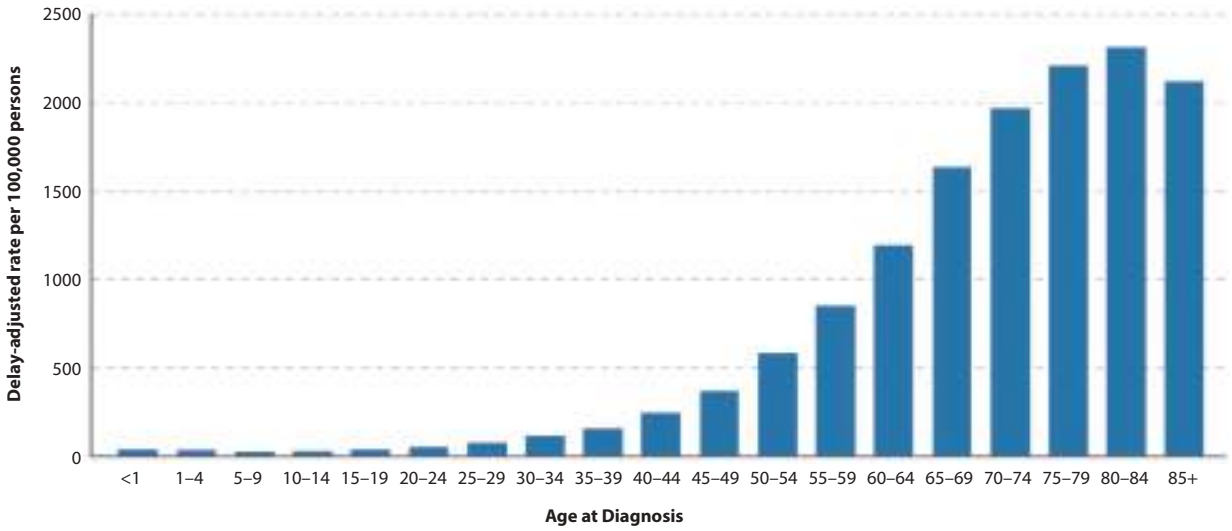


FIGURE 35.2 Incidence rates by age at diagnosis, all cancer types. (From National Cancer Institute 2021. ***Age and Cancer Risk***. Reproduced by permission of NCI.)

Physical activity must be differentiated from the term "exercise," which refers to "a type of physical activity that involves planned, structured, and repetitive bodily movement to maintain or improve one or more components of physical fitness."[8] Physical activity, however, is defined as "any bodily movement produced by contracting skeletal muscles, with a concomitant increase in energy expenditure."[8] The U.S. Physical Activity Guidelines recommend that healthy children and adolescents engage in at least 60 minutes of enjoyable moderate-to-vigorous intensity physical activity every day.[7] Adults should engage in at least 150 minutes a week of moderate intensity physical activity, with at least 2 days a week of muscle-strengthening activities, whereas older adults (>65 years old) should also

add activities that improve their balance.[7] According to the American College of Sports Medicine (ACSM), moderate intensity is performed at a level that allows an evident increase in a person's heart rate and breathing, while still being able to hold a conversation that could not be maintained at vigorous intensity.[9] Physical inactivity is a major public health problem and should be avoided at all costs.

Patients with cancer who are not engaging in regular physical activity expose themselves to a higher risk of chronic diseases or premature death, justifying the need for specific guidelines in exercise and oncology. The American Cancer Society (ACS) issued guidelines for nutrition and physical activity for cancer prevention,[10] while the ACSM recently endorsed the updated consensus statement and guidelines on exercise for adult patients with cancer and survivors.[11] In pediatric oncology, the first guidelines on exercise were published in 2021,[12] which testifies not only to the emergent nature of the research field but also to the willingness to include exercise in the continuum of health and disease prevention. Clinicians and researchers support physical activity as an integral strategy across the cancer prevention continuum. It is important, however, to understand the key role of physical activity at different levels of prevention, regardless of the age of the patients.

35.2.2 Role of Physical Activity in Primary Prevention

Primary prevention is defined as preventing a cancer before it occurs, through measures such as healthy lifestyle behavior to reduce behavioral risk factors associated with the disease. The World Health Organization states that between 30% and 50% of cancers can be prevented by avoiding risk factors and that cancer risk can be reduced by engaging in regular physical activity.[13] Studies have reported that modifiable and preventable lifestyle-related behaviors (e.g., tobacco use, poor diet, physical inactivity, alcohol consumption) are the underlying cause of half of all deaths in the United States.[14,15] Several other studies have also shown that physical inactivity and unhealthy behaviors are associated with higher mortality rates,[16] while physical activity is associated with lower mortality rates.[17,18]

Back in 1985, the pioneering work of Dr. Rose E. Frisch found that women who engaged in athletic training had a lower risk of breast cancer and cancer of the reproductive organs, such as cancers of the uterus, ovaries, cervix and vagina, compared with their non-athletic counterparts.[19] Since then, several studies and meta-analyses have been published showing that physical activity is associated with a lower risk of many cancer types. A systematic review and meta-analysis highlighted that running was associated with a reduction of 23% in cancer mortality.[20] Researchers at the American Cancer Society and the National Cancer Institute pooled data from 12 prospective U.S. and European cohort studies for a total of 1.44 million adults and showed that leisure-time physical activity was associated with a lower risk of developing 13 cancers: esophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, head and neck, rectal, bladder, and breast.[21]

Emerging data have suggested that physical activity enhances patients' inflammatory and immune function.[22] In fact, there are several biological mechanisms that can explain how physical activity has an effect on cancer risk and prevention. For example, physical activity has the potential of reducing the amount of adipose tissue and the production of sex hormones, insulin, leptin, and inflammatory markers, which has the effect of reducing exposure to carcinogenic hormones and peptides, reducing the risk of cancer.[23] Physical activity–mediated reduction of biologically available sex hormones has been described as playing a significant role in decreasing the risk of developing cancer in different sites, such as breast, prostate, endometrium, ovary, and testis.[24]

The effects of physical activity have been described as multifactorial, and patients' age, gender, and body composition should also be taken into consideration when clinicians and researchers want to understand the underlying mechanisms of physical activity. Regarding this aspect, there is a very large field of research focusing on the effects of physical activity on immune function.[25] It is important for the audience to note that the scientific evidence in this regard is mainly derived from animal studies or studies in adults with cancer. Thus, many mechanisms remain to be explored, and some mechanisms are still in the hypothesis stage in adults. Some of the biological mechanisms have been, however, described by Zhu and collaborators (Figure 35.3).[26] Unfortunately, our knowledge of the mechanisms by which physical activity reduces the risk of cancer in children, adolescents, and young adults is still limited.

35.2.3 Role of Physical Activity in Secondary Prevention

Secondary prevention is defined as reducing the impact of a cancer that has already occurred through interventions such as physical activity to reduce the impact of cancer on patients' health, psychosocial, and physical function. Cancer affects patients in many areas of their lives, both personally and professionally. In comparison with the general population (without cancer), patients with cancer may experience anxiety, pain, depressive symptoms, fatigue, physical function impairment, and low health-related quality of life.[27,28] Symptom burden is even more severe in patients with advanced cancer.[28] In children with cancer, both physical and mental health are affected during cancer. It has been reported that at least 70% of them will experience at least two distressing symptoms during their treatment.[29] Adolescents and young adults are more likely to have a lower or impaired health-related quality of life compared with their healthy counterparts.[30] This is a symptom that lasts several years after the end of treatment.

Strong evidence is in favor of regular physical activity in patients with cancer to improve patient-reported

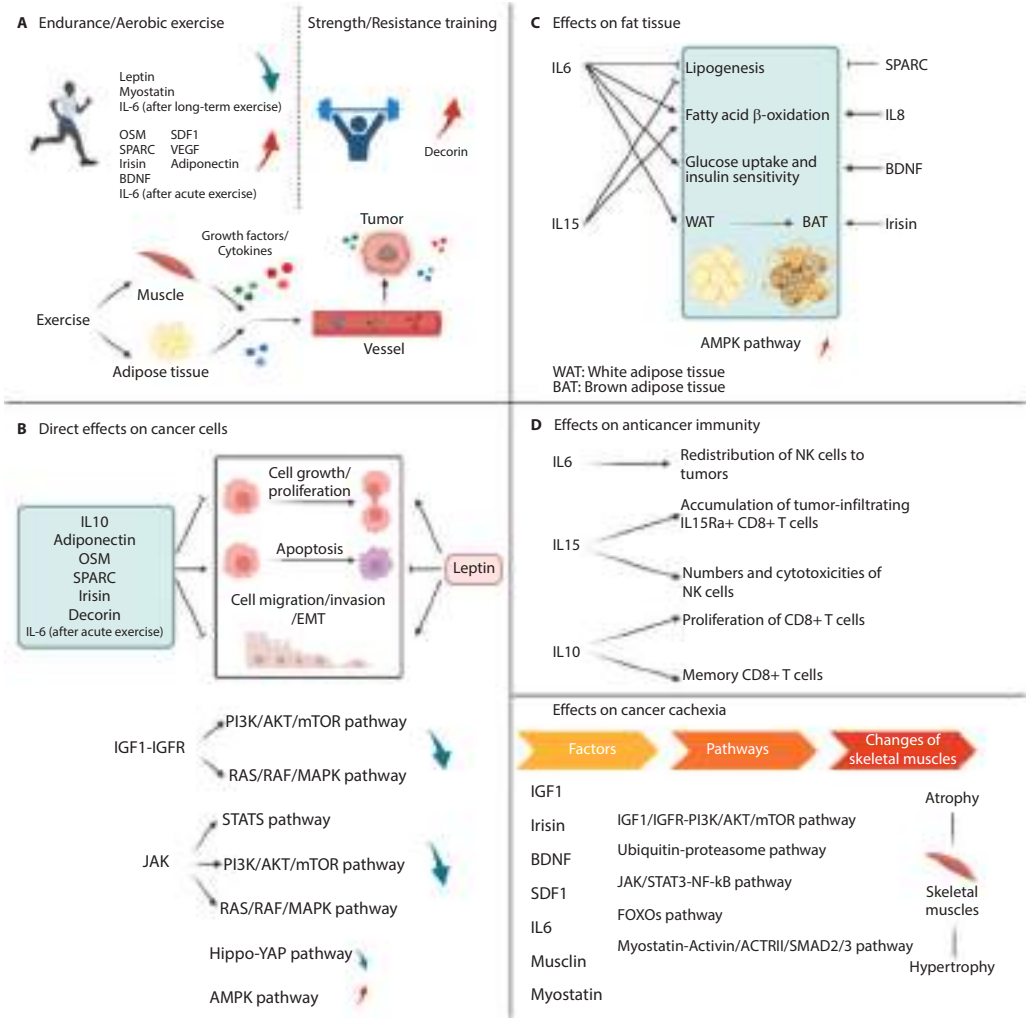


FIGURE 35.3 Biological mechanisms involved in the association between physical activity and cancer. (From Zhu, C., Ma, H., He, A., Li, Y., He, C., & Xia, Y. (2022). Exercise in cancer prevention and anticancer therapy: Efficacy, molecular mechanisms and clinical information. ***Cancer Letters***, 215814. Reproduced by permission of Elsevier.)

outcomes, including fatigue, anxiety, depressive symptoms, health-related quality of life, and physical function.[11] A recent study showed that treatment-related symptoms (e.g., fatigue) vary daily in patients with cancer and that physical activity should be adapted accordingly.[31] Cancer-related fatigue affects almost every adult patient with cancer,[32] a rate similar to the one observed in pediatric oncology.[33] A meta-analysis showed that physical activity is significantly more effective to reduce cancer-related fatigue than the available pharmaceutical options.[34] Physical activity can also improve patients' health status and long-term outcomes. A longitudinal study of 4,643 women diagnosed with invasive breast cancer showed that women engaging in regular physical activity before their diagnosis had lower breast cancer mortality and lower all-cause mortality.[35] Even if they were inactive before their cancer diagnosis, women who increased or maintained physical activity had lower all-cause mortality.[35] These findings strengthen the impact of physical activity on cancer.

To better understand its impact, mechanisms by which physical activity would influence cancer (incidence and symptoms) have been and continue to be explored. Before the 1990s, the role of physical activity had been studied in elderly women, showing its influence on natural killer cell tumor cytotoxicity.[36] This study generated many hypotheses, of which one of the best known involves the role of physical activity in increasing the number or improving the function of natural killer cells that play a role in tumor suppression.[37] Further, physical activity may increase the antioxidant capacity of the cells, reduce oxidative stress, improve DNA repair, and reduce cell proliferation, as well as improve apoptosis to block the initiation of cancer cells and fight their replication in the human body.[38,39] In animal models, it has been shown that physical activity inhibits tumor initiation and tumor multiplicity in addition to changing the tumor microenvironment.[38] Studies have suggested that engaging in regular physical activity improves immune function and the body's overall cancer control, regardless of the patient's age.[37,40,41]

35.2.4 Role of Physical Activity in Tertiary Prevention

Tertiary prevention is defined as managing the long-term impact and complex health problems related to a cancer that has already occurred through interventions such as physical activity to prevent long-term problems and cancer recurrence. Physical activity plays an important role in oncology (adults and pediatrics) to help patients with cancer recover their autonomy by improving their physical function. Patients who engage in regular physical activity give themselves a chance to increase their longevity as well as their physical and mental health. Pooled data from the National Cancer Institute Cohort Consortium in 6 prospective cohort studies for a total of 654,827 adults showed that leisure-time physical activity was associated with a longer life expectancy (up to 4.5 years).[42]

Throughout 26 studies of patients with breast, colorectal, and prostate cancers, it has been observed that those who are physically active reduce their risk of cancer-specific mortality by 37% compared with patients who are not active.[43] In adult survivors of childhood cancer, increased physical activity over eight years is associated with a 40% reduction in all-cause mortality.[44] Findings from the Childhood Cancer Survivor Study (CCSS) cohort have shown that a decreased risk for all-cause mortality is associated with being physically active more than three days per week, with a lower risk of death among females.[45] In colorectal cancer, patients engaging in regular physical activity, in addition to avoiding risk factors (tobacco use, alcohol consumption, overweight/obesity) and modifying their eating habits, have the potential to reduce cancer-specific and overall mortality by up to 40%.[46] They are also more likely to significantly increase their health-related quality of life compared with those who do not engage in regular physical activity.[46] Similar observations are reported in breast cancer survivors, since physical activity has been associated with better health-related quality of life, better reported symptoms (e.g., fatigue, pain, sexual function), and better survival.[47–49] Physical activity seems to be powerful enough to decrease patients' likelihood of dying.

A systematic review and meta-analysis reported that physical activity in cancer survivors was significantly associated with a reduction in the risk of recurrence by over 50%.[50] Patients with breast, colorectal, and prostate cancers engaging in regular physical activity decreased their risks of recurrence and recurrence/cancer-specific death.[43] Mechanistically, physical activity may boost the immune system of patients with cancer, as observed in patients with breast or colon cancers.[51, 52] Moreover, physical activity has been associated with reduced insulin secretion, insulin-like growth factor-1 (IGF-1) production, and insulin resistance, which can lead to enhanced normal cell division and inhibit cell death in patients with cancer.[52,53] Regulation of IGF-1 concentrations and signaling, natural killer cell function, and inflammation have been identified as key cancer biomarkers positively affected by physical activity. Other mechanisms related to physical activity also have to be taken into consideration, such as gene suppression and oxidative stress reduction, which play an important role in gastric and colorectal cancers, respectively.[54]

Furthermore, it seems crystal clear that physical activity should be promoted and implemented in oncology, and clinicians must understand and be educated on current guidelines surrounding physical activity practice after a cancer diagnosis.

35.3 PHYSICAL ACTIVITY GUIDELINES AND PRACTICE BEFORE AND AFTER A DIAGNOSIS OF CANCER

The focus of physical activity intervention shifts across the cancer control continuum. Courneya and Friedenreich have developed the Physical Activity and Cancer Control Framework (Figure 35.4), which clarifies the categories

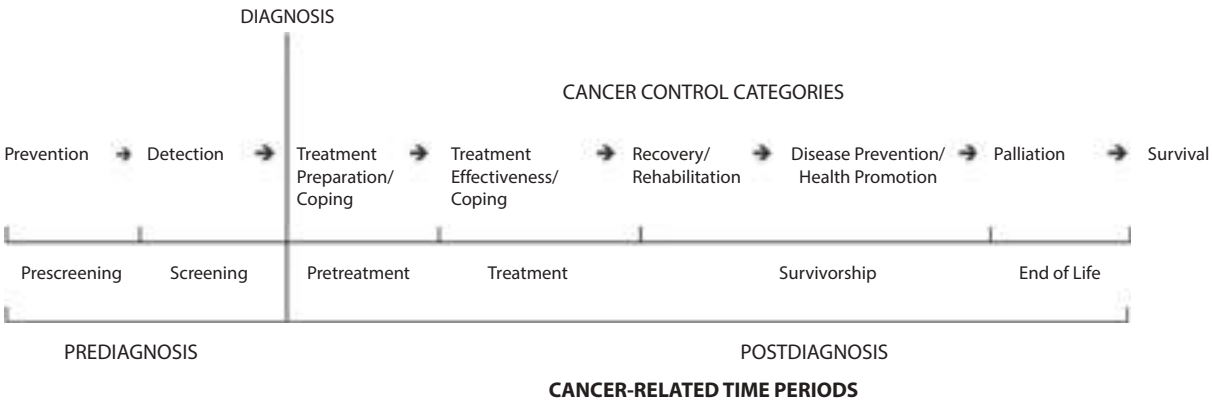


FIGURE 35.4 Physical activity and cancer control framework. (From Courneya, K. S., & Friedenreich, C. M. (2007, November). Physical activity and cancer control. In ***Seminars in Oncology Nursing*** (Vol. 23, No. 4, pp. 242–252). WB Saunders. Reproduced by permission of Elsevier.)

of outcomes that might be the focus of physical activity interventions from the point of primary prevention, immediately after diagnosis, throughout treatment and recovery, and through the end of life.[55]. Given this framework, it follows that physical activity guidance is distinct for patients from diagnosis to the end of treatment versus post treatment through the end of life. For example, the outcomes of greatest interest during the pretreatment time frame might be addressing anxiety and increasing muscle mass and physical function. By contrast, outcomes of greatest interest during active treatment would be coping with symptoms and improving treatment tolerance. In turn, during the recovery time frame, there would be a return to focus on body composition and physical function.

35.3.1 Physical Activity Guidelines and Practice During and After Cancer Treatment

Multiple organizations have reviewed the scientific evidence and drawn the conclusion that exercise should be recommended during cancer treatment, including the National Comprehensive Cancer Network, American Cancer Society, Exercise Sport Science Australia, Clinical Oncology Society of Australia, American College of Sports Medicine, and the American Society of Clinical Oncology.[11,56–60] In particular, the ACSM reviewed 16 cancer health-related outcomes to discern whether there was randomized controlled trial evidence that exercise would benefit these outcomes during and after cancer treatment.[11] The reviewed outcomes included anxiety, depression, fatigue, health-related quality of life, breast cancer–related lymphedema, physical function, bone health, sleep, cardiotoxicity, chemotherapy-induced peripheral neuropathy, cognitive function, falls, nausea, pain, sexual function, and treatment tolerance. Systematic reviews of randomized controlled trials or individual randomized controlled trials were reviewed. If at least 5 trials with at least 150 participants showed an effect that was statistically significant, heterogeneity of effects was reviewed. With no heterogeneity, or heterogeneity with more promising results from recent trials, the expert panel chose to make a FITT prescription (Frequency, Intensity, Time, and Type) for the cancer health-related outcome. The eight outcomes for which there was sufficient evidence included anxiety, depression, fatigue, health-related quality of life, breast cancer–related lymphedema, physical function, bone health, and sleep. For these cancer health-related outcomes, the exercise prescription for patients during cancer treatment can be summarized as three times weekly moderate intensity aerobic exercise of 30 minutes in duration and two times weekly progressive resistance training. More specifics are provided in Figure 35.5. The ACSM guidelines are unique in that they provide greater specificity for the exercise prescription during treatment, which can be helpful when translating these recommendations into clinical practice.

35.3.2 Physical Activity Guidelines for Primary and Secondary Prevention of Cancer

The U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee (PAGAC) and the ACSM both reviewed the observational epidemiologic evidence regarding the relationship between physical activity and primary or secondary prevention of several common types of cancer.[61,62] Both reviews concluded that there is strong evidence of a reduction of incidence of seven common types of cancer for those who are more physically active, including colon, breast, kidney, endometrium, bladder, stomach, and esophageal adenocarcinoma. There is also moderate evidence of an inverse association between physical activity and incident lung cancer. The magnitude of the preventive effect generally ranges from 10% to 20%.

The U.S. PAGAC and ACSM Roundtable also reviewed the epidemiologic evidence regarding the role of physical activity and cancer-specific and all-cause mortality.[61,62] The review included many cancer sites (breast, colorectal, prostate, endometrium, ovarian, kidney, lung, melanoma, non-Hodgkin lymphoma, childhood cancers, esophageal, gastric, and malignant glioma). Review of meta-analyses and pooled analyses suggests that post-diagnosis physical activity is associated with a substantive prevention of cancer-specific mortality and all-cause mortality for breast, colorectal, and prostate cancers. The magnitude of these secondary prevention effects ranged from 30% to 45%, a notably larger effect than observed for primary prevention. The lack of effects for other examined cancers is thought to be largely due to lack of studies examining post-diagnosis physical activity and survival outcomes in those cancer sites.

35.3.3 Models of Exercise Oncology Practice during and after Treatment

Given the proliferation of clinical guidelines stating that exercise should be prescribed to those who have had a cancer diagnosis, both during and after treatment, it becomes important to describe how such programming would be delivered in cancer treatment settings. In the United States, qualified exercise oncology professionals are not yet covered by third party payers. This influences how exercise oncology is practiced in the United States. There are other countries in which qualified exercise oncology professionals are paid through a national insurance scheme, including the United Kingdom and Australia. In those countries, the challenges to practice center around triage, referral, and recommendations (issues addressed in the next section of this chapter). Herein, we describe how exercise oncology is typically practiced in the United States. There are three common models: group fitness, exercise consultation, and formal exercise programming. Each is described in the following. Notably, all three can be offered through telehealth. Referral into these programs includes self-referral and referrals from clinicians.

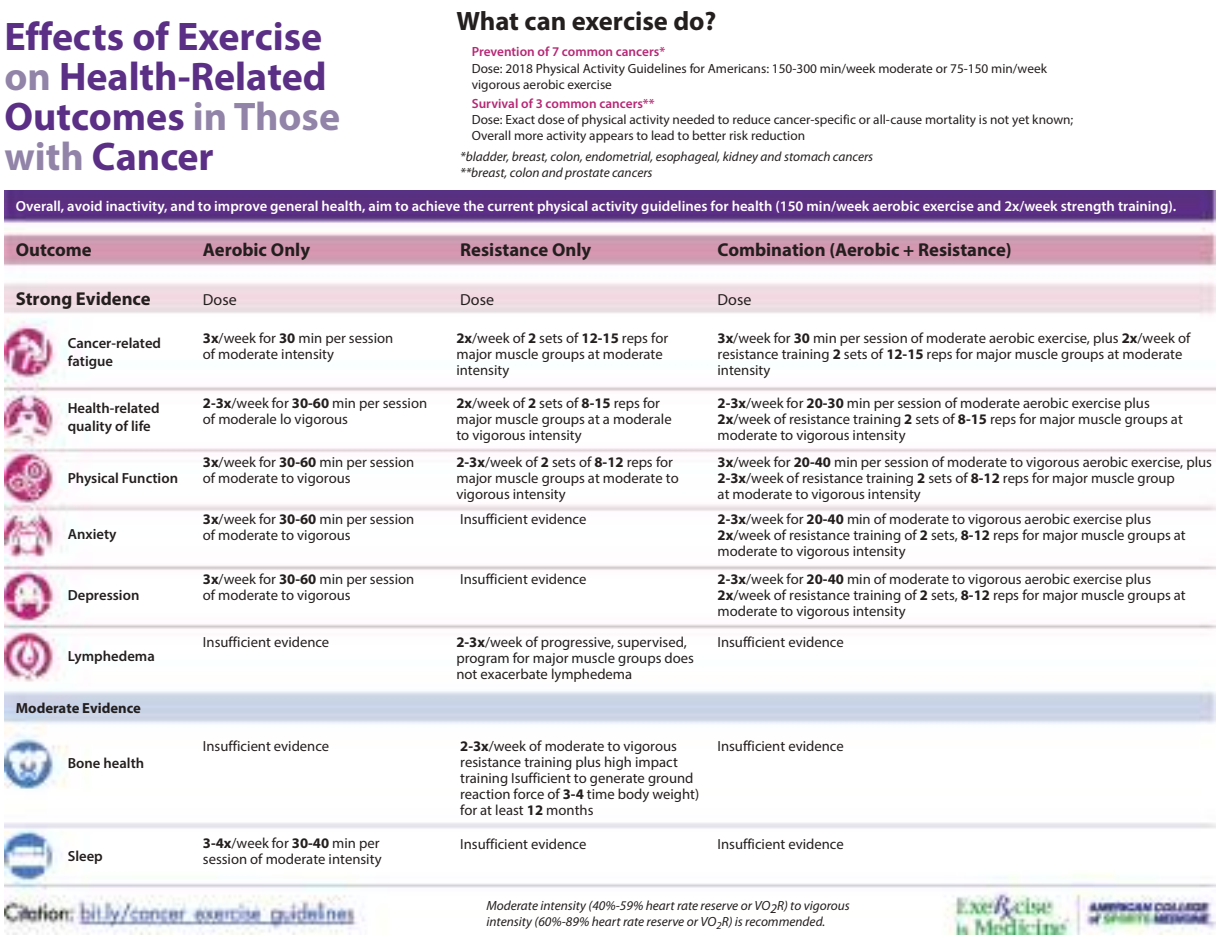


FIGURE 35.5 American College of Sports Medicine guidelines for specific cancer health-related outcomes. (From Campbell, K. L., Winters-Stone, K., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., ... & Schmitz, K. H. (2019). Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. ***Medicine and Science in Sports and Exercise***, 51(11), 2375. Reproduced by permission of Wolters Kluwer Health, Inc.)

Group Fitness. The examples of this approach include LiveStrong at the YMCA and Fitsteps for Life in Texas. These programs are generally supported by charity fundraisers and offered to patients and survivors at no cost. The programs generally include two in-person (or virtual synchronous) exercise sessions per week, led by a staff person with special training to provide exercise training to cancer patients and survivors. At present, the LiveStrong at the YMCA program is the largest in the United States, having served over 68,000 patients and survivors.[63] The program is carried out in groups, runs for 12 weeks, twice weekly, and is generally offered two to four times per year by YMCAs. There is documented efficacy of the LiveStrong program to improve physiologic and psychosocial outcomes.[64]

Exercise Consultation. An example of this approach is the Cancer Wellness for Life program in Kansas (www.cancerwellnessforlife.com). The program is paid for by the health system through a contract to the exercise oncology professionals and is offered to patients free of charge. The exercise oncology professionals contact referred patients to discuss goals and plans, to carry out a baseline triage to discern the need for outpatient rehabilitation, and to perform a baseline assessment prior to developing a personalized exercise plan. There are multiple community settings in which the patient can carry out the exercise plan (including their home). The exercise oncology team can check in with patients periodically to update the exercise plan as needed.

Formal Exercise Programming. An example of this approach is Maple Tree Cancer Alliance, which has over 55 locations across the United States (www.mapletreecanceralliance.org). The program is paid for either by charity fundraising or by health system investment and is offered to patients free of charge. An initial consultation/evaluation discerns whether outpatient rehabilitation is needed for specific impairments. The baseline evaluation is used to develop a personalized exercise plan. Patients come to the centers where this program is offered once weekly to perform the exercise program under the supervision of a qualified exercise oncology professional, and they are given exercise homework to do in between the sessions. The program is available for prehabilitation (pre treatment), during treatment (12 weeks), immediately post treatment

(12 weeks), and longer post treatment (12 weeks). All sessions are one on one with a qualified exercise oncology professional.

35.3.4 The Role of the Clinician in Triage, Referral, and Recommendations

One of the most challenging issues in making exercise standard of care, as has been suggested by multiple expert panels from multiple organizations, is getting clinicians to make referrals into exercise programming during and after cancer treatment. There are multiple reasons for this: 1) lack of education of oncology clinical staff regarding the effectiveness of exercise for multiple clinical outcomes during and after cancer treatment; 2) lack of time to talk to patients about exercise during busy oncology clinical encounters; 3) lack of clarity regarding who should be referred to outpatient rehabilitation versus exercise programming. Recently published evidence underscores that most oncologists agree they should be talking to their patients about exercise,[65] but that only 14.7% of patients are getting referrals to exercise from their oncology care team.[66] The challenge of lack of time and lack of clarity regarding trial to outpatient rehabilitation versus exercise could be solved by inserting an exercise oncology staff member to talk about exercise and carry out the triage process, as is the case with the consultation model and formal exercise program approaches described earlier.

There is a newly validated triage tool that could be included in this process and that would ease this challenge, called "EXCEEDS-S"[67] (Figure 35.6). The tool is patient facing but could be completed in the presence of an exercise oncology professional so that appropriate referrals could then be made. There is also a new directory of exercise oncology and rehabilitation programs developed by the ACSM to which patients can be referred upon completion of the EXCEEDS-S triage tool. The directory will only show patients programs that would be appropriate for them, based on answers to the EXCEEDS-S tool (www.exerciseismedicine.org/eim-in-action/moving-through-cancer/exercise-program-registry).

35.3.5 Cost and Healthcare Outcomes

The rising cost of cancer care is a primary focus for patients, payers, and providers. Over the past 40 years, the mean monthly cost of cancer drugs has risen from less than $100 in 1965–1969 to more than $10,000.[68] Finding innovative ways to reduce this cost burden is of value from the patient, payer, and societal perspective. Given that many competing cancer treatment modalities exist, it is essential to ensure that scarce healthcare resources are allocated in the most effective way to benefit cancer patients by considering the cost-effectiveness, sustainability, and economic aspects. Cost-effectiveness analysis (CEA) is a widely used analytical tool to choose between two alternative treatments by comparing the cost relative to the effectiveness.[69,70] CEA is increasingly being considered in developing cancer treatment guidelines.[71,72]

A search in PubMed using keywords "cost effectiveness cancer exercise" yielded 250+ hits (we also tried other keyword combinations to increase our search results). For the hundreds of hits, we reviewed all the titles/abstracts (and full contents when needed) to identify truly relevant studies. Only a few of the identified studies conducted genuine cost-effectiveness analyses (others just merely mentioned the concept that exercise might be cost-effective without actually conducting a CEA). Among the small number of existing CEA studies, almost all are conducted in other countries, including the United Kingdom, the Netherlands, Australia, etc.[73–79] Results consistently favor exercise programming, with a trend toward more formal and supervised programs being most cost-effective, perhaps because they garner the greatest physiologic benefit. Unfortunately, these results may or may not be applicable to the U.S. healthcare environment, given large differences in organization of care and payment structure. We found only one study that is based on U.S. patient-level data, with a focus on lung cancer survivors, that documented organizational-level cost-effectiveness of a lifestyle intervention that included exercise.[80]

It seems that despite international guidelines promoting the implementation of exercise in cancer treatment,[11,81] little is known about its cost-effectiveness. Understanding cost-effectiveness would facilitate incorporating exercise as a standard (and furthermore, reimbursable) form of treatment. It is unquestionably important to study the efficacy of exercise among cancer patients, given the high prevalence of cancer and far-reaching benefits of exercise. Nevertheless, to ensure the feasibility and economic sustainability of the exercise intervention, formal CEA is essential. Recent data from an uncontrolled pragmatic exercise oncology trial supports further economic evaluation of exercise oncology programming. The intervention cost approximately $191/patient, and the authors observe cost savings of $3,513 when comparing emergency department and hospitalization costs for patients who receive a consultative intervention (described earlier) as compared with matched comparison patients.[82]

35.4 PHYSICAL ACTIVITY BEHAVIOR CHANGE

35.4.1 Epidemiology of Physical Activity

The fight against cancer is a long-term public health issue in which physical activity plays an important part. The prevalence of physical inactivity among cancer-free American adults has reached 25% in the last few years.[83] The U.S. Department of Health and Human Services has identified, however, that approximately 80% of men and women are insufficiently active in the general population.[84] There is an equally frightening observation in children and adolescents.[85,86] Low levels of physical activity have been associated with chronic diseases, such as cardiovascular diseases

The Exercise in Cancer Evaluation and Decision Support - Survivor (EXCEEDS-S) Tool

Directions: Answer "yes" or "no" to the questions below. When you answer "yes", review the corresponding recommendation. Use the ACSM Exercise is Medicine, Moving Through Cancer registry[2] to locate a program near you.

Note: Always discuss with your doctor before starting a new exercise program.

Question	Answer	Recommendation
1. Do any of the following limit your ability to complete daily activities including work, hobbies, home care, socializing, and caring for yourself or loved ones? ☐ Difficulty with any of the following activities: • getting in or out of a vehicle, or using public transportation • walking one block without using a mobility aid like a cane or a walker • moving or reaching with your arms ☐ Difficulty being without a caregiver or another person who can assist you with activities ☐ New or worsening of any of the following conditions: • muscle weaknesses or coordination • difficulty with eating or drinking • difficulty with memory, multitasking, or thinking • numbness or loss of sensation in feet or hands • dizziness or blurred vision, or feeling lightheaded or disoriented ☐ Moderate to high pain that you rate as 7 out of 10 (0 = no pain, 10 = highest pain) ☐ Moderate to high fatigue that you rate as 7 out of 10 (0 = no fatigue, 10 = highest fatigue)	**Yes** **No**	**Outpatient cancer rehabilitation**
Continue to the next section if you answered "no" above or if there are no recommended programs in your area		
2. Have you fallen in the past 6 months?	**Yes** **No**	**Clinically supervised exercise program**
3. In the past 3 months, have you had any of the following cancer treatments? ☐ Surgery ☐ Stem cell transplant ☐ Chemotherapy ☐ Targeted therapy or immunotherapy ☐ Radiation therapy or brachytherapy	**Yes** **No**	
4. In the past week, have you experienced any of the following conditions? ☐ Mild daily fatigue that you rate as 3 to 6 out of 10 (0 = no fatigue, 10 = highest fatigue) ☐ Tingling sensation or loss of feeling in your feet or hands ☐ Difficulty with memory, multitasking, or thinking ☐ Dizziness after you stand up from either sitting in a chair or from lying down ☐ Nausea or frequent vomiting/diarrhea that interferes with daily activities ☐ Frequent feelings of dehydration ☐ Loss or gain of more than 5% body weight ☐ Lack of voluntary control over urination or defecation (incontinence) ☐ Persistent heaviness or swelling in your arm(s), leg(s), or trunk (lymphedema) ☐ Immunosuppression due to anemia, neutropenia, or thrombocytopenia	**Yes** **No**	
Continue to the next section if you answered "no" above or if there are no recommended programs in your area		
5. Do you currently have or are you planning to receive a catheter? *Including but not limited to: peripherally Inserted Central Cather (PICC), port, intraperitoneal catheter, or ostomy*	**Yes** **No**	**Cancer-specific community-based exercise program**
6. Confidence for independent exercise *Would you describe yourself as "highly confident" that you will exercise at moderate or vigorous intensity for 30 minutes, at least 3 times a week, for the next 12 weeks without receiving support from an exercise professional?*	**Yes** **No**	
Continue to the next section if you answered "no" above or if there are no recommended programs in your area		
Independent exercise *Try to do at least 150 minutes of moderate-intensity physical activity every week* *Examples: brisk walk, water aerobics, casual biking, doubles tennis*		

[1] https://www.exerciseismedicine.org/eim-in-action/moving-through-cancer/exercise-program-registry/

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FIGURE 35.6 Validated triage tool "The Exercise in Cancer Evaluation and Decision Support - Survivor (EXCEEDS-S) Tool." (From Covington, K. R., Marshall, T., Campbell, G., Williams, G. R., Fu, J. B., Kendig, T. D., ... & Pergolotti, M. (2021). Development of the exercise in cancer evaluation and decision support (EXCEEDS) algorithm. ***Supportive Care in Cancer***, 29(11), 6469–6480. Reproduced by permission of Springer Nature.)

and cancer.[87] According to the World Health Organization, sedentary behavior is the fourth leading risk factor for death worldwide and is responsible for almost a quarter of cancers.[88] A cohort study in 334,161 European men and women showed that physical inactivity was a larger contributor to all-cause mortality than obesity (considered to be one of the most important risk factors for cancer).[89] The authors also suggested that "efforts to encourage even small increases in activity in inactive individuals may be beneficial to public health,"[89] reinforcing the benefits of exercise for the general population.

From our youngest age, physical activity should be part of our good habits. Children need more daily physical activity than adults to ensure optimal development. It is during childhood that the chronic adaptations associated with training are intended to be more effective and beneficial in the long term (i.e., adulthood).[90] Physical activity during childhood and adulthood has been described as a key health behavior to prevent chronic diseases.[91] While it was historically recommended to avoid physical activity when diagnosed with an illness, the safety of exercise for those with chronic conditions, including cancer, has been established, and the following message is now highly endorsed by the Centers for Disease Control and Prevention: "Some activity is better than none."[92]

In oncology, physical activity programs are designed to support patients by enhancing their health behavior in order to replace their unhealthy lifestyle habits or risky health behaviors. One of the challenges is to design a program that will favor patients' adherence to physical activity, whether during or after cancer treatments. Several factors can predict physical activity adherence, such as baseline physical fitness, pretreatment fatigue level, treatment-related mood disturbance, and marital status.[93] Nevertheless, self-efficacy, or patients' belief that they can change their behavior, is a key concept in motivating the patient to maintain their behavior.[94] It has been shown that individuals who have control over their behavior are more likely to engage in physical activity than those who do not have control.[95,96] This aspect is reinforced in pediatric patients, especially in adolescents, who want to have control of their lives and indirectly, of their behavior. To help their patients, researchers and clinicians have started implementing lifestyle interventions. These types of interventions provide information to patients regarding physical activity–related benefits, goal-setting, self-monitoring, and how to increase physical activity.[97]

Patients' knowledge about the benefits of physical activity is also an important key factor in their adherence to this health behavior. Patient education starts by explaining why physical activity is important and how it can be done and adapted to patients' health status. For some patients, physical activity is construed as engaging in a sport or competition instead of being performed for one's health. For example, walking is associated with a reduction of 11% in all-cause mortality, 20% in cardiovascular mortality, and 9% in cancer mortality.[20,98] The U.S. Department of Health and Human Services made a call to action in 2015, focusing on walking to help Americans increase their moderate-to-vigorous physical activity, and prevent and reduce their risk of chronic diseases and premature death.[99]

Therefore, clinicians should encourage their patients to engage in regular physical activity, in addition to enable patients' self-efficacy and enjoyment.[100] Developing fun, safe, appropriate, and personalized physical activity programs is not just for children. Doing so is important for everyone to increase adoption of and adherence to better long-term health behaviors. To reach this goal, a key factor is working with patients, and for them to be actors in their changes and in overcoming the barriers they face.

35.4.2 Barriers to Physical Activity

Barriers to physical activity must be understood and recognized to better understand and support patients with cancer and survivors. As also observed in the general population, many patients, regardless of their age, are sometimes unable to maintain regular daily physical activity, affecting their quality of life and wellbeing. In adult cancer survivors, the most common barriers are difficulty getting motivated, lack of self-discipline, health issues, and adverse effects from treatment, such as fatigue and pain.[101,102] Similar observations are reported in childhood cancer survivors. Almost 50% report that they are "simply too tired" to be active, while nearly 22% report that "pain prevents them from being active."[103]

Cancer-related fatigue is a common and multifactorial symptom, and above all, the most debilitating side effect during and after treatment. All cancer survivors (children, adolescents, and adults) will experience this symptom at least once in their life. The National Comprehensive Cancer Network defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[104] This symptom cannot be resolved by sleep and is a major barrier to maintaining regular physical activity in patients with cancer and survivors. In 646 cancer survivors, cancer-related fatigue was significantly associated with depressive symptoms, anxiety, sleep difficulties, adjustment to the illness, pain, dyspnea, age, and lack of social support.[105] Regular physical activity has been shown to have benefits for cancer-related fatigue.[34]

Cancer-related pain is also a barrier to adherence to regular physical activity. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[106] Pain in oncology is a complex phenomenon, and the perception of pain varies from one patient to another. Its evolution and the effectiveness of treatments to address patients' pain depend on many biological, psychological,

and social factors.[107] It is reported that all cancer patients will, at some point in their lives, have a painful experience. A report from the St. Jude Lifetime Cohort Study observed that almost one in two adult survivors of childhood cancer still experience pain.[108] Physical activity, in addition to pain medication, has strong potential to reduce patients' pain.[109]

Thus, various obstacles and barriers can prevent the practice and maintenance of a physically active lifestyle. In order to enhance patients' health and physical activity, these barriers have to be recognized, especially since a lot can happen in the life of a patient living with and beyond cancer. Time restrictions due to medical examinations and school commitments can also prevent regular physical activity, as observed in children and adolescents diagnosed with cancer.[110]

35.4.3 Health Equity and Physical Activity

Physical activity has not always been available to everyone, and while one might think it is now accessible to everyone, it still is not. The Centers for Disease Control and Prevention published the U.S. physical inactivity prevalence maps by race and ethnicity and showed that non-Hispanic Asian adults had the lowest prevalence of physical inactivity (~20%), followed by non-Hispanic Whites (23%), non-Hispanic American Indians/Alaska Natives (~29%), non-Hispanic Blacks (30%), and Hispanic adults (~32%).[111] It has also been reported that non-Hispanic Blacks, Hispanics and other non-White adults, people with lower levels of education, and unemployed individuals have lower levels of leisure-time physical activity.[112] Thus, enhancing physical activity participation requires a comprehensive effort, and personal beliefs and awareness are vital to consider when physical activity programs are designed in oncology settings. The Centers for Disease Control and Prevention also highlight that the place of residence plays an important role in increasing the prevalence of physical inactivity.[111] The lack of safe space, time, and social support has also been pointed out by their recent report.[111]

The distinction between sex and gender should also be considered when establishing a physical activity program in oncology. In childhood cancer survivors, it has been observed that female survivors have a lower cardiorespiratory fitness level than male survivors, and that this difference increases with childhood cancer survivors' age.[113] Cardiorespiratory fitness is an important parameter in exercise physiology and an excellent predictor of cardiac health in patients with cancer. Efforts must be pursued to make physical activity equally accessible to all genders.[114] To support our point, a systematic review shows gaps in the understanding of cancer among LGBTI adolescents and young adults. This review discusses in particular the unique disparities in access to healthcare in this population.[115] Clinicians and researchers have the opportunity to avoid making this mistake in exercise and oncology settings.

35.5 Opportunities in Physical Activity and Cancer Research

In the last two decades, evidence on the benefits of physical activity on health has caught the attention of the general population. The 2018 U.S. physical activity guidelines for Americans document where the U.S. government stands on physical activity, sedentary behavior, and health.[7] Nevertheless, the implementation of physical activity in standard patient care in oncology is still in its early stages. Important work remains to be done in the field of implementation and health services research to make physical activity available as a standard of care in patients with cancer and survivors. To reach this goal, clinicians, public policy, and researchers must work together for the benefit of all.

The exercise oncology field is well recognized as a multidisciplinary field where collaborations between researchers and clinicians are needed.[116] It is also a field that could benefit from more multi-site projects to extend the scope of research findings. A question that the scientific community regularly asks is related to the significance of results and their generalizability to other populations. In many cases, samples are too small to answer this question positively, and significance and generalizability could depend on the research focus. In adolescent and young adult patients with cancer, the literature points out the heterogeneity of samples and the small sample sizes. Multi-site projects could help recruit more participants. They could also help to have more exercise oncology clinical trials that are representative of the ethnicity, race, sex, and geographical location of patients diagnosed with cancer.

Implementing multi-site multidisciplinary projects could be a great way to address gaps in knowledge and also for collaborations between different research fields. For example, chemotherapy-related cardiotoxicity is well documented in childhood cancer survivors,[117] and the fields of exercise and cardio-oncology, mainly in childhood cancer survivors, would benefit from working together. Indeed, subclinical cardiac dysfunction has been reported only a few years after the end of cancer treatments,[118] and it could be prevented by engaging in regular physical activity.[119,120] Unfortunately, this seems to be just the tip of the iceberg, and Figure 35.7 emphasizes the need for the fields of exercise and cardio-oncology to work together; physical activity having shown promising benefits on chemotherapy-related cardiomyopathy both during and after treatments.[121–123] This is only one example of the need for multidisciplinarity to make forward progress in the field of exercise oncology.

To address these complex challenges between fields, transdisciplinary research is required, along with more efficacy research to better understand biological mechanisms in human subjects.[26] And, it is time to translate animal research to exercise oncology clinical trials. The ACSM Roundtable has nicely highlighted that there is insufficient evidence in human subjects regarding the benefits of exercise and cardiotoxicity, chemotherapy-induced peripheral

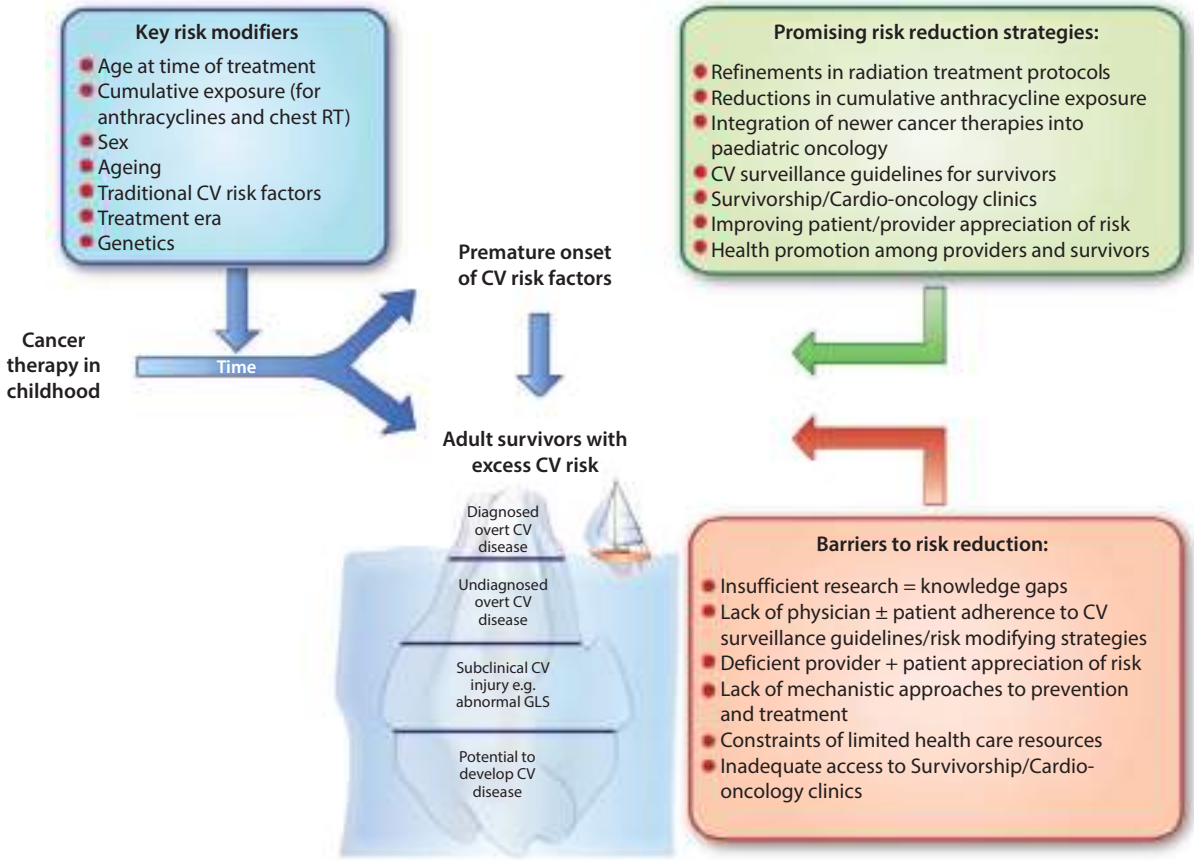


FIGURE 35.7 Association between cancer treatments and excessive cardiovascular disease risk. (From Groarke, J. D. (2018). Cardiovascular vulnerability of childhood cancer survivors: time to progress from risk observation to risk modification. ***European Heart Journal***. Reproduced by permission of Oxford University Press.)

neuropathy, cognitive function, falls, nausea, pain, sexual function, and treatment tolerance, despite animal studies that have presented promising results.[11] The complexity of what needs to happen next is an excellent opportunity for clinicians and researchers to work together in order to generate more research questions and answers in the field of exercise oncology.

35.6 CONCLUSION

Physical activity prevents and manages chronic diseases, in addition to providing a myriad of other physical and mental health benefits. Clinicians and researchers have been working together to demonstrate that engaging in regular physical activity and adopting a healthy lifestyle has benefits for patients living with and beyond cancer. In the last decades, multiple systematic reviews of randomized controlled trials or individual randomized controlled trials have been published and reviewed to prompt strong international exercise guidelines in exercise, as presented by the ACSM. Nevertheless, while the field of exercise and oncology in adults continues to progress and nears the discovery of biological mechanisms in exercise and cancer, the field of exercise and pediatric oncology is still in its early stages, and promising findings have been reported. This chapter has presented the state of evidence-based medicine in exercise, in addition to suggesting great opportunities for future research in exercise oncology. Important challenges remain for clinicians, including the key role that they can play in making exercise the standard of care.

CLINICAL APPLICATIONS

- Although significant progress has been made in understanding biological mechanisms, more research is needed to understand these mechanisms in exercise and cancer, in particular in human subjects.
- Triage referral and recommendations in exercise oncology remain a challenging issue in making exercise the standard of care.
- Clinicians and researchers have the opportunity to work together to reduce disparities in access to exercise in the healthcare setting.
- Emerging evidence suggests that exercise in oncology might be cost-effective; however, more research is required.

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36 The Health Consequences of Tobacco Use and Addiction: Assessment and Treatment

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KEY POINTS

- Tobacco smoking is addictive and harmful to every organ in the body, and continued smoking causes the loss of an average of ten years of life.
- Clinical practice guidelines recommend implementation of the "5 As" with every smoker.
- The "5 As" are Ask, Advise, Assess, Assist, and Arrange (a follow-up).
- Meta-analyses have demonstrated the efficacy and safety of numerous pharmacotherapies and different types of behavioral support or counseling.
- Because tobacco smoking is so harmful, even brief interventions with smokers remain among the most cost-effective healthcare interventions (top equal with childhood immunization).

36.1 CIGARETTE SMOKING AND HEALTH

At the time of the landmark 1964 U.S. Surgeon General's report on tobacco and health, over 50% of men and 30% of women were cigarette smokers.[1] Substantial public health efforts over decades (including educating the public about the health effects, increases in cigarette taxes, smoke-free air legislation, age-of-sale laws, etc.) have succeeded in consistently reducing the prevalence of cigarette smoking, such that by 2020, 14% of men and 11% of women in the United States smoke cigarettes "every day or some days." In addition, 3.7% used electronic cigarettes, 3.5% smoked cigars, and 2.3% used smokeless tobacco products.[2]

While the prevalence of cigarette smoking has been declining in most high-income countries over recent decades, it remains a major cause of premature death and disease. It has been estimated that tobacco smoking causes over 400,000 premature deaths per year in the United States,[3,4], and over 6 million premature deaths per year worldwide.[5,6] In addition, for every case of premature death caused by tobacco smoking each year in the United States, there are approximately 20 cases of non-fatal serious smoking-caused illness in someone who does not die in that year.[7] The vast majority of these illnesses (59%) are chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD).

The net effect of these smoking-caused diseases is that the continuing smoker is likely to die an average of ten years earlier than a never-smoker.[8] The approximate doubling of mortality risks for smokers is evident at age 50 (6% of smokers have already died, versus 3% of never-smokers) and continues past age 70 (by which time 42% of smokers have died, versus 19% of never-smokers).

While over 90% of smokers are aware that smoking cigarettes causes lung cancer (with a 20-fold excess risk), there is less awareness that smoking increases cancer risks at 9 other sites (mouth, esophagus, stomach, pancreas, larynx, cervix, bladder, kidney, and acute myeloid leukemia). The age-adjusted risk of death from COPD is tenfold higher for smokers than for never-smokers. This effect is relatively easy for smokers to understand, but there is less awareness that smokers have approximately threefold the risks of death from ischemic heart disease, stroke, and atherosclerosis at ages 35–64.[4]

36.2 HEALTH BENEFITS OF SMOKING CESSATION

The 1990 U.S. Surgeon General's report reviewed the health benefits of ceasing tobacco use and concluded that smoking cessation has major health benefits for men and women of all ages. For example, smokers who quit smoking by age 50 have one-half the risk of dying in the next 15 years, compared with continuing smokers.[9] The timescale for reduction in risks of disease after smoking cessation varies with each disease and even with the stage of the disease. Thus, the excess risk of death from coronary heart disease will be cut in half within a year of stopping smoking, but the same level of risk reduction may take 10–15 years for lung cancer.[9]

Lung function declines with age after reaching adulthood in non-smokers, but it declines at a significantly faster rate for smokers. However, when a smoker stops smoking, the rate of decline of lung function normalizes to a rate similar to that for never-smokers. Figure 36.1 is based on data from various epidemiological studies[10–14] but is primarily designed to help clinicians educate people who smoke about the potential benefits for lung function from

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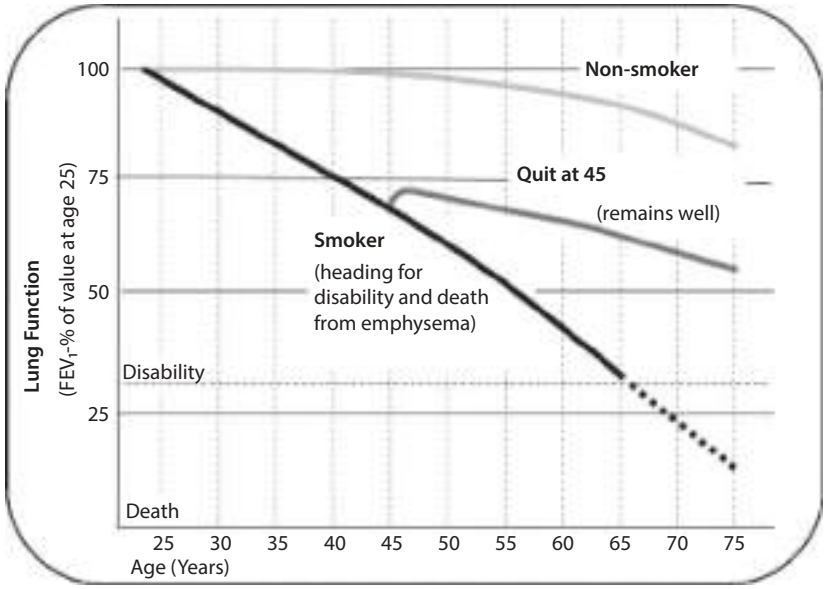


FIGURE 36.1 Schematic diagram illustrating effects of smoking cessation on lung function.

successfully quitting smoking and the likelihood of a small improvement in lung function followed by a significantly slower age-related decline.[14]

Overall, for most people who smoke cigarettes, the single best thing they could do to improve their health is to quit smoking completely. In the United States, the tobacco treatment strategy often referred to as "the 5 As" has been recommended in treatment guidelines since 2008.[15] The five steps proposed by this mnemonic are summarized here:

1. ASK about tobacco use.
2. ADVISE about the importance of quitting.
3. ASSESS motivation to change and dependence.
4. ASSIST to quit by providing treatment.
5. ARRANGE a follow-up.

The rest of this chapter will provide suggestions of practical evidence-based methods for implementing the 5 As.

36.3 "ASK": SCREENING FOR USE OF TOBACCO OR NICOTINE PRODUCTS

Screening: While cigarettes remain the nicotine products most commonly used by adults, other products and dual product use have become very common among young people over recent decades. In 2020, 17.3% of current tobacco users reported using two or more products.[2] For this reason when screening for current tobacco use, it is important to ask about all nicotine product use, using questions like the following:

(a) Have you used a nicotine or tobacco product some days or every day in the past 30 days? Yes No
(b) Which of the following products have you used some days or everyday in the past 30 days?
(a) *Cigarettes (manufactured or "roll-your-own" cigarettes)*
(b) *Cigars (e.g., large cigar or little cigar/cigarillo)*
(c) *Smokeless tobacco (e.g., snuff, chew, or snus)*
(d) *Electronic cigarette (e.g., Juul, NJOY, nicotine vape, mod device, etc.)*
(e) *Hookah or waterpipe*
(f) *Pipe*
(g) *Heat-not-burn cigarettes (e.g., electronic product that heats tobacco without burning it, e.g., IQOS)*
(h) *Nicotine pouches (oral nicotine pouch product not containing tobacco, e.g., Zyn, On!, etc.)*
(i) *Nicotine replacement therapy products (e.g., nicotine patch, gum, lozenge, inhaler, spray)*
(j) *Traditional tobacco product (e.g., gutka or paan from southeast Asia, or Iqmik from Alaska)*
(k) *Other nicotine products (please list type of products you have used not mentioned above).*

36.4 "ADVISE": BRIEF MOTIVATIONAL INTERVENTIONS AND ADVICE

It may seem more sensible to conduct a more detailed assessment prior to giving smoking cessation advice. This also relates to the fact that some aspects of assessment may also contain a motivational component. For example, the measurement of exhaled carbon monoxide (eCO) is often used as an assessment of recent smoke intake, but it can also be considered as one of many potential interventions designed to enhance motivation to take steps toward quitting smoking. Motivational Interviewing (MI) is a directive patient-centered style of counseling, designed to help people to explore and resolve ambivalence about behavior change. For some patients, assessment of their eCO, dependence, motivations, barriers, etc. can provide information that can be discussed in a way that may help increase their motivation to quit. However, the evidence of efficacy of MI

or Motivational Enhancement Therapy in terms of having a direct effect on boosting quit rates in clinical trials is not strong.[16]

Many busy clinicians now choose to ask questions designed to assess motivation to quit (e.g., "how much do you want to quit smoking?") *after* they have first of all delivered a positive statement of advice, emphasizing the importance of treatment. Here is an example of a brief, simple piece of advice that can be provided after identifying that a patient is a current tobacco smoker:[17]

> *"As your clinician, I want you to know that the single best thing you can do for your health right now is to quit smoking. Every year that you continue smoking likely reduces your healthy lifespan by around 3 months. I understand that it may not be an easy thing to do, but there are now treatments that have been shown to be effective, and I am familiar with those treatments and can help provide them. I believe it is very important for your health that we get started on this."*

When this type of accurate but encouraging advice is followed up with a question about interest in quitting, it is more likely to receive a positive response, which can lead directly to a more detailed assessment and discussion about treatment options.

36.5 "ASSESS": ASSESS FREQUENCY OF USE

Once the products being used have been identified, it is important to assess the frequency of use of every product that is currently being used, using the following questions:

> *"On how many days out of the past 30 did you use xxx product?"*
>
> *"In the past 30 days, how many cigarettes have you smoked per day, on average?"*

36.6 ASSESSING ADDICTION/DEPENDENCE

Nicotine addiction, like other psychoactive drug addictions, is characterized by continued compulsive nicotine seeking and use, which would be very difficult to control were the person to seriously try to stop using or believe that continued use may be harmful.

With regard to cigarette addiction (by far the most widely used nicotine product across the world), the question of attempting to quit, or being aware of the health risks, does not usually arise. Almost all cigarette smokers are aware that cigarette smoking can cause serious diseases like lung cancer, and the average 40-year-old smoker who started in their teens will have made more than 20 failed quit attempts.[18] Nicotine addiction differs from some other addictions in that there is often an unpleasant withdrawal syndrome on abruptly ceasing nicotine use, characterized by dysphoric mood, increased appetite, and poor concentration, that peaks in the first week and has largely resolved within three to four weeks of complete abstinence.

Some common characteristics of other addictions are less prominent for nicotine addiction because in most contexts, nicotine use is legal, and because nicotine use does not typically cause a general impairment in cognitive abilities or consciousness. For these reasons, nicotine addiction is less commonly accompanied by legal problems, loss of employment, or loss of the right to drive a motor vehicle.

With this definition, nicotine addiction can be identified by its behavioral characteristics even if the person has not yet made a serious quit attempt or has not yet experienced a serious health problem caused by their nicotine or tobacco use.

36.6.1 Assessment Using Criteria from the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders

Whereas DSM-4 required at least 3 out of 7 criteria for the diagnosis of tobacco dependence, DSM5 requires only 2 out of 11 criteria to meet diagnostic criteria for tobacco use disorder (TUD). The 11 basic criteria for DSM-5, translated into an easy-to-administer questionnaire, are shown in Table 36.1. TUD is considered of "mild" severity when two or three criteria are met, "moderate" severity when four or five criteria are met, and "severe" when six or more criteria are met.

An analysis of a representative sample of 6,793 exclusive cigarette smokers found a close relationship between cigarette smoking frequency and severity of DSM5 TUD (as assessed by the number of symptoms endorsed).[19] As shown in Figure 36.2, even among those who smoke less than weekly, 18% of those who typically smoke only one or two cigarettes on a smoking day met TUD criteria. Figure 36.2 shows a clear relationship between frequency of cigarette smoking and the proportion of cigarette smokers meeting DSM-5 TUD criteria, which becomes relatively flat above ten cigarettes per day (CPD), at around 90%. Notably, almost two-thirds of those smoking only one to four CPD met TUD criteria, as did the majority (64.1%) of those smoking on three to six days per week and a substantial minority (26.3%) of individuals who smoke less than once per week. DSM-5 states that TUD is considered of "moderate" severity when four or more criteria are met, and this study found that this is typically at ten or more cigarettes per day.

Question	Answer	Score
How soon after you wake up do you smoke your first cigarette of the day?	Within 5 minutes	3
	6–30 minutes	2
	31–60 minutes	1
	>60 minutes	0
How many cigarettes per day do you smoke?	<10	0
	11–20	1
	21–30	2
	>31	3

The most widely used questionnaire measure of cigarette dependence in smoking cessation research is the

TABLE 36.1

Questions That May Be Used to Assess DSM-5 Tobacco Use Disorder. There Are 11 Items; Each "Yes" on Items 1–10 Counts as One Criterion Met, and at Least 3 "Yes" Answers on Item 11A or a "Yes" on 11B Counts as One Criterion Met. The Total Severity Score Is Number of Criteria Met Out of 11.

The following questions are about experiences that some people have had when using cigarettes (or insert other nicotine product here). Please answer "yes" to each question if this has happened to you in the past 12 months:

1. Did you have a period when you often used your cigarettes more or longer than you intended to?
   Y N
2. Did you more than once TRY to stop or cut down on your cigarette use but found you couldn't do it?
   Y N
3. Did you have a period of time when you spent a lot of time making sure you had enough cigarettes available?
   Y N
4. Did you have a very strong desire or urge to smoke a cigarette?
   Y N
5. Did you continue to use your cigarettes even though it was causing you problems at school or home or work?
   Y N
6. Did you continue to smoke your cigarettes even though it was causing you problems in one or more relationships?
   Y N
7. Did you give up on any activities that you were interested in or that gave you pleasure because cigarettes were not permitted at the activity or because you had spent required money on cigarettes instead?
   Y N
8. Did you more than once use a cigarette in a situation that could have been dangerous, for example, driving a car, riding a motorbike, using machinery, boating, etc.?
   Y N
9. Did you continue to use cigarettes even though you knew it was causing you a health problem or making a health problem worse?
   Y N
10. Did you increase your cigarette use because the amount you used didn't give you the same effect anymore?
    Y N
11. (a) When you cut down on heavy or prolonged use of cigarettes or stopped smoking for over 24 hours did you have any of the following withdrawal symptoms:(*3 or more withdrawal symptoms required)*
    a. Irritability, frustration, or anger Y N
    b. Feeling tense or anxious Y N
    c. Difficulty concentrating Y N
    d. Increased appetite Y N
    e. Feeling restlessness Y N
    f. Feeling low or depressed Y N
    g. Had difficulty sleeping Y N
1. 11 (b) Did you continue smoking in order to avoid experiencing these types of withdrawal symptoms that may occur if you quit or cut down significantly?
   Y N

Fagerstrom Test for Cigarette Dependence (FTND). The FTND is a six-item questionnaire producing a score from 0 to 10. Numerous studies have found that a baseline FTCD score is moderately predictive of which smokers are more likely to succeed in quitting during a quit attempt (i.e., the lower the dependence score, the greater the chances of quitting smoking). The score also has significant correlations with severity of withdrawal symptoms and biochemical measures of nicotine exposure (e.g., plasma cotinine). Many studies have found that the two items in the FTND that measure the "**Heaviness of Smoking Index**" (cigarettes per day, and time to first cigarette of the day) perform about as well as the total score from six items in predicting quit success rates.[20,21]. So, a simple, practical way to assess cigarette addiction is to use the Heaviness of Smoking Index, such that a score of zero implies very low or no addiction, and a higher score implies more severe addiction.

36.6.2 Assessing Motivation to Quit

It is respectful of patient autonomy to ask about the level of interest in quitting smoking with a few straightforward questions:

> e.g., *"How much do you want to stop smoking?" (a) Not at all, (b) I am somewhat interested, (c) I am very much interested in quitting soon.*

Previous models of "stage-matched" interventions[22] have intuitive appeal to practitioners, but the strict interpretation of the model has been criticized on numerous grounds.[23] Perhaps the main problem has been the implication that if a patient states (or more commonly, checks a box implying) that they do not want to quit smoking in the next few months, then no further attempts to encourage the patient to quit should be pursued at that time. This may be an opportunity

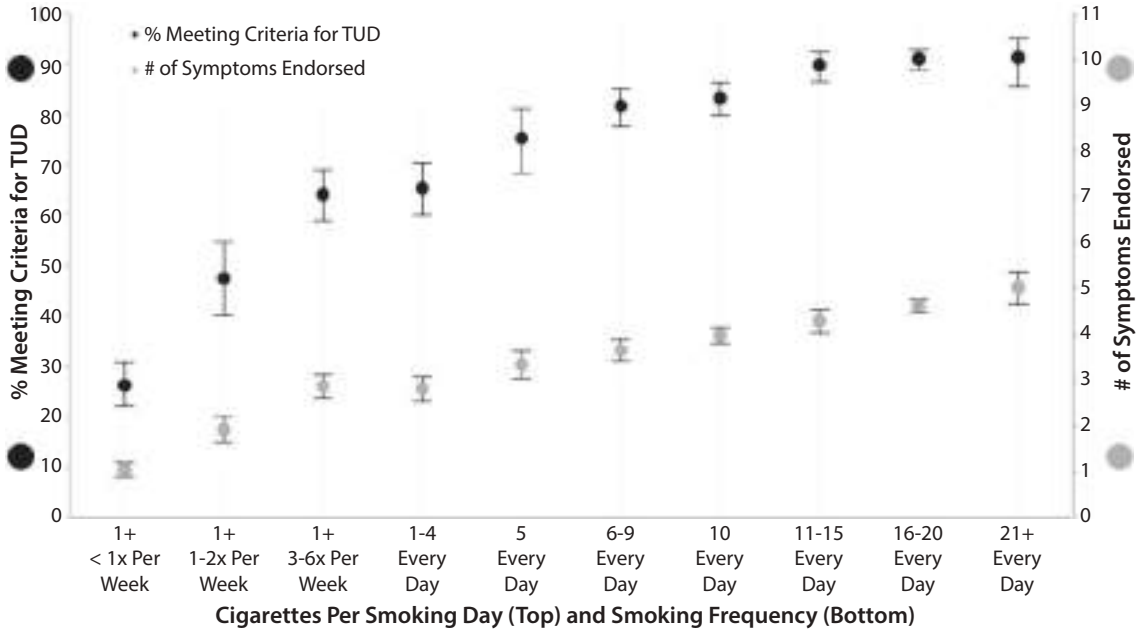


FIGURE 36.2 Percentage of smokers meeting DSM-5 criteria for Tobacco Use Disorder and mean number of DSM-5 criteria endorsed, by cigarette smoking frequency, in a large representative sample of U.S. exclusive cigarette smokers (n = 6,793). (From Oliver. J. and Foulds, J., ***Am. J. Prev. Med.***, 60(5), 726–728, 2021.)

missed, as such models do not reflect the frequent observation that people sometimes change their behavior and plans quite suddenly, and sometimes in response to seemingly small triggers.[24] So, modern models of assessment and intervention on tobacco use see it as more effective to identify motivational tools and offer evidence-based interventions that give some reasonable hope of success if an attempt at quitting or reducing smoking is to be pursued.

36.6.3 Biochemical Assessment

While numerous measures relating to tobacco use and toxicant exposure can be collected from body fluids (e.g., cotinine as a measure of nicotine exposure, or NNAL as a measure of carcinogen exposure), the most practically useful biochemical measure is assessment of exhaled carbon-monoxide (eCO). Exhaled CO can be easily measured in a few minutes using a relatively inexpensive portable device and has become a widely used method for assessing tobacco smoke exposure and validating self- reports of smoking cessation.[25] The typical eCO of smokers is around 20 ppm but can range from 5 to 80 ppm depending on the heaviness and recency of smoking. Over 90% of non-smokers in a low pollution environment have an eCO lower than 5 ppm, and most are in the range 0–3 ppm. A major advantage of routine use of eCO monitors in tobacco dependence treatment is that patients are more likely to be completely honest about their smoking behavior, as they know it will likely be measured by the CO monitor. For some people, the measurement of a high baseline eCO, then being informed that it will likely be much lower at subsequent visits after smoking cessation, can help boost motivation and attendance at treatment sessions. It can serve a similar monitoring and motivational function as measurement of blood cholesterol, blood pressure, or body weight. For example, here is a script used in one study of group smoking cessation treatment:[14]

> *"Your exhaled carbon-monoxide reading was 20. This is much higher than that of a non-smoker (typically 0–4). It means that the carbon-monoxide from inhaled cigarette smoking is binding to the red blood cells that carry oxygen in your blood and displacing oxygen. This means that your heart has to do more work to supply oxygen to your body, and it is part of the reason why smoking causes serious cardiovascular diseases such as heart attack or a stroke. It is very important to get that number down. The good news is that when you stop smoking the concentration of carbon-monoxide in your body will return to that of a never-smoker within a week. So it is really important that you attend all the stop-smoking group meetings, use the nicotine patches and succeed in stopping smoking. We will measure your CO levels at every appointment and you will be able to see the improvement when you quit smoking."*

36.7 CHRONIC CARE MODEL: TREATING TOBACCO DEPENDENCE AS A LIFE-THREATENING CHRONIC ILLNESS

An important part of modern conceptualizations of tobacco treatment is to adopt a chronic care approach. Tobacco use is seen as a chronic illness (much like asthma or diabetes), and treatment is seen as a long-term process, with the clinician offering to assist in the process for as long as it takes.[17,26] It is understood that changing the plan may be necessary at times, and every day without tobacco use is counted as a success (as compared with conceptualization of a single attempt that

either succeeds or fails in quickly resulting in complete abstinence). In this model, it is emphasized that although a target "quit date" may be arranged, the clinician explicitly expects that it may take a few months or longer before the patient feels confident in their abstinence from tobacco.

36.8 EVIDENCE-BASED INTERVENTIONS: ASSIST

The evidence is very clear that a combination of behavioral support plus pharmacologic therapy results in the highest quit rates.[15] The evidence suggests that there is a dose–response effect for the number of counseling sessions from a trained counselor (at least up to four or five sessions), and also that either varenicline or combination nicotine replacement therapy (NRT) (typically the nicotine patch plus a short acting NRT product like gum, lozenge, nasal spray, or inhaler) has the best outcomes.[27] Therefore, for smokers who have been assessed as being at least moderately dependent, they should be encouraged to use the most intensive level of counseling and pharmacotherapy available. However, in practice, many countries' healthcare systems have limitations on the counseling services available, and there may also be limitations on the types of medication the individual is willing to use, based on prior experience, cost, side effects, etc.

36.8.1 Summary of the Evidence for Various Pharmacotherapies for Smoking Cessation

Meta-analyses carried out for the 2008 U.S. Clinical Practice Guideline on Tobacco Use and Dependence[15] and subsequent updates carried out by the Cochrane Tobacco Addiction review group (and others) have confirmed a fairly consistent pattern of results from randomized clinical trials.[27]

Pharmacologic methods

Method (number of trials)	Versus placebo unless otherwise noted Risk ratio (95% CI)
First-line pharmacotherapies	
Nicotine replacement	
Any NRT product[133]	1.55 (1.49–1.61)
Combination (versus individual products(	1.25 (1.15–1.36)
Patch[51]	1.64 (1.53–1.75)
Gum[56]	1.49 (1.40–1.60)
Lozenge[8]	1.52 (1.32–1.74)
Inhaler[4]	1.90 (1.36–2.67)
Nasal spray[4]	2.02 (1.49–2.73)
Varenicline[7,27]	2.24 (2.06–2.43)
Bupropion SR[45]	1.64 (1.52–1.77)

CI: confidence interval.
Source: adapted from Rigotti et al, 2022.[27]

These studies have found that all of the Food and Drug Administration (FDA)-approved nicotine replacement therapies, as well as bupropion and varenicline, increase the chances of patients achieving long-term abstinence (6–12 months or longer) as compared with placebo or no pharmacotherapy. However, it has become clear that varenicline is the most effective single pharmacotherapy, which is approximately equal to combination pharmacotherapies (e.g., nicotine patch plus nicotine gum), which is significantly more efficacious than any other single pharmacotherapy.

The clearest evidence for the superior efficacy of varenicline versus nicotine replacement therapy or bupropion was provided from the EAGLES randomized trial.[28] This trial is by far the largest placebo-controlled, double-blind randomized clinical trial comparing different medications head-to-head (n = 8,141) and also including a large group of people with a history of mental disorders (n = 4,116). It found that within both the psychiatric and non-psychiatric cohorts, varenicline produced superior quit rates to bupropion or the nicotine patch, even though both of these therapies had significantly higher quit rates than placebo, both at the end of drug treatment (12 weeks) and after 12 weeks of medication (24 weeks), as shown in Figure 36.3.[28]

The evidence is so strong for the safety and efficacy of these FDA-approved pharmacotherapies that it would nowadays be considered sub-standard treatment not to recommend pharmacotherapy when trying to treat tobacco dependence, outside potential patient choice or population groups without clear supportive evidence (e.g., minors, pregnant women, very light smokers [e.g., <5 cigarettes per day]).

36.8.2 Summary of Evidence of Efficacy of Various Behavioral Treatments

There is clear evidence that brief advice (lasting less than 15 minutes) can improve quit rates, largely by increasing quit attempts, and that more intensive individual and group counseling can provide higher quit rates. All these proven counseling modalities tend to produce higher quit rates when added to pharmacotherapy than either counseling or pharmacotherapy alone.

Efficacy of behavioral methods

Method (number of trials)	Versus minimal or usual care unless otherwise noted Risk ratio (95% CI)
Behavioral counseling	
Individual counseling[27]	1.57 (1.40–1.77)
Group counseling[13]	1.88 (1.52–2.33)
Telephone quit line counseling[13]	1.38 (1.19–1.61)
Clinician counseling	
Brief advice[17]	1.66 (1.42–1.94)
Brief counseling[11]	1.86 (1.60–2.15)
Brief counseling (versus brief advice)	1.37 (1.20–1.56)
Counseling added to pharmacotherapy[65]	1.15 (1.08–1.22)vs. pharmacotherapy alone

Source: adapted from Rigotti et al, 2022.[27]

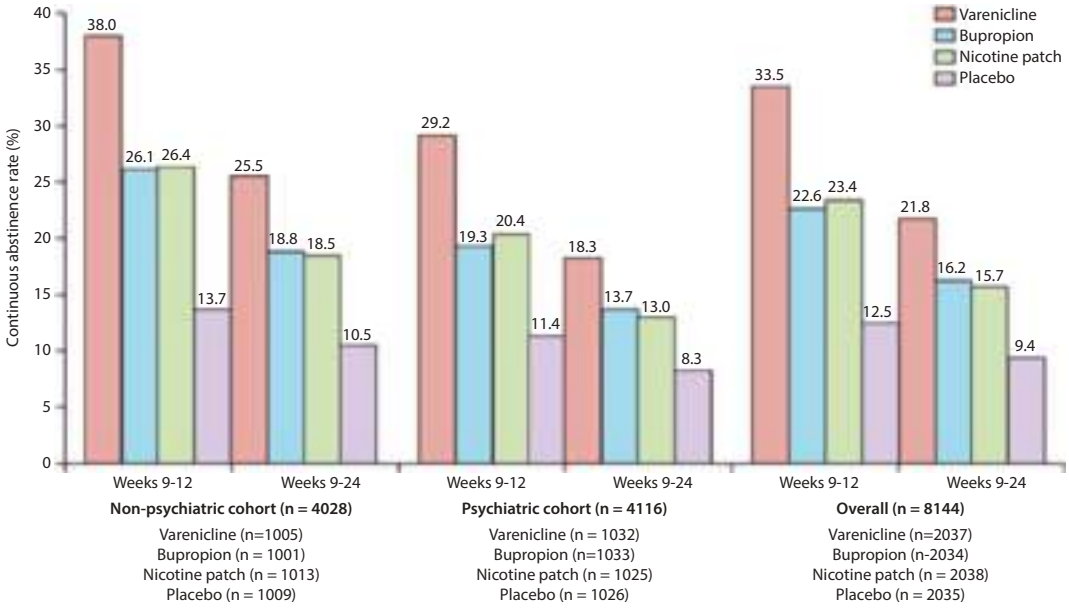


FIGURE 36.3 Continuous abstinence rates for weeks 9–12 and 9–24. Analyses based on the all-randomized population, in a randomized, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up at 140 centers in 16 countries. (From Rigotti, N. et al., ***JAMA***, 327(6), 566–577, 2022.)

Although there are fewer studies or less clear evidence for other types of behavioral intervention, there is evidence to support the efficacy of interventions based on structured text messaging to cell-phones[29] as well as internet-based treatment[30] and real-time video counseling. There is also very solid evidence supporting the efficacy of financial incentives, although these can be practically difficult to implement.

Overall, it appears that most behavioral interventions that encourage a structured quit attempt and provide encouragement to persist with the quit attempt are likely to be helpful. Relatively intensive in-person interventions appear to result in the highest short-term quit rates (e.g. at one- to three-month follow-ups), but they also require relatively high motivation and time commitment on the part of patients, and so can be more difficult to implement in a manner that has "reach" in the sense of being able to help a large number of smokers in the local target community to quit smoking.

One aspect of smoking cessation treatment that appears to be fairly clearly supported in the literature is recommending a specific "target quit date" when the smoker will quit smoking completely, rather than having a more gradual reduction toward quitting.[31] Clinical experience also suggests that little is gained by including an extended "preparation" phase prior to attempting to quit completely, other than the allowing sufficient time for the patient to obtain and understand how to use adjunctive pharmacotherapy. While gradual reduction appeals to many smokers and makes intuitive sense, it is unclear why it appears to be less successful. It is possible that it simply delays the time frame when the individual actually quits, such that fewer smokers actually reach that point.

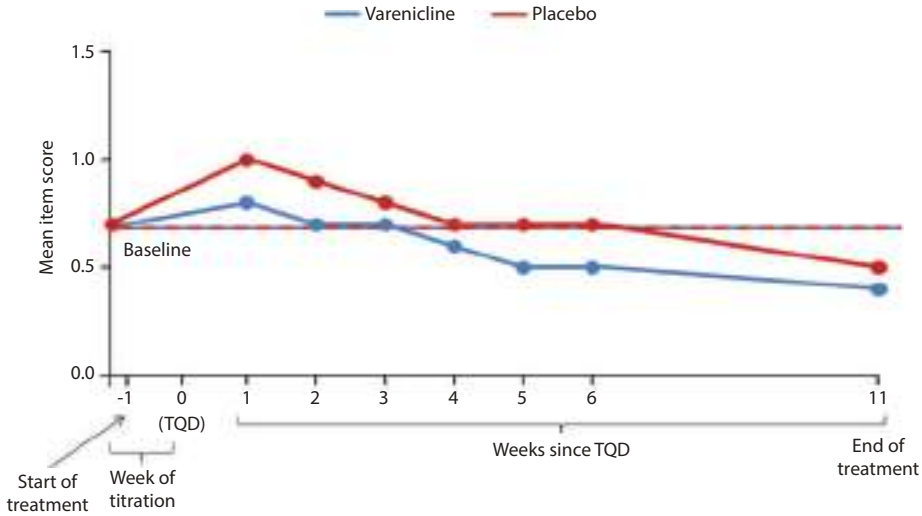
36.9 ADDITIONAL CONSIDERATIONS WHEN PROVIDING TOBACCO CESSATION INTERVENTIONS

There are additional components of tobacco cessation treatment that are not yet very clearly supported by evidence but are becoming more widely supported, both by the evidence and by clinical experience.

1. **Social support.** Sessions with a trained professional are a formal type of social support, as is the support provided in a formal group-based smoking cessation program. There is evidence that the more social support provided, the better the outcomes. For example, in group treatment, it appears that "group-oriented" groups, in which group members support each other and group cohesion is encouraged, do better than "class-style" smoking cessation groups, in which the therapist does most of the talking with less group interaction/support.[32] Similarly, even something as simple as seeing smokers who want to quit in pairs with a "buddy" appears to result in higher quit rates than seeing them individually.[33] Even when it is not feasible to provide within-treatment social support, it appears worthwhile to encourage smokers to consider how they might maximize the social support

in their own life (e.g., by telling supportive friends or family about their quit attempt and seeking their support).

2. **Management of withdrawal and craving**. The primary mechanism of all the pharmacotherapies is that they reduce the severity of nicotine withdrawal symptoms and also the severity and frequency of cravings for a cigarette. The dosing guidelines for each medication are based on the doses selected for the clinical trials. However, it is clear that there are large individual differences in dependence and that the standard dose of some medications, particularly the intermittently administered medicines like nicotine gum, inhaler, etc., may not be sufficient to minimize withdrawal symptoms and cravings. This is likely part of the reason why 4 mg gum often has better smoking cessation outcomes than 2 mg, and why the patch plus another NRT has better outcomes than the patch alone. So, it appears that, particularly for more addicted smokers, it is important to ensure that they are using enough pharmacotherapy to adequately treat withdrawal symptoms and cravings.
   Figure 36.4 is from Foulds et al 2013[34] and shows the severity rating of the withdrawal symptom "feeling restless" in participants in 8 randomized double-blind placebo-controlled trials of varenicline for smoking cessation, with 2,403 randomized to varenicline and 1,434 to placebo. It shows that for smokers attempting to quit on placebo, restlessness peaked at week 1 and had returned to baseline by week 4, and was significantly lower in smokers randomized to use varenicline. Similar effects were found for depressed mood, irritability, anxiety, and difficulty concentrating, and these results are consistent with other similar studies (although this is the largest placebo-controlled analysis of individual nicotine withdrawal symptoms over time).
   Given that nicotine withdrawal symptoms have largely resolved within four to six weeks after the target quit date, this is the time frame in which both pharmacological and social support should be focused. This is not to say that these treatment components are not needed after six weeks (they certainly are), but many smokers relapse and give up on their quit attempt within the first few weeks due to the severity of withdrawal and craving in those first few weeks.
3. **Novel pharmacotherapies, not yet approved by FDA for smoking cessation**. No new smoking cessation drugs have been approved in the United States for over ten years. The non-approved medication with the best evidence to date is called "Cytisine" and is actually the drug on which varenicline was originally based. Cytisine is a plant-based alkaloid with a very similar mechanism of action to varenicline and has been used for decades in Eastern Europe. Trials in Poland and New Zealand suggest a similar efficacy to varenicline,[35, 36] and a U.S. trial is ongoing.
4. **Non-smoked nicotine delivery products classified in the United States as "tobacco products."** In the U.S. regulatory system, many tobacco products are allowed on the market subject to marketing approval from the FDA – Center for Tobacco Products. These products are not allowed to make therapeutic claims (for that, they would need to



Significant difference $P<0.0001$ between varenicline and placebo at all post-baseline time points.
Figure based on observed mean values; statistical analysis based on multivariate repeated measures model controlling for baseline, visit, and treatment by visit interaction

FIGURE 36.4 Mean ratings of restlessness at baseline and then up to 11 weeks after attempting to quit smoking, while using e ither varenicline (n = 2,403) or placebo (n = 1,434) in randomized double-blind clinical trials. (From West, R. et al., ***Addiction***, 93(7), 1007–1011, 1998.)

apply via the "therapeutics" part of FDA), but once they have marketing authorization, they can then apply for "modified risk" status, which would allow them to use labeling stating that they have lower health risks than cigarettes or other products. Although these products are not allowed to make claims about smoking cessation, there is evidence that some can function in a very similar manner to nicotine replacement therapy (e.g., snus smokeless tobacco, nicotine pouches, and electronic cigarettes). The product in this category with the strongest evidence for smoking cessation efficacy is electronic cigarettes.

Electronic cigarettes (or "e-cigs") are electronic devices that transform a liquid containing nicotine into an aerosol that is inhaled via a mouthpiece. The aerosol contains chemicals such as glycerin and propylene glycol in addition to additives and nicotine. They deliver far lower levels of harmful toxicants than cigarettes, but the long-term health effects are not known.[37] A recent Cochrane review of their efficacy for smoking cessation found significant positive effects on smoking cessation as compared with NRT, placebo, and no treatment.[38] Their use for smoking cessation remains controversial, and although they are not yet considered as "first-line" treatments, a patient who wants to try them or who has already succeeded in quitting smoking by switching to an e-cig should not be strongly discouraged. They should be congratulated for quitting smoking and offered assistance to withdraw from e-cig use when they feel ready.

5. **Assessment of non-cigarette nicotine product use and dependence**

As mentioned earlier, the use of alternative tobacco products such as snus, nicotine pouches, heat-not-burn cigarettes, and electronic cigarettes is becoming more common, particularly among young people. For some of these products, the FDA has already determined that they are likely much less harmful than cigarettes and has authorized modified risk claims (e.g., General Snus, Iqos "heat-not-burn" cigarettes, and VLNC reduced nicotine cigarettes). However, for most of these products, the long-term risks are uncertain, and generally, it would be wise for users to consider quitting when they feel ready and confident that they will not relapse to combustible tobacco use. However, there may be a challenge in assessing how dependent the patient is on these alternative products. It was partly for this reason that dependence assessment questionnaires have been developed for use with any nicotine product. One example is the Penn State Nicotine Dependence Index (PSNDI),[39] which has been widely used to assess cigarette and electronic cigarette dependence and can easily be adapted for other products by simply replacing the word "cigarette" with the appropriate product name in the questions.

The cigarette version of the PSNDI was found to be at least as predictive of short-term cessation success as the Fagerstom Test for Cigarette Dependence in a controlled trial of group treatment plus NRT for smoking cessation.[14] As shown in Figure 36.5, those with a baseline PSCDI score of 0–10 were about three times as likely to be cigarette abstinent a month later as compared to those smokers with a baseline PSCDI score of 15–20.

Scores on the electronic cigarette version of this questionnaire[39] were found to be correlated with the concentration of nicotine being used in the liquid in electronic cigarettes and to predict which electronic cigarette users had quit using e-cigs a year later,[40,41] suggesting construct validity of the measure for e-cig users. Those allocated to a high dose e-cig (36 mg/ml) in a double-blind randomized controlled trial had higher Penn State Electronic Cigarette Dependence Index (PSECDI) scores after six months than those randomized to zero or 8 mg/ml, which also supports the validity of the questionnaire.[42] The PSECDI has shown good internal consistency[43] and test-retest reliability after a month (+0.78),[42] and correlates highly (around +0.7) with other measures of e-cig dependence.[44] The PSECDI questions are shown in the table.

Penn State Electronic Cigarette Dependence Index (PSECDI)

1. How many times per day do you usually use your electronic cigarette* (*assume that one "time" consists of around 15 puffs or lasts around 10 minutes*) times

(Scoring: 0–4 times/day = 0, 5–9 = 1, 10–14 = 2, 15–19 = 3, 20–29 = 4, 30+ = 5)

2. On days that you can use your electronic cigarette freely, how soon after you wake up do you first use your electronic cigarette?* minutes

(Scoring: < 5 minutes = 5, 6–15 = 4, 16–30 = 3, 31–60 = 2, 61–120 = 1, 121+ = 0)

3. Do you sometimes awaken at night to use your electronic cigarette? +

(Scoring: Yes = 1, No = 0)

4. If yes, how many nights per week do you typically awaken to use your electronic cigarette? +

(Scoring: 0-1 nights = 0, 2-3 nights = 1, 4+ nights = 2)

5. Do you use your electronic cigarette now because it is really hard to quit (using e-cigs)? ♦

(Scoring: Yes = 1, No = 0)

6. Do you ever have strong cravings to use your electronic cigarette? ♦

(Scoring: Yes = 1, No = 0)

7. Over the past week, how strong have the urges to use your electronic cigarette been? •

(Scoring: None/Slight = 0, Moderate/Strong= 1, Very Strong/Extremely Strong = 2)

8. Is it hard to keep from using your electronic cigarette in places where you are not supposed to? ♦

(Scoring: Yes = 1, No = 0)

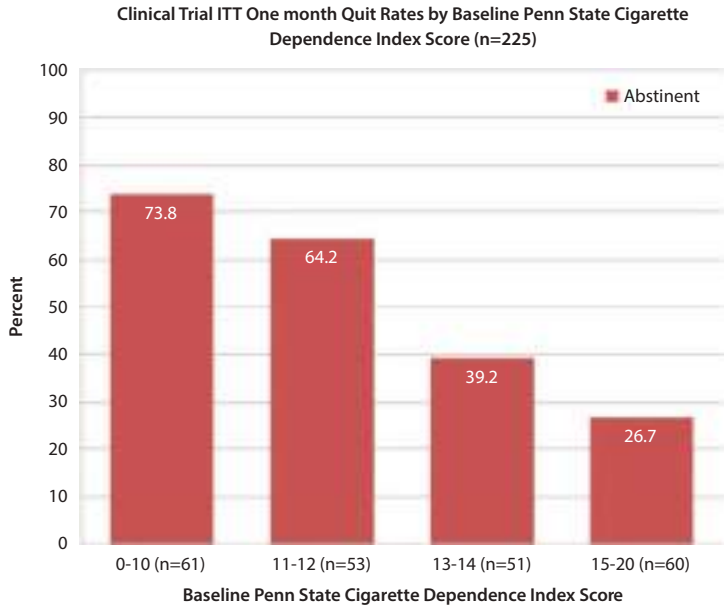


FIGURE 36.5 One-month cigarette abstinence rates (eCO-verified) in smokers participating in group treatment plus transdermal nicotine patches, by baseline score on the Penn State Cigarette Dependence Index.[14, 39]

When you haven't used an electronic cigarette for a while or when you tried to stop using.…

9. Did you feel more irritable because you couldn't use your electronic cigarette? ♦

(Scoring: Yes = 1, No = 0)

10. Did you feel nervous, restless, or anxious because you couldn't use your electronic cigarette? ♦

(Scoring: Yes = 1, No = 0)

Total score indicates dependence as follows: 0–3 = not dependent, 4–8 = low dependence, 9–12 = medium dependence, 13 or more = high dependence

While some of the older tobacco products have known health risks and can reasonably be treated much like cigarettes (e.g., cigars), for other, newer products, the picture is less clear. However, some of the large-scale smoking cessation treatment providers, such as telephone quitline vendors and other research organizations, have gained experience helping other product users to quit, and initial trials have been published. For example, Truth Initiative has recently published a large randomized trial showing efficacy of a fully automated text messaging program for vaping cessation that delivers social support and behavioral coping skills training, as compared with a no-treatment control group, among young[18–24] e-cig users (24.1% vs. 18.6% at seven months).[45]

36.10 CONCLUSION

Tobacco smoking remains the single biggest cause of premature death in high-income countries, causing an average loss of ten years of life for continuing smokers. Quitting smoking by age 35 can avoid the vast majority of the health effects from smoking. The primary reason people continue to smoke despite awareness of the health risks is addiction to nicotine. All patients should be asked about their nicotine product use and if they are smoking, provided with clear advice on the health benefits of quitting and available treatments. Dependence can be assessed with just a few questions, and smokers can be assisted to quit with counseling and evidence-based pharmacotherapy. Smokers treated with intensive pharmacotherapy and counseling are four times more likely to quit smoking long term and less likely to die in the next 15 years.[46] Non-combusted tobacco products are significantly less harmful to health than cigarettes, and switching to these from smoked products will likely reduce health risks. If a clinician does not have the time or expertise to provide tobacco counseling, then providing brief advice and referral to specialist counseling (which could include the national quitline) is still a very worthwhile intervention. These interventions should be continued and repeated as necessary within a chronic care model for tobacco dependence treatment.

KEY CLINICAL POINTS

- Tobacco dependence treatment is an extremely cost-effective, life-saving intervention.
- Every patient should be ASKed about their use of nicotine products.
- Smokers should be ADVISEd about the health benefits of quitting and offered effective treatments.
- Dependence on tobacco products can be ASSESSed with a few questions.
- Intensive counseling and pharmacotherapy quadruple the chances of long-term cessation as compared with usual care, and even brief interventions can ASSIST patients to quit.

- A chronic care model for tobacco treatment should be used, with follow-ups ARRANGEd and the intensity of the intervention increased and repeated if necessary.

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37 The Role of Integrative Medicine in Cancer Prevention and Survivorship

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KEY POINTS

- Understanding of Integrative, Complementary and Alternative Medicine therapies
- Regulatory and quality differences between prescription medication and dietary supplements
- Review of the clinical evidence regarding the use of dietary supplements for cancer treatment and prevention
- Summary of the clinical research on the use of mind body practices (ex. Meditation) and acupuncture, massage, music therapy, and yoga
- Acupuncture is another safe and effective therapy that has been shown to be beneficial for symptoms of pain and nausea.

37.1 INTRODUCTION

Integrative, Complementary, and Alternative Medicine (ICAM) has become increasingly popular in Western medicine. According to the National Center for Complementary and Integrative Health (NCCIH), "if a non-mainstream approach is used together with conventional medicine, it's considered complementary," while "if a non-mainstream approach is used in place of conventional medicine, it's considered alternative."[1] Meanwhile, integrative medicine intertwines complementary and conventional medicine and emphasizes the use of multimodal approaches to treat the entire person in an evidence-based manner.[1] While some people use alternative medicine alone, this is backed by very little evidence-based research. This chapter concentrates on integrative medicine, or the use of complementary medicine modalities with Western medicine, focusing solely on evidence-based clinical research. The NCCIH divides ICAM modalities into three main categories: nutrition, psychological, and physical. Nutrition approaches focus on food as medicine and encompass special diets, dietary patterns, and natural products (i.e., dietary supplements such as vitamins, minerals, herbs, and botanicals). Psychological aspects include mindfulness and spirituality, while physical modalities include massage and spinal manipulation, and increasingly popular is the combination of psychological and physical approaches known as mind and body practices, including acupuncture, massage therapy, mindfulness, meditation, music therapy, and yoga (see Figure 37.1).[1]

The use of ICAM has become increasingly popular. According to the 2012 National Health Interview Survey, 59 million Americans over the age of 4 used at least one complementary health approach, equating to 30.2 billion dollars in out-of-pocket expenses.[2] Dietary supplements and yoga appeared to be the most popular modalities in 2017, with 57.6% and 14.2% of adults reporting their usage, respectively.[3,4] Cancer patients and survivors in particular increasingly look to ICAM in attempt to decrease recurrence, manage the side effects of treatment, and manage and treat other comorbidities.[5] More specifically, approximately one-third of cancer patients reported using ICAM in the last 12 months in 2019, with herbal supplements being the most commonly used modality. Of the cancer patients using ICAM, 29.3% did not disclose their ICAM use to their physicians.[6] This high use of herbal supplements, in combination with lack of disclosure to their healthcare providers, is worrisome not only because dietary supplements are not thoroughly regulated, and thus may have quality and safety issues, but also because many have drug interactions and the potential for negative outcomes. Therefore, it is important for physicians to discuss ICAM with their patients to ensure they are using ICAM in safe and effective ways. This also requires educating physicians on the various ICAM modalities, such as their safety, efficacy, and effects on the body and on other conventional treatments. Additionally, further research needs to be done to determine the mechanisms, effectiveness, safety, side effects, and treatment interactions for each modality.[1] A list of evidence-based research sources of various ICAM modalities can be found in Table 37.1. Dietary approaches will be covered in another chapter, while this chapter will focus mainly on the dietary supplements category within nutrition and mind and body practices.

37.2 DIETARY SUPPLEMENTS

The Dietary Supplement Health and Education Act (DSHEA) of 1994 states that dietary supplements are intended to be taken by mouth, contain one or more dietary ingredients or their constituents, supplement the diet, and are clearly labeled on the front panel as being a dietary

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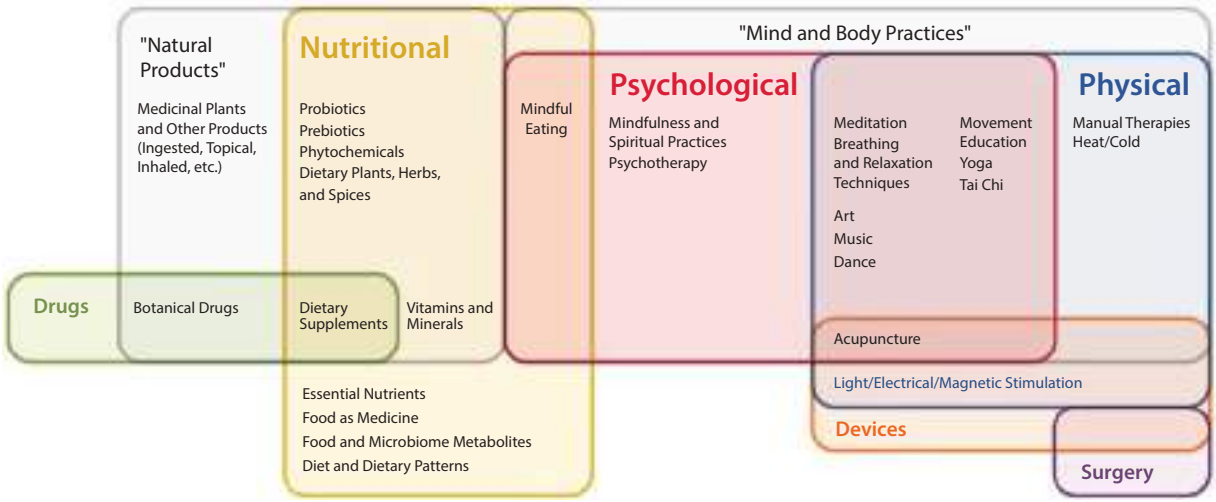


FIGURE 37.1 Examples of complementary health approaches that fall within the categories: Psychological, Physical, and Nutritional. (From Complementary, Alternative, or Integrative Health: What's In a Name? www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name. Updated April 2021. Accessed April 22, 2022.)

TABLE 37.1
Evidence-Based Research Sources of ICAM Modalities

Organization	URL
American Cancer Society	www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/index
The Center for Mind–Body Medicine	https://cmbm.org/about/
Cochrane Review Organization	www.cochrane.org
Linus Pauling Micronutrient Information Center	http://lpi.oregonstate.edu/infocenter/
Memorial Sloan-Kettering Cancer Center – About Herbs, Botanicals & Other Products	www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
Natural Medicines Database	https://naturalmedicines.therapeuticresearch.com/
NIH	www.cancer.gov/camwww.nccih.nih.gov/health/herbsataglancehttps://ods.od.nih.govwww.cancer.gov
University of Texas MD Anderson Cancer Center Complementary/Integrative Medicine Education Resources	www.mdanderson.org/CIMER

supplement.[7] Unlike prescription drugs, which are marketed as disease modifying and must be proven safe and effective for intended use before being marketed, dietary supplements are not allowed to have claims of any disease modifying components and do not require the same level of premarket review and approval.[8] Under DSHEA, the federal government is not required to approve dietary supplements for safety or efficacy before they are sold on the market. Instead, the federal government is responsible for monitoring the marketplace for unsafe dietary supplements and products making misleading claims, which means that Food and Drug Administration (FDA) regulation is mostly post-market.[7,–10]

In 2019, 35.8% of cancer patients reported using herbal supplements in the last 12 months.[6] Different than many other ICAM modalities, dietary supplements run the risk of causing biological harm via potential lack of quality control of the products, metabolic and immunologic interactions, drug interactions, organ damage and toxicity, and potential tumorigenesis and cancer growth. Thus, more regulation and quality control on the dietary supplement industry needs to be instituted, in addition to further scientific research on their mechanisms of action and effects on cancer prevention, initiation, growth, and treatment. Currently, there is a lack of data, as well as mixed data, in the realm of dietary supplement research, particularly as it applies to cancer prevention and survivorship. The following section outlines dietary supplements with peer-reviewed clinical research, focusing on randomized controlled clinical trials and large meta-analyses specific to cancer outcomes.

37.2.1 Calcium

Calcium is the most widely used mineral supplement,[11] yet the data remain somewhat mixed regarding calcium and cancer prevention. One large randomized clinical trial

consisting of 2,303 women found that calcium supplementation does not significantly decrease cancer risk.[12] This is in alignment with the Women's Health Initiative, a double-blind placebo-controlled study of 36,282 postmenopausal women, which found calcium supplementation to have no significant effects on the risk of developing colorectal, breast, or total invasive cancers.[13] Conversely, two meta-analyses found calcium supplementation to lead to a decrease in colorectal adenoma (precancerous polyps) and colorectal adenoma recurrence risk.[14,15] In regard to colon cancer incidence, one meta-analysis found calcium supplementation to reduce the risk of colorectal cancer,[11] while another meta-analysis showed that calcium supplementation has a ten-year lag before intake has an effect on colorectal cancer prevention, which could contribute to the variable data.[16] Before further conclusions can be drawn, more randomized controlled clinical trials need to be done to determine calcium's role in cancer prevention, specifically as it pertains to colorectal cancer, as the data remain mixed.

37.2.2 Curcumin

Curcumin is a compound that comes from a natural root spice, turmeric (*Curcuma longa*), which is part of the ginger family. It has been associated with antioxidant and anti-inflammatory properties.[17] It has been studied for several different cancer types with variable results. A double-blind randomized controlled study of 36 patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) found that curcumin may reduce light chain proteins and random urinary protein concentrations, suggesting that it may decrease the risk of disease progression.[18] Two randomized clinical trials studied curcumin's effects on oral potentially malignant disorders. One study consisting of 223 patients with oral leukoplakia found 3.6 g/day of curcumin supplementation over six months to have a positive clinical response (67.5% vs. 55.3%),[19] while the other, consisting of 60 patients, found a positive clinical response in those receiving a combination of curcumin and green tea supplements (65%) but no significant benefits in the patients solely taking 950 mg/day of curcumin for three months (55%).[20] A prospective phase II clinical treatment trial of pancreatic cancer found that 2,000 mg of curcumin supplementation per day in addition to gemcitabine therapy produced a better response rate in advanced pancreatic cancer patients compared with historical data.[21] Another study of 25 patients with advanced pancreatic cancer found that treatment with 8 grams of daily oral curcumin generated a clinical response in 2 of the patients, in one of whom it was sustained for >18 months.[22] A randomized double-blind pilot study on muscle-invasive bladder cancer found that 180 mg/day of curcumin supplementation during chemotherapy produced no significant changes.[23] Curcumin has also been studied to reduce side effects and improve quality of life. A study of curcumin given during radiation reported a reduction in radiation-related dermatitis in breast cancer patients.[17] Another randomized double-blind placebo-controlled study of 80 patients with solid tumors undergoing chemotherapy found that 180 mg/day of curcumin supplementation over eight weeks improved quality of life and suppressed systemic inflammation.[24]

The data relating to curcumin and prostate cancer remain mixed. One random double-blind placebo-controlled study of 82 men with prostate cancer on intermittent androgen deprivation therapy found that 1,440 mg/day of curcumin supplementation over six months did not lead to significant changes in time off from androgen deprivation therapy, but did lead to fewer patients with prostate-specific antigen (PSA) elevation during curcumin therapy,[25] while another study found that 120 mg/day of curcumin supplementation three days before and during radiotherapy produced no significant differences in tumor response or in side effects.[26] Similarly, another randomized phase II study of men with metastatic castration-resistant prostate cancer found that 6 g/day of oral curcumin supplementation for seven days every three weeks, in addition to docetaxel, had no significant effects;[27] thus, more research needs to be done on curcumin and prostate cancer before conclusions can be drawn, as data remain mixed, and dosage in many of the studies is stratified. A review on curcumin found that it may cause disease stabilization in advanced pancreatic, biliary, and colon cancers.[28] Further large randomized clinical trials on curcumin's effects on cancer prevention, interaction with cancer treatments, effects on treatment-related symptoms, and dosing studies need to be done before it can be recommended.

37.2.3 Ginger

Ginger (*Zingiber officinale*) is a common spice used for culinary and medicinal purposes.[29] While there are no substantial studies demonstrating ginger's antitumor effects, it has been shown to serve an antiemetic function by increasing gastric tone, motility, and emptying;[30] thus, ginger supplements have been associated with decreased nausea and vomiting severity in breast cancer patients.[31,32] A study examining 576 adult cancer patients found 0.5–1.0 g of ginger supplementation to have the greatest reduction in acute nausea severity related to chemotherapy.[33] The American Society of Clinical Oncology (ASCO) states that based on the Society for Integrative Oncology's (SIO) guidelines, ginger can be considered as an adjunct to antiemetic pharmacology for nausea and vomiting during chemotherapy (Grade C).[34]

37.2.4 Ginseng

Korean red ginseng (KRG) is a product of ginseng (*Panax ginseng*), a vegetable root. The main therapeutic effects come from ginsenosides, a group of phytochemicals that inhibit cell proliferation and migration, as well as angiogenesis, and can reverse drug resistance.[35] In a phase III

double-blind randomized clinical trial consisting of 436 colorectal cancer patients receiving chemotherapy, cancer-related fatigue was significantly reduced in the treatment arm taking 2,000 mg/day of KRG compared with the placebo.[36] Another double-blind randomized trial of 364 fatigued cancer survivors found 2,000 mg of Wisconsin ginseng (*Panax quinquefolius*) to significantly decrease fatigue over eight weeks.[37] In a double-blind randomized clinical trial of 55 premenopausal women with gynecological cancer, 3 g/day of KRG decreased the sexual complaints after gynecological surgery but did not significantly decrease menopausal symptoms compared with the placebo group.[38] The ASCO states that based on the SIO guidelines, ginseng can be considered to improve fatigue during treatment (Grade C).[34]

37.2.5 Green Tea

The main component implicated in green tea's (*Camellia sinensis*) therapeutic effects is epigallocatechin gallate (EGCG) due to its potential to promote antioxidant activity, inhibit angiogenesis, downregulate oncogenes, and upregulate tumor suppressor genes, though molecular mechanisms remain unclear.[39] Two meta-analyses on breast cancer and green tea consumption found risk decreased by 15–27%.[39, 40]A phase II randomized controlled trial found high doses of green tea extract (750 mg/m^2 and 1,000 mg/m^2) to have higher clinical response rates in patients with high-risk oral premalignant lesions compared with the placebo arm over 12 weeks.[41]A phase II randomized controlled trial of 60 men at high risk of developing prostate cancer suggested that 3 daily treatments of 200 mg of green tea catechin capsules can have up to 90% efficacy in chemoprevention.[42] However, another phase II clinical trial found that 6 g of oral green tea per day increased PSA levels in 43% of the men studied and produced green tea–related toxicities, such as diarrhea, nausea, and insomnia, in 69% of the patients.[43] Additionally, evidence exists that EGCG may antagonize bortezomib, a chemotherapeutic used to treat myeloma and some lymphomas, as well as reports of hepatoxicity.[28, 44] While some studies have shown green tea to have promising results, data still remain inconsistent; thus, further studies examining its long-term effects, interactions with chemotherapeutics, and effects on other cancer types are needed.

37.2.6 Lycopene

Lycopene is a carotenoid and antioxidant found in some vegetables and fruits, such as tomatoes, watermelon, and papayas. Proposed mechanisms include scavenging reactive oxygen species (ROS), upregulation of detoxifying systems, disrupting the cell cycle, and altering signal transduction.[45] Supplementation has been associated with prostate cancer prevention via decreasing PSA levels and inflammatory markers,[46–49] ultimately leading to a 20–45% reduction in prostate cancer risk.[50] One phase II clinical trial of 13 men with advanced castrate-resistant adenocarcinoma of the prostate found that 30 mg/day of lycopene supplementation and 75 mg/m^2 of docetaxel every 21 days could lead to a 50% reduction in PSA levels, suggesting that lycopene can be an adjunct to chemotherapy.[51] Another double-blind randomized phase II trial of 84 men with low-risk prostate cancer found that while 30 mg/day of lycopene supplementation had no effect on prostate gene expression, it did modulate the metabolism of androgen, estrogen, and arachidonic acid, as well as modulating Nrf-2 mediated oxidative stress.[52] Another phase II randomized clinical trial of 26 men with prostate cancer found that 30 mg/day of lycopene supplementation three weeks before prostatectomy may decrease the growth of prostate cancer, though the results were not statistically significant, and the sample size was small.[53] Other phase II clinical trials have found 30 mg/day of lycopene supplementation to have no clinical benefits on prostate cancer.[54–56] Due to the relatively small sample sizes and variable results, further research needs to be done before conclusions can be drawn in order to be able to determine the therapeutic effect and mechanism of action.

37.2.7 Melatonin

Melatonin is a hormone responsible for sleep-wake cycles. A randomized double-blind clinical trial found that 20 mg of melatonin before and during the first cycle of adjuvant chemotherapy for breast cancer might have a neuroprotective effect on cognitive function in 36 women over a ten-day period.[57] One review on melatonin as an adjunct to chemotherapy found improvements in tumor remission and one-year survival, and decreases in radiation and chemotherapy side effects, such as thrombocytopenia, neurotoxicity, nausea, vomiting, and fatigue.[58] Another review included clinical trials of melatonin with chemotherapy and in supportive care scenarios.[59] However, the majority of these studies come from a single institution in Italy, and the randomized chemotherapy treatment trials have been limited in size, thus making the results difficult to interpret. More research with larger clinical trials needs to be done to determine melatonin's true efficacy.

37.2.8 Omega-3 Fatty Acids/Fish Oils

Omega-3 fatty acids are essential fatty acids that cannot be synthesized by the body and therefore, must be consumed in the diet via whole food sources or supplementation. Two specific types of long chain omega-3 fatty acids found in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Some studies have shown that they may have antitumor activity. For example, one phase II double-blind randomized clinical trial consisting of 84 men with low-risk prostate cancer found that 3 g of fish oil containing EPA and DHA can modulate the metabolism of androgen, estrogen, and arachidonic acid, in addition to modulating Nrf-2 mediated oxidative stress, though it had no effect on prostate gene expression.[52] However, other

studies have shown that another omega-3 fatty acid, 16:4 (n-3) (hexadeca-4,7,10,13-tetraenoic), found in commercial fish oil supplements may antagonize platinum compounds in some chemotherapeutics.[28] Two reviews of omega-3 fatty acids and breast cancer point to an association between high omega-3 fatty acid consumption and/or a high omega-3:omega-6 fatty acid ratio in the diet and a decreased risk of breast cancer of up to 27%.[60,61] In addition, two other studies indicate that EPA and DHA may have antitumor activity in lung, breast, prostate, and colorectal cancers.[28,52] Adequate levels of omega-3 fatty acids can be achieved by including fish in the diet; thus, fish oil and EPA/DHA supplements should be avoided until more research is done.[28]

37.2.9 Pomegranate

Pomegranate (*Punica granatum*) contains polyphenols, which have been shown to have antioxidant and anti-inflammatory properites.[29] Pomegranate extract has been a major subject of study in men with prostate cancer. A phase II study involving 46 men with rising PSA after surgery or radiotherapy found that 8 ounces of daily pomegranate juice can increase the average PSA doubling times from 15 to 54 months, lead to a 12% decrease in cell proliferation, increase apoptosis by 17%, increase serum nitric oxide by 23%, and significantly reduce oxidative states, leading to overall better outcomes.[62] Similar results were found in another phase II study that found PSA doubling time to be longer in men with recurrent prostate cancer taking both low and high doses (1 g and 3 g, respectively) of pomegranate extract compared with placebo group over a six-month period.[63] This is in contrast with a phase II double-blind randomized controlled trial involving 98 men with prostate cancer that found no significant differences in PSA doubling times between men drinking 500 mL and then 250 mL of daily pomegranate juice over eight weeks and those in the control arm,[64] and with a double-blind randomized study that found no difference in PSA doubling times, oxidative stress biomarkers, and other markers of prostate cancer between men taking 2,000 mg of PomX, which contains 1,200 mg of polyphenol from pomegranate extract (equal to 16 oz of pomegranate juice), and the control arm.[65] While some studies have shown promising data for men at high risk of developing prostate cancer or those with prostate cancer, others have shown pomegranate juice and/or extract to have no effect; thus, it needs to be examined further before definitive conclusions can be drawn.

37.2.10 Probiotics

Probiotics are live organisms that can be consumed via whole food sources or supplementation. They can alter the gut microbiome and intestinal flora, strengthen the bowel epithelial barrier, change the pH of the intestines, and modulate the immune system.[66] Probiotics have been implicated in reducing post-operative side effects in patients with colorectal cancer. A randomized double-blind controlled study was stopped early due to the efficacy of LactoLevure by Unipharm, a four-strain probiotic regimen, which improved post-operative complications such as pneumonia, surgical site infections, and anastomotic leakage as well as reducing time of hospital discharge.[67] This is consistent with other controlled trials that found a three-strain eight-culture probiotic containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus*, BIO-THREE by Toa Pharmaceuticals, and HEXBIO by B-Crobes to decrease surgical site infections,[66,68] promote normal gut function, and decrease the time in the hospital after colorectal cancer surgery.[66,69] Additionally, a randomized clinical trial of 30 metastatic renal cell carcinoma patients found that *Clostridium butyricum* may improve clinical outcomes when used as an adjunct to nivolumab and ipilimumab therapies.[70] Research regarding probiotics and colorectal cancer treatment-related side effects appears promising, though the best probiotic strain and dose remain unclear.

37.2.11 Selenium

Selenium is a trace mineral found in whole food sources, such as Brazil nuts, seafood, and organ meats, but can also be taken as a supplement.[71] SELECT, a double-blind randomized controlled trial looking at over 35,000 men for prostate cancer prevention, found 200 µg/day of oral selenium supplementation to have a 1.09 hazard ratio risk of prostate cancer, which was not statistically significant.[72] There have been no other large randomized clinical trials looking at selenium's effects on prostate cancer or any other types of cancer; thus, more research is warranted.

37.2.12 Soy

Soy, which contains isoflavones, has been widely consumed in Asian cultures for centuries and has been associated with positive health benefits, such as decreased heart disease and type 2 diabetes.[29] One phase II study of 41 men with high PSA levels found that 100 mg of oral soy isoflavone per day can lead to stabilization of PSA.[73] Meanwhile, a randomized placebo-controlled study of 140 women with early-stage breast cancer found soy protein supplementation to negatively alter gene expression of cell cycle transcripts that promote cell proliferation, thus raising concern that soy could potentially negatively impact breast cancer progression.[74] A meta-analysis of 14 cohorts or case-controlled studies on soy and soy isoflavones found a 26% decreased risk of prostate cancer in those with a high soy intake.[75] For women with breast cancer or at risk for breast cancer, current studies do not indicate any significant risk with dietary soy in moderation.[76, 77] The ASCO states that based on the SIO guidelines, soy is not recommended to improve hot flashes in breast cancer patients due to the lack of effect (Grade D).[34] Further research on soy and soy isoflavones' effects on different cancer types needs to be done, as its impacts may be cancer type specific.

37.2.13 Vitamin A/β-Carotene

β-carotene is a precursor of Vitamin A (or a provitamin A carotenoid), which is found in foods such as carrots, tomatoes, and leafy green vegetables.[78] The results of a large double-blind randomized controlled trial known as ATBC, which consisted of over 29,000 male smokers, found a higher incidence of lung cancer in those taking β-carotene supplements and an 8% increase in total mortality.[79] Similarly, CARET, a randomized double-blind controlled trial of over 18,000 smokers and workers exposed to asbestos, found those taking β-carotene and retinol (Vitamin A) supplements to have a 1.28 increased relative risk of lung cancer compared with the placebo arm and a 1.46 increase in relative risk of death from lung cancer, forcing the trial to be stopped 21 months earlier than intended.[80] One small study in pediatric leukemia and lymphomas treated with high-dose methotrexate noted a possible reduction in drug-induced D-xylose malabsorption but no other side effects.[81] Additionally, a meta-analysis of dietary supplements and primary prevention trials found that Vitamin A supplementation is associated with a 16% increased risk for overall cancer incidence.[11] However, several meta-analyses on carotenoids and breast cancer have found that high serum β-carotene levels and increased dietary intake and supplementation are associated with 17–30% reduction in breast cancer,[82–84] while others found an increased risk of disease progression and death[85] or overall inconclusiveness.[86] The U.S. Preventative Services Task Force advises against the use of β-carotene supplements for the prevention of cancer, as β-carotene is associated with a negative effect on lung cancer incidence, especially in high-risk populations.[87]

37.2.14 Vitamin B

Vitamin B is a broad term for eight B vitamins, including B6 (pyridoxine), B9 (folate), and B12 (cobalamin), which have been studied in relation to cancer. A large randomized clinical trial consisting of over 2,500 participants, known as B-PROOF, found a significant increase in colorectal cancer in patients taking B9 and B12 supplements.[88]Additionally, a large trial consisting of 1,134 breast cancer patients using B12 supplements both before and during treatment found that their use was significantly associated with poorer disease-free survival and overall survival.[89] On the other hand, a large randomized trial of 5,442 women at high risk for cardiovascular disease found no significant effect on overall risk of total invasive cancer or breast cancer in those taking combined Vitamin B6, folate, and B12 supplements.[90] A meta-analysis of Vitamin B9 found that it was associated with a 18% decreased risk in developing hormone receptor negative breast cancer, and that supplementation was associated with a 55% decreased risk in those with the *BRCA1* mutation.[78] It should also be noted that anti-folate therapies (methotrexate and pemetrexed) are commonly utilized as a cancer treatment, and supplementation with folate during such treatment would potentially impact the efficacy of these therapies. Because the data on B vitamins remain mixed and are highly specific to the different types of Vitamin B, more research needs to be done before conclusions can be drawn.

37.2.15 Vitamin C

Vitamin C, or ascorbate, is commonly found in citrus fruits and taken as a dietary supplement. Two double-blind randomized controlled trials consisting of 100 and 150 patients, respectively, looked at the effects of Vitamin C on advanced cancer. Both found high-dose (10 g) oral Vitamin C to have no effects on advanced cancer in terms of symptoms, performance status, appetite, weight, disease progression, or survival, suggesting that Vitamin C has no effect on advanced malignant cancers.[91,92] Several studies have looked at the effects of intravenous Vitamin C on cancer, though intravenous Vitamin C is not considered a dietary supplement, and the data are limited and mixed.[93,94] Thus, there is still a need for large double-blind randomized clinical trials.

37.2.16 Vitamin D

Vitamin D is a hormone that requires sunlight exposure for synthesis and is well known for its role in calcium metabolism.[28] A large randomized clinical trial of 2,303 post-menopausal women showed that Vitamin D supplementation had no effect on breast cancer risk,[12] while a meta-analysis on Vitamin D and breast cancer found Vitamin D supplementation to be associated with a decreased risk of breast cancer and that deficiency is associated with increased risk.[95] A more recent study of Vitamin D supplement, called the Vitamin D and Omega-3 Trial (VITAL), with over 25,000 participants showed no benefit in regard to cancer risk.[96] Calcitriol, the active metabolite of Vitamin D, has inconclusive data, but a summary of studies points to no effects on tumor growth.[28] However, it should be used cautiously, if at all, concurrently with chemotherapeutics like docetaxel, as the incidence of toxicity, such as gastrointestinal issues (nausea, vomiting, diarrhea, constipation, etc.), febrile neutropenia, and pneumonia, was found to be increased.[97] Further studies on Vitamin D and its metabolites need to be done before decisive conclusions can be drawn, although if patients are deficient in Vitamin D, supplementation is reasonable.

37.2.17 Vitamin E

Vitamin E, or α-tocopherol, is an antioxidant found in foods such as nuts, seeds, and plant-based oils. SELECT, a double-blind randomized controlled trial looking at prostate cancer prevention that included over 35,000 men, found Vitamin E supplementation to result in a 1.6-fold increase in relative risk of prostate cancer and a 1.17 hazard ratio, which were both statistically significant.[72] Another large double-blind randomized controlled trial involving Vitamin

E supplementation and lung cancer in over 29,000 male smokers found no reduction in incidence in lung cancer, but did find fewer cases of prostate and colorectal cancers and more cases of bladder, stomach, and other cancers in the supplementation group over the placebo, leading the group to conclude that Vitamin E has no beneficial effects on lung cancer prevention.[79] Similarly, a randomized controlled double-blind study of over 39,000 women found Vitamin E to have no significant effect on breast, lung, colon, or total cancer incidence, death, or total mortality.[98] The U.S. Preventative Services Task Force advises against the use of Vitamin E supplements for the prevention of cancer, as it has no known effects on cancer prevention.[87]

37.3 SUMMARY: DIETARY SUPPLEMENTS

In conclusion, while some dietary supplements may have the potential for cancer prevention or antitumor effects, the majority have inconclusive data, mixed data, or potentially harmful effects on tumor development and growth, as well as drug interactions that can negatively impact chemotherapy. Additionally, not all dietary supplements are created equal. Under DSHEA, manufacturers are primarily responsible for ensuring the safety, proper labeling, and truthful claims for dietary supplements.[7,9] Thus, overall compliance with DSHEA law prior to marketing a product falls on the manufacturer, which is a potential reason why there may be issues/concerns with the quality and safety of dietary supplements that have been improperly manufactured. Because of these factors, physicians should be aware of the effects of popular dietary supplements on cancer and chemotherapeutics and discuss the use of dietary supplements with their patients to prevent any potential negative outcomes, especially when referencing β-carotene, Vitamin E, and potentially Vitamin B12, as these have been shown to cause substantial harm to cancer patients.[87–89]

37.4 MIND AND BODY PRACTICES

According to the NCCIH, "Mind and body practices are a large and diverse group of procedures or techniques that are administered or taught by a trained practitioner or teacher."[99] These include massage therapy, acupuncture, yoga, and music therapy. Despite these practices having small risk profiles, the data on their effects on cancer prevention is negligible and therefore not included in the following paragraphs. While survivorship studies exist, they are somewhat limited. Their data are summarized in the remainder of this chapter, as well as grades given to each modality that are endorsed by the ASCO based on the SIO guidelines that specifically focus on breast cancer patients (Table 37.2).

Mind and body practices are mainly used to control stress and for symptom management. The reduction of stress can not only be essential to improve patients' quality of life but can also play a role in cancer growth and progression, which can be exacerbated by chronic stress via the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. For example, increased levels of norepinephrine and cortisol can promote invasion, angiogenesis, inflammation, and immune dysregulation, and negatively impact chemotherapy drugs.[100] Thus, using mind and body practices to lower chronic stress levels, often associated with cancer diagnoses, can potentially impact cancer survivorship, in addition to increasing quality of life. One of the greatest obstacles to mind and body research is the difficulty of creating a "sham" group, as factors such as the impact of a healing presence cannot be discounted.

TABLE 37.2
ASCO Endorsed Grading Scale for Integrative Therapies

Grade	Definition
A	"High certainty that the net benefit is substantial"
B	"High certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial"
C	"Evidence is equivocal or that there is at least moderate certainty that the net benefit is small"
D	"No demonstrated effect"

Source: Greenlee, H. et al., *CA Cancer J. Clin*., 67(3), 194–232, 2017.

37.4.1 Acupuncture

The theory behind the traditional Chinese medicine practice of acupuncture is that disease disrupts the body's energy (qi), and stimulation of points via acupuncture can help restore the balance. This involves the placement of needles in the skin at specific places correlating to meridians on the body to regulate the flow of qi.[101] Proposed mechanisms of action for acupuncture's therapeutic effects include mediation through opioidergic and/or monoaminergic neurotransmission and the pituitary system.[102] Imaging studies in humans have shown that acupuncture stimulation activates numerous brain structures, including the limbic system and deep gray structures, which can potentially lead to a decrease in nociception.[103–105] When performed appropriately by a licensed practitioner, acupuncture is safe and has minimal side effects, limited to needle pain, tiredness, and bleeding.[106,107]

Its main benefits for cancer patients surround symptom management, though the outcomes are dependent on the symptom. For example, a randomized controlled trial consisting of 226 women with early-stage breast cancer showed a statistically significant reduction in aromatase inhibitor–related joint pain in patients who received 12 acupuncture sessions over six weeks, compared with the women who received sham acupuncture or no acupuncture.[108] Another large randomized clinical trial by Shen et al. focused on 104 women with high-risk breast cancer

and found electroacupuncture to significantly decrease the number of emesis episodes compared with minimal needling or antiemetic pharmacology after five days, but these differences dissipated by day 9.[109]Additionally, four reviews found that acupuncture reduces cancer-related pain,[110–113] while two other reviews found not enough statistically significant evidence to draw this conclusion,[106,114] and a review by Paley et al. found that acupuncture's effect on pain management varied by cancer type.[115] A meta-analysis by Tao et al. found that acupuncture can also increase quality of life and reduce symptoms such as pain, fatigue, sleep disturbance, and gastrointestinal discomfort,[112] while two reviews found decreases in fatigue, chemotherapy-induced nausea and vomiting, and leukopenia.[106,116]

While other studies focus on the benefits of acupuncture more generally than just cancer, many of their findings can be applied to cancer patients. For example, a randomized trial of 245 patients with migraines found acupuncture to significantly reduce the number of migraines over sham acupuncture and no acupuncture, implying that it may be beneficial for migraine prophylaxis.[117] A meta-analysis of 29 trials involving 17,922 patients with chronic pain found that acupuncture significantly decreased pain over sham acupuncture and no acupuncture.[118] ASCO/SIO guidelines state that electroacupuncture can be considered as an adjunct therapy to antiemetic pharmacology to control chemotherapy-related vomiting (Grade B), while Grade C evidence exists for treatment of anxiety, mood disturbance and depressive symptoms, post-treatment fatigue, pain, quality of life, and hot flashes.[34]

37.4.2 Massage Therapy

Massage therapy in the context of cancer patients can be used to alleviate symptoms and should be done by a licensed practitioner with training in oncology massage. It is important that the practitioner knows how to avoid vulnerable areas, such as those that have been exposed to radiation, are sites of surgery, or have lymphedema, and the importance of doing so. A randomized trial of 380 patients with advanced cancer with moderate to severe pain found that six 30-minute massage therapy sessions over 2 weeks could significantly reduce pain and mood compared with simple-touch sessions, while sustained pain, quality of life, symptom distress, and medication analgesics were not significantly different.[119] Meanwhile, other studies have shown that massage therapy can decrease pain, fatigue, anxiety, nausea, and depression from 42.9% to 59.9% in cancer patients, though the effects are relatively short term.[116,120–123] There is also evidence that massage therapy can decrease cortisol levels, which can contribute to a decline in stress.[124,125] More research needs to be done to better understand massage therapy's biological effects on cancer-related symptoms. ASCO/SIO guidelines recommend massage therapy to improve mood disturbances (Grade B) and state that it can be considered for anxiety reduction (Grade C).[34]

37.4.3 Meditation and Mindfulness

Mindfulness meditation is the practice of bringing one's attention to the present via thoughts, feelings, emotions, and physical presence with openness, which can be taught via an eight-week Mindfulness-Based Stress Reduction (MSBR) course. A clinical trial of 229 women found that MSBR significantly improved total mood, quality of life, and well-being compared with the control group in women who had undergone breast cancer treatment.[126] Another randomized controlled trial examining breast cancer survivors found mindfulness awareness practices to significantly reduce stress, pro-inflammatory gene expression, inflammatory signaling, fatigue, sleep disturbance, and vasomotor symptoms, though these effects, aside from cancer-related distress, did not persist at a three-month follow-up.[127] Six other studies found that meditation can also significantly decrease anxiety, fatigue, and depression in cancer patients,[116,128–132] as well as leading to stress reduction and improving overall quality of life.[116,133] ASCO/SIO guidelines recommend meditation to reduce anxiety (Grade A), treat mood disturbance and depressive symptoms (Grade A), and improve quality of life (Grade A).[34]

37.4.4 Music Therapy

The purpose of music therapy is to benefit from the therapeutic aspects of music, which can include stress management, decreasing pain, and expressing emotions via the nonverbal, creative, structural, and emotional qualities of music with a trained music therapist. This ideally should be an active process, where the patient creates or describes their feelings via music, rather than a passive practice where the patient just listens.[134] Music therapy has been associated with decreasing cancer-related pain, fatigue, depression, and anxiety, while increasing overall quality of life,[116,135–138] though the mechanisms of these effects are not well researched or understood. One proposed theory based on imaging studies showed music to affect the limbic and paralimbic structures that play a part in pain, anxiety, and depression.[139] ASCO/SIO guidelines recommend music therapy to reduce anxiety (Grade B) and to improve mood disturbance (Grade B), while stating that it can be considered for pain management (Grade C).[34]

37.4.5 Yoga

Yoga involves the combination of breath control, meditation, and physical movements. A randomized controlled trial of 410 cancer survivors found that two 75-minute yoga sessions per week can improve sleep, something that is often impaired in cancer survivors.[140] A randomized controlled trial of early-stage breast cancer patients found that yoga can lead to significantly lower levels of serum IgA and CD56 % post-operatively, suggesting that yoga may prevent immune suppression after surgery.[141] One meta-analysis of randomized controlled trials found that yoga significantly

decreased depression, distress, and stress in cancer patients, though the number of studies analyzed was limited to ten, which varied in quality.[142] Another review of 13 randomized controlled trials found yoga to improve cancer patients' mental health, quality of life, and treatment-related side effects, while decreasing stress, anxiety, and depression,[143] which supports a review by Greenlee et al. that also found an improvement in quality of life and decrease in distress, anxiety, and depression in cancer patients who practiced yoga.[116] Similarly, Cramer et al.'s meta-analysis of 23 randomized controlled trials found that yoga can improve quality of life and decrease fatigue and sleep disturbances in the short term, but did not affect depression or anxiety.[144] ASCO/SIO guidelines recommend yoga to reduce anxiety (Grade B), improve mood disturbance and depressive symptoms (Grade B), and improve quality of life (Grade B). They also state that yoga can be considered for post-treatment fatigue (Grade C) and that gentle yoga can be considered to improve sleep (Grade C).[34]

37.5 CONCLUSION

With an increasing number of cancer patients using a variety of ICAM modalities, it is essential that physicians discuss with their patients the benefits, safety, and efficacy of various practices. This is especially true when patients are interested in taking dietary supplements, as some can have negative effects on tumor prevention or tumorigenesis, have drug interactions, or have biological mechanisms of action that are not thoroughly researched or understood. While mind and body practices have a much lower risk profile and appear to have beneficial effects on cancer and chemotherapy-related symptoms, more research needs to be done on their biological mechanisms of action, in addition to their effects on symptom management, as the data remain mixed. It is important that healthcare providers are knowledgeable about the various ICAM modalities and can integrate evidence-based approaches into their patients' conventional care when appropriate.

CLINICAL RECOMMENDATIONS

- Herbs and supplements should be used cautiously, and some studies have shown potential harmful effects, including vitamins A, B12, and E, which should be avoided in high doses.
- Mind body practices, especially meditation, are generally safe and can be effective for the adjunct treatment of cancer-related symptoms such as stress/anxiety and sleep.
- Acupuncture is another safe and effective therapy that has been shown to be beneficial for symptoms of pain and nausea.
- Dietary supplement regulation and compliance is the responsibility of the manufacturer; thus, the quality and safety of dietary supplements vary, and therefore, physicians should be knowledgeable about the popular products and their effects. Patients should look for independent verification of quality, such as USP tested products.
- For many dietary supplements, the effects on cancer prevention, survivorship, drug interactions, and treatment-related symptoms need to be studied before further conclusions can be drawn.

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38 Cancer Prevention Vaccines

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KEY POINTS

- On an annual basis, there are more than two million cases of cancer attributable to infectious agents globally.
- Vaccines targeted at viral surface proteins are available to protect against infection and prevent viral mediated malignant transformation.
- Hepatitis B virus vaccine is safe, effective, prevents hepatitis B virus infection, and when administered to newborn and young children, prevents development of hepatitis B virus–mediated hepatocellular cancer.
- Human papilloma virus vaccine is safe and effective, and when given to adolescents before initiation of sexual activity, prevents high-risk HPV infection of cervix, vulva, vagina, penis, and oropharynx and prevents cancer development in these tissues.
- Many tumor cells have unique antigens, which are serving as a focus for the development of vaccines to prevent, destroy, and/or block tumor cell progression.

38.1 CANCER PREVENTION VACCINES TARGETED AT INFECTIOUS AGENTS

The International Agency for Research on Cancer (IARC) recently estimated that the worldwide annual incidence of cancer attributable to infections was 2.2 million cases for an age standardized incidence rate of 25.0 cases per 100,000 person-years.[1] The prevalence of cancers attributable to infections was greatest in East Asia and sub-Saharan Africa. On a worldwide basis, most common cancers attributable to infectious causes were due to *Helicobacter pylori*, 810,000 cases; human papilloma virus, 690,000 cases; hepatitis B virus, 360,000 cases; and hepatitis C virus, 160,000 cases. In the United States, there were 81,000 cancers attributable to infectious agents, including *Helicobacter pylori*, 18,000; human papilloma virus, 35,000; hepatitis B virus, 2,100; and hepatitis C, 20,000.[1] As discussed later, highly effective vaccines are available to prevent infections with hepatitis B virus and human papilloma viruses and eliminate their carcinogenic effects.

38.2 HEPATITIS B VIRUS–ASSOCIATED CANCERS

Hepatitis B virus (HBV) is a hepatotropic, double stranded, DNA virus, which can cause acute and chronic hepatic infections. HBV infection may be accompanied by signs of acute hepatitis, including abdominal pain, jaundice (yellowing of skin), dark urine, clay-colored stools, fever, appetite loss, and fatigue.[2] Acute HBV hepatitis is usually self-limiting and clears within six months in non-endemic areas, whereas a limited number of patients, 1–5%, may progress to chronic infection.[3] In endemic countries where neonatal HBV infection is common, the development of chronic infection is more prevalent and may occur in 20–30% of those infected.[4] HBV chronic infections may be asymptomatic or symptomatic; however, 15–40% of chronically infected persons progress to cirrhosis, liver failure, and hepatocellular cancer (HCC).[4–7]

HBV is spread through direct contact with body fluids, including blood, saliva, semen, and vaginal secretions, by way of perinatal, percutaneous, sexual, and other forms of close contact. In endemic areas such as Africa, Eastern Europe, and Asia, perinatal, vertical transmission from mother to neonate is one of the most common routes of HBV spread.[3,5,7]

In the United States, prior to the launching of the HBV vaccine in 1982, there were an estimated 200,000 new cases of HBV infection per year.[7,8] On a worldwide basis, chronic HBV infection (persisting for six months or more) is estimated to affect 257–291 million persons.[6,9] The risk of becoming a chronic carrier of HBV is increased in those infected at younger ages.[5,7]

HBV is a major cause of HCC in most parts of Asia, South America, and Africa, accounting for an estimated 60% of cases, whereas in the United States, HBV is associated with 20% of HCC.[10,11] Studies in Taiwan have shown that death from cirrhosis and/or HCC may occur in 25% of patients who become chronic HBV carriers, stemming from infections acquired during infancy or childhood.[12] The number of global deaths due to HBV-associated HCC in 1990 was estimated at 210,200, increasing to 341,400 by 2010.[13] A 2013 study estimated that HBV was associated with 680,000 deaths per year, of which 300,000 were due to HCC.[14]

HBV-induced hepatic inflammation is mediated in part by the HBV pre s protein, which distributes to the endoplasmic reticulum, where it promotes cellular and oxidative stress, leading to cellular and DNA damage. A major element of chronic HBV toxicity is due to the viral genome being incorporated into host DNA, resulting in insertional mutagenesis, chromosomal rearrangement, and oncogene activation. HBV may also produce epigenetic effects associated with aberrant DNA methylation. In addition, viral

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protein HBx activates multiple cellular mitogen signaling genes, including Il-6, TNF, TGF-β, and EGFR. Thus, HBV promotes hepatocyte proliferation, which in the presence of viral-induced DNA damage and mutations, leads to hepatic carcinogenesis.[4,10]

The HBV genome codes for three viral surface antigens: Pre-S1, which is the large HBs antigen envelope protein; Pre-S2, the medium HBs antigen envelope protein; and S, which is the small HBs antigen envelope protein. The S protein has been used to produce several monovalent viral surface antigen vaccines (1AHBV), and the S, Pre-S1, and Pre-S2 proteins have been combined to produce a trivalent viral surface antigen vaccine (3AHBV). HBV vaccines are composed of recombinant protein molecules produced in a *Saccharomyces cerevisiae* system.[15–17] The vaccines are free of viral DNA. Three monovalent vaccines, Engerix-B®, Recombivax HB®, and Heplisav-B®, and one trivalent vaccine, PreHevbrio®, are all Food and Drug Administration (FDA) approved in the United States, and all are highly immunogenic.[18] Both monovalent and trivalent vaccines are administered by intramuscular injection, with three doses given over a six-month period. The second dose usually follows the first dose after one month, and the third dose six months after the first. In a series of 18–45-year-old healthy adults administered three vaccine doses, 94.8% of those receiving 1AHBV achieved sero-protection, whereas among those immunized with 3AHBV, 99.3% achieved sero-protection.[17]

Vaccination against HBV is associated with mild to moderate injection site reactions, including pain, tenderness, itching, redness, and swelling, which are usually of short duration and self-limiting, lasting one to two days. Site reactions were greater with 3AHBV vaccines compared with 1AHBV vaccine. Systemic effects, including limited fatigue, headaches, fever, and vertigo, were also of short duration. Among individuals receiving 3AHBV, 85% and 68%, respectively, had local and systemic reactions, whereas among those receiving 1AHBV, 65.9% and 60.1% showed local and systemic reactions.[17] HBV vaccination is not associated with long-term adverse effects. Early concerns of associated demyelinating disorders have not been substantiated.[19,20]

Because of the prevalence of neonatal and early childhood HBV infection, HBV vaccination is recommended to be initiated within 24 hours of birth for all medically stable infants, followed by administration of two additional doses within 6 months. For individuals not vaccinated in infancy, HBV vaccination is recommended for those up to 59 years of age and also for those over 60 with risk factors for HBV infections, such as contact with HBV infected people, people who inject drugs, people who have HIV, men who have sex with men, and people with end stage renal disease, especially those receiving hemodialysis.[21] Immunization provides lifelong immunity, and there are no recommendations for boosters beyond the initial three dose immunization regimen.

Since the institution of HBV vaccination of newborns in the 1980s, the incidence of HBV-associated HCC has been reduced among individuals who were vaccinated at birth compared with non-vaccinated children. Cases of HBV in the United States progressively decreased from 25,916 new cases of HBV reported in 1987, for an annual incidence of 10.7 cases per 100,000 individuals per year, to 6,212 reported cases in 2009, for an annual incidence rate of 2.1 per 100,000, to 0.9–1.1 per 100,000 in 2009, and to 0.7 per 100,000 in 2020.[3,22] The U.S. National Health and Nutrition Examination Survey (NHANES), in three different studies conducted from 1988 to 2016, estimated that chronic HBV infection remained stable at 0.3–0.35% of the U.S. population, with prevalence being greatest in foreign born persons compared with those born in the United States.[6]

Comparing the NHANES data survey from 1999–2006 with 1988–1994, there was a 68% decrease in new HBV infections and a 79% decrease in chronic HBV infections among children 6–19 years of age. In contrast, there was no statistical difference in overall or chronic HBV infection in individuals over 50 years of age.[7]

However, on a worldwide basis, as of 2019, there were still an estimated 1.5 million new cases of HBV infection per year, 296 million people with chronic HBV infection, and 820,000 deaths annually from liver cirrhosis and HCC.[23] The overall worldwide incidence of HCC is increasing at a rapid rate, stemming from multiple etiologic factors, including alcohol, aflatoxin, viruses such as HBV and HCV, and the obesity pandemic–associated non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).[10,13,24] In 2020, there were 900,000 new cases of HCC, 632,320 in men and 273,357 in women.[25] The incidence of HBV related HCC deaths continued to increase from 210,200 in 1990 to 341,400 in 2010, presumably a reflection of chronic HBV infection acquired before the availability of HB vaccines.[13]

Although the overall incidence of HCC and even HBV-associated HCC may be increasing in many countries, those that have shown early uptake of neonatal HBV vaccination are beginning to show signs of a decrease or stabilization of HBV-associated HCC. For example, in Singapore, where perinatal HBV vaccination was introduced in 1984, liver cancer decreased from 27.1 per 100,000 population members in a 1993–1997 cohort to 17 cases per 100,000 population in a 2006–2012 group.[26] In the United States, age standardized death rates for HBV-associated HCC decreased by 0.2% annually from 2.35 cases per 100,000 population to 2.31 cases in 2019.[27] While the overall incidence of HCC is continuing to increase, it is expected that the contribution of HBV will continue decreasing as children vaccinated in the perinatal period progress into adulthood.[9]

38.3 HUMAN PAPILLOMA VIRUS–ASSOCIATED CANCERS

Human papilloma viruses (HPV) are a family of over 200 double stranded DNA viruses that are epithelial tropic, infecting both cutaneous and mucosal tissues. Acute

infections are usually asymptomatic and clear spontaneously. HPV may become persistent, either in an extrachromosomal, nuclear episomal form or integrated into host DNA.[28–30] Chronic HPV cutaneous infections may lead to common skin warts, whereas chronic infections of mucosal tissue with HPV may lead to diseases such as anogenital warts and malignancies, including cervical, vaginal, vulvar, anal, and oropharyngeal cancers.[31] Although 14 types of HPV are considered high risk for anogenital warts and malignancies in humans, HPV 16 and HPV 18 are most frequently associated with human cancers.[32,33]

HPV infection is most commonly transmitted through sexual contact, including vaginal, penile, anal, and oral sex, as well as by other forms of intimate skin contact.[30] Although HPV infection may occur before initiation of sexual activity, it increases rapidly thereafter. A study in Tanzania showed 11.6% HPV positivity among 15–16-year-old girls who reported having had no sexual activity.[34] Among 15–16-year-old unvaccinated girls, the median time from initiation of sexual activity to first HPV infection was found to be 4.9 months, and 9.3 months to first infection with high-risk HPV. The median duration of new HPV infections was 6 months.[35] A prospective study of U.S. college women showed that the cumulative incidence of HPV infection reached 38.9% within 24 months after first sexual intercourse, with 10.4% of the infections being caused by HPV 16.[36]

Prior to the introduction of HPV vaccines, the prevalence of infections in the United States was estimated at 79 million persons, with 14 million new cases annually, almost half of which occurred in individuals 15–24 years old.[37]

In a NHANES U.S. population based national study conducted from 2003 to 2008, using self-collected cervical-vaginal smears obtained from 1,921 women, the overall HPV prevalence among 14–59-year-old women was 26.8%. The prevalence was 33.8% among 14–34-year-olds and was highest at 44.8% among those women 20-–24 years old. Sexually active women were 39.6% positive among 14–19-year-olds and 49.3% among 20–30-year-olds. High-risk HPV types were identified in 15.2% of women. HPV 16 was detected in 1.6% and HPV 18 in 0.8% of women aged 14–59.[38] These studies confirm that genital HPV infection is common in women, even among adolescents, and increases when individuals become sexually active.

A subsequent NHANES study was conducted in 2013–2014 to identify the prevalence of genital HPV among adult men aged 18–59 years old. Analysis of self-collected penile swabs from 1,868 men identified HPV infection prevalence of 45.2%, with 25.1% showing at least one high-risk HPV type; 4.3% were positive for HPV 16 and 1.7% for HPV 18. On a population basis, these numbers extrapolated to 3.3 million men infected with HPV 16 in the United States and 1.3 million with HPV 18.[37]

A NHANES study of U.S. adults aged 18–69 years old from 2011 to 2014 showed a 7.3% prevalence of oral HPV, 11.5% among men and 3.3% among women. The prevalence of high-risk oral HPV was 4.0% overall, 6.8% among men and 1.2% among women.[30]

The U.S. Centers for Disease Control (CDC), using data from 2015–2019, reported an average of 47,199 HPV-associated cancers annually, of which 26,177 occurred in women and 21,022 in men. In the United States, HPV is considered to be responsible for 91% of cervical cancer, 91% of anal cancer, 69% of vulvar cancer, 75% of vaginal cancer, 63% of penile cancer, and 70% of oropharyngeal cancer.[39] In 2019, 300,000 women died of cervical cancer on a worldwide basis.[40]

Integration of the HPV virus into host DNA drives expression of two viral early genes, E-6 and E-7.[28] These viral early genes are expressed in cervical tissues from women with chronic infections, in cervical carcinoma cell lines, and in clinical samples of cervical carcinoma, where they promote cancer by inactivating the two tumor suppressor proteins, p53 and Rb[41] and by increasing telomerase, which promotes tumor cell survival.[42]

HPV vaccines have been developed to protect against HPV 16 and 18, which are responsible for 70% of cervical cancers, and against HPV 31, 33, 45, 52, and 58, which are responsible for 20% of cervical cancers. HPV 6 and 11 are responsible for anogenital warts. A bivalent vaccine, 2vHPV, Cervarix®, was developed to protect against HPV 16 and 18. A quadrivalent vaccine, 4vHPV, Gardasil®, was developed against HPV 6, 11, 16, and 18. Following up on the success of these vaccines, the nine-valent (9vHPV) Gardasil9® was developed against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 to provide more comprehensive protection against all HPV types associated with cervical, vaginal, vulvar, penile, and oropharyngeal cancers.[33]

HPV vaccines consist of recombinant proteins that form the outer viral capsid layer of the HPV, which self-assemble into virus like particles. The vaccines are free of any DNA that could cause infection or development of cancer. Vaccines are produced using *Saccharomyces cerevisiae* systems and contain yeast proteins. Immunization with the viral proteins stimulates antibody production capable of preventing HPV infection. Immunization with the 4vHPV vaccine provided 100% protection against HPV 16 and 18 infection. The 9vHPV vaccine, Gardasil9®, protects against the nine HPV types included in the vaccine.[33,43]

Clinical trials demonstrate strong safety profiles for both Gardasil® and Cervarix® vaccines, with transient symptoms of injection site pain, swelling, and/or redness along with systemic symptoms of headache and fatigue. Pregnant women who receive Cervarix® treatment compared with Gardasil® showed no significant increase in miscarriages. However, a non-significant increase in miscarriages was noted in pregnancies conceived within three months of Cervarix® vaccination. Immunization with Gardasil® compared with control vaccine resulted in no differences in live births, spontaneous abortion, or congenital abnormalities.[43]

Gardasil9® was subsequently shown to be immunologically non-inferior to Gardasil® in eliciting antibody response among women who were not infected at the time of vaccination.[43] Mild, transient pain, swelling, redness, and itching at the injection site were more common with

Gardasil9® than with Gardasil®. Adverse systemic effects from the two agents were similar.[43] Gardasil9® was more effective than Gardasil® at protecting against cervical, vaginal, or vulvar cancer.[33]

HPV vaccine is administered by intramuscular injection. In the United States, Gardasil9® is now the only HPV vaccine available and is recommended for routine immunization of both sexes by ages 11–12 years, before initiation of sexual activity, to protect against HPV infection. Gardasil9® should be administered as two doses separated by six months. A third dose is required if the first two doses are given at less than six-month intervals. The CDC further recommends vaccination for everyone up to 26 years of age, with three doses given for those who start vaccination after age 15. Vaccination may be given to adults 27–45 years of age who have not been previously vaccinated and who are at high-risk for infection. Pregnant women should not be vaccinated.[29,44]

In a NHANES study of 4,727 women who were 26 years old or younger in 2006, of whom 38% were vaccinated by 2018, the prevalence of HPV 16 and HPV 18 was reduced from 5% in unvaccinated women to 3.4% in women who were vaccinated after initiation of sexual activity, and to less than 1% in women vaccinated before initiation of sexual activity. These studies clearly show the importance of vaccination before initiation of sexual activity to prevent HPV infection.[45] The prevalence of HPV 6, 11, 16, and 18 decreased by 88% among women aged 14–19 years old and by 71% among those 20–24 years old within one decade after the quadrivalent vaccine introduction.[46] Similar studies have shown that vaccination before initiation of sexual activity prevents cervical cancer caused by HPV 16 and HPV 18. However, vaccine efficacy in preventing cancer decreases as vaccination age increases to 19.[47] Emphasizing the need for early age vaccination, estimates based on model studies predict that the lifetime risk of cervical cancer can be decreased by 55% for women vaccinated by age 9, but only by 6% among women vaccinated at age 45.[47]

A 2017 review of the first decade of experience with HPV vaccine showed significant immunogenicity and improvement in HPV infections and related pathologies.[48,49]. Cervarix®, Gardasil®, and Gardasil9® were each shown to produce high antibody titers to the specific HPV type virus like particle contained in the vaccine. Antibody titers have been shown to be persistent after five to ten years, and both Gardasil® and Cervarix® have been shown to extend protection against HPV 16 and HPV 18 infections for at least five to ten years, respectively.[49] Immunization with type specific vaccine did not induce clearance of already infected women.[49] In a 2011–2014 NHANES study of men and women, oropharyngeal HPV infection with HPV 6, 11, 16, and 18 was reduced by 88% in vaccinated versus unvaccinated individuals.[50]

Among women 15/16–26 years old, Gardasil® and Cervarix® have been shown to be 98% protective against development of HPV 16/18-associated grade 2 cervical intra-epithelial neoplasia (CIN 2). Gardasil9® was shown to be further 100% protective against CIN 2 associated with HPV 31, 38, and 55, as well as 53% protective against CIN 2 due to any HPV type. Gardasil® and Cervarix® are 43% and 83% protective against grade 3 CIN caused by any HPV type.[33,43]

In an international trial of 14,215 women 16–26 years of age, randomized to immunization with three injections of either Gardasil® or Gardasil9® and then followed for 48 months, Gardasil9® was shown to be non-inferior to Gardasil® for preventing high-grade intra-epithelial neoplasms and malignant cervical, vulvar, and vaginal disease related to HPV 16 and 18. Among women immunized with Gardasil®, there were 30 cases of high-grade CIN and 27 cases of cervical cancer related to HPV 31, 33, 45, 52, and 58 compared with 1 case of high-grade CIN and only 1 case of cancer in women receiving Gardasil9®. Risk reduction was 96.7% and 96.3%, respectively, for high-grade disease and cancer related to HPV 31, 33, 45, 52, and 58. This study clearly showed that prophylactic administration of Gardasil9® protected against development of high-grade intra-epithelial neoplasms and cancer caused by the HPV types included in the vaccine over a 48-month period.[33] A Swedish national registry study composed of nearly 1.7 million women 16–30 years of age compared 527,871 who received at least one dose of quadrivalent HPV vaccine with 1,145,112 unvaccinated women of the same age. Women were followed for 11 years from 2006 to 2017 or until they reached 31 years of age. There were 538 cases of invasive cervical cancer, for an incidence rate of 5.27 cases per 100,000 person-years, among unvaccinated women compared with 19 cases in vaccinated women, for an incidence rate of 0.73 cases per 100,000 person-years in the latter. Of the cases that occurred in vaccinated women, only 2 were in those vaccinated before age 17, while 17 occurred in women vaccinated between 17 and 30 years of age. Overall, there was an 86% reduction in invasive cervical cancer in women receiving quadrivalent vaccine, with best results when those vaccines were given at younger ages.[51] Studies have not yet been reported demonstrating that HPV vaccination protects against oropharyngeal cancer; however, since the vaccine protects against the virus types associated with these malignancies, it is expected that they will be shown to prevent development of the cancers as well.[52]

Overall, HPV vaccines have been shown to be highly immunogenic, to produce long lasting seropositivity of antibodies to effectively reduce HPV vaccine type specific infections of cervix, vulva, vagina, penis, and oropharynx, and to further protect against development of cervical intra-epithelial neoplasia and invasive carcinoma. Long-term protection by these vaccines against HPV infection, resultant high-grade disease, and cancer remains to be determined. Thus, although HPV- and HBV-related cancers are preventable, strategies to increase uptake of the vaccines and eliminate these diseases need to be improved.

In the United States, 86.3% of U.S. born children are vaccinated against HBV, while 40.3% of adults aged 19–49 and 19.1% of adults over 50 are vaccinated.[53,21] HBV

vaccination rates vary by country, with an overall global estimate of 42% vaccination.[23] Only 58.6% of U.S. adolescents have completed HPV vaccination, while worldwide, fewer than 15% of girls have been vaccinated.[54,55] Thus, we have witnessed the contribution of vaccines to the control of two major cancer classes attributable to infectious agents, with great promise if more cancer preventive vaccines were to be targeted at both infectious agents and unique tumor cell antigens.

38.4 STATUS OF CANCER PREVENTION VACCINES TARGETED AT TUMOR CELL ANTIGENS

It has long been recognized that tumor cells express unique or mutated "neo"-antigens and/or over-express surface structures that are only minimally present on normal, non-malignant cells. Thus, it was hypothesized that the immune system provided continuous surveillance that could detect neoantigens and eradicate neoplastic cells before they became actual tumors,[56] and that when this "immune surveillance" was weakened in patients who were iatrogenically immunosuppressed to prevent rejection of transplanted organs[57] and in those with intrinsic immune deficiencies, higher incidences of cancers resulted.[58] It became apparent, therefore, that tumors somehow protected themselves from immune attack, but the mechanisms by which they evaded the immune system were unknown. Early attempts to stimulate immune eradication of tumors involved non-specific inflammatory stimuli such as bacterial toxins;[59] cross-immunization with tumor cells from different individuals;[60] isolation, amplification, and stimulation *in vitro* of tumor infiltrating lymphocytes;[61] and administration of stimulatory cytokines such as IL-2 *in vivo*.[62] With improved understanding of the induction and regulation of immune responses, research in the 1970s began to focus on dendritic cells and attempts to stimulate antigen presentation for induction of helper and cytotoxic T-cells. To avoid tumor microenvironments, which may be immunosuppressive or tolerogenic *in vivo*, *ex vivo* conditions were developed in which peripheral blood monocytes could be differentiated into activated antigen-presenting dendritic cells by culturing with toll-like receptor agonists and/or immunostimulating cytokines, together with tumor antigens, to activate and induce proliferation of tumor-specific T-cells. This approach is exemplified by Provenge® (Sipuleucel-T), approved in the United States in 2010, in which autologous peripheral blood cells are collected by leukapheresis and cultured *in vitro* with a proprietary recombinant fusion protein consisting of prostatic acid phosphatase and GM-CSF (Prescribing Information, Dendreon Inc., Seal Beach, CA). In this case, the tumor antigen, prostatic acid phosphatase, is expressed by 95% of all prostate cancers. However, this and other attempts at immunotherapy had only limited success because besides developing defenses that enable them to evade immune detection, tumor microenvironments may also inhibit T-cell proliferation and cytotoxic lymphocyte attack. As tumors grow, they often develop progressively immunosuppressive microenvironments due to hypoxic and other metabolic stresses, shedding of exosomes and cell fragments, and chronic inflammation with prolonged NF-κB activation. These changes favor differentiation of macrophages into the M2 phenotype with diminished antigen-presenting activity, increased concentrations of suppressive cytokines such as interleukin (IL)-10 and transforming growth factor beta (TGF-β), and exhaustion and apoptosis of T-cells.[63]

Research in the 1990s led to elucidation of the need for co-stimulation to induce T-cell responses and the discovery that in addition to co-stimulatory molecules, there were also inhibitory surface proteins on T-cells, antigen-presenting cells, and target cells. It soon became apparent that integration of these various stimulatory and inhibitory (so-called "check-point") signals determined the extent of T-cell activation, and that using antibodies to block inhibitory molecules such as CTLA-4 could unleash potent anti-tumor immune responses.[64] Thus, tumors can become established and grow when co-stimulatory molecules are down-regulated and/or inhibitory molecule expression is increased. This realization led to the introduction and increasing use of "check-point inhibitors" such as ipilimumab (anti-CTLA-4), pembrolizumab (anti-PD1), nivolimumab (anti-PD1), and atezolimumab (anti-PD-L1) as immunotherapeutics for a wide variety of cancers. In turn, the success of check-point inhibitor immunotherapy has led to increased interest in the use of vaccines, now in combination with check-point inhibitors, to focus the immune response on tumor-specific antigens and to unleash its effectors. Development of autoimmune complications is one risk of this and other immunotherapy approaches.[65]

Considerable evidence suggests that many nascent tumors are eliminated by immune surveillance before they become clinically apparent.[58] Demonstration that mice with targeted knockouts of important immune effector genes such as interferon-γ and perforin have an increased incidence of spontaneous and carcinogen-induced tumors supports the importance and highlights the mechanisms of immune surveillance.[66] Many individuals without cancer have been found to have established T-cell memory and/or pre-existing antibodies against tumor antigens, which can effectively inhibit tumor growth in animal models.[67] Such antigens include mutated and/or over-expressed cell surface growth factor receptors, mucins and adherence proteins, and even intracellular growth-regulating proteins such as cyclins and transcription factors, which actually drive tumor growth.[68–70] The latter types of intracellular proteins may be processed through proteosomes into peptides, which can be presented on class I MHC molecules as targets for CD8-effector lymphocytes,[71] but may require phagocytosis of tumor cells or their fragments by macrophages in order to be presented on class II molecules to stimulate CD4 T-helper cells—a process that is often impaired in the tumor microenvironment.[72] Several

studies suggest that the presence of activated T-cells and other immunologic reactants in and/or adjacent to premalignant lesions is associated with decreased incidence of tumor formation and better long-term prognosis if cancer does develop. Immunization with HPV antigens in Freund's adjuvant led to regression of premalignant intraepithelial vulvar lesions.[73] Similarly, the presence of autoantibodies against MUC1 in heavy smokers and others who are at risk for, but have not yet been diagnosed with, carcinomas also suggests that active immune surveillance is effective in preventing or delaying the development of malignancies.[68]

Thus, current efforts in the immunoprevention of non-virally induced cancers focus on the detection of premalignant lesions and blocking their progression to invasive malignant tumors.[74–76] Two main avenues of attack include identification of appropriate neoantigens and optimizing presentation to achieve effective responses. Approaches to antigen identification include characterizing and cataloging shared proteins and epitopes on premalignant tissues through such efforts as the "Precancer Genome Atlas"[77,78] and the "Cancer Epitope Database and Analysis Resource (CEDAR)."[79] It is hoped that this could yield off-the shelf vaccines useful for many patients and potentially, multiple types of tumors that share common mutations or over-expressed antigens. For example, detection of microsatellite instability and proteins with frame-shift mutations (i.e., in Lynch Syndrome patients) could potentially identify frequently occurring neoantigens, which could be targeted.[80] A potentially important approach toward personalized vaccines tailored for presentation on a patient's own HLA molecules includes subtraction of whole exome sequences of a patient's healthy cells from sequences of that patient's own tumor, accompanied by informatic/machine learning tools to optimize tumor-specific, HLA-binding sequences.

The success of mRNA vaccines against the SARS-coronavirus responsible for the COVID-19 pandemic has suggested that individual epitope sequences or sequences for multiple epitopes could be linked together and incorporated into optimized nucleic acid–based vaccines[71,75,81] rather than translated into peptides or fusion proteins with different solubility and administration requirements. The injection of stabilized and adjuvanted nucleic acid–based vaccines remotely from the tumor microenvironment should stimulate and expand T-cells to prevent progression of premalignant lesions and in patients with established disease, eradicate residual tumor cells and prevent metastases and recurrence.[82,83] Other approaches to increase the antigenicity of tumor vaccines include the use of extracellular vesicles bearing tumor antigens, incorporation of tumor lysate antigens into nanoparticles comprised of yeast or bacterial cell walls, and other strategies designed to promote phagocytosis and stimulate antigen presentation.[84] These strategies are often used in combination with cytokines intended to further stimulate T-cell activation by dendritic cells.

Thus, advances in basic immunology, tumor biology, and vaccine technology have come together to illuminate a bright future in immunologic approaches to the prevention and treatment of cancer.

KEY CLINICAL POINTS

- Hepatitis B vaccine should be administered to prevent infection with HBV and consequent hepatocellular cancer.
- Hepatitis B vaccine should be administered according to the following CDC guidelines:[21]
  - All newborns
  - All persons under 19 years of age who have not been vaccinated
  - Adults 19–59 years old
  - Adults 60 years and older with risk factors for hepatitis B virus infection
- Human papilloma vaccine is recommended to prevent human papilloma virus infection and consequent anogenital warts as well as cervical, vaginal, vulvar, penile, and oropharyngeal cancers.
- Human papilloma vaccine should be administered according to the following CDC guidelines:[29]
  - All children, boys and girls, by 11–12 years of age, starting at age 9 to ensure vaccination before exposure to HPV through sexual activity.
  - Catch-up vaccination is recommended up to age 26 years.
  - Vaccination may be of benefit to individuals 27–45 years old who are not adequately vaccinated and who have not been exposed to HPV infection.
- HBV and HPV vaccines are not effective for treating acquired infections or virus-attributable cancers.

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39 Lifestyle Approaches To Obesity Management for Cancer Control

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KEY POINTS

- Overweight and obesity are at pandemic proportions in the United States and worldwide.
- Overweight and obesity promote, accelerate, and worsen the prognosis of multiple malignancies.
- Overweight and obesity account for 14% of all cancer deaths in men and 20% in women.
- Obesity control can prevent and/or reduce incidence of many cancers.
- Metabolic-bariatric surgery is the most effective and durable approach to weight loss in markedly obese patients. Its role in cancer prevention will be reviewed.

39.1 INTRODUCTION

Obesity is a major health problem in the United States and worldwide.[1,2] On a global basis, obesity has reached pandemic proportions, with an estimated 650 million obese adults and more than 110 million obese children.[3–5] Successive reports by the U.S. National Health and Nutrition Examination Survey (NHANES) from 1960–1962 through 2017–2018 indicate that obesity in the United States has increased more than threefold among women and more than fourfold among men.[6] In the United States, 42.5% of adults have obesity, another 31.1% are overweight, and almost 10% have severe obesity.[6] Childhood obesity is also increasing, affecting over 17% of U.S. children in 2018.[7]. These figures are alarming in that overweight and obesity are associated with increased risk for many health problems, including heart disease, stroke, Type II diabetes mellitus, musculoskeletal disorders, cancer, and many others.[5] In addition, each year, there are 2.8 million deaths worldwide, and over 300,000 in the United States, as a result of overweight or obesity.[8–10] Thus, obesity and its consequences are a major cause of morbidity and mortality. Further cause for alarm is the cost of obesity-associated diseases, which in the United States has been estimated at $173 billion annually, or an increase per individual of $1,861 per year above average healthcare costs.[11].

The terms "overweight" and "obesity" are used to describe the condition where an individual carries more weight, usually as fat mass, than the average normal person of the same height and gender. These weight comparisons are commonly expressed using the term "body mass index" (BMI), calculated as weight in kilograms divided by height in meters squared (BMI = weight [kg] ÷ height [m]$^{2)}$). BMI can be easily determined using readily available websites.[12]. Individuals with a BMI lower than 18.5 kg/m2 are considered underweight and may be subject to unique health problems associated with malnutrition and nutritional deficiencies.[13–15] Individuals with a BMI of 18.5 to 24.9 are considered normal and usually serve as the reference range for conditions associated with elevated BMI. Individuals with a BMI of 25–29.9 are considered overweight, and those with a BMI of 30 or over are considered obese. Obesity is sometimes further divided into BMI 30.0–34.9 kg/m^2 as type 1 obesity, BMI 35–39.9 kg/m^2 as type 2 obesity, and BMI ≥40 kg/m^2 as severe or morbid obesity.

Prior to 1962, only 14.3% of the U.S. adult population was estimated to be obese.[16] More recent U.S. data indicate the prevalence of obesity to be 42.5% in adults and 19.7% in those under 20, with no differences noted between adult men and women.[6,17,18] Obesity rates in the United States show a regional distribution, with higher prevalence in the eastern United States and even higher rates in the south, reaching greater than 38% in the Mississippi Delta states of Alabama, Louisiana, and Mississippi; and in Appalachia, where the prevalence of obesity is greater than 40% in Kentucky and West Virginia. Obesity likewise has an ethnic distribution, with the highest prevalence in non-Hispanic Black Americans (49.9%), followed by Hispanics (45.6%) and non-Hispanic Whites (41.4%), and is lowest among non-Hispanic Asians (16.1%).[18]

Although the United States is in the unenviable position of leading the world in prevalence of overweight and obesity, similar trends occur in countries throughout Europe, Australia, and the Middle East. In contrast, the prevalence of obesity in sub-Saharan Africa, India, and China is significantly lower; however, these countries are showing marked increases in the incidence of obesity, especially in urban areas where residents acquire Western lifestyles.[4]

The public is well aware of the impact of obesity on heart disease, stroke, and diabetes and engaged in multiple strategies to reduce these comorbidities. However, a 2017 report from the American Institute of Cancer Research (AICR) indicated that only 50% of Americans were aware that obesity stimulates cancer growth.[19] An important alert and awakening subsequently came from the American

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Cancer Society, which in a series of landmark reports based on a prospective observational study of more than one million U.S. adults, showed that overweight and obesity were associated with increased cancer incidence and deaths. They identified that obesity-associated cancers accounted for 14% of all cancer deaths in men and 20% in women.[20–22] The International Agency for Cancer Research (IACR) subsequently convened an expert panel, which upon review of extensive epidemiologic data, concluded there was sufficient evidence to link 13 human malignancies to excess body fatness.[23] These obesity-associated cancers include esophageal adenocarcinoma, gastric cardia cancer, colon and rectal cancer, liver cancer, gall bladder and pancreatic cancer, post-menopausal breast, corpus uteri, ovarian, renal cell, and thyroid cancers, meningioma, and multiple myeloma.[23] In addition, there is suggestive but not conclusive evidence that other malignancies, including prostate cancer, lung cancer, and some hematologic malignancies, especially acute promyelocytic leukemia, may be associated with obesity.[24–28]

A more recent report, using Mendelian randomization studies of germline genetic determinants of lifetime expectancy of body fatness, reported causal association of adult obesity with six cancers, including esophageal adenocarcinoma, colorectal cancer, and cancers of endometrium, ovary, kidney and pancreas.[29,30] These studies also suggested a potential link of obesity to lung cancer, which may be obfuscated by tobacco use, and development of cachexia in association with disease development and progression. Studies of association with breast cancer were mixed because of pre- and post-menopausal breast cancer. Mendelian randomization studies had insufficient data to link obesity with cancers of gall bladder, gastrocardia, or multiple myeloma.[29,30]

Improved awareness and understanding of how excess fat, overweight, and obesity as well as high fat diets promote cancer development and progression should contribute to improved lifestyle efforts to control obesity, reduce cancer risk, and mitigate some of its effects on prognosis. Adipose tissue was once considered a storage depot where reserve energy was maintained in the form of fats (triglycerides) to be released and utilized by peripheral tissues in times of energy demand or periods of restricted food availability. However, it was shown that adipose tissue, composed of adipocytes, stromal fibroblasts, and vascular, immune, and hematopoietic cells, is intensely metabolic, with multiple physiologic functions, including appetite regulation, inflammation, modulation of insulin sensitivity, nutrient uptake and storage, and other processes as well.[31–34] Obesity-associated aberrations in these physiologic functions result in multiple and overlapping pathophysiologic mechanisms by which obesity promotes cancer.[3536]

39.2 MECHANISMS OF OBESITY'S IMPACT ON CANCER

In considering the multiple mechanisms by which obesity affects cancer (Figure 39.1), it is important to note that obesity does not initiate the carcinogenic process, but rather, obesity promotes and accelerates cancer progression.[36,37] As adipose tissue expands in association with overweight and

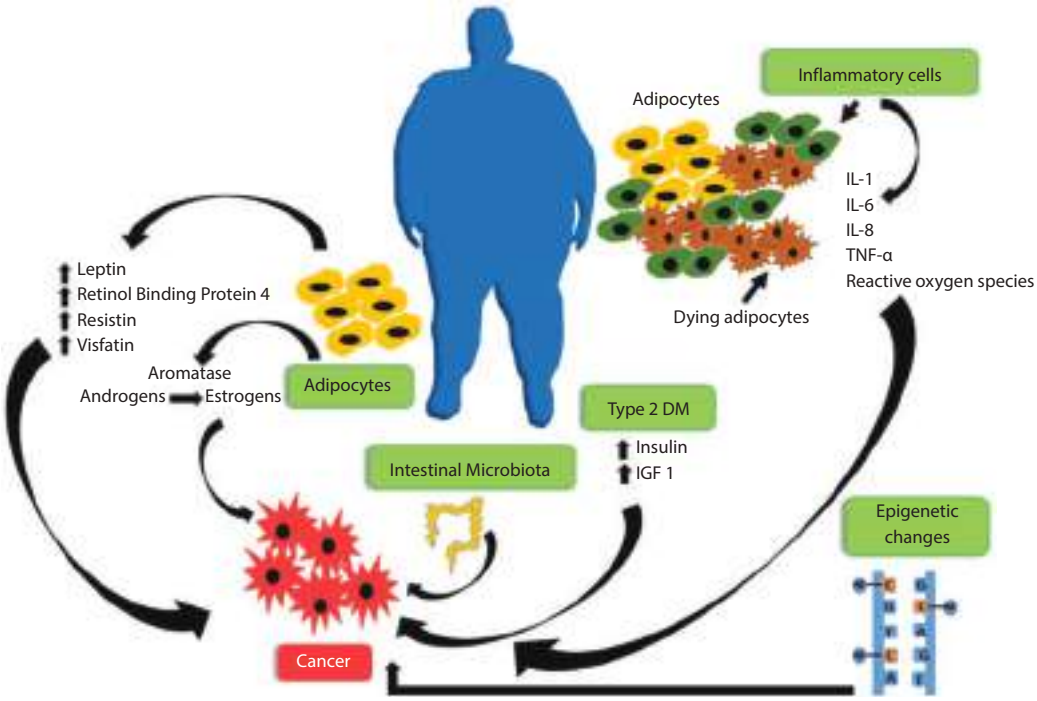


FIGURE 39.1 Mechanisms of cancer obesity. (From Bruno, D.S. and Berger, N.A., ***Ann. Transl. Med.***, 8(Suppl 1), S13, 2020. doi: 10.21037/atm.2019.09.26. PMID: 32309417; PMCID: PMC7154324. Used with permission from the author.)

obesity, adipocytes, the fat containing cells, enlarge, and some undergo cell death and become surrounded by pro-inflammatory macrophages to form crown-like structures (CLS), which generate cellular and humoral pro-inflammatory factors, including lipids, cytokines, interleukin (IL)-6, IL-1, and tumor necrosis factor alpha (TNFα).[38] These in turn further act to provide cellular and humoral growth-promoting microenvironments that lead to insulin resistance.[32,33] In addition, adipose tissue is responsible for the synthesis and secretion of a number of adipokines, proteins that under normal conditions have a variety of physiologic functions.[34,39].These include leptin, which under normal conditions increases in proportion to fat cell mass and has an anorexigenic effect, that is, it down-regulates appetite;[40] adiponectin, which increases in response to calorie restriction and has an orexogenic or appetite stimulating function;[41] and retinol binding protein 4 (RBP4), which facilitates vitamin A uptake and transport.[42] Increased levels of these adipokines, such as leptin and RBP4, promote tumor cell growth by stimulating cell proliferation, survival, and invasion.[43,44]. In contrast, adiponectin, which suppresses cell proliferation and stimulates apoptotic cell death, is decreased in obesity.[41]

Levels of insulin and insulin like growth factor (IGF-1) are usually increased in obesity, where they may contribute to tumor growth.[33,34] While the normal physiologic function of insulin is to stimulate cellular glucose uptake and utilization, insulin can also stimulate cell growth.[45,46] Thus, elevated levels of insulin secreted by the pancreas in response to insulin resistance may have the pathophysiologic effect of promoting tumor cell growth and cancer progression.[45,46]. IGF-1, synthesized mostly by the liver, has a structure similar to insulin and commonly functions to stimulate normal tissue growth. [46] Elevated levels of IGF-1 may likewise contribute to the pathophysiologic mechanism by which obesity promotes tumor cell growth and cancer progression.[46]

Aromatase, the enzyme responsible for converting androstenedione to estrone and estrogen, is found in many organs, including adipose tissue. As a result of the increased adipose tissue associated with obesity, increased aromatase produces increased estrogen, which promotes the growth of breast cancer.[47,48] Another process by which obesity promotes tumor growth is mediated by the intestinal microbiome, which harbors a great number and extensive variety of bacteria whose concentration and metabolic products are highly dependent on both the composition and quantity of our dietary intake and nutritional status. Shifts in these populations, such as increases in bacteroidetes or decreases in firmicutes, promoted by high fat diets, may lead to metabolic changes and circulating toxins that promote cancer growth.[49] Obesity may also predispose to cancer by mechanical factors, such as stretching of diaphragmatic muscles, leading to hiatal hernia and gastro-esophageal reflux disease, thereby predisposing to esophageal adenocarcinoma.[50–52] It has recently been shown that adipocytes (fat cells) can take up and metabolize cancer chemotherapeutic agents, thereby reducing available chemotherapy in the tumor microenvironment. Thus, the increase in adipocyte number and size associated with obesity, along with their ability to reduce tumor exposure to chemotherapeutic agents, provides a mechanism for tumor cells to escape and survive chemotherapy.[53]

Many of the effects just described are the result of alterations in metabolic, hormonal, or pro-inflammatory signaling pathways associated with obesity. These pathways may be regulated in relatively rapid response to changes in nutritional status. Obesity may also alter cellular messaging by more stable epigenetic processes in which modification of the DNA or its supporting chromatin proteins changes the genetic readout without altering the genetic sequence.[54–56] Such alterations include chemical modifications like methylation of DNA or methylation, acetylation, or other changes in chromosomal proteins that alter their structure and function.[54–56] Epigenetic changes that shift cellular metabolism to fatty acid synthesis and oxidation for generation of energy and cellular building blocks to promote growth in tissues with predisposing genetic mutations have been shown to occur after as little as three days of high fat diet feeding.[57],[58] Studies also suggest that high fat obesogenic diets may contribute to epigenetic suppression of immune responses to tumors.[58, 59]

Epigenetic changes may persist after nutritional status changes.[60,61] They may become heritable, through multiple generations of cell division, and may even become transgenerational, passing from parent to offspring.[60–62] It is now becoming apparent that lifestyle phenomena such as starvation, obesity, and physical activity may alter epigenetic factors that affect individuals and the ,pathophysiology of chronic conditions like obesity, diabetes and cancer.[55,63,64] For example, obesity has been shown to induce epigenetic, structural changes in the organization and structure of chromatin in colon epithelium that alter the binding of transcription factors promoting colon development and growth.[65] While these changes do not directly promote tumor growth, they induce chromatin structural remodeling that enhanced cell-signaling pathways driving cancer progression.[65] The sustainability of these epigenetic changes suggested the possibility that the tumor promoting effects of obesity, at any stage of life, may contribute to cancer progression at later ages, leading to the need for epigenetic targeted therapy.[56] The importance of considering both the metabolic, hormonal, and pro-inflammatory effects of obesity and the epigenetic effects is that the former may be largely eliminated or reversed with weight loss, whereas the latter may be more durable. Thus, while elimination of obesity and restoration of normal body weight is desirable at any time of life, it may not always reverse all cancer promoting consequences of obesity. Moreover, the rapid onset of epigenetic changes following initiation of obesogenic diets and their durability indicate potential problems with weight cycling, that is, recurrent weight loss and weight gain; also known as yo-yo dieting.

In studies on the effects of obesity on adverse health outcomes, it is noteworthy that not all adipose tissue has

the same metabolic, hormonal, or pro-inflammatory activity, and likewise, not all adipose tissue has the same tumor promoting activities. Visceral fat, consisting of the fat in and around abdominal organs, is more intensely metabolic and pro-inflammatory, produces more pro-inflammatory cytokines such as TNFα and IL-6, and is more likely to stimulate insulin resistance, diabetes, and cardiovascular disease than subcutaneous fat, which lies directly under the skin.[66–68] Visceral fat has been epidemiologically linked to tumor promotion in humans.[69,70] In mouse models, surgery to remove visceral fat depots has been shown to reduce development of the intestinal tumors[71] and ultraviolet light induced skin carcinogenesis.[72] However, this surgery is not practical in humans. Although liposuction removes subcutaneous fat, it has been used primarily for cosmetic body contouring[73] but has not been shown to produce sustained body weight loss or to reduce risk for many of the pathophysiologic consequences of obesity. Caloric restriction, on the other hand, is likely to reduce both subcutaneous and visceral adipose mass and to reduce risk of obesity-associated comorbidities. In preclinical animal model studies, prevention of obesity by calorie control or weight loss after calorie restriction, following diet-induced obesity, has been shown to reduce or delay the incidence of tumors.[74]

Other studies demonstrate that the tumor promoting effects of obesity can be reduced by pharmacologic interference with obesity-mediated growth promotion and pro-inflammatory pathways. For example, blockade of insulin or IGF-1 receptors[75] and molecular interference with leptin receptor[76] counteract the promotion of breast cancer by obesity. Likewise, both genetic and pharmacologic interference with pro-inflammatory activity of the complement system counteracts obesity-mediated progression of colorectal tumors.[57]

While obesity itself is associated with an increased risk for cancer, it is also clear that different dietary fats may have different effects on cancer development. Murine models and human epidemiologic studies indicate that not all dietary fat is equal in influencing obesity and cancer risk. For example, saturated coconut oil and corn oil promote tumor growth, while equal amounts of olive oil promote obesity but not tumor growth.[57] Further, high fat lard-based diets fed to obesity resistant BALB/C mice promoted the growth and metastasis of mammary carcinoma.[77] In general, tumor promoting fatty acids include medium chain saturated fatty acids, such as lauric and myristic acids; long chain saturated fatty acids, including palmitic and stearic acid; and ω6 polyunsaturated fatty acids, linoleic and arachidonic acids. In contrast, unsaturated fatty acids, including oleic and conjugated linoleic acid, and ω3 polyunsaturated fatty acids, including eicosapentaenoic, docosahexaenoic, and α-linolenic acid, have anti-inflammatory properties that function as tumor suppressors.[78]

Studies with animal models indicating that different types of dietary fat may impact tumor growth have been shown to be clinically relevant. For example, consumption of high quantities of olive oil was associated with decreased risk of upper aerodigestive and breast cancer.[79] Increasing ω-3 PUFAs has been shown to alter the risk of several malignancies, including breast, colon, lung, and prostate cancer.[80,81] A high fat walnut-based diet decreased risk for pancreatic cancer and cancer metastasis.[82, 83]

High carbohydrate diets leading to hyperglycemia and insulin resistance, especially in obese and/or diabetic individuals, have been shown in model, epidemiologic, and clinical studies to contribute to cancer progression and its adverse effects.[84–86] While obesity is associated with the increasing incidence of esophageal adenocarcinoma, increased carbohydrate consumption appears to be a contributing factor.[85] Recent studies further indicate that the consumption of high-fructose corn syrup drinks may contribute to the development of obesity and colorectal tumor growth.[87,88] At the clinical level, in patients with stage III colon cancer and elevated BMI who had failed adjuvant chemotherapy, increased glycemic and carbohydrate loads led to shorter overall survival.[86]

39.3 STRATEGIES TO DISRUPT THE OBESITY–CANCER LINKAGE

From a clinical perspective, the most effective way to prevent the increased cancer risk associated with obesity is by maintaining a lean body mass throughout life, using prudent lifestyle practices of dietary regulation and regular physical activity. For individuals who are overweight or obese, reducing the excess obesity-associated comorbid risk factors should primarily be addressed by lifestyle modifications to lose weight and restore normal body mass. Studies to demonstrate the clinical effectiveness of this approach are limited; however, they do indicate that intentional weight reduction by lifestyle modification, in morbidly obese patients, is associated with normalization of circulating cancer risk factors, including estrogens, insulins, IGF-1, and inflammatory markers such as IL-6, TNFα, and others.[89–91] It is noteworthy that these effects occurred with sustained weight loss. As noted earlier, in discussion of diet-induced epigenetic changes, weight cycling, repeated cycles of loss then regain of excess weight, has not been shown to effectively reduce obesity-associated cancer risk. It may in fact have the opposite effect of increasing risk for breast cancer, renal cell cancer, and non-Hodgkin lymphoma in post-menopausal women.[92]

While studies indicate that intentional weight loss can reduce obesity-associated biomarkers, there have been limited randomized controlled studies to evaluate whether dietary interventions can improve cancer risks or outcomes. In general, studies to alter dietary composition have not been effective at primary prevention of breast cancer occurrence or secondary prevention of tumor recurrence except when interventions were accompanied by weight loss.[93–99] In the prospective Woman's Health Initiative, an

observational study of 61,395 women ≥50 years old, followed for a median 11.4 years, weight loss ≥5% was associated with 12% lower risk of breast cancer, hazard ratio (HR) = 0.88 (95% confidence interval [CI]: 0.78–0.98).[100] The Pooling Project of Prospective Studies on diet and cancer examined the impact of weight loss on the incidence of breast cancer in 180,855 women over age 50, reported in ten studies from the United States, Australia, and Japan. For women not taking post-menopausal hormones, with weight loss and maintenance of greater than or equal to 9 kg, there was a 32% lower incidence of breast cancer, HR = 0.68 (95% CI: 0.50–0.93). A trend to reduced cancer incidence was even noted with sustained weight loss of 2–4.5 kg, HR = 0.82 (95% CI: 0.70–0.96).[101] Although demonstrating a decreased risk of breast cancer associated with weight loss, these studies did not provide comparisons to randomized groups of control patients.

In the LookAHEAD randomized clinical trial, 4,859 patients with obesity, mean BMI 36 kg/m^2, and Type II diabetes mellitus, mean age 58 years old, were divided into either an intensive lifestyle intervention (ILI) targeted at 7% weight loss and maintenance or a diabetic support and education (DSE) control group.[102, 103] After median 11-year follow-up, the cumulative incidence of obesity-associated cancers was 6.1 cases per 1,000 person-years in the ILI group compared with 7.3 cases per 1,000 person-years in the DSE group for HR = 0.84 (95% CI: 0.68–1.04). The 16% reduction in cancer risk for ILI, however, did not reach statistical significance. There were no differences between male and female patients, no specific differences in any tumor type, and no differences in overall or non-obesity-associated cancers. Although not statistically significant, the trend of 16% reduction was considered to provide important evidence that obesity-associated cancer promotion may be reversed by weight loss. The marginal effect resulting from this RCT involving 4,859 patients at 16 institutions with 11-year median follow-up, coupled with the difficulty of monitoring weight regulation by behavioral alterations ,illustrates the problems in conducting large-scale randomized control studies of cancer impact associated with lifestyle approaches to weight loss.[102,103]

The beneficial consequences of intentional weight loss have been most successfully demonstrated by bariatric surgery, in which obese patients undergo one of several surgical procedures to reduce and/or bypass gastric function and capacity.[104,105] Because of the profound metabolic changes associated with these procedures, they have more recently been referred to as metabolic-bariatric surgery (MBS).[105,106] With appropriate post-surgical management, these procedures are among the most successful in achieving sustained weight loss and reduction of comorbidities associated with obesity.[107–110] In the Swedish Obese Subject (SOS) prospective study, comparing the outcomes in 2,010 MBS treated patients with 2,036 controls, surgery was associated with 40% reduction in cancer incidence after 10.9 years' follow-up.[107,108] In a retrospective single practice study from Utah of 7,925 patients who underwent gastric bypass surgery, the surgical intervention showed a 60% decrease in cancer mortality compared with 7,955 controls.[111]

In a follow-up period of 16 years, overall mortality in the SOS study was reduced in patients undergoing surgery compared with medically managed obese patients. Cancer was noted to be the most common cause of death, with 47 cancer deaths in the control group compared with 29 in the surgery group. The number of first-time cancer diagnoses, 117 in the surgery group, was lower than in the controls 169.[108] MBS has been shown to reduce risk of endometrial cancer in severely obese patients.[112] In a recent retrospective study of 22,198 subjects who had MBS for severe obesity compared with 66,427 matched controls, surgically treated patients had a 33% lower incidence of new cancers over a three-year follow-up period compared with controls.[113] The risk reduction was greater for obesity-associated cancers, including post-menopausal breast, colon, endometrial, and pancreatic cancer.[113]

The recently reported SPLENDID (Surgical Procedures and Long Term Effectiveness in Neoplastic Disease Incidence and Death) trial describes a single-institution (Cleveland Clinic) retrospective observational cohort study that provides important new insights regarding the contribution of MBS to protection against cancer development and further demonstrates the importance of weight loss in the process.[114] Among 30,318 patients, 18–80 years old, BMI 35–80 kg/m^2, 5,383 who underwent MBS between 2004 and 2017 were matched 1:5 with 25,265 patients subject to conventional non-surgical obesity management. Among patients followed for median 6.1 years, there were 93 cases of obesity-associated cancers among MBS patients, for an incidence of 3.0 per 1,000 person-years, compared with 780 cases of obesity-associated cancers among controls, for an incidence of 4.6 per 1,000 person-years. The cumulative ten-year incidence for obesity-associated cancers was 2.9% among MBS patients compared with 4.9% in non-surgical controls, for adjusted HR = 0.68 (95% CI: 0.53–0.87) for obesity-associated cancers. The ten-year cumulative incidence for all cancers was 6.8% with MBS, compared with 8.3% in controls, for adjusted HR = 0.83 (95% CI: 0.69–0.99) for all cancers. There were 21 cancer deaths, 0.8% ten-year mortality, among MBS patients compared with 205 deaths in controls, 1.4% ten-year mortality, for adjusted HR = 0.52 (95% CI: 0.31–0.88). Reduced risk of cancer incidence with MBS was noted for both Black patients, adjusted HR = 0.47 (95% CI: 0.27–0.84) and White patients, adjusted HR = 0.71 (95% CI: 0.55–0.93). The study found similar cancer protective effects of sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB). MBS was associated with a decrease in most types of obesity-associated cancers and showed a statistically significant reduction in endometrial cancer. An important aspect of the SPLENDID study was that it provided strong evidence that protection against cancer was associated with degree of weight loss, with those achieving less than 24% weight loss showing the highest cumulative cancer incidence (6%), while those with greater than 39% weight reduction showed the lowest (1%) cancer incidence.

In summary, the SPLENDID study provides strong evidence that MBS is associated with a significantly lower incidence of obesity-associated cancers and all cancers, as well as decreased cancer-related deaths. The cancer protective effects extended to both Black and White patients and were clearly demonstrated to be associated with degree of weight loss.[114]

In more recent years, several programs have focused on the potential role of MBS to prevent specific cancers. Liver cancer has been a particular interest, since the obesity pandemic has been accompanied by a rapid increase in non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and cirrhosis, all of which function as precursors to liver cancer and more specifically, to hepatocellular cancer. Importantly, NAFLD, NASH, and cirrhosis are important precursors of liver cancer that can be evaluated in response to MBS.[115–117]

In 2017, a consortium of 110 academic medical centers and their 338 affiliated hospitals in the United States conducted a retrospective administrative database study comparing the presence of liver cancer among hospital admissions with and without MBS over a three-year period, 2011–2015.[118] Among 15,534,065 patients who never had MBS, there were 74,404 patients with liver cancer, for a prevalence of 477.72 cases per 100,000 admissions, compared with 336 diagnoses of liver cancer among 178,192 patients who had MBS, for a prevalence of 188.56 cases per 100,000 admissions. The reported prevalence ratio (PR) = 0.39 (95% CI: 0.35–0.44) suggests a 61% decrease in prevalence of liver cancer in patients who had undergone MBS. The association persisted for sex, race, and ethnicity.[118] In a retrospective survey of 2,881,414 patients with morbid obesity in the United States, the Nationwide Inpatient Sample (NIS) database, sponsored by the U.S. Agency for Healthcare Research and Quality (AHRQ) from 2004 to 2014, 230,956 patients who had undergone MBS were propensity matched with same number of non-surgical patients.[119] Compared to non-surgical patients, where there were 18 cases of hepatocellular carcinoma (HCC), those with MBS had 10 or fewer cases of HCC, for PR = 0.11 (95% CI: 0.63–0.48), accounting for an 89% decrease in the prevalence of HCC associated with MBS. Patients with MBS compared with non-surgical patients were also noted to have 75% decreased hospital mortality.[119] In another retrospective review from a single institution, University of Virginia, in which patients with obesity were followed for up to 12 years, 2,052 MBS patients were compared with 2,055 propensity matched non-surgical patients. MBS was associated with the development of a lower incidence of NASH, from 212 cases (10%) in non-surgical controls to 123 cases (6%) in MBS patients, odds ratio (OR) = 0.52 (95% CI: 0.40–0.68), for 48% reduction in NASH. The incidence of HCC decreased from seven cases (0.3%) in controls to one case (0.05%) in MBS patients.[120] In a meta-analysis of 9 reported MBS studies among patients with NALFD, NASH, and general obesity, BMI 40–47 kg/m^2, with a maximum 24-year follow-up, the incidence of HCC among 239,924 patients who had NALFD and underwent MBS was 0.051 cases/1,000 person-years compared with non-surgical controls, 0.34 cases/1,000 person-years, for a pooled adjusted OR = 0.63 (95% CI: 0.53–0.75), indicating that MBS decreased HCC incidence by 37%.[121]

To evaluate the impact of obesity and NAFLD and subsequent cancer outcomes and protective effects of MBS, a survey was performed of over 230 million unique patient medical records in the IBM Watson Health Market Scans Commercial Claims and Encounters Database from 2005 to 2014. A total of 98,090 patients were identified, 18–64 years old, with severe obesity, BMI $\geq$ 40 kg/m^2 and NAFLD, of whom 33,435 underwent MBS. After 96 months' follow-up, there were 1,898 incident cases cancer among 64,655 non-surgical patients and 925 incident cancers among 33,435 MBS patients, adjusted HR = 0.82 (95% CI: 0.76–0.89) for an 18% reduction in incidence for all cancers and adjusted HR = 0.65 (95% CI: 0.57–0.77) for a 25% reduction in obesity-associated cancers. There were 49 cases in total of HCC, resulting in adjusted HR = 0.48 (95% CI: 0.24–0.89) for 52% reduction. Reductions were also reported for colon cancer, pancreatic cancer, thyroid cancer, multiple myeloma, and endometrial cancer. Of all cancers in this group, endometrial cancer showed the greatest adjusted risk reduction of 52%, adjusted HR = 0.48 (95% CI: 0.31–0.73). Interestingly, risk reduction was greater in patients with cirrhosis compared with those without.[122]

Collectively, these five retrospective database surveys and meta-analysis indicate that in patients with obesity, MBS, compared with non-surgical controls, is associated with 37–89% decreased occurrence of HCC and/or liver cancer as well as a 48% reduction in NASH. The decrease in development of NASH appears to be a major benefit of MBS. While the actual case numbers of HCC and liver cancers are small, their prevention by MBS may become increasingly important, as the incidence of NASH and NAFLD and consequent liver cancer are expected to continue to increase in association with the obesity pandemic.[123]

The prevention of obesity-associated female cancers by MBS has also been an important area of inquiry. In a follow-up to earlier reports in which the SOS study indicated predominant cancer protective effects of MBS in women but not in men, the investigators reported an extended follow-up of 18.1 years median, 26 years maximum for female-specific cancers, including breast, endometrial, ovarian, cervix, and other gynecologic malignancies, among 1,420 women from the SOS surgical cohort and 1,442 contemporaneously matched controls.[124] The MBS group had an incidence of 205 new cancers compared with 267 in the control group, for adjusted HR = 0.71 (95% CI: 0.5–0.85), 29% protection. For female-specific cancers, there were 97 cases in the MBS group compared with 135 in controls, for adjusted HR = 0.68 (95% CI: 0.52–0.88). The MBS group compared with controls showed a decrease in breast, endometrial, and

ovarian cancer. However, only the decrease in endometrial cancer reached statistical significance: adjusted HR = 0.56 (95% CI: 0.35–0.89), 44% reduction in risk. Thus, multiple studies have now shown reduction in endometrial cancer in patients undergoing MBS.[110,112,114,122,124] Interestingly, the reduction in female-specific cancers in the SOS study was associated with elevated baseline insulin levels. Based on a number needed to treat (NNT) analysis, the authors determined the need to conduct MBS surgery in 56 patients to prevent the occurrence of 1 female-specific case of cancer over ten years[124].

Bariatric surgery has also been successful in achieving weight loss in cancer survivors[125] following primary treatment of malignancy, but long-term effects on recurrence and on overall or disease related survival have not yet been reported. Bariatric surgery to reduce weight during active treatment of malignancy has not been reported in enough numbers to evaluate its potential for mitigating adverse prognostic effects in patients with cancer.

In summary, dietary interventions have resulted in modest weight loss, improvement in cancer biomarkers, decrease in incidence of several cancers, and extended overall survival.[89–93,95–99] In an RCT of ILI weight loss, there was a trend to reduced cancer incidence that did not reach statistical significance.[102,103] In contrast, MBS has produced greater and more sustained weight loss and greater reduction in cancer risk.[107–114] The limited benefits of dietary interventions compared with MBS serve to emphasize the importance of significant and sustained weight loss and restoration of lean body mass to reduce cancer incidence among overweight and obese patients. Cancer prevention associated with MBS has been most notably, and most consistently, demonstrated for endometrial and hepatocellular cancers.[112–114,118,119,121,122,124] The persistence of some degree of elevated cancer risk after weight loss may be associated with lasting epigenetic consequences of obesity and may require specific targeted therapy to reverse. While those possibilities are in development, increased cancer risk associated with overweight and obesity is most effectively prevented by maintaining lean body mass throughout life and by emphasizing the necessity for adopting prudent lifestyle practices, including diet modulation, avoidance of pro-inflammatory foods, and regular physical activity.

39.4 LIFESTYLE RECOMMENDATIONS TO DISRUPT THE OBESITY–CANCER LINKAGE

39.4.1 Recommendations for Lifestyle Modifications for Primary Cancer Prevention

As previously discussed, maintaining a healthy BMI (18.5 to 24.9 kg/m^2) throughout life is as important to prevent certain common types of cancer as is avoidance of tobacco consumption. While there are multiple guidelines and recommendations on what constitutes a healthy approach to weight management, the most important behaviors focus on diet and physical activity. As any excessive energy consumption will be stored as fat, it is fundamental for successful weight loss to decrease the number of calories ingested while increasing physical activity. For persons striving to keep their current weight, expenditure and consumption of calories should be relatively balanced. Provided that endocrine disorders affecting basal metabolic rate do not play a role in one's health (i.e., hypothyroidism), the simple math of keeping energy expenditure greater than energy consumption should suffice as a rough guide.

A number of guidelines on physical activity and diet for cancer prevention are accessible to the general public and health practitioners (Table 39.1). Further descriptions are available in the accompanying chapters on the Importance of Nutrition in Cancer (Chapter 40) and in the chapter on Exercise Oncology (Chapter 35). The vast majority of recommendations focus on maintaining a lean body weight and avoiding obesity and were created using the best currently available data and a multitude of studies of mostly cohort nature that have validated the benefits of adhering to such guidelines for cancer prevention. In this section, we provide a compilation of current guidelines while adding personal recommendations on nutrition and physical activity to decrease cancer risk.

39.4.1.1 Achieve and Maintain a Lean Weight across Life Span

A BMI between 18.5 and 24.9 is considered healthy, as it is associated with decreased risk for developing many diseases, such as type 2 diabetes mellitus (DM), hypertension,

TABLE 39.1
Obesity Cancer Guidelines

American Cancer Society Guidelines for Nutrition and Physical Activity	www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html
American Institute for Cancer Research—Cancer Prevention Recommendation	www.aicr.org/cancer-prevention/
National Heart, Lung and Blood Institute	www.nhlbi.nih.gov/health/educational/lose_wt/BMI/ob_evtbl.htm
US Department of Health and Human Services: President's Council of Fitness, Sports and Nutrition	https://health.gov/our-work/nutrition-physical-activity/presidents-council

coronary artery disease, strokes, and of course, many cancers.[4,126,127] As previously noted, individuals should strive to achieve and keep a lean body weight throughout life, including childhood and elderly years, since increased weight at any time of life may result in obesity at later stages and may also have long lasting epigenetic effects. In a recent meta-analysis of 50 prospective studies, adult weight gain was significantly associated with increased risk for post-menopausal breast cancer, endometrial and ovarian cancers, as well as colon cancer in men.[128] In adolescents, overweight and obesity have been associated with increased risk for colon cancer[129] and colon cancer–related death.[130] And even though the overall incidence of colon cancer has decreased since the late 1990s, colorectal cancer rates have actually increased among younger patients ages 20 to 49.[131]

In adolescents and children over age 2, a BMI between the 5th and 85th percentiles is considered healthy. BMIs between the 85th and 95th percentiles are considered overweight, and above the 95th percentile obese. Childhood obesity predicts not only adulthood obesity but also type 2 DM and abdominal obesity.[132] For the overweight or obese, controversy exists as to which is more effective, rapid or gradual weight loss; however, whichever approach is taken, it is quite clear that long-term management is essential for maintenance.[133,134]

Since 1 pound is equal to 3,500 calories, in order to lose 1–2 pounds in one week, one must decrease the ingestion of calories by 500–1,000 calories per day on average. Making lifelong lifestyle changes is recommended by all national guidelines and leading experts to modify energy balance and maintain a healthy weight.

39.4.1.2 Avoid High-Calorie Foods and Sugary Drinks

A major contributor to the obesity epidemic is the availability and appeal of energy-dense foods, which are defined as having an energy content of at least 225 kcal per 100 grams. The densest micronutrient is fat, as each gram of fat = 9 calories. Each gram of protein and carbohydrate, on the other hand, corresponds to 4 calories.[135] Naturally, for the same amount of calories, a person can consume a much larger portion of food lower in energy density than a food higher in energy density. As an example, oranges have one-quarter of the energy density of one fried egg. In general, foods with the lowest energy density tend to be high in water and fiber content and very low in fat (fruits and vegetables). The consumption of energy-dense foods should be done sparingly.[136] Sugary drinks should be avoided completely, and so should fast foods. Fruit juices should also be limited. Fruits are best eaten whole.[136]

39.4.1.3 Prioritize Healthy Eating Patterns—Rich in Whole Foods, Plant-Based Elements

Because vegetables, legumes, whole grains, and fruits are very high in fiber and water and overall low in fat, they are the perfect example of low energy dense foods that promote healthy weight loss or weight maintenance. They should be consumed mostly whole, with minimal if any processing, including juicing. Processing such as juicing reduces the fiber content that promotes gastric stretching and feeling of satisfaction after eating while concentrating carbohydrates and calories.

39.4.1.4 Physical Activity

Physical activity has many health benefits. Not only does it "burn calories," but also, exercise can enhance muscle mass, leading to increased baseline metabolic rate, aiding in weight loss maintenance. It can also decrease levels of growth factor hormones such as insulin and IGF-1, improve lipid profile, and increase bone mineral density. Many studies have validated a protective effect of exercise in breast cancer,[137] even more so with vigorous activity.[138] Similar associations have been reported for colon[139] and endometrial cancers.[140] For more information, see Chapter 35.

39.4.1.5 Maintain Good Sleep Hygiene

Sleep may play a more important role in weight management than is credited. For natural successful sleep to occur, a highly structured circadian interplay of biological mechanisms, such as melatonin release in response to environmental cues such as dimming of lights/darkening, needs to occur. Lack of adequate sleep has been associated with many diseases, including obesity. Recently, it has been demonstrated that sleep restriction can in fact activate the endocannabinoid system, which modulates appetite and food intake,[141] as well as other appetite stimulating hormones such as ghrelin,[142] leading to an increase in BMI.[143] Sleep deprivation also worsens insulin sensitivity and is a risk factor for type 2 DM.[144] Short sleep duration has been associated with colorectal adenomas[145] and cancer.[146] In breast cancer patients with hormone receptor positive tumors, shorter sleep correlated with higher likelihood for systemic relapse.[147] The initial recommended approach to chronic insomnia is cognitive behavioral therapy, which mostly addresses healthy sleep practices and relaxation training.[148] It can lead to significant and durable symptom control.[149] It may be necessary to address an existing psychiatric disorder and to use pharmacotherapy when cognitive behavioral therapy alone does not effectively control insomnia.[150]

39.4.1.6 Lose Weight If You Are Overweight or Obese

As previously discussed, weight loss is achieved if a caloric deficit is created by restricting the intake of calories with or without increasing the energy expenditure with exercise. Clinicians should screen all adults for overweight and obesity and counsel on weight loss, referring patients to weight management programs if needed. It is important to stress that even 5–10% weight loss is already associated with substantial health benefits.[151] Also, small but meaningful weight loss can boost energy levels and improve mobility, self-esteem, and mood, leading to greater adherence to lifestyle modifications.

39.4.1.6.1 Weight Management Programs

Typically focusing on behavioral treatment, weight management programs offer a comprehensive approach to obesity and overweight, including a large element of coaching. Following individualized assessment, subjects commonly engage in both individual and group sessions aiming to educate and develop strategies to overcome barriers to lifestyle modifications. Patients are encouraged to establish weight loss goals and to develop a plan for reduced caloric intake and increased physical activity as well as self-monitoring strategies. Individuals are encouraged to engage in a steady and slow weight-loss process of 1–2 pounds per week, as very rapid weight loss (more than 3 pounds per week) can be associated with health hazards such as gallstones.

39.4.1.6.2 Metabolic-Bariatric Surgery

Morbidly obese individuals (BMI $\geq$ 40 kg/m^2) or obese subjects with a BMI $\geq$ 35 kg/m^2 who also have comorbidities (type 2 DM, for instance) and despite behavioral treatment cannot achieve target health outcomes are typically referred for a consultation with a bariatric surgeon.[152] Compared with lifestyle modifications, MBS leads to greater weight loss and higher rates of successful control of metabolic syndrome indicators, such as glucose intolerance/type 2 DM.[153] MBS also reduces development of NASH. On average, patients undergoing MBS lose 60% of excess body weight, with more than 80% of patients achieving either complete resolution or improvement of type 2 DM.[154]

There are different types of operations, with different technical challenges, complications, and morbidity.[104] The RYGB and the sleeve gastrectomy procedures typically have higher success rates when compared with gastric banding.[155,156] As with any medical intervention, failures can also occur, and re-operation may be required. For individuals undergoing operations leading to significant anatomical changes, such as the RYGB surgery, vitamin deficiencies can develop,[157] and monitoring and replacement for life (vitamin B12, iron, vitamin D) may be indicated.

Existing data are still conflicting in regard to whether bariatric surgery affects cancer-related mortality, in part due to the limitations of the studies reported, which are mostly of cohort nature and with short follow-ups. Some studies have demonstrated at least a 50–60% reduction in cancer-related deaths,[111,114,158,159] while others have found no effects.[160] In contrast, several Swedish studies suggest that MBS patients may have a higher incidence of colon cancer especially at ten years following surgery.[161,162] In these studies, it is noteworthy that the reported increased incidence of colon cancer is for obese patients who underwent MBS compared with the overall background population calculated by standardized incidence ratios (SIR).[163] In a follow-up study of five Nordic countries, Denmark, Finland, Iceland, Norway and Sweden, the same group using the SIR comparison approach found that patients with obesity, with or without MBS, showed increased colon cancer relative to the background population. However, when patients with obesity who underwent MBS were compared with control patients with obesity but no surgery, there was no significant increase in colon or rectal cancer after ten-year follow-up. A trend to increase in colon cancer was noted 14 years after surgery. Of interest, this study showed a marked reduction in uterine cancer in MBS patients compared with controls, HR = 0.69 (95% CI: 0.56–0.84).[163] In contrast, in a long-term, 22.2-year median follow-up of 4,047 patients (2,007 MBS and 2,040 contemporaneous controls) in the SOS study, there were 58 cases of colorectal cancer in the surgery group compared with 67 cases in the control group, adjusted HR = 0.89 (95% CI: 0.62–1.29), demonstrating that bariatric surgery was not associated with altered colorectal cancer risk.[164]

In summary, MBS provides proof of principle that significant and sustained weight loss can reduce cancer risk, particularly endometrial and hepatocellular cancers. However, because of the radical nature, high cost, and intensive follow-up care for those undergoing the procedure, there remains insufficient evidence to recommend for or against MBS primarily for cancer risk reduction. Moreover, the need to treat more than 50 patients to prevent 1 case of cancer is prohibitive.[124] Nevertheless, MBS actually constitutes an important option for treatment of severe and refractory obesity and its associated metabolic conditions,[107,109,110,114] with the potential for cancer risk reduction as an added incentive.

39.4.1.7 Follow Cancer Screening Guidelines

While people who are overweight or obese have a tendency to avoid cancer screening, it is important to remember that obesity increases the risk for cancer occurrence and that early detection increases the chance of cure and decreases the need for more extensive therapies that can cause unwanted side effects and complications. Moreover, patients with obesity who successfully undergo and maintain weight loss still remain susceptible to common causes of cancer. Accordingly, it is important that all individuals, especially those who are overweight or obese, follow recommended screening guidelines for breast, colorectal, lung, and gynecologic cancers.[165–171]

39.4.2 Guidelines for Secondary Prevention in Cancer Survivors

Cancer survivorship is, by definition, life after a diagnosis of cancer. From the time of diagnosis onward, treatment goals should focus not only on cure or lengthening survival, but also on decreasing and treating complications related to therapy, surveying for progression or recurrence of the original cancer, as well as preventing and detecting new primary cancers. With improvement in screening and treatment of different types of malignancies, the numbers of cancer survivors have increased substantially over the past decades. Currently, there are more than 18.1 million survivors in

the United States. They are projected to increase to 22.5 million by 2032.[172,173]. Two-thirds of cancer survivors are over 65, and many of them potentially face substantial challenges not only in recovering and living with sequelae from their diagnosis and treatment but also working on instituting and maintaining lifestyle modifications that can lead to improved health outcomes. In this section, we focus on the impact of obesity in cancer survivorship and potential strategies to address this health problem.

39.4.2.1 Secondary Prevention of Cancers

Obesity is a risk factor for cancer recurrence after initial diagnosis and treatment and can lead to worse outcomes.[174–176] Obese cancer survivors are more likely to develop complications from cancer treatment,[177–179] including lymphedema and post-operative complications. They are also more likely to develop new primary malignancies.[180] Therefore, following an initial cancer diagnosis, obesity should be aggressively treated as a risk factor that needs to be controlled as much as tobacco use.

39.4.2.2 Avoid Weight Gain After Cancer Diagnosis

Many interventions aiming to control and treat cancers can lead to deleterious weight gain. The etiology of weight gain following cancer diagnosis is multifactorial. It includes:

- Use of medications to prevent nausea and reactions to chemotherapy that are notorious for inducing increased appetite and weight gain (corticosteroids).
- Development of fatigue as a cancer symptom or a side effect of the treatments provided (chemotherapy, hormonal therapy, and radiotherapy) that decreases physical mobility and ability to exercise.
- Development of side effects such as neuropathy, myalgia, and arthralgia that can make regular forms of exercise a painful and challenging endeavor.
- Use of hormonal manipulation (especially in the case of breast and prostate cancers) leading to decrease in muscle mass and sarcopenic obesity (obesity with depleted muscle mass).
- Gastrointestinal side effects such as dysgeusia (taste bud changes), nausea, diarrhea, and constipation that lead to perversion of natural food choices and may skew food intake toward unhealthy food groups.
- Sleep dysfunction is a common manifestation of cancer and/or side effect from treatment, and as previously discussed, can contribute to weight gain.

The authors recommend that following a diagnosis of cancer, all the aforementioned strategies to control weight and obtain/keep lean body weight are developed and/or strengthened. Some other considerations specific to cancer survivorship include the following.

39.4.2.3 Use Exercise as a Tool to Decrease Obesity

Different forms of exercise activity have been studied in cancer survivors to combat side effects from treatment.[181,182]. While in the recent past, oncology patients were frequently told to rest and conserve energy, currently, they are told to be as active as possible. It is best to combine and diversify aerobic, resistance, and mindfulness-based exercise to achieve maximal health benefits and fight side effects. There is no single exercise prescription that fits all cases, and the type and level of activity should be tailored to individual needs and limitations.

Both aerobic and resistance training exercise can improve cancer-related fatigue,[183–186] a highly prevalent symptom that often persists after cancer-directed therapy is complete.[187] Positive effects of physical activity seem to be dose-related, with moderate- or vigorous-intensity exercise displaying a more pronounced impact.[188]

39.4.2.4 Use Exercise to Increase Cancer Survival Odds

The biological reasons for the protective effects of exercise may be more complex than simply weight management. For instance, there is evidence that exercise can modulate circulating levels of growth factors such as IGF-1[189] and insulin[190] as well as endogenous hormones such as estradiol.[191] For a detailed review on exercise for cancer prevention, refer to Chapter 35 on Exercise Oncology.

39.4.2.5 Make Dietary Changes to Achieve Weight Loss

Two clinical studies in breast cancer survivors have addressed the impact of dietary intervention on breast cancer recurrence and overall survival. The Women's Healthy Eating and Living (WHEL) study looked at the effects on breast cancer outcomes and overall survival of increasing the consumption of fruits and vegetables and decreasing the consumption of dietary fat. In this cohort of pre- and post-menopausal women, there were no differences in outcomes between the intervention and the control group[96] in terms of weight loss, progression free survival, or overall mortality. It is noteworthy, however, that the WHEL study was not designed to achieve weight loss. In contrast, the Women's Initiative in Nutrition Study (WINS) addressed the impact of decreasing all dietary fat to 15% of total energy intake and found a 24% lower risk of breast cancer recurrence; however, this was not statistically significant. Nonetheless, a secondary analysis found a 42% lower recurrence risk in the hormonal receptor negative breast cancer patients. Of note, even though the study did not target weight reduction, there was nonetheless a mean weight loss of 6 pounds in the intervention group.[98] These studies suggest that while dietary change alone was not sufficient to reduce the risk for breast cancer, risk may be reduced when diet change is accompanied by weight loss. The contrasting results in the WINS and WHEL studies may also be attributable, in part, to the fact that WINS focused on post-menopausal

women, while WHEL studied both pre-and post-menopausal women, along with other differences.[94] An ongoing initiative, the Breast Cancer Weight Loss (BWEL) study, is a randomized controlled study to specifically evaluate caloric restriction and exercise initiated after a diagnosis of breast cancer, targeted at achieving and maintaining ≥10% weight loss to decrease the risk of reoccurrence in overweight or obese pre- and post-menopausal women with early stage breast cancer.[192] Results of the BWEL study are anxiously awaited. Nonetheless, a recent expert panel convened by the American Society of Clinical Oncology concluded that there was an insufficient amount of evidence based on RCTs to recommend for or against intentional weight loss to improve outcomes. Accordingly, they recommend that patients with cancer should follow guidelines to support general health for patients undergoing active cancer therapy.[193]

39.4.2.6 Invest in Sleep Hygiene

Insomnia is an often-non-recognized symptom in cancer survivors. While many patients are insomniacs by the time of cancer diagnosis, many develop this symptom as a consequence of adjusting to the diagnosis, side effects from therapy, or cancer-related symptoms. As such, insomnia should be addressed in every cancer survivor and treated.

39.4.3 Type 2 Diabetes Mellitus and Cancer Risk

Obesity is a major risk factor for the development of type 2 DM. Type 2 DM is a condition defined by resistance to insulin, leading to sustained hyperinsulinemia and hyperglycemia, and it has been associated with an increased risk for different types of malignancies, including pancreatic, colon, endometrial, breast, and hepatobiliary cancers.[194] One of the working hypotheses for the increased cancer risk seen in diabetics is the cancer promoting effect of insulin and IGF-1, the levels of which are typically elevated in this population. These hormones can activate mitogenic pathways, affecting tumor microenvironment and cell-signaling pathways that lead to tumor growth and progression.[195] Type 2 DM is associated with excess mortality in a multitude of cancer types, including colorectal, breast, pancreatic, gastric, liver, endometrial, and even lung cancers.[196–198]

Metformin is commonly the first drug used for treatment of type 2 DM. Through activation of the AMP-activated protein kinase (AMPK) pathway,[199] it can decrease the production of glucose in the liver. It also increases insulin sensitivity and lowers its circulating levels. AMPK regulates cell metabolism and becomes activated when there is shortage of energy, and also acts as a tumor suppressor.[200] Through AMPK activation, metformin may exert cancer prevention properties and has been implicated in reducing the incidence of certain types of cancers in diabetics, including pancreatic, breast, and liver cancers.[201, 202] Many prospective studies were conducted to explore the chemopreventive properties of this drug. In the MA32 randomized, placebo controlled, double blind trial, involving 3,649 nondiabetic women undergoing usual treatment for breast cancer and followed for eight years, there was no statistically significant difference based on adjuvant therapy with Metformin versus placebo for disease free survival, overall survival, distant relapse free survival, or breast cancer free survival.[203] In an earlier trial of Metformin versus placebo in patients with Barrett's Esophagus, a precursor to esophageal adenocarcinoma, Metformin had no significant impact on cell proliferation, apoptosis, or phosphorylated S6 kinase, a biomarker of insulin pathway activation.[204] Thus, while Metformin has lost its apparent promise as a cancer preventive agent, it remains an important asset for managing type 2 DM in patients with or without cancer.

39.4.4 Special Considerations

The doses of most antineoplastic agents are traditionally calculated based on the body surface area (BSA), using the weight and height of the individual. Deviating from standard dosing and dose-intensity can compromise long-term outcomes and survival of cancer patients, particularly when treating with curative intent. In that regard, the American Society of Clinical Oncology (ASCO) has issued guidelines for treating oncologists on how to dose chemotherapy agents in the ever-growing obese population. ASCO recommends that chemotherapy agents are dosed on a full weight basis, and that ideal body weight or adjusted body weight are not used for dosing.[205] Obese cancer patients should be aware of this recommendation and ensure that treating oncologists are knowledgeable in this regard.

39.5 CONCLUSIONS

Obesity is a risk factor for many types of malignancies, including the highly prevalent post-menopausal breast and colorectal cancers. Excessive adipose tissue can contribute to tumor progression through a variety of mechanisms, including inflammatory, hormonal, and epigenetic alterations. Therefore, maintaining a healthy BMI across the lifespan is essential for cancer prevention. This can be achieved by adherence to national guidelines on diet and physical exercise. Since even after an initial cancer diagnosis, obesity may impact cancer-related outcomes, achieving and keeping a healthy weight constitutes a key priority in cancer survivorship.

39.6 RECOMMENDATIONS FOR LIFESTYLE MODIFICATIONS FOR CANCER PREVENTION

- Achieve and maintain a lean weight across the lifespan
  - Healthy BMI for adults: 18.5–24.9 kg/m^2
  - Adolescents and children over age 2: BMI between 5th and 85th percentile for the age

- If overweight or obese, lose weight gradually.
  - Weight loss goal: 1–2 pounds per week
- Avoid calorie-dense foods and sugary drinks.
  - Drink more water and avoid high glycemic foods such as desserts, sodas, white breads.
  - Prioritize healthy eating patterns, eating plant-based whole foods that are not calorie- but nutrient-dense (high in vitamins and minerals) and high in fiber content.
  - Consume at least five portions of vegetables and fruits of different colors (dark leafy greens, orange, red, yellow, and purple) daily.
  - Use legumes (beans) as a major source of protein.
- Limit the amount of certain animal-derived foods.
  - Red meat (beef, pork, lamb, goat) should be limited to <500 grams/week. If consuming animal protein, prioritize fish and poultry.
- Consider adopting a well-balanced vegetarian or vegan (whole foods, completely plant-based) diet.
  - Whole foods and a plant-based diet aid in weight loss and maintenance of healthy weight through avoidance of calorie-dense foods while providing ample amounts of protein, minerals, and vitamins.
- Engage in physical exercise.
  - Aim for at least 150 minutes of moderate exercise (brisk walk, biking, yoga) or 75 minutes of vigorous exercise (swimming, running/jogging) per week.
- Avoid completely the use of tobacco and if drinking alcohol, use in moderation.
  - Men should limit alcohol intake to up to two drinks per day and women to less than one drink per day.
  - One standard drink = 5 oz. glass of wine, 1.5 oz. hard liquor, 12 oz. beer.
  - Alcohol is a calorie-dense drink and can lead to weight gain.
- Prioritize sleep.
  - Aim for seven to eight hours of sleep every night.
- Avoid dietary supplements unless prescribed by a physician.
  - Obtain all vitamins and minerals from your diet. People following a strict plant-based diet (vegan diet) require oral B12 supplementation.
- If unable to lose weight by making all the aforementioned recommendations, consider joining a weight management program.
  - Achieving and keeping a healthy BMI should be a priority.
  - Discuss with primary care provider metabolic-bariatric surgery evaluation if behavior modifications fail to promote meaningful weight loss.

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40 The Importance of Nutrition in Cancer Prevention

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KEY POINTS

- Eat a plant-based diet rich in a variety of vegetables, fruits, whole grains, pulses, legumes, roots, and tubers.
- Limit or avoid the consumption of red and processed meat, alcohol, foods preserved by salting, and foods that are energy dense and nutrient poor.
- Eat a varied and balanced diet, eating foods from across all food groups rather than relying on supplements to protect against cancer.

40.1 INTRODUCTION

Cancer is the leading cause of death worldwide, accounting for one in six deaths in 2020.[1] Some cancers are found to be hereditary, but most are influenced by age, environmental, and lifestyle factors, accounting for up to 90% of the lifetime risk of developing cancer.[2] This large non-hereditary influence on risk indicates that primary risk factors associated with carcinogenesis are potentially modifiable for most cancers. Doll and Peto's seminal 1981 publication "The Causes of Cancer" introduced a framework of studying cancer prevention through modifiable environmental and lifestyle interventions, estimating that at least 35% of the cancer burden at the time was attributable to dietary factors.[3] They highlighted dietary factors hypothesized as protective against cancer and those, such as overnutrition and alcohol, that could increase risk.

The association between nutrition and cancer has been hypothesized since at least the 1800s.[4] Data have shown that nutrition is highly associated with cancer risk and that dietary patterns can either increase or decrease this risk. The National Academy of Sciences (NAS) published the first major institutional report on diet, nutrition, and cancer. This report provided the first evidence-based dietary guidelines for the prevention of cancer, recommending a decrease in dietary fat intake, an increase in plant-based foods, and not consuming nutrients through supplements.[5] Food groups and macronutrients such as protein, carbohydrates, and fats have been a focus in studying the impact of diet on cancer. Additionally, observational and prospective epidemiological studies have shown associations of individual micronutrients such as vitamins, minerals, and phytochemicals (defined here as chemicals from plants that may impact health but are not essential nutrients) with decreasing cancer risk, leading to several seminal clinical trials investigating the effects of supplements. However, many of the clinical trials investigating the potential anticancer effect of specific supplements or dietary components have yielded mixed results.[6] Understanding that foods and nutrients are consumed in combination and not in isolation, there has been a more recent shift to investigating the effect of diet as a whole, or dietary patterns, and cancer risk. Studying dietary patterns aims to dynamically capture food consumption over time and study interventions based on the concerted effect of nutrition. This can include measuring what and how much is consumed as well as when and how often.

There are current limitations in regard to making general evidence-based dietary recommendations for cancer prevention due to robust heterogeneity in cancer incidence, methodology for data collection, and shifts in dietary patterns over time. The influence of nutrition for the prevention of cancer can vary by cancer type. Additionally, dietary patterns are typically assessed through either an *a-priori* approach, using a dietary hypothesis and a standardized scoring system to evaluate adherence to the pattern, or an *a-posteriori* approach, by collecting dietary data, which are statistically analyzed to generate groupings of patterns observed.[7] In research assessing dietary patterns, individual dietary components are not evaluated for contribution to cancer risk. Dietary pattern research holds both potential for clinical effectiveness as well as challenges for well-defined intervention research. Gold standard dietary intervention studies are randomized, double-blinded, provision-controlled trials in which all foods and liquids are provided to participants for the duration of the study, which can be very difficult to carry out.

There now exist multiple national and international tools for researching dietary recommendations and making guidelines for cancer prevention as well as application tools to aid in public health messaging and adherence to guidelines. In the United States, the Dietary Guidelines for Americans is released every five years and now includes a section for cancer risk reduction. The National Cancer Institute (NCI) has created dietary assessment resources for research, which includes the commonly used Healthy Eating Index (HEI-2015) to evaluate dietary patterns, updated in 2015 in collaboration with the United States

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Department of Agriculture (USDA).[8] One of the most impactful research and public health messaging efforts on nutrition and cancer prevention was established by the World Cancer Research Fund International (WCRF), a not-for-profit organization network between the American Institute for Cancer Research in the US (AICR), World Cancer Research Fund United Kingdom, Wereld Kanker Onderzoek Fonds in the Netherlands, and World Cancer Research Fund Hong Kong. The WCRF established the Global Cancer Update Programme (CUP) to analyze how diet, nutrition, and physical activity impact cancer risk and survival. The CUP has now published three expert reports (1997, 2007, and 2018) comprising comprehensive analyses and leading to the development of the WCRF/AICR Cancer Prevention Recommendations.[9] These recommendations emphasize increased consumption of plant-based foods and limitation of certain foods and fluids to decrease cancer risk (Figure 40.1). In 2019, NCI also developed a standardized 2018 WCRF/AICR score that can be used by researchers to evaluate adherence to the recommendations and associations with cancer-related outcomes.[10] Recent use of this scoring system demonstrated that adherence to the 2018 WCRF/AICR recommendations substantially reduces total cancer risk. However, a high percentage of the study population had a low adherence score, indicating a significant opportunity to improve cancer prevention.[11]

40.2 SUPPLEMENTS

The 2018 WCRF/AICR Cancer Prevention Recommendations state directly: Do not use supplements for cancer prevention, consistently with the messaging recommended by the NAS in 1982. In the United States, supplement use is common and has increased over the past ten years in all adult age groups.[12] According to the National Health and Nutrition Examination Survey, over 57% of adults and 80% of women aged 60 and over use dietary supplements, most commonly multivitamin-mineral supplements, vitamin D, and omega-3 fatty acid supplements.[12] Dietary supplements are critical tools for the treatment of nutrient deficiencies and related conditions, but in the context of sufficiency, could lead to negative outcomes related to excessive and isolated intake.

Observational epidemiological studies among some human populations have generated hypotheses regarding the potential relationships between nutrients and cancer outcomes. The direct testing of these hypotheses to assess the impact of dietary supplements in cancer prevention is mostly limited to *in vitro* cell and preclinical animal studies. Specific micronutrients and phytochemicals are capable of modifying aspects of carcinogenesis in some cancers. There have been a variety of randomized control trials (RCTs) investigating dietary supplements, mainly antioxidants, folic acid and/or vitamin B, and vitamin D and/or

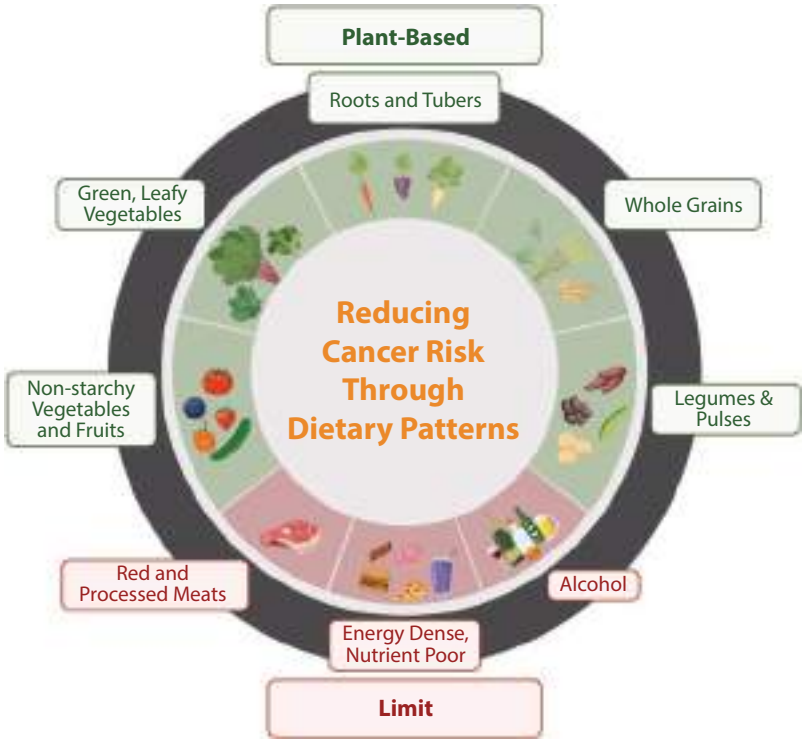


FIGURE 40.1 Nutrition is a key strategy for cancer prevention. Current recommendations encourage reducing cancer risk through dietary patterns that incorporate a plant-based diet and limit intake of components identified as increasing cancer risk. Multiple components of a plant-based diet have been identified in decreasing cancer risk, such as non-starchy vegetables and fruits, green, leafy vegetables, roots and tubers, whole grains, and legumes and pulses. Components recommended to limit include red and processed meats, energy, dense nutrient-poor items, and alcohol. Figure 40.1 was created using Biorender.com.

calcium, for the prevention of certain cancers. These studies have generally produced null results, with some even showing increased risk of certain cancers with supplement use.

In the case of antioxidants, β-carotene/retinoids, α-tocopherol/vitamin E, vitamin C, vitamin A, and selenium have been used in several cancer prevention clinical trials over the past 30 years.[13–28] The data from nearly all these studies showed that the supplement and/or combination of supplements did not protect against the incidence of the cancer being investigated. Furthermore, several of the studies reported increased risks with supplementation. There were some surprising results in which initial trials indicated potential protection against cancer incidence and mortality when studied as secondary endpoints, but when those were directly tested in follow-up studies, the effect was not seen. Further investigations have found that the initial trials were more successful because there were baseline deficiencies within the populations and that supplementation on top of sufficiency had no additional benefit.[29]

There have been only a few RCTs evaluating the effect of folic acid/vitamin B supplementation or vitamin D and/or calcium supplementation in the prevention of cancer. Clinical trials using folic acid supplementation with or without other B vitamins with cancer prevention as a primary endpoint or in a secondary analysis have mostly shown that the supplementation was not protective and in some cases, may have tumor-promoting effects.[30–34] Short-term RCTs using vitamin D and/or calcium supplementation have shown mixed results regarding cancer outcomes,[35–40] and given the short study period and sample size, there is insufficient evidence to draw cancer prevention conclusions. Overall, the potential effects of supplementation on cancer risk have been difficult to identify given the variable baseline nutrient status and dietary backgrounds of individuals, variation in supplement formulations and doses, study duration, and differential effects between tissue and cancer types.

40.3 PLANT-BASED DIETARY PATTERNS

Plant-based dietary patterns emphasize the consumption of a variety of fruits, vegetables, whole grains and cereals, nuts, seeds, legumes, herbs, and spices. Additionally, plant-based dietary patterns may encompass diverse constellations of a variety of plants as well as quantity. They are vaguely described as infrequent consumption of animal products along with frequent consumption of plant-based foods. Plants are rich in bioactive compounds, including fibers, vitamins, minerals, and polyphenols, that have been associated with anti-cancer properties and/or reduced cancer incidence as individual compounds, food components, and whole foods. As noted in the previous section, multiple expert panels/reports have concluded over the years that these bioactive compounds are most beneficial when consumed as whole foods.

Whole grains are grains and grain products that include the bran, endosperm, and germ layers, contributing soluble and insoluble fibers, protein, starch (carbohydrate), fats, and micronutrients, particularly B vitamins (e.g., thiamin, niacin, and folate), and phytochemicals to the diet. Conversely, refined grains have been processed in a way that removes some or all the nutrient-rich outer bran layer and inner germ core, to isolate the starchy carbohydrate middle endosperm layer. Notably, refined grains are often enriched with B vitamins and iron and may have variable nutrient and fiber status depending on the degree of processing. Whole grain and fiber intake are consistently associated with a reduced risk of gastrointestinal cancers. including colorectal,[41] colon, gastric, pancreatic, and esophageal cancers.[42,43] Investigations assessing the risk of cancer with high intake of refined grains are currently limited and potentially biased by the definition and types of refined grains studied. There have only been a few meta-analyses investigating the association of refined grain intake and cancer, yielding mixed results.[42] Importantly, there have not been studies to distinguish between refined grains that also contain high amounts of fat and/or sugar, such as cookies, doughnuts, and pizza, versus those that are considered staple foods, such as bread, non-sugary cereals, and pastas.[42]

Fruits and vegetables also contain varying levels and types of soluble and insoluble fibers, macronutrients, micronutrients, and phytochemicals. Fruits and vegetables can be classified using a botanical definition, where a fruit is precisely the mature ovary of a seed from the flower of a plant, or a culinary definition, in which fruits are considered to be sweet or sour while vegetables are non-sweet or more savory. Like the Continuous Update Project, this chapter will discuss fruits and vegetables from a culinary perspective that is commonly understood by consumers. In addition, vegetables are often discussed in dietary recommendations as starchy (e.g., corn, potatoes, acorn and butternut squash) or non-starchy vegetables (e.g., leafy greens, eggplant, tomatoes, peppers, onions, summer squash, asparagus). Starchy vegetables contain higher amounts of carbohydrate and less fiber, but still contain various micronutrients and phytochemicals. Like whole grains, a higher intake of non-starchy vegetables and fruit is associated with a decreased risk of gastrointestinal cancers.[9] Additionally, non-starchy vegetables and fruit intake are associated with a decreased risk of lung cancer, breast cancer, and bladder cancer. However, higher intakes of vegetables preserved by salting (e.g., kimchi, olives, cucumbers, canned vegetables with salt) are associated with an increased risk of gastric and possibly nasopharynx cancers.[9]

In plant-based diets, soybeans and other legumes such as beans, nuts, peas, and lentils are major protein sources. Like whole grains, vegetables, fruits, and legumes contribute various levels of macronutrients, micronutrients, fiber, and phytochemicals. Thus, higher intakes of these fiber-containing foods are associated with decreased gastrointestinal cancer risk.[9,41,44,45] Soybeans and soy-containing products contain naturally occurring isoflavonoids

that act as phytoestrogens and antioxidants in mammals. Due to their similarity to estrogen and differences in how rodents, a common preclinical research model, metabolize phytoestrogens compared with humans, there is a common misconception that soy may increase the risk of certain types of cancers, including hormone sensitive breast and prostate cancer. However, moderate intakes of soy and soy-containing products are associated with a decreased risk of breast cancer and do not increase the risk of recurrence of breast cancer.[46–48] Nuts, seeds, and legumes also contribute mono- and polyunsaturated fatty acids to the diet. Diets with a higher ratio of omega-3 to omega-6 polyunsaturated fatty acids have been associated with a lower risk of cancer than diets higher in omega-6 and saturated fats.[49]

Due to the differences in nutrient profiles, plant-based diets encourage intake of a variety of whole grains, vegetables, fruits, legumes, nuts, and seeds to constitute most of one's food intake. Plant-based dietary patterns can be achieved by following several different diets, including vegan diets that are free of animal products or vegetarian diets that may include animal products such as eggs and dairy (i.e., lacto-ovo vegetarian) or fish (i.e., pescatarian). Additionally, flexible vegetarian (i.e., flexitarian), Mediterranean diets, and other dietary patterns such as The New American Plate recommended by the AICR contain more animal products than vegan diets but still encourage a plant-based diet, with the majority of dietary intake coming from whole grains, vegetables, fruit, legumes, nuts, and seeds. In a recent meta-analysis, the highest adherence to a Mediterranean diet was inversely associated with a lower risk of cancer mortality and in the incidence of several cancers, including colorectal, liver, gastric, breast, head and neck, and prostate.[50] To date, the scientific evidence does not support one specific plant-based diet over the other for reduction in cancer risk. Individuals should be encouraged to follow the plant-based dietary pattern that fits their lifestyle and personal preferences and to which they can routinely adhere.

40.4 ENERGY BALANCE

Plant-based diets are typically more nutrient dense and less calorically dense (kcal per unit weight of food) than other dietary patterns. Thus, in addition to the nutrients provided, plant-based diets may facilitate a reduction in cancer risk by aiding in maintaining a healthy body weight. The first 2018 WCRF/AICR Cancer Prevention Recommendation is to be a healthy weight. Six of the other recommendations (be physically active, eat a plant-based diet, limit fast foods, limit red and processed meats, cut down on sugary drinks, and limit alcohol consumption) can influence energy balance and the healthy weight recommendation.

Overweight and obesity describe increasing states of the amount and/or distribution of body fat above a recommended range identified with improved health outcomes. Chronic positive energy balance due to an excess of energy intake from foods and drinks results in increased body fatness, obesity, and metabolic alterations. The mechanisms linking obesity and cancer are multifactorial and are not yet fully elucidated. Obesity induces chronic inflammation and insulin resistance, leading to increased levels of cytokines and growth hormones promoting cancer initiation and progression. Indeed, overweight, obesity, and metabolic syndrome are associated with increased incidence of at least 13 cancers.[51] According to the 2018 WCRF/AICR report, there is convincing evidence to support a causal relationship with increased adult weight gain and body fatness and the incidence of esophagus, pancreas, liver, colorectal, postmenopausal breast, endometrial, and kidney cancers,[52] Furthermore, their investigations have found strong evidence to support a probable causal relationship between adult body fatness and the risk of mouth, pharynx, larynx, stomach, gallbladder, ovary, and prostate cancers.[52] In contrast, the effect of body fatness in premenopausal breast cancer may lower risk. This paradoxical relationship is likely multifactorial and related to circulating estrogen concentrations, adipocytokines, inflammatory status, and insulin-signaling pathway activation.[53]

A Western diet or Standard American Diet dietary pattern is typically energy dense, consisting of large portions of processed foods, red and processed meats, and high fat and high sugar foods. In contrast to plant-based diets, the Standard American Diet is typically lower in whole grains, vegetables, and fruit. Thus, these dietary patterns are often associated with increased body fatness and increased risk of cancer, including colorectal cancer and hormone sensitive, postmenopausal breast cancer.[54]

40.5 PROCESSED FOODS

Food processing is a critical tool for providing foods to consumers—this tool can be used minimally or extensively, with a wide range of approaches. In general, processed foods are often criticized and their nutritious contributions called into question, but as defined by multiple regulatory systems and food science teachings, processed foods encompass a wide range of products. The U.S. Department of Agriculture defines a processed food as one that has undergone any changes from its natural state.[55] This could include milling, cutting, pasteurizing, cooking, canning, drying, fermenting, packaging, and addition of other ingredients. Thus, most of the foods within our food supply have been processed to some degree, and not all foods with some processing are unhealthy. Food processing can increase food safety and extend the shelf life of foods. Some food processing methods can preserve (e.g., freezing) or enhance (e.g., enrichment and fortification) the nutritional properties of foods. Other food processing methods can decrease the nutritional properties of foods and incorporate less nutritionally desirable ingredients such as added salt, sugars, and saturated and trans fats.

Multiple classification systems have been developed to describe the type and extent of food processing in

order to study the relationship between food processing and health. Currently, these frameworks vary in what is defined as processed and how the level of processing may influence health outcomes, but most do not include nutrient profiling parameters. One framework was developed as a part of the large multi-center European Prospective Investigation into Cancer and Nutrition (EPIC) in connection with the International Agency for Research on Cancer, referred to as the IARC-EPIC system.[56] The IARC-EPIC system bases food processing on the level of physical change made to the food per type of food and not the technique used, including how food is modified and prepared in the home. Conversely, the NOVA system, originally described in 2010[57] and revised over the years, classifies food based on the extent and purpose of the industrial processing.

Processed foods can be made by adding salt, oil, sugar, or other processed culinary ingredients. Processed food also includes preservation methods such as canning, curing, smoking, bottling, and non-alcoholic fermentation. Intake of foods preserved by salting, including pickled and/or fermented vegetables and salted fish, is associated with an increased risk of nasopharynx and stomach cancers.[9,58] Ultra-processed foods or highly processed foods are processed in such a way that nutrient density decreases and energy density increases through the addition of sugars and fats. Typically, these foods are ready-to-eat, such as sugar sweetened beverages, cookies and package baked goods, salty snacks, fast food, and frozen dinners. The consumption of ultra-processed foods is inversely related to diet quality. It is estimated that on average, Americans consume more than half of their calories from ultra-processed foods.[59] Due to increased energy density, habitual consumption of ultra-processed foods contributes to positive energy balance, weight gain, and increased body fatness. Ultra-processed food intake is associated with higher overall cancer risk and breast cancer risk.[60]

40.6 RED AND PROCESSED MEATS

Epidemiological data has long supported the association between red and processed meat intake and colorectal cancer.[61] In 2015, the IARC classified processed meat as a carcinogen.[62] A critical evaluation of the epidemiological studies investigating processed meat intake and cancer risk cautions such associations due to lack of scientific rigor. The 2018 WCRF/AICR report acknowledged the methodological limitations of the epidemiological studies and therefore considered the available mechanistic evidence as well in their recommendations regarding processed meat. Processed meat intake is strongly associated with an increase in colorectal cancer and may be associated with an increased risk of nasopharynx, esophageal, lung, stomach, and pancreatic cancers.[9,63,64] Additional controversy has emerged based on regional differences, in which investigations in some populations of Asian countries have not shown significant increases in colorectal cancer risk with red and processed meat intake.[65]

The associations between red meat, its specific components, and cancer risk indicate potential complexity.[66] Consumption of red meat, including beef, pork, sheep, horse, and goat, is probably a cause of colorectal cancer. One suggested mechanism is that red meat is higher in heme iron than poultry or seafood. Heme iron can increase the production of reactive oxygen species and formation of nitroso compounds that can lead to DNA damage within the gastrointestinal tract. Additionally, gastrointestinal carcinogens, including heterocyclic amines and polycyclic aromatic hydrocarbons, can be formed when meat is cooked well-done at high temperatures. However, these compounds can be formed in red and white meats and may not explain the association of red meat consumption and colorectal cancer. Most preclinical studies testing these potential mechanisms used concentrations of these compounds in excess of those found in human diets. Also, the semi-purified animal diets that were used did not include potentially protective compounds present in a variety of whole foods.[67] Another potential mechanism focuses on the interaction of red and processed meats with the gut microbiota and the impact on colorectal cancer.[68] From these data, it remains unclear whether red and processed meats are causes of dysbiosis of the microbe–host relationship or only increase risk if a pre-existing dysbiosis exists,[68] potentially indicating why there could be dramatic regional differences in the association of red and processed meats and cancer.[65] More evidence from rigorously designed studies is needed to fully understand the relationship between red meat consumption and cancer risk. In addition to iron, red meat is an excellent source of protein, vitamin B12 (almost exclusively found in animal products), niacin, vitamin B6, zinc, and phosphorus.[69] To balance risk versus benefit, the 2018 AICR/WCRF recommends limiting intake of red meat to 12 to 18 ounces (or three portions) per week in conjunction with a plant-based diet.

40.7 ALCOHOL

Alcoholic drinks include beers, wine, spirits, fermented milks, mead, and cider. On average, worldwide, adults consume one alcoholic drink per day (~14 grams of pure alcohol); however, alcohol consumption varies widely between and within different populations across the world. The National Toxicology Program of the U.S. Department of Health and Human Services classifies alcohol as a known human carcinogen.[70] Ethanol increases reactive oxygen species production in cells, and ethanol is metabolized to acetaldehyde. Both reactive oxygen species and acetaldehyde can damage DNA and proteins, increasing carcinogenic potential. Alcohol also decreases the absorption and utilization of several micronutrients associated with cancer risk (e.g., vitamin A, B complex, C, D, and E) and increases estrogen levels.[71] Although alcohol intake is often confounded with tobacco use, there is strong

TABLE 40.1
Clinical Nutrition Recommendations for Cancer Prevention and Control

Recommendation	Strategies for Implementation
Use a patient-centered treatment approach	• Use SMART (Specific, Measurable, Achievable, Relevant, and Time-Bound) goals; set personalized goals for each individual • Consider and address socio-economic barriers • Treat emotional or disordered eating behaviors • Consider consultation with or referral to other healthcare providers or agencies that can assist in treating or managing nutrition-related problems
Achieve and maintain a healthy weight throughout the lifecycle	• Consume a nutrient-dense, balanced diet • Participate in physical activity or exercise most days of the week • Follow obesity treatment guidelines considering lifestyle, pharmacological, and surgical treatment options as appropriate[78–80]

Eat a plant-based diet	• Balance meals and snacks according to The New American Plate with at least two-thirds of the plate being vegetables, fruits, whole grains, and beans and one-third or less animal protein
	• Follow a vegan, vegetarian, or Mediterranean dietary pattern
	• Consume 30 g/d of fiber from food sources
	• Eat a variety of:
	  • fruits (e.g., berries, oranges, apples, avocado)
	  • non-starchy vegetables (e.g., broccoli, okra, asparagus, peppers, cabbage)
	  • green, leafy vegetables (e.g., spinach, lettuce, kale)
	  • roots and tubers (e.g., carrots, sweet potatoes, turnips, beets)
	  • whole grains (e.g., brown rice, wheats, oats, barley, and rye)
	  • legumes and pulses (e.g., beans and lentils)

Limit consumption of red and processed meat	• Limit intake of red meat (e.g., beef, pork, lamb) to 12 to 18 ounces (or three portions) per week • Eat little, if any, processed meat (e.g., bacon, hot dog, sausage, pepperoni, deli meats)
Limit consumption of sugar sweetened beverages (e.g., soda, sweet tea, juices)	• Enjoy mostly low-calorie beverages such as water, sparkling water, and unsweet tea
Limit or avoid alcohol consumption	• It is best not to drink alcohol
Limit consumption of processed foods high in fat, starches, or sugars	• Limit consumption of "fast foods," many pre- prepared or packaged foods, baked goods, desserts, and candy • Consume fresh, frozen, or no salt added vegetable options • Prepare more meals at home and avoid adding fat, sugar, and salt during and after cooking • When eating out, choose foods lower in fat and sugar • Eat fruit or yogurt as a sweet food option
Do not use supplements for cancer prevention	• Aim to meet nutritional needs through diet alone • Use macro- and micro-nutrient supplementation to correct known deficiencies • Do not mega-dose or use high-dose dietary supplements

Source: Data from World Cancer Research Fund International and American Institute for Cancer Research, *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective: A Summary of the Third Expert Report*. World Cancer Research Fund International, London, 2018 and Shams-White, M.M., et al., *Nutrients*, 11(7), 2019.

evidence supporting the positive association between alcohol intake and the risk of mouth, pharynx, larynx, esophagus, liver, colorectal, and postmenopausal breast cancer.[9,72,73] Alcohol may also increase the risk of lung, pancreas, and skin cancers, although current evidence is limited.[9] Although the consumption of up to two alcoholic drinks per day may be protective against kidney cancers, most cancer prevention dietary recommendations endorse limiting or complete avoidance of alcohol.[9,74] In the United States, most alcohol related policies are regulated at the state level. More restrictive policy environments are associated with lower rates of most alcohol-attributable cancers.[71]

CLINICAL APPLICATIONS

There are important aspects regarding the incorporation of changes in dietary patterns to reduce cancer risk. While increased adherence to recommendations corresponds to decreased risk, adherence needs to be considered on a continuous scale with a goal of identifying what can be manageably changed in a sustainable way for an individual. Health and eating behaviors are multifactorial and are influenced at the individual, interpersonal, organizational, community, and public policy levels. Such factors include health status, knowledge, skills, motivation, preferences, social support, time constraints, food availability and accessibility, cultural

and societal norms, food environment, food pricing, media advertising, and public policy. Notably, over half of patients with obesity experience weight discrimination and bias, significantly reducing their access to quality healthcare and inducing additional barriers to improving health.[75] Additionally, there is a complex influence of economic and social injustices on dietary patterns and health status. The USDA found that the prevalence of cancer increases as the severity of food insecurity increases.[76] Often, food insecurity limits access to affordable, nutritious foods while incentivizing energy-dense, nutrient-poor foods.

Understanding the psychosocial aspects of food choices and behavioral changes is important. Many behaviors cannot be addressed in a single session or by solely providing a written handout, as knowledge alone is a poor predictor of behavior.[77] Patients are likely to benefit from a multidisciplinary treatment team (e.g., physician or advanced practice provider, dietitian, social worker, and/or psychologist) to meet their needs. Together, patients can make incremental, realistic, and sustainable changes building toward a lifestyle that contributes to overall cancer risk reduction. Furthermore, organizations and individuals at national, state, and local levels should work collaboratively to advocate for, develop, and implement policies to increase access to affordable healthy foods for all individuals throughout the lifecycle.

The diverse field of nutrition and cancer progression is burgeoning. The understanding of the pathology of carcinogenesis for different cancer types has improved, and the appreciation for the interaction between dietary components and health and disease has widened. There remains a need for RCTs that incorporate robust dietary information and the effect on specific cancers to offer evidence for the potential causative relationship between dietary patterns and different types of cancers. This effort will be made possible with improved tools and technologies to capture food intake and dietary patterns. Investigations into the nutritional components and quality of food between different sources and levels of processing and preparation offer insights into how we can make healthier choices even within the same types of foods. Efforts to highlight food insecurity and weight and health stigma bring to light the structural barriers people face regarding their nutrition and health. A person-centered approach to find ways to shift dietary patterns toward plant-based incorporation and limited intake of alcohol, nutrient-poor/energy-dense foods, and red and processed meats are recommended for reducing cancer risk (Table 40.1 and Figure 40.1).

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Part VII

Obesity and Weight Management



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41 Exercise Management for the Patient with Obesity

John M. Jakicic, PhD

KEY POINTS

- Physical activity contributes to the prevention of weight gain and a lower risk of developing obesity as an adult. Thus, physical activity should be emphasized in efforts focused on the primary prevention of weight gain and obesity.
- Physical activity can result in weight loss, even without a concurrent reduction in energy intake, and the magnitude of weight loss is dependent on the dose of physical activity.
- Physical activity is a key contributor to enhancing weight loss maintenance and the prevention of weight regain, which supports the need for intervention efforts focused on continued engagement in an adequate dose of physical activity for these outcomes.
- Moderate-to-vigorous-intensity physical activity is most strongly associated with weight loss and prevention of weight regain; however, a concurrent increase in light-intensity physical activity may result in additional weight control benefits.
- Physical activity is an important lifestyle behavior to include within medical-based treatments of obesity, which may include bariatric surgery and pharmacotherapy.
- Independently of body weight and obesity status, physical activity contributes to a variety of health benefits, which justifies its importance as a key lifestyle behavior for health in patients of optimal body weight and in patients with overweight or obesity.

41.1 INTRODUCTION

Overweight and obesity are significant public health problems, given the association between excess body weight and many chronic diseases, which include cardiovascular disease, diabetes, some forms of cancer, musculoskeletal disorders, and others.[1,2] Thus, public health approaches and interventions are needed to prevent overweight and obesity, and to reduce body weight in adults who are already diagnosed with overweight or obesity. The cornerstone of these approaches is lifestyle factors that contribute to optimal energy balance to prevent weight gain, and energy imbalance that results in an energy deficit to promote weight loss. One of the key lifestyle factors that have been implicated in these prevention and treatment efforts is physical activity.[3–5] This may result in important health benefits to patients.

41.2 EFFECT OF PHYSICAL ACTIVITY ON PREVENTION OF WEIGHT GAIN

Given the high prevalence of overweight and obesity in adults, much of the clinical emphasis is typically on effective treatments for weight loss. However, from a public health perspective, it is also important to consider effective approaches to prevent weight gain in order to reduce the onset of overweight and obesity.

There is evidence that physical activity may be an important lifestyle behavior that can contribute to these prevention efforts.[3,4,6] For example, there is cross-sectional evidence to support that an inverse relationship exists between physical activity and both body mass index (BMI)[7–13] and body fatness.[7,9,11–14] There are also prospective data from the NHANES-I Epidemiology Follow-Up Study,[15] Aerobics Center Longitudinal Study,[16] Women's Health Study,[17] and Harvard Alumni Study[18] to support the importance of physical activity for the prevention of weight gain. Others have also demonstrated that physical activity is important for maintaining a healthy body weight, defined as a BMI of $\geq$18.5 to <25 kg m^2,[19] and for reducing the odds of developing obesity.[20] Moreover, there may be a threshold of physical activity that is needed to prevent significant weight gain, defined as a weight gain of at least 3% of current body weight, with this threshold ranging from 150 to 250 minutes per week.[21]

The findings from prospective and randomized studies that were at least one year in duration to support that physical activity contributes to the prevention of weight gain were reviewed by the U.S. Department of Health and Human Services 2018 Physical Activity Guidelines Advisory Committee.[3,4] This review concluded that "there is strong evidence to demonstrate a relationship between greater amounts of physical activity and attenuation of weight gain in adults."[3,4] This review also supported that the evidence for the association and attenuation of weight gain in adults was most pronounced when physical activity exceeds 150 minutes per week, and when physical activity

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is at a moderate-to-vigorous intensity compared with less intense physical activity (e.g., light-intensity physical activity).[3,4] Moreover, despite the increased public health emphasis on reducing sedentary behavior, there is limited evidence to support that reducing sedentary behavior, without a concurrent increase in moderate-to-vigorous physical activity, will impact efforts to prevent weight gain.[22]

41.3 EFFECT OF PHYSICAL ACTIVITY ON WEIGHT LOSS

41.3.1 Physical Activity without a Concurrent Prescribed Reduction in Energy Intake

Physical activity has been recommended as a key behavior within interventions that target overweight and obesity.[2] However, the effects of physical activity on weight loss, when not coupled with a concurrent reduction in energy intake, appear to be on average quite modest.[23,24] For example, average weight loss of 2% at 6 months and 1% at 18 months was reported in a study of overweight adults who were prescribed home-based physical activity without a prescribed reduction in energy intake.[25] This is also consistent with the 0.5–3.0-kg weight loss in response to 180–270 minutes per week of physical activity that was reported based on a systematic review in the 2008 Physical Activity Guidelines Advisory Committee Report.[26] This systematic review also reported that weight loss did not occur when physical activity was reported to be less than 150 minutes per week.

Despite the modest average effect of physical activity on weight loss, there may be a dose–response effect, with the magnitude of weight loss increasing as the dose of physical activity increases. For example, a systematic review of the literature conducted for the 2009 Position Stand of the American College of Sports Medicine (ACSM)[21] concluded that there was no significant change in body weight in response to <150 minutes per week of physical activity, whereas a change of 2.0–3.0 kg and 5.0–7.5 kg was observed with >150 and 225–420 minutes per week of physical activity, respectively.

Donnelly et al. also reported on the findings from a randomized study that was 10 months in duration, with 5 days per week of supervised aerobic exercise that progressed to either 400 or 600 kcal per session. Results showed that weight loss was 3.9 ± 4.9 kg and 5.2 ± 5.6 kg in the 400 and 600 kcal per session conditions, respectively, with the no exercise control group showing a small weight gain (0.5 ± 3.5 kg).[27] A similar pattern was observed in this study for reduction in body fat. However, the additional weight or fat loss achieved within the 600 kcal per session condition was not statistically greater than the weight and fat loss achieved within the 400 kcal per session condition. These findings may suggest that significant weight loss can be achieved with progressively increasing engagement in aerobic physical activity to 400 kcal per session (equivalent to approximately 30–50 minutes per session at a moderate-to-vigorous intensity); however, increasing the energy expenditure to 600 kcal per session (approximately 45–65 minutes per session) may result in modest additional weight and fat loss.

41.3.2 Physical Activity Combined with a Prescribed Reduction in Energy Intake

It is recommended that within the context of a comprehensive behavioral weight loss intervention, a diet focused on reduced energy intake be coupled with an increase in physical activity.[1,2] There is an abundance of studies to support that physical activity, when added to a modest energy restricted diet, will result in greater weight loss than a modest energy restricted diet that does not also include physical activity. For example, results from a six-month weight loss intervention showed that the combination of both reduced energy intake and increased physical activity was associated with an increase in weight loss.[28] Moreover, findings from the multi-center Look AHEAD Study showed that within a comprehensive behavioral weight loss intervention, physical activity was a significant predictor of weight loss achieved at one year.[29] Examination of the scientific evidence further suggests that the addition of physical activity to an energy restricted diet will result in an additional 1.0–3.0 kg beyond what is achieved with an energy restricted diet alone.[23,24,30] While this magnitude of additional weight loss appears to be modest, Curioni and Lourenco[31] have suggested that the combination of physical activity and an energy restricted diet results in approximately 20% greater weight loss than the weight loss achieved with an energy restricted diet alone.

Despite the findings that behavioral interventions, on average, are effective for initial weight loss, the maintenance of weight loss is less than optimal.[32] Thus, there is a clinical and public health need for interventions targeting weight loss maintenance to be more effective. This is a particularly important health-related area that may highlight the important of physical activity, as physical activity appears to be important for enhancing weight loss beyond the initial six months of treatment, improving long-term weight loss maintenance, and minimizing weight regain.[21,33] An important observation is that relatively high levels of physical activity may be necessary to improve long-term weight loss,[34–41] and the magnitude of physical activity to enhance long-term weight loss and to minimize weight regain is recommended to be 200–300 minutes per week at a moderate-to-vigorous intensity.[21,33] The higher level of physical activity may be a particularly important behavior to achieve an initial weight loss of ≥10% at six months and to sustain this magnitude of weight loss at the conclusion of the 24-month intervention period.[42]

It is important to highlight a few important considerations that are pertinent to the association between physical activity and long-term weight loss and weight loss maintenance. First, most of the evidence for this association is supported

by data from secondary analyses or observational studies.[34–42] However, randomized studies do not necessarily support that the higher dose of physical activity contributes to improved long-term weight loss. For example, Washburn et al. reported that following a 3-month intervention, weight loss after an additional 12-month period did not differ when physical activity was prescribed at 150, 225, or 300 minutes per week.[43] Moreover, recent findings from a randomized study conducted in our laboratory showed that weight loss at 12 months did not differ when a reduced energy diet was combined with prescribed physical activity of either 150 minutes per week (−10.1 [95% confidence interval, CI: −11.5 to −8.8] kg) or 250 minutes per week (−9.4 [95% CI: −10.8 to −8.0] kg), and neither of these differed from weight loss achieved with a reduced energy diet without prescribed physical activity (−9.4 [95% CI: −10.8 to −8.0] kg).[44] These findings may suggest that the influence of physical activity on long-term weight loss and weight loss maintenance is observed when interventions exceed 12 months in duration. Moreover, this may support the need for effective intervention strategies that enhance initial engagement in physical activity and support continued physical activity beyond 12 months in adults with overweight or obesity.

41.4 ALTERNATIVE TYPES OF PHYSICAL ACTIVITY

41.4.1 Daily Steps of Physical Activity

There has been a proliferation of wearable devices that monitor and provide feedback on physical activity, and a common metric included in these devices is steps of daily movement. These devices are upgrades to the simple technology included in pedometers, which also monitor and provide feedback on steps of physical activity. It has been shown that providing a device, similar to a pedometer, to monitor and provide feedback on steps of activity resulted in an increase of 2,100 to 3,000 steps per day.[21,45] This increase in steps per day resulted in modest weight loss equivalent to 2–3 kg[21] or a reduction in waist circumference.[45] These findings were observed in studies where there was no concurrent prescription to decrease energy intake.

Creasy et al.[46] examined the effect of prescribing physical activity as steps per day within the context of a comprehensive behavioral weight loss intervention. Steps per day was the prescribed physical activity, to progress to 10,000 steps per day, with a target of at least 25% of those steps accumulated in bouts that were at least 10 minutes in duration at a moderate-to-vigorous intensity. Results after 12 weeks showed that participants achieved 10,323 ± 2,538 steps per day, with 36% of daily steps performed in bouts of at least 10 minutes in duration and at a moderate-to-vigorous intensity. Moreover, there was no difference in short-term weight loss achieved with the step-based physical activity prescription compared with a traditional structured physical activity prescription. There is also evidence to support that 10,000 steps per day, with at least 35% of the steps performed in bouts of at least 10 minutes and at a moderate-to-vigorous intensity, is associated with enhanced long-term weight loss and weight loss maintenance.[47] This may suggest that a step-based physical activity prescription is a viable method of prescribing physical activity for adults with overweight or obesity.

41.4.2 Resistance Exercise

While most of the research related to the effect of physical activity, in the absence of restrictions in energy intake, has focused on cardiovascular (aerobic) forms of physical activity, there is a body of literature on the effects of resistance exercise on weight loss. It has been proposed that the pathway by which resistance exercise may influence body weight is through an increase in lean mass, which may increase resting metabolic rate and also increase strength, which will result in an increase in free-living physical activity.[21] In combination, these may result in an increase in total daily energy expenditure, which may then have an effect on body weight regulation.[21]

There is evidence from studies of resistance exercise of a modest, but significant, increase in lean mass when this form of activity is not coupled with a concurrent reduction in energy intake.[48] However, this increase in lean mass is not observed when resistance exercise is coupled with a concurrent reduction in energy intake.[49, 50] Nonetheless, even in the presence of a concurrent reduction in energy intake, resistance exercise has been shown to increase muscular strength,[49] and it may also result in beneficial enhancements in the structure of skeletal muscle.[51] This may suggest that resistance exercise can be beneficial in enhancing strength and function in adults with overweight or obesity.

Despite the potential benefits of resistance exercise, systematic reviews have shown that this form of physical activity has modest effects on weight loss without a concurrent reduction in energy intake.[21, 52]. Moreover, within the context of dietary restriction, resistance exercise is not superior to aerobic forms of physical activity for weight loss.[52] There are few long-term trials of the effects of resistance exercise on weight loss,[52] and the inclusion of resistance exercise may not enhance the maintenance of diet-induced weight loss.[53]

Despite the above-mentioned potential benefits of resistance exercise, systematic reviews have concluded that resistance exercise has a modest influence on weight loss when performed in the absence of reductions in energy intake.[21, 52] One potential explanation for this lack of an effect of resistance exercise on weight loss is that the potential increase in lean mass may offset the reduction in the loss of fat mass, and this may result in absolute body weight remaining unchanged.[54–57] Moreover, it has been suggested that the energy expenditure resulting from resistance exercise may have been insufficient to result in weight loss in studies that have been relatively short in duration (e.g., six months or less).[21,26] There are limited data available from longer-term studies,[52] and the limited data available do not

support that resistance exercise enhances the maintenance of weight loss resulting from an energy restricted diet.[53]

The evidence does not support that resistance exercise is superior to aerobic forms of physical activity for either short-term or long-term weight loss, either without energy restriction or when coupled with energy restriction.[52] However, there is evidence to support that resistance exercise may reduce subcutaneous abdominal adiposity,[58] which has been shown to be associated with reduced cardiometabolic health risk.

41.4.3 Yoga

Yoga participation is a form of physical activity that may have the potential to contribute to weight loss and the treatment of obesity. Within the context of yoga, there are many styles and components that may need to be considered when determining if this is a form of physical activity that can impact body weight regulation.

A major aspect of yoga practice is the asanas (poses), and how these asanas are performed can impact energy expenditure, which may then also have implications for body weight control. Some styles of yoga perform the asanas in a manner that holds the body in a static manner prior to moving to the next asana, and this style of yoga typically elicits energy expenditure that is consistent with light-intensity physical activity (1.5 to 3.0 metabolic equivalents [METs]).[59] An alternative style of yoga is one in which the asanas flow from movement to movement in a continuous manner, rather than being held statically, and this stye of yoga elicits an energy expenditure that consistent with moderate-to-vigorous-intensity physical activity (e.g., ≥3.0 METs).[60] Thus, given these differences in energy expenditure, the style of yoga may have different effects on body weight.

There have been few studies that have examined the effects of different styles of yoga, within the context of a comprehensive intervention program that includes a prescribed energy-reduced diet, on weight loss in adults with overweight or obesity. A study conducted in our laboratory compared a restorative hatha style of yoga with a vinyasa style of yoga within the context of a six-month comprehensive behavioral weight loss intervention.[61] There was no significant difference in weight loss between these styles of yoga. However, as expected, participants reported that vinyasa yoga rather than the restorative hatha style of yoga was more likely to elicit an effort similar to brisk walking.

Another recent study examined whether adding 12 weeks of yoga following an initial 12 weeks of a behavioral weight loss intervention enhanced weight loss that was observed at 6 months.[62] This study showed that the additional yoga at 12 weeks to a behavioral weight loss intervention resulted in greater weight loss at 6 months (9.0 kg vs. 6.7 kg) compared with not receiving the addition of yoga. However, these findings need to be interpreted with caution, given that the comparison group was not provided with an additional physical activity intervention at 12 weeks. This is a limitation, given that other studies have shown that the addition of other forms of physical activity after initial weight loss can also enhance subsequent measures of weight loss.[30] Thus, it is unclear whether the additional weight loss observed is a result of specifically adding yoga to the intervention or whether adding any form of physical activity would have resulted in a similar finding. Thus, the effects of yoga on weight loss are currently inconclusive. Moreover, there is a lack of evidence supporting the efficacy of yoga for weight loss beyond a six-month intervention.

41.5 PHYSICAL ACTIVITY INTENSITY

Within the context of interventions for weight loss, physical activity has typically been prescribed at a moderate-to-vigorous intensity. Greater improvements in cardiorespiratory fitness are observed with vigorous compared with moderate-intensity physical activity.[37,63] However, when controlling for energy expenditure, there does not appear to be a difference in weight loss achieved with the inclusion of moderate-intensity compared with vigorous-intensity physical activity.[37,63] This suggests that physical activity energy expenditure, rather than physical activity intensity, makes the greatest contribution to weight loss. Thus, strategies to enhance physical activity energy expenditure may need to be the emphasis of interventions focused on weight loss and the treatment of obesity.

An alternative form of physical activity that has gained popularity is high-intensity interval training (HIIT). This has been defined as "episodic short bouts of high intensity exercise separated by short periods of recovery at a lower intensity."[64] Studies have shown that HIIT is not superior to other forms of moderate-to-vigorous-intensity physical activity for changes in weight, body fatness, or lean mass.[64–66] Thus, provided that it is not contraindicated, HIIT may provide an alternative to traditional physical activity prescriptions for adults with overweight or obesity.

The term "nonexercise activity thermogenesis" (NEAT) is used to describe energy expenditure that does not result from sleeping, eating, or structured periods of exercise.[67] This form of physical activity may be comprised mostly of light-intensity physical activity rather than moderate-to-vigorous physical activity. Within the context of obesity treatment and weight loss, light-intensity physical activity may provide weight loss benefits in addition to what is achieved with moderate-to-vigorous physical activity. For example, Jakicic et al.[28] found that the amount of light-intensity physical activity, in combination with moderate-to-vigorous physical activity and reduced energy intake, was predictive of weight loss achieved during a six-month behavioral weight loss intervention. Secondary data analysis also showed that light-intensity physical activity, in combination with moderate-to-vigorous physical activity, was associated with long-term weight loss and enhanced weight loss maintenance.[39] In an additional study conducted in our laboratory, we again have shown that light-intensity physical activity, in combination with

moderate-to-vigorous intensity physical activity, is associated with weight loss achieved at both 6 and 12 months of a comprehensive behavioral weight loss intervention.[68] These findings suggest that interventions for weight loss should emphasize the need for moderate-to-vigorous intensity physical activity, and there should also be an emphases on increasing participation in lifestyle forms of light-intensity physical activity.

Within the context of physical activity intensity, consideration of the influence of reducing sedentary behavior warrants consideration. The reduction in sedentary behavior has gained considerable attention relative to its association with enhancing a variety of health-related outcomes.[22,26,69] Despite the potential health benefits of reducing sedentary behavior, there is limited evidence to support that reducing sedentary behavior alone will have a positive impact on measures of weight control or obesity.[70–72] Studies that have examined sedentary behavior within the context of a comprehensive behavioral weight loss intervention have also not shown an association between reduced sedentary behavior and weight loss.[28] This may be a result of a minimal increase in energy expenditure with the change in posture from sedentary (lying or sitting) to non-sedentary (standing), whereas changing from sedentary to movement (walking) results in a substantial increase in energy expenditure.[73] Thus, for weight loss, reducing sedentary behavior in combination with increasing movement appears to be needed and should be recommended for patients with overweight or obesity.

41.6 DURATION OF PHYSICAL ACTIVITY BOUTS

Until recently, public health guidelines have recommended that physical activity be accumulated in bouts of 8-–10 minutes to have favorable benefits on a variety of health-related outcomes.[26, 74] However, evidence reported in the 2018 Physical Activity Guidelines Advisory Committee Report support that bouts even shorter than 8–10 minutes in duration are associated with a variety of health benefits.[4,75] Included in these health benefits are measures of obesity that include BMI,[7–9,11] and body fatness.[7,9,11–13] However, these findings may need to be interpreted with caution, given that they are supported primarily by evidence from cross-sectional studies. When prospective studies are examined, the evidence supports that physical activity accumulated in bouts of at least 10 minutes is associated with a lower incidence of obesity, whereas this finding was not supported when examining physical activity accumulated in bouts of a shorter duration.[76] Moreover, secondary data analysis from an intervention study supports that moderate-to-vigorous physical activity performed in bouts of at least 10 minutes in duration was associated with greater weight loss at 18 months, with physical activity accumulated in bouts less than 10 minutes in duration not being associated with weight loss.[39,47] These findings may suggest that adults with overweight or obesity can realize health benefits with physical activity accumulated in bouts less than 10 minutes in duration; however, to enhance weight loss, physical activity may need to be accumulated in bouts of at least 10 minutes.

41.7 THE TIMING OF PHYSICAL ACTIVITY BOUTS

Evidence has started to emerge related to the time of day when physical activity occurs and its relationship with obesity-related outcomes. There is a circadian clock in muscle tissue, and it has been suggested that physical activity may impact this pathway, which may further impact substrate metabolism.[77] This potential influence on substrate metabolism, along with other potential pathways that have yet to be determined, may provide a variety of biological pathways by which the time of day when physical activity is performed may influence body weight. There are few studies that have specifically examined whether the timing of physical activity influences weight loss, with the limited data results primarily from secondary data analyses.[78] In the context of a 10-month supervised physical activity study, when the majority of physical activity was performed between 7:00 and 11:59 AM, the weight loss was 7.2 kg, whereas when the majority of physical activity was performed between 3:00 and 7:00 PM, the weight loss was 2.1 kg. Given that this was a supervised physical activity study, sessions were not offered after 7:00 PM, so it is unclear how structured periods of physical activity performed after 7:00 PM would influence weight loss. Moreover, this study did not include measures of potential mechanisms that may have contributed to these findings.

Schumacher et al. examined whether consistency of the time of day when physical activity was performed was associated with greater physical activity participation in participants in the National Weight Control Registry.[79] This study showed that regardless of the time of day when physical activity was performed, being consistent with that time of day resulted in greater physical activity compared with participants who were not consistent with the time of day of their physical activity. Creasy et al. reported that patients defined as weight loss maintainers engaged in higher amounts of moderate-to-vigorous physical activity, with more of this occurring in the morning hours, compared with control participants with obesity or without obesity.[80] In adults who had bariatric surgery, a greater amount of physical activity performed in the morning hours was associated with greater overall physical activity.[81] This greater amount of physical activity, which may be influenced by the time of day or consistency of when physical activity is performed, may contribute to increased energy expenditure, which may influence body weight regulation. These findings may support that there is a behavioral influence, and not only a biological influence, for how the time of day when physical activity is performed may contribute to the effects of physical activity on body weight regulation and the treatment of obesity.

From a clinical perspective, these findings may suggest that consistency of when physical activity is performed should be an important behavioral target that can enhance physical activity participation and result in greater energy expenditure. Moreover, when feasible, there may be some additional benefit from physical activity being consistently performed in the early hours of the day. However, the specific mechanisms by which physical activity timing may influence body weight regulation have not been confirmed, and the findings from the observational studies warrant confirmation from appropriately designed and rigorous research studies.

41.8 THE ROLE OF PHYSICAL ACTIVITY IN THE MEDICAL TREATMENT OF OBESITY

41.8.1 The Role of Physical Activity in Surgically Induced Weight Loss

Bariatric surgery has become a more common treatment for obesity[82] and results in highly significant weight loss compared with nonsurgical interventions for weight loss.[83] While there is limited additional weight loss observed in the short term (<6 months) following bariatric surgery with the addition of physical activity,[84,85] the existing evidence does support that surgically induced weight loss is enhanced with physical activity at 12 months and beyond.[85–88] Thus, patients who undergo bariatric surgery may benefit from physical activity to enhance long-term weight loss, and therefore, physical activity should be included within a treatment plan for these patients.

41.8.2 The Role of Physical Activity in Pharmaceutically Induced Weight Loss

There is a pipeline of pharmaceutical agents focused on weight loss for the treatment of obesity. These medications have varying degrees of effectiveness; however, recent trials have shown that current pharmaceutical agents can be highly effective for weight loss. For example, liraglutide and semaglutide are glucagon-like peptide-1 analogues that are currently approved for weight loss, and 68 weeks of liraglutide resulted in mean weight loss of 6.4%, while semaglutide resulted in mean weight loss of 15.8%, from baseline body weight.[89] Within these pharmaceutical approaches for weight loss, patients were also prescribed an energy restricted diet and a prescription to engage in physical activity of at least 150 minutes per week. While most of these pharmaceutical trials do not specifically report on the adherence to the physical activity recommendation or how adherence to the physical activity recommendation may be associated with weight loss, it is important to highlight that physical activity is a component of the comprehensive treatment plan. Moreover, regardless of whether physical activity significantly contributes to the weight loss observed in response to these pharmaceutical agents, as highlighted later, physical activity may contribute to other health-related outcomes in patients with obesity, and these health benefits may be independent of weight loss.

41.9 WEIGHT LOSS VARIABILITY IN RESPONSE TO PHYSICAL ACTIVITY

There is a high degree of individual variability in weight loss in response to physical activity,[90] and this has been observed even in studies that included structured periods of highly controlled exercise.[91] There are a variety of factors that may contribute to this variability in weight loss with physical activity. There may be biological factors that contribute to this variability, and this is supported in studies of twins, in which there was small variability within a pair of biological twins but greater variability within non-biological pairs of twins.[92] There is evidence of inter-individual variability in energy intake in response to physical activity, with some individuals experiencing an increase in energy intake and others experiencing a reduction in energy intake in response to physical activity, which can contribute to variability in energy balance.[93,94] There are also genetic[95–97] and psychosocial factors[98,99] that are associated with physical activity engagement, and these may further contribute to weight loss response with physical activity. These factors are important to consider when there is less than the expected weight loss in response to physical activity in adults with overweight or obesity, and clinicians should be cautious about attributing this lack of weight loss response solely to the possibility of lack of compliance by the patient. Rather, exploring potential causes of this lack of weight loss response to physical activity warrants careful consideration on behalf of the clinician.

41.10 PHYSICAL ACTIVITY, FITNESS, AND HEALTH OUTCOMES

41.10.1 Effects on Mortality and Cardiovascular Disease

There is a substantial body of evidence to support that a higher level of cardiorespiratory fitness is associated with reduced risk of mortality. This association between cardiorespiratory fitness and reduced risk of mortality may be present even when adjusting for body mass index[100–104] or body fatness.[105,106] However, there is also evidence to support that fitness will not completely ameliorate the risk of a higher level of BMI or body fatness on these outcomes.[107–109] Thus, to maximize the reduction in mortality and cardiovascular disease, public health and clinical approaches should focus on both weight loss and enhancing cardiorespiratory fitness in adults with overweight or obesity.

More recently, secondary analyses examining the association between physical activity and cardiovascular disease outcomes from the Look AHEAD Study have been reported.[110] These result showed a significant inverse

association between objectively measured physical activity and outcomes of cardiovascular disease in patients with type 2 diabetes, and these results remained significant after controlling for a variety of covariates that included weight loss. However, an important finding from these analyses was that the association between change in physical activity and cardiovascular disease was not present after one year of observation but was present after four years of observation. Other studies have also shown that the association between physical activity and cardiovascular disease in prospective studies was observed for periods beyond one year.[111] These findings may suggest that for physical activity to reduce the onset of cardiovascular disease, physical activity needs to be sustained for relatively long periods (e.g., more than one year), and therefore, strategies to enhance long-term engagement in physical activity are needed.

41.10.2 Effects on Risk Factors for Cardiovascular Disease

41.10.2.1 Left Ventricular Mass

A clinically prognostic indicator of cardiovascular disease is the left ventricular mass of the cardiac tissue.[112,113] When measured by either echocardiography[114] or cardiac magnetic resonance imaging,[115, 116] BMI is positively associated with left ventricular mass. This association between BMI and left ventricular mass may reflect a maladaptive response that contributes to the association between obesity and cardiovascular disease. Jakicic et al. recently reported that weight loss induced by an energy restricted diet resulted in significant reduction in left ventricular mass in middle-aged adults.[44] However, when physical activity was combined with the energy restricted diet, there was a blunting of the reduction in the left ventricular mass. Moreover, cross-sectional evidence from this same study showed that cardiorespiratory fitness was associated with greater left ventricular mass in adults with overweight or obesity.[116] Thus, combining physical activity with weight loss that results in an increase in cardiorespiratory fitness, which is associated with a greater left ventricular mass, may reflect a clinically adaptive response that indicates an improvement in cardiac structure and function. This may provide an explanation of why both weight loss and physical activity, in combination, contribute to reduced risk of cardiovascular disease.

41.10.2.2 Blood Pressure

Hypertension is a risk factor for cardiovascular disease. Whether interventions should target treatment of obesity, low fitness, or the combination of obesity and low fitness to reduce resting blood pressure is an important clinical question. Some studies have reported that both obesity and low cardiorespiratory fitness are significantly associated with the risk of developing hypertenstion.[117] However, other studies report that when both a measure of obesity and cardiorespiratory fitness are considered in the same analysis, the measure of obesity and not cardiorespiratory fitness is associated with systolic blood pressure.[118,119] In response to a 12-month weight loss intervention in adults with overweight or obesity, a reduction in systolic blood pressure was reported, and a similar reduction was observed with weight loss induced by an energy restricted diet alone or when this same diet was combined with physical activity.[44] However, there is also evidence to support that structured periods of physical activity can significantly decrease blood pressure.[120] Thus, collectively, it may be important to target both weight loss and physical activity, which elicits an increase in cardiorespiratory fitness, to maximize reduction in blood pressure.

41.10.2.3 Lipids

Abnormal blood lipids are risk factors for cardiovascular disease, and there is an association between obesity and blood lipids.[2] Thus, interventions that target the treatment of obesity may contribute to improved lipid profiles, which are associated with reduced risk for cardiovascular disease. However, there are inconsistent results regarding the potential effect of physical activity on changes in blood lipids. For example, weight loss induced by an energy restricted diet resulted in favorable improvements in blood lipids; however, the addition of physical activity to the same diet did not result in further improvements in blood lipids in adults with overweight or obesity.[44] Similar results have been shown in other studies of weight loss and physical activity.[30] However, these findings are in contrast to the results from the CALERIE Study, which reported that the addition of physical activity to calorie restriction resulted in reductions in total cholesterol and low-density lipoprotein (LDL), and these reductions were not reported with calorie restriction that did not include physical activity.[121] Moreover, in the absence of dietary restriction or weight loss, physical activity has a modest effect on blood lipids,[122,123] while other studies have reported no influence of physical activity on changes in blood lipids.[128]

41.10.2.4 Inflammatory Markers

Biomarkers of inflammation and anti-inflammation contribute to the processes of atherosclerosis.[124] Studies have shown that physical activity is not associated with improvements in markers of inflammation,[123, 125] and cardiorespiratory fitness has also been shown not to be associated with markers of inflammation.[126] These findings support that physical activity may not be the preferred therapy for improving measures of inflammation in adults with overweight or obesity.

41.10.2.5 Cardiorespiratory Fitness

As highlighted in the preceding sections, cardiorespiratory fitness may be a clinically meaningful correlate of a variety of health-related outcomes, and some evidence supports that these benefits are observed even when excess body weight is present. Thus, engagement in physical activity is needed to realize improvements in cardiorespiratory fitness, and this is also observed in adults with overweight or obesity.[25,127]

Improvement in cardiorespiratory fitness is seen in response to a sufficient dose of physical activity regardless of whether that dose of physical activity also results in weight loss.[128] However, an important clinical observation is that cardiorespiratory fitness does not improve significantly with weight loss in the absence of physical activity.[49,128] These findings support the need for clinicians to prescribe engagement in physical activity to enhance cardiorespiratory fitness in adults with overweight or obesity, regardless of whether physical activity contributes to weight loss.

SUMMARY AND CLINICAL APPLICATIONS

Physical activity is a key lifestyle behavior that contributes to numerous health-related benefits.[70] These health-related benefits include prevention of weight gain, weight loss in the presence of overweight or obesity, and additional health-related benefits even in the presence of excess body weight or when weight loss is not achieved. The summary of the evidence presented supports the following:

- Physical activity contributes to the prevention of weight gain and can also contribute to a reduced incidence of developing obesity, and these benefits are typically observed when physical activity is at least 150 minutes per week and performed at a moderate-to-vigorous intensity.
- Physical activity, when not combined with a prescribed energy restricted diet, results in an average short-term weight loss (typically less than six months) of approximately 0.5–3.0 kg; however, the magnitude of weight loss occurs in a dose–response manner and is dependent on the dose of physical activity.
- When combined with a reduction in energy intake, physical activity can enhance weight loss by approximately 20% beyond the magnitude of weight loss achieved through a reduction in energy intake alone.
- Physical activity engagement at a sufficient dose is an important contributor to enhancing long-term weight loss and prevention of weight regain following initial weight loss.
- The evidence supports that moderate-to-vigorous-intensity physical activity is most strongly associated with weight loss and prevention of weight regain; however, the addition of light-intensity physical activity can further contribute to weight loss or weight loss maintenance.
- While there is some evidence that moderate-to-vigorous physical activity that is accumulated in bouts of less than 10 minutes per bout may contribute to effective weight control, the scientific evidence supports accumulation of physical activity performed in at least 10 minutes per bout is more strongly associated with enhance weight loss and weight loss maintenance.
- It is important that physical activity be included within medical treatments for obesity, which include bariatric surgery and pharmacotherapy.
- Physical activity contributes additional health benefits beyond weight loss, and many of these benefits can be realized in adults with overweight or obesity, even without a significant reduction in body weight.

Given these findings, physical activity should be included in the treatment plan for obesity and related health conditions. Physicians, other healthcare providers, public health professionals, and health-fitness professionals should prioritize the inclusion of physical activity within the treatment of patients with overweight or obesity to optimize health-related benefits.

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42 Dietary Management of Overweight and Obesity

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KEY POINTS

- Behavioral intervention is the cornerstone of treatment plans for people with overweight or obesity; Registered Dietitian Nutritionists (RDNs) use an ongoing, dynamic process to collect data and continually analyze the patient during medical nutrition therapy.
- Nutrition assessment includes the use of equations and tools to estimate resting energy expenditure and energy intake balanced with an understanding of patient-specific environmental and behavioral factors.
- Evidence for particular dietary interventions varies and includes various ways to reduce energy intake while maintaining realistic expectations and enjoyment; there is no one-size-fits-all approach, so individual interventions can be tailored based on assessment and then monitored and adjusted accordingly.
- The chronic, relapsing nature of the disease of obesity requires long-term strategies and a commitment to shared decision making and a trusting partnership between each patient and their healthcare team.

42.1 INTRODUCTION

As the majority of American adults today live with overweight or obesity, managing obesity, or abnormal/excess body fat, as a chronic disease is one of today's greatest healthcare challenges. Rates of obesity and associated health conditions and healthcare costs continue to impact society. Obesity has been described as a chronic, relapsing disease process that is rarely, if ever, cured.[1] While target outcomes for weight management vary across individuals, modest weight losses of 5–10% are associated with improvements in cardiovascular risk factors.[2] As described in other chapters of this text, surgery and medications are important tools in the treatment of obesity. However, behavioral intervention remains a cornerstone of obesity care and plays a role in all treatment plans, irrespective of the severity of obesity or treatment modality. Dietary modification is a key component of behavioral intervention for weight management. While there is no one-size-fits-all dietary pattern for weight management, appropriate dietary patterns provide essential nutrients to achieve and maintain optimal nutritional status while simultaneously producing an energy deficit to yield a weight loss consistent with patients' goals. Importantly, appropriate dietary modifications also balance eating enjoyment with reductions in energy consumption to promote sustainable eating patterns. This chapter will help guide clinicians through the dietary assessment, intervention, monitoring, and evaluation of patients with overweight and obesity.

42.2 MEDICAL ASSESSMENT

Accurate assessment of weight status requires an office environment sensitive to the unique needs of patients with obesity. This includes having appropriately sized furniture, equipment, gowns, and scales that can weigh patients of all sizes. The assessment of overweight or obesity involves annual measurement of anthropometrics, including height, weight, and calculation of body mass index (BMI; calculated as kg/m^2), to classify overweight and obesity using current classification methods. Weight and height are measured with the patient wearing light clothing or an examination gown and no shoes. Patients identified as having overweight (BMI >25 kg/m^2) or obesity (BMI >30 kg/m^2), as well as those who may benefit from nutrition counseling, should be referred to a Registered Dietitian Nutritionist (RDN) for medical nutrition therapy (MNT).[3]

Measuring waist circumference in patients with BMI ≤35 kg/m^2 is recommended to provide additional information about other medical conditions associated with obesity, such as cardiovascular risk (>88 cm or >35 in for women; >102 cm or >40 in for men).[4] A medical history and exam should query for cardiovascular risk factors like high blood pressure, hyperlipidemia, and hyperglycemia. The measurement of blood pressure, lipids, and glucose to assess for cardiovascular risk enables treatment to be matched to risk profile.[4] These markers are also critical to assess because they provide additional baseline measures besides weight from which patients' progress can be monitored and evaluated. This is important to help patients remain adherent to treatment plans during times of weight plateaus or when weight changes are not as expected.

During the medical examination and history, genetic syndromes as well as endocrine disorders such as

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hypothyroidism, Cushing's disease, polycystic ovary syndrome, and other metabolic conditions should be ruled out as contributing reasons for a patient's weight status. Acquiring medication history is also essential in identifying if any drugs are associated with weight gain and can be modified. For female patients, it is also important to inquire about the possibility of pregnancy before making weight loss recommendations. The Institute of Medicine has set guidelines for total and rate of weight gain during pregnancy by pre-pregnancy BMI.[5] Recommendations for weight gain during pregnancy should be individualized based on pre-pregnancy BMI to improve pregnancy outcome, avoid excessive maternal postpartum weight retention, and reduce risk of the child acquiring chronic disease later in life.[6]

42.3 NUTRITION ASSESSMENT

MNT by the RDN will include a comprehensive nutrition assessment to obtain, verify, and interpret data needed to identify nutrition-related problems, their causes, and their significance. It is an ongoing, nonlinear and dynamic process that involves data collection and continual analysis of the patient's status compared with specified criteria.[7] The RDN should assess food- and nutrition-related history, anthropometric measurements, biochemical data, medical tests and procedures, nutrition-focused physical findings, and client history in order to individualize the comprehensive weight management treatment.[8]

Assessment of food and nutrition-related history includes asking questions about beliefs and attitudes, including food preferences and motivation, food environment, access to fruits and vegetables, dietary behaviors, eating out, screen time, past dieting history, food allergies, medications, dietary supplements, and physical activity. The patient's weight history, family medical and health history, social history, living situation, and socio-economic status are all factors to consider in a thorough assessment. Weight history includes questions about highest and lowest adult body weight, usual body weight (within the last six months), body composition assessments, and finally, the individuals' stated preferred or desired body weight. Consideration of individual factors such as eating disorders or disordered eating behaviors, dieting history, pregnancy, and if a patient is receiving treatment for other health conditions that impact diet (e.g., chemotherapy, management of diabetes, renal disease) are part of determining the appropriateness of a weight management plan.

Many RDNs are becoming proficient in performing nutrition-focused physical assessment,[9] an examination of the body and physical function to help determine nutritional status, signs of malnutrition, and nutrient deficiencies. A systems-based exam of regions of the body (i.e., skin, nails, hair/head, eyes, mouth, neck/chest) can help identify declining nutrition status and micronutrient deficiencies even when malnutrition is not present.[9] Assessment of body composition (fat mass and fat-free mass) can further help individualize the dietary intervention for weight loss. Because interventions aim to reduce fat mass while preserving fat-free mass, periodic assessment of body composition changes can help to measure changes during the intervention. Body composition testing can help provide additional, objective data beyond weight/BMI to reinforce effectiveness and encourage patients to continue with their eating pattern. Available technology or devices may vary based on availability, cost, and accessibility, but include dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA).

42.4 DIETARY ASSESSMENT

42.4.1 Determining Energy Expenditure

Determining a patient's energy needs is a critical first step to creating a personalized dietary plan that creates the energy deficit needed for weight loss. Typically, an energy deficit of 500–750 kcal/day is recommended.[3] Energy needs can be determined by first assessing total energy expenditure. An individual's total energy expenditure consists of three components: basal energy expenditure, thermic effect of food, and an adjustment factor for the physical activity level. The assessment of energy expended in the basal state is impractical. Resting energy expenditure (REE), or resting metabolic rate (RMR), however, is practical to assess. REE is considered to be ~10% above the basal state. This substitution works well in practice because the thermal effect of food, which is also difficult to measure, is approximately 10% of total energy expenditure. The overestimation of REE compared with basal energy expenditure can be substituted for the thermic effect of food. Therefore, determining energy expenditure requires assessment or estimation of both RMR and energy expended through physical activity.

RMR should be measured through indirect calorimetry whenever possible.[3] Although reasonably priced, handheld medical devices enable measurement of RMR in the primary care setting; however, there are often times when measurement is not possible. The Mifflin-St. Jeor Equation (MSJE) is the most accurate predictive formula available for adults and has been found to predict RMR within 10% of measured in most individuals.[3,10,11] Online and mobile applications utilizing the MSJE make the calculation of energy needs particularly convenient and accessible. The simplified MSJE for males and females[11] is as follows:

$$\text{For females, REE} = 10 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 5 \times \text{age (y)} - 161$$

$$\text{For males, REE} = 10 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 5 \times \text{age (y)} + 5$$

To complete the estimation of total energy expenditure, physical activity level must be estimated. Assess the patient's current activity level and apply the appropriate activity factor of REE × 1.2 (sedentary), × 1.4 (low active to moderate), and × 1.6 (active). Subsequent adjustments for intentional activity or exercise (such as walking, biking, dancing, exercise routines, etc.) are added as individuals

engage in these activities and can be adjusted per day or averaged per week.

Given the depth of the physical activity and nutrition fields, separate examination of each of these areas is necessitated, and the specific role of physical activity in weight management will be discussed in more detail in other chapters. However, it is important to recognize that as the most modifiable components of energy balance, both physical activity and diet are inherent components of weight management that complement each other to create an energy deficit. In practice, the lines between physical activity and eating habits are more blurred. and clinicians must assess both areas. The assessment of energy expenditure is a natural opportunity for the RDN to assess a patient's physical activity and sedentary behaviors. The assessment of activity patterns is crucial to being able to tailor recommendations. Although it is difficult to lose weight through increased physical activity alone, physical activity is a critical factor in the maintenance of weight loss.[12] Additionally, inactivity is predictive of cardiovascular outcomes, and physical activity has many other benefits outside a simple "calories in, calories out" equation. As such, establishing regular physical activity routines is important at all weight management stages and levels of health and fitness.

42.4.2 Determining Energy Intake

Once energy needs are determined, it is important to assess an individual's total energy intake and dietary composition. There are multiple ways to assess this, including 24-hour recall, food frequency questionnaires, food records, and digital photography. Strengths and limitations of these methods are listed in Table 42.1.

Regardless of the method of dietary assessment, the goal is to determine a representative pattern from which dietary interventions and recommendations can be made. The establishment of such a pattern requires inquiry into not just what patients eat, but the time, place, and occasion of eating, as well as the method of preparation and portion size of foods eaten. These are important factors to determine sustainable changes. Mobile applications are now widely available for assessment and self-monitoring of dietary intake. Patients may find tracking their intake more sustainable when using technology to assist in collection and monitoring. Some apps are also able to seamlessly connect with electronic medical records or portals, which can provide real-time data from which providers can work with patients to utilize to tailor treatment plans. Real-time data are also helpful in overcoming limitations of self-report methods, which can be prone to error.

42.4.3 Determining Eating Environment and Readiness for Intervention

The practicalities of a patient's eating environment are important to assess. Recommendations are more relevant and feasible when the clinician understands the patient's access to food, food budget, delineation of responsibility for

TABLE 42.1
Dietary Intake Assessment Methods

Method	Strengths	Limitations
Food Record/Food Diary *Patients are asked to prospectively record intake for a specified period of time*	• Doesn't rely on patient memory • Can be completed in advance of dietetic visit • Portion sizes can be measured at time of consumption • Data can be entered into dietary analysis program • Records of multiple days provide valid measure of usual intake for most nutrients	• Patient intake may change as a result of keeping a food record • Requires patient to be literate, numerate, and have portion size knowledge • High patient burden, time consuming • Relies on self-reported information
24-hr Recall *Patients are retrospectively asked about intake from the past 24 hours*	• Unlikely to modify behavior • Inexpensive • Low patient burden • No patient literacy requirement • Can be conducted in person or by telephone • Data can be entered into dietary analysis program	• Dependent on patient memory • Relies on self-reported information • Requires skilled interviewer • High inter-interviewer variability • Time consuming • Not representative of usual intake
Food Frequency Questionnaire *Patients complete a survey that retrospectively queries how often certain foods/beverages were consumed in a specified period of time*	• Low patient burden • Quick, inexpensive • Easily standardized • Useful screening tool	• Requires patient to be literate and numerate • Dependent on patient memory • Can be cognitively difficult for patient because food lists are not meal-based • Doesn't provide valid estimate of total intake or meal patterns
Diet History *Patients are interviewed about their usual eating habits*	• No patient literacy requirement • Low patient burden • Enables assessment of meal patterning, usual nutrient and food group intake in one interview	• Dependent on patient memory • Requires skilled interviewer • Time consuming

shopping and preparation, location of meals, cultural food practices, and with whom meals are eaten. Assessing the environment may help the clinician and the patient identify potential barriers to carrying out recommendations.

Although recommendations may focus on timing and meal frequency, there is limited evidence to support such recommendations for weight loss.[3] Consistently with the principles of energy balance, solely changing the frequency of meals, without decreasing total energy intake, does not appear to induce a change in weight. For example, increased eating frequency has been associated with increased energy intake through snacks, and individuals rarely compensate at mealtimes for previously eaten snacks.[13] Lower-calorie (<200 calories) snacks can help patients meet restricted energy intake goals. Breakfast consumption has not been found to lead to greater weight loss in randomized control trials.[3] However, research looking at the relationship between circadian rhythm and weight loss has indicated that eating a higher proportion of total energy intake earlier in the day may be helpful in weight loss.[14] Importantly, different timing strategies may be helpful for different individuals to adhere to reduced caloric intake. Assessing patients' schedules and lifestyle patterns can aid in the determination of how patients may be most successful in incorporating recommendations into their day.

Current guidelines also recommend assessment of motivation, readiness, and self-efficacy for weight management, based on behavior change theories and models (e.g., cognitive-behavioral therapy, transtheoretical model, and social cognitive theory/social learning theory). Patient motivation is a key component of success in a weight loss program and is essential for any weight loss treatment. Motivational Interviewing is a collaborative, goal-oriented method of communication between a practitioner and a client with a focus on drawing out a client's personal motives by allowing a person to find answers on his or her own. Motivational Interviewing is believed to enhance motivation and self-efficacy, which are both considered to be key for making and sustaining behavior changes.[8,11] Asking a patient to rate on a scale from 0 to 10 the importance of behavior change and their confidence in being able to make the change is a quick tool clinicians can use to gauge a patient's readiness to change.

42.5 DIETARY INTERVENTION

Before beginning intervention, it is critical for the RDN to discuss expectations and set realistic weight loss goals together with the patient's input. As little as a 3–5% weight loss has been shown to improve clinical cardiovascular markers, and 5–10% weight loss improves even more cardiovascular risk factors.[4] While clinically meaningful, this amount of weight loss may differ from a patient's expectation. Addressing this potential mismatch prior to treatment can be important to a patient's success. Utilizing body composition measurements to look at reduction in body fat and increases or maintenance of muscle mass during weight loss may be more motivating and related to changes within a patient's control, rather than total body weight loss.

Many dietary approaches exist that facilitate the reduction of energy consumption. However, there is no one ideal dietary composition for weight loss or weight maintenance.[3] Low- and very low-calorie diets focus specifically on the creation of an energy deficit. Very low-calorie diets (≤800 kcal/day) are only appropriate for use among patients with a BMI ≥30. While very low-calorie diets have been shown to produce significantly greater weight loss than low-calorie (>800 kcal/day, usually 1,200–1,600 kcal/day) diets in the short term, long-term weight loss is equivalent between the two diets.[3] Meal replacements (liquids, bars, frozen entrees) are an effective strategy to increase adherence to the energy restriction imposed by either diet and are helpful with long-term weight management.[3] Meal replacements, which are generally formulated products such as shakes or portion controlled entrees, have value because they provide a regulated amount of calories per serving, are usually fortified with essential nutrients and fiber, and are economical, safe, and convenient to use. They also provide a departure from normal eating patterns and can serve as a venue for reeducation about and/or reformulation of what foods can be substituted or reintroduced.

Other dietary approaches achieve a caloric deficit through the restriction of particular foods or macronutrients. Results of randomized control trials indicate no difference in the rate or magnitude of weight loss between diets of differing macronutrient composition when caloric intake is held constant.[3] On the individual level, however, it is likely that some approaches will be superior to others at helping a patient achieve the necessary caloric deficit and adhere to the diet long term. Additionally, cardio-metabolic outcomes may differ based on the dietary approach taken. For example, greater reductions in low-density lipoprotein cholesterol have been achieved through a low-fat diet compared with a low-carbohydrate diet; however, low-carbohydrate diets have produced a greater reduction in triglycerides and a larger increase in high-density lipoprotein cholesterol than a low-fat diet of equivalent energy restriction.[4] In addition to weight loss, the Dietary Approaches to Stop Hypertension (DASH) diet with energy restriction produces reductions in blood pressure, and the Mediterranean diet with energy restriction may also result in cardiovascular risk factor improvements greater than those seen with low-fat diets.[3] As discussed in another chapter, dietary patterns described in the Dietary Guidelines for Americans 2020–2025 coupled with energy restriction can be a good starting point for patients.

Eating foods with low energy density, the ratio of energy in a food to the weight of the food (kcal/g), may be a strategy for appetite control and subsequent achievement of energy restriction, as it allows a greater amount of food to be eaten relative to energy consumed. It is important to note that for an energy deficit to occur using this strategy, high energy density foods must be replaced by lower energy density foods.[15] Randomized controlled trials have shown

that solely increasing fruits and vegetables (foods with low energy density) does not produce weight loss.[16] Although the low energy density approach warrants further research, a lack of standardized methods and consensus on how to include beverages prohibits conclusions from being drawn on the efficacy of this strategy for weight loss at this time.[17]

Similarly, because people typically do not compensate for energy consumed from beverages by reducing their energy from foods, it is recommended that caloric beverages be reduced or eliminated from the diet. For example, reducing sugar sweetened beverage consumption has been shown in randomized controlled trials to aid in weight loss[18]. Nonnutritive sweeteners and fat substitutes have a role in the dietary management of overweight and obese individuals, primarily because they can potentially lower caloric intake overall. For this reason, nonnutritive sweeteners have been endorsed by the Academy of Nutrition and Dietetics as a strategy to reduce energy intake by replacing sugar.[19] It is important that sugar and fat substitutes are used in the context of a regular diet, used in moderation and balance with other foods, are appreciated for total energy and nutrient value, and do not replace other nutritious foods.[19,20]

Finally, while total energy intake is of central importance, reductions in intake are too often accompanied by a decline in essential nutrients and overall quality of the diet. Dietary supplements should be considered when eating patterns are compromised, erratic, limited in choices, or <1,200 kcal/day.[3] Vitamin and mineral supplements should not be used in lieu of a healthy diet, and their use should be evaluated on a case-by-case basis.

Regardless of the dietary approach taken, close collaboration with the patient will help to create a realistic diet plan that takes into consideration weight loss and adequate nutrition. The dietary intervention should begin with the patient's usual pattern in mind. The diet plan should build on the strengths of the patient's current diet and incorporate modifications necessary to manage comorbid conditions. The usual food pattern derived from food records can be used to determine recommendations for change. Realistic strategies (e.g., increasing or decreasing food groups, assessing portion sizes, changing or substituting foods, especially of high caloric and/or high fat value, altering eating patterns when feasible, etc.) to impose a practical energy deficit should be decided upon through collaboration with the patient.

Although the concept of energy balance seems straightforward, great individual variation exists in weight loss treatment response and maintenance of weight loss. Dietary intake is complicated by the complex interplay between behavioral, psychological, and environmental factors. Individual variations in microbiome have been suggested to explain some of the individual variation in how much energy is absorbed from foods.[21] Established genetic and epigenetic variability underscores the importance of individualizing dietary intervention; however, it is unknown how to do this effectively.[22] Long-term adherence to dietary interventions is affected by how well the diet composition meets the most important of these established needs. The magnitude of weight loss achieved in the first few months of treatment is the best predictor of overall outcomes.[23,24] For these reasons, realistic goals and expectations for weight loss need to be addressed prior to beginning intervention, dietary approaches taken need to be decided on iteratively with the patient, and patient progress should be regularly monitored so that adjustments can be made as needed.

42.6 INTENSITY OF INTERVENTION

After dietary intervention and appropriate weight loss goals are determined with the patient, discussion about the intensity of the intervention is important. The American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) Guideline recommends referral for comprehensive lifestyle intervention for all patients encouraged to lose weight, including those for whom medical or surgical intervention is recommended.[4] Frequency of contact is an important characteristic in achievement of weight loss. There is strong evidence for at least 14 MNT encounters (group or individual) with an RDN over a period of at least six months.[4] High intensity, comprehensive weight loss interventions produce on average a weight loss approaching 5–10% of initial weight.[4] Energy needs change as weight is lost. Continual monitoring and evaluation of energy requirements enables adjustments to energy intake recommendations to be made as needed. This will help to prevent the weight loss plateau that occurs around six months for many patients. For weight maintenance after weight loss, there is also strong evidence for monthly visits of MNT over at least one year.[4] Alternative modes of delivery, including electronically providing visits through phone, internet, or telehealth technology, may be indicated.

If patients are unable to meet health and weight loss goals, more intensive behavioral treatment, pharmacology, or evaluation for bariatric surgery should be considered as appropriate. It is important to note that dietary intervention plays an important role in all these treatment approaches. Working with the patient's medical team, the RDN can tailor the dietary approach to be appropriate for the patient's specific treatment plan.

For those with a BMI ≥27 kg/m^2 and an obesity-related comorbid condition, or a BMI ≥30 kg/m^2, pharmacotherapy can be considered as adjunctive to comprehensive lifestyle intervention to achieve targeted weight loss and health goals.[4] Clinicians should be aware of the current Food and Drug Administration (FDA)-approved medications indicated for weight loss through appetite suppression or absorption of fat. The potential risk of the medication should be weighed against the potential benefit of weight loss for the individual. Patients taking weight loss medications may be more likely to consistently adhere to a lower-calorie diet, increase physical activity, and experience weight loss and maintenance.[4] Newer GLP-1 agonists and GIP anti-obesity medications used for diabetes and obesity have been considered "game changers" for obesity care and

should become part of all healthcare providers' arsenal of tools to help patients lose and maintain weight loss, as well as improving metabolic health.

At this point in time, the obesity care community is still using BMI to assess whether patients are candidates for the next level of care, but more targeted protocols and algorithms are expected to become available in the near future that rely on more accurate assessment of adiposity and body composition, rather than weight and BMI alone. Patients who have a BMI ≥35 kg/m^2 with obesity-related comorbid conditions or BMI ≥40 kg/m^2 and who are motivated to lose weight but for whom behavioral treatment has not resulted in sufficient weight loss should be offered a referral to an experienced bariatric surgeon with an interdisciplinary team of medical, nutritional, and psychological professionals for evaluation.[4] Several factors are involved in the decision to undergo surgery: patient motivation, treatment adherence, operative risk, optimization of comorbid conditions, and insurance coverage.[4] Although bariatric surgery is the most clinically and cost-effective treatment for severe obesity, fewer than 1–2% of patients with severe obesity undergo surgery. The decision to discuss surgical options is subjective and inconsistent among providers, likely due to bias toward people with obesity and stigma associated with having surgery.

Patients rely on recommendations from primary care providers and other healthcare practitioners for treatment recommendations for chronic diseases, including obesity.[25] Providers often incorrectly assume that people with obesity are well aware of their excess weight and report feeling ineffective at helping patients with obesity lose weight.[25] It is important for clinicians to be compassionate, recognizing the complexities of the disease of obesity and following a shared decision-making approach. It is imperative that healthcare providers tell patients when their weight is a health concern, that there are treatment options for overweight and obesity, that the provider recommends treatment, and that the provider will support the patient throughout treatment and maintenance.[4]

42.7 CONCLUSIONS

A number of dietary approaches have produced weight loss in the short term; however, long-term maintenance of weight loss remains a critical challenge. The patient's ability to adhere to a diet long term is an important factor to consider when selecting the dietary intervention. Successful selection of the dietary approach taken in MNT depends on thorough assessment, monitoring, and evaluation of a patient's eating behaviors, environment, and level of readiness for intervention. Despite the critical role of dietary intervention in the treatment of obesity, reimbursement for MNT weight management varies by state and insurance provider. Future directions include continued progress in reimbursement for MNT for weight management by RDNs, consideration of "non-diet" approaches for people with obesity (e.g., intuitive eating), counseling to modify behavior, and greater focus on preventing weight recurrence after weight loss. It is critical that patients have a relationship with their healthcare team based in trust that the provider will continue to work with them, without judgment, even if they experience weight recurrence. Like other chronic conditions, management of obesity will be lifelong and will require change in approach by provider and patient alike.

PRACTICAL APPLICATIONS

- Clinicians have a variety of tools available for nutrition assessment, most notably, referral to RDNs to provide medical nutrition therapy for weight loss and maintenance.
- While nutrition assessment includes objective assessment of anthropometric data such as weight, waist circumference, and resting energy expenditure, clinicians should spend time discussing eating behaviors, environment, preferences, motivation, access, living situation, and history of disordered eating in order to individualize treatment recommendations.
- Dietary interventions generally reduce calorie intake through mechanisms designed to manipulate total calories, specific macronutrients, caloric density or texture of foods, or timing of eating occasions. Utilizing a shared decision-making approach will help create a realistic plan together with the patient that is both grounded in evidence and considerate of the patient's preferences, which can help with longer-term adherence to the plan.
- It is important that providers appreciate their role as a trusted member of the patient's long-term care team and facilitate continual follow-up and monitoring in order to recommend changes based on response, as well as to increase intensity to include pharmacology or surgical intervention when appropriate.

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43 A Clinical Approach to Pharmacological Management of the Patient with Obesity

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43.1 INTRODUCTION

The current obesity management guidelines highlight the role of pharmacotherapy in the management of people with excess adipose tissue (with a body mass index [BMI] at or above 30 kg/m^2 or a BMI at or above 27kg/m^2 with at least one comorbidity).[1,2] The recommendations are very clear in stating that weight loss drugs should be used as approved by the U.S. Food and Drug Administration (FDA) as adjuvants to lifestyle interventions. The guidelines cite comprehensive lifestyle interventions as the most effective. These include diet, activity changes, and behavior change counseling during frequent visits, followed by weight maintenance interventions with a medical team.

However, medical providers are often reluctant to prescribe weight loss drugs for reasons of safety, probably due to the scandal caused by Fen-Phen in 1997. This drug contained Fenfluramine, which caused valvular heart defects and subsequently was taken off the market. How about present times? Are the available weight loss drugs still the same? Currently, the FDA requires all weight loss drugs to be studied long term for serious cardiac side effects in a large population before approval.[3] More than this, three of the five drugs approved for long-term management of weight loss include drugs approved and used safely for other indications for a long time without concerns for safety.[4,5]

This chapter will discuss the FDA-approved pharmacological treatment of obesity with detailed clinical considerations for medical providers who are considering pharmacological therapy in the management of patients with excess adipose tissue.

43.2 DRUGS APPROVED FOR PHARMACOLOGICAL MANAGEMENT OF OBESITY

Currently, there is one drug approved for short-term management of obesity and five drugs approved for long-term management of obesity. We will discuss the indications, mechanisms, efficacy, side effects, black box warning, contraindications, formulations, titration schedule, and practical considerations for each of them, beginning with the most recent ones approved by the FDA.

43.2.1 Semaglutide (Trade Name Wegovy)

Indications: Semaglutide is indicated for chronic weight management as an adjunct to lifestyle changes in adults with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of at least one weight-related comorbidity.[6]

Mechanism: Semaglutide is a GLP-1 analog that is distributed to and activates neurons from brain regions involved in the regulation of food intake. Semaglutide acts to decrease weight by decreasing calorie intake, likely mediated by increased satiety and decreased appetite.[6]

A double-blind parallel-group trial of 72 adults with obesity treated for 20 weeks showed that Semaglutide significantly decreased ad libitum energy intake by 35% more compared with placebo ($p < 0.0001$). It also produced better control of eating and weaker food craving ($p < 0.05$).[7]

Efficacy: The weight loss effect of Semaglutide 2.4 mg weekly was studied in a double-blind, placebo-controlled trial of 1,961 adult subjects with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of one or more weight-related coexisting conditions (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) but excluded patients with diabetes. The intervention and placebo subjects received lifestyle change intervention, which included counseling sessions every 4 weeks, daily self-recording of dietary intake and activity, and advice for a low-calorie diet (500 kcal/day less than the estimated energy expenditure levels at randomization) and increased physical activity (150 minutes/week of walking or similar activities). After 68 weeks of treatment, Semaglutide caused 12.4% body weight loss, more than the placebo control. Importantly, significantly more subjects achieved 5% or more weight loss (86.4% vs. 31.5% in intervention vs. placebo); 10% or more weight loss (69.1% vs. 12.0% in intervention vs. placebo); and 15% or more weight loss (50.5% vs. 4.9% in intervention vs. placebo).[8]

There were several other health benefits observed. Semaglutide caused a 0.45% decrease in HbA1C compared with a 0.15% decrease in the control group. In patients with prediabetes, significantly more patients with prediabetes in the intervention group (84.1%) vs. placebo (47.8%) experienced a return to normoglycemia. Systolic and diastolic blood pressure decreased with Semaglutide (5.1 mmHg and

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2.4 mmHg more, respectively, compared with the control group). Total cholesterol decreased by 0.97 compared with baseline, and high-density lipoprotein (HDL) cholesterol increased by 1.04 more than control (ratio of week 68 to baseline). As expected, there was a significant decrease in the detrimental impact of weight on quality of life in the Semaglutide group versus placebo (14.7 vs. 5.2 points in physical function score, $p < 0.001$).[8]

Side effects: Common side effects include nausea, diarrhea, constipation, vomiting, headache, dyspepsia, gastroenteritis, gastroesophageal reflux disease, abdominal pain, flatulence, eructation, fatigue, and dizziness. Patients with diabetes mellites can develop hypoglycemia. Serious adverse reactions include thyroid C-cell tumor, acute pancreatitis, acute gallbladder disease, acute kidney injury, hypersensitivity reaction, diabetic retinopathy complications in patients with type 2 diabetes, heart rate increase, and suicidal behavior and ideation.[6]

It is important to note that gastrointestinal side effects were the most common ones, and those were mild to moderate and transient,[8] which should reassure patients interested in this treatment.

Black box warning: Semaglutide has a black box warning for use in patients with personal/family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.[6]

Contraindications: Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN2), or hypersensitivity to Semaglutide or any other excipients in Wegovy. Semaglutide should not be used concomitantly with another GLP-1 receptor agonist. It should not be used two months before planned pregnancy, during pregnancy, or in the pediatric population,[6]

Formulations: The trade name is Wegovy, which is a prefilled injection pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg. Semaglutide is to be administered subcutaneously (abdomen, thigh, or upper arm) once a week on the same day each week, at any time of day, regardless of meal timing.[6]

Titration schedule: Medical providers are instructed to start with 0.25 mg once weekly for four weeks, and then increase the dose every four weeks to 0.5 mg, 1 mg, 1.7 mg, and finally, 2.4 mg as the maintenance dose. If patients do not tolerate the dose escalation due to side effects, then consider keeping the same dose or decreasing the dose for another four-week interval. If after all these, the patient cannot tolerate the maintenance dose, then discontinue the treatment.[6]

Monitoring: It is recommended to monitor blood glucose in patients with diabetes mellitus, especially those also treated with insulin and/or the insulin secretagogue, to avoid hypoglycemia. Additionally, monitoring heart rate, renal function, depression, and suicidal thoughts before initiating the treatment and at regular intervals is recommended.[6]

Practical considerations: Semaglutide was approved by the FDA in 2021 for long-term weight loss. However, Semaglutide (administered either as an injectable for 1 mg weekly as Ozempic or orally 14 mg daily as Rybelsus) has been used since 2018 and 2019, respectively, for the treatment of type 2 diabetes.

43.2.2 Liraglutide (Trade Name Saxenda)

Indications: Liraglutide is indicated as an adjunct to lifestyle changes in adults with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of at least one weight-related comorbidity.[4]

Mechanism: Liraglutide is a human glucagon-like peptide-1 (GLP-1) analog, which delays gastric emptying, increases satiety, and decreases appetite.[4]

Efficacy: The weight loss effect of Liraglutide 3 mg/day was studied in a double-blind, placebo-controlled trial of 3,731 subjects with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of hyperlipidemia or hypertension (HTN) with lifestyle change counseling. After 56 weeks of treatment, Liraglutide caused 5.6 kg more body weight loss than the placebo control. In addition, Liraglutide treatment was accompanied by an improvement in the cardiometabolic profile.[9]

Liraglutide has additional benefits in patients with prediabetes or type 2 diabetes and obesity. A large double-blind, placebo-controlled trial in 2,254 subjects with prediabetes and a BMI at or above 30 kg/m^2, or at or above 27 kg/m^2 in the presence of comorbidities, was undertaken for three years. A lower proportion of conversion to type 2 diabetes was observed in the Liraglutide group (2%) compared with the control group (6%), with a hazard ratio being calculated at 0.21 (95% confidence interval [CI] 0.13–0.34). In addition, the subjects with prediabetes treated with Liraglutide lost significantly more weight compared with placebo (4.3% difference).[10] In 1,361 subjects with type 2 diabetes with overweight or obesity, Liraglutide for 56 weeks caused 6% weight loss (for the 3 mg/day dosage) and 4.7% weight loss (for the 1.8 mg/day dosage), compared with 2% weight loss in the placebo group.[11]

Liraglutide also has additional benefits for patients with obstructive sleep apnea, as shown by a study where the apnea-hypopnea index improved after a 32-week study of treatment (−12.2 vs. −6.1 events h^{-1}), and this improvement was related to the degree of weight loss. This study also demonstrated that Liraglutide produced a significantly larger percentage of weight loss compared with placebo (4.3% difference) and an improvement in HbA1C and systolic blood pressure.[12]

Side effects: Common side effects include nausea, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, flatulence, and insomnia. Serious adverse reactions include thyroid C-cell tumor, medullary thyroid carcinoma, papillary thyroid carcinoma, colorectal malignancy, first-degree atrial ventricular block, and pancreatitis.[4]

It is important to note that a large double-blind trial studied the cardiovascular side effects of Liraglutide in

9,340 subjects with type 2 diabetes and with high cardiovascular risk followed for 3.8 years. Death from a cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke occurred in significantly fewer subjects treated with Liraglutide (13.0%) compared with placebo (14.9%), with a hazard ratio of 0.87 (95% CI 0.78 to 0.97). The rate of death from cardiovascular events was lower in the Liraglutide (4.7%) compared with the placebo group (6%). There was no significant difference in the rate of nonfatal stroke, myocardial infarction, and pancreatitis in the Liraglutide compared with the placebo group.[13]

Black box warning: Liraglutide has a black box warning for use in patients with personal/family history of medullary thyroid carcinoma or in patients with MEN2.[4]

Contraindications: Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or MEN2, hypersensitivity to Liraglutide, or pregnancy, and should not be used concomitantly with insulin or another GLP-1 receptor agonist.[4]

Formulations: The trade name is Saxenda, which is a prefilled injection pen with multiple doses of 0.6 mg increments. One pen has 3 ml solution, which contains 6 mg/ml of active drug. Liraglutide is to be administered subcutaneously (abdomen, thigh, or upper arm) daily at any time of day, regardless of meal timing. Liraglutide should be used with caution in patients with renal or hepatic impairment.[4]

Titration schedule: Medical providers are instructed to start with 0.6 mg/day for one week, then increase the dose weekly to 1.2 mg, then 1.8 mg, then 2.4 mg until the maximum dose of 3 mg/day is reached.[4]

Monitoring: It is recommended to monitor blood glucose in patients with diabetes in order to avoid hypoglycemia. If after 16 weeks of treatment the patient has not lost at least 4% of initial body weight, it is recommended to discontinue the drug and consider alternative treatment options for obesity.[4]

Practical considerations: Liraglutide was approved by the FDA in 2014 for long-term weight loss; however, a different dosage (lower) of Liraglutide has been used as Victoza since 2010 for the treatment of type 2 diabetes.

43.2.3 Naltrexone-Bupropion ER (Trade Name Contrave)

Indications: Naltrexone-Bupropion is indicated as an adjunct to lifestyle changes in adults with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of at least one weight-related comorbidity.[14]

Mechanism: Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for depression and smoking cessation that acts on the reward pathways. Naltrexone is an opioid receptor antagonist approved for alcohol and opioid dependence, which in this combination antagonizes the feedback loop that limits the anorectic effects of Bupropion. Therefore, the combination drug works synergistically to suppress appetite and decrease food cravings.[14]

Efficacy: The efficacy of this drug was studied in a 56-week double-blind, placebo-controlled study in 1,496 subjects with obesity or overweight (BMI at or above 27 kg/m^2) with at least one weight-related comorbidity. The combination of Naltrexone 32 mg/day and Bupropion 360 mg/day caused a significant weight loss of 6.4% versus 1.2% in the placebo-controlled group. Additionally, the combination drug caused an improvement in several cardiometabolic risk factors and increased control of eating impulses.[15]

The drug was also studied in 505 subjects with overweight/obesity and type 2 diabetes in a double-blinded, placebo-controlled trial. Naltrexone 32 mg-Bupropion 360 mg once daily for 56 weeks caused 5% weight loss compared with 1.8% in placebo, and 44.5% of subjects achieved more than 5% weight loss compared with 18.9% in placebo. Interestingly, the drug achieved a significantly greater reduction in HbA1C (−0.6%) compared with placebo (−0.1%). The percentage of subjects achieving the recommended American Diabetes Association target of 7% HbA1C was doubled in the treatment group compared with placebo (44.1% vs. 26.3%). More than this, the treatment group observed an improvement in cardiovascular risk factors, triglycerides, and HDL cholesterol.[16]

Side effects: Common side effects include nausea, vomiting, constipation, headache, dizziness, and insomnia. Serious adverse reactions include neuropsychiatric disorders, homicidal ideation, suicidality, depression exacerbation, HTN, hepatotoxicity, and closed angle glaucoma.[14]

Black box warning: Naltrexone-Bupropion ER has a black box warning for use in patients with major depression disorders or other psychiatric disorders, as it may cause suicidality.[14] However, we note that three large studies showed that there was no increase in depression or suicidal events compared with placebo.[15–17]

Contraindications: Naltrexone-Bupropion is contraindicated in patients with uncontrolled HTN, seizure disorders, anorexia nervosa, bulimia, and chronic opioid use, in patients taking Bupropion containing products, or MAOI (during or within 14 days of discontinuation), and in patients undergoing abrupt discontinuation of alcohol, benzodiazepine, barbiturates, and antiepileptic drugs.[14]

Formulations: The trade name is Contrave, and it is dispensed in 8 mg Naltrexone HCl/90 mg Bupropion HCl extended release tablets.[14] The maximum dose is 32 mg Naltrexone HCl and 360 mg Bupropion HCl for the general population; however, patients with renal and hepatic impairment need dose adjustment.

Titration schedule: Naltrexone-Bupropion is to be taken as two tablets twice a day by mouth. Patients should be started with one tablet in the morning for one week, then one tablet twice a day for one week, then two tablets in the morning and one tablet in the evening for one week, followed by two tablets twice a day as the maximum dose from then on as tolerated.[14]

Monitoring: Patients with HTN should be monitored for changes in blood pressure and heart rate. If the patient has

not lost at least 5% of initial body weight in 12 weeks, then the drug should be discontinued, and alternative management of obesity should be investigated.[14]

Practical considerations: Naltrexone-Bupropion was FDA approved for long-term management of obesity in 2014. However, both component drugs have been approved by the FDA for almost 25 years, which speaks to the safety of this combination drug.

43.2.4 Phentermine-Topiramate ER (Trade Name Qsymia)

Indications: Phentermine-Topiramate was approved as an adjunct to lifestyle changes in adults with a BMI at or above 30 kg/m^2 or at or above 27 kg/m^2 in the presence of at least one weight-related comorbidity.[5]

Mechanism: Phentermine-Topiramate is a combination of the appetite suppressant Phentermine together with the anticonvulsant Topiramate, which acts on gamma-aminobutyric acid (GABA) receptors to decrease appetite and increase satiety.[5]

Efficacy: A 56-week phase 3 study of Phentermine-Topiramate was conducted in 2,487 adults who had overweight or obesity with two or more of the following comorbidities: HTN, dyslipidemia, type 2 diabetes, prediabetes, or abdominal obesity.[18] The drug doses were once-daily Phentermine 7.5 mg plus Topiramate 46.0 mg, or Phentermine 15.0 mg plus Topiramate 92.0 mg. All subjects received counseling for lifestyle management. The change in body weight was minimal in the placebo group (−1.4 kg), but was significant and dose-dependent in the drug groups (−8.1 kg and −10.2 kg, respectively).[18] Selected subjects (676) completed an additional 52 weeks of either active drug (Phentermine/Topiramate 7.5/46 mg, 15/93 mg) or placebo, in addition to lifestyle therapy. This length of treatment was not only well tolerated but caused significantly more weight loss and clinically significant improvement in systolic and diastolic blood pressure, triglycerides, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and insulin sensitivity compared with placebo. Interestingly, the incidence rate of diabetes significantly decreased in the Phentermine-Topiramate 15/93 mg group.[1]

Side effects: At the higher dose, Phentermine-Topiramate causes dry mouth and paresthesia, constipation, insomnia, dizziness and dysgeusia, anxiety-related adverse events, and depression-related adverse events.[18] Due to the Phentermine component, rare serious adverse reactions include cardiac ischemia, tachycardia, pulmonary HTN, psychosis (see the Phentermine section for more information), and potential for abuse and dependence.[5]

Black box warning: None.[5]

Contraindications: Phentermine-Topiramate should not be used in pediatric patients; pregnant and lactating patients; patients with uncontrolled HTN, arrhythmia, heart failure, hyperthyroidism, glaucoma, agitated states, history of stroke, coronary artery disease, drug abuse, or reactions to sympathomimetic amines; or within 14 days of treatment with monoamine oxidase inhibitor. Caution for use in women of childbearing age.[5]

Formulations: The trade name is Qsymia, and it is dispensed in 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg of Phentermine and Topiramate ER combination, respectively. The two largest dosages are contraindicated in patients with moderate or severe renal or hepatic impairment.[5]

Titration schedule: Phentermine-Topiramate is to be taken once a day in the morning. Medical providers are instructed to start with the lowest dose and increase to the next dose in 14 days. Due to the Topiramate component, medication should not be discontinued abruptly, to avoid seizures, which occur in patients with a predisposition to seizures.[5]

Monitoring: Discontinue if after 12 weeks, the weight loss is less than 3% (with 7.5 mg/46 mg dosage) or 5% (with 15 mg/92 mg). Due to the Phentermine component, patients should be monitored for changes in heart rate and blood pressure. Because Topiramate increases the risk for cleft palate in pregnant women in the first trimester, there is a required negative pregnancy test before the beginning of the treatment and every four weeks after that. Patients should avoid concomitant use of alcohol; monitor irregular bleeding in women using oral contraceptives and potassium in patients using non-potassium sparing diuretics.[5]

Practical considerations: Phentermine-Topiramate ER combination was approved in 2012; however, both drugs have been FDA approved and used individually for more than 20 years: Phentermine for short-term weight loss and Topiramate for seizures and migraines.

43.2.5 Orlistat (Trade Name Xenical™, Alli™)

Indications: Orlistat is indicated for the management of obesity in conjunction with a reduced-calorie diet.[19]

Mechanism: Orlistat acts through inactivating gastrointestinal lipase, thereby partially inhibiting the digestion of fat. This action results in a decrease in fat absorption and energy intake, and the promotion of malabsorption.[19]

Efficacy: In a two-year study, subjects treated with Orlistat (120 mg three times a day) lost nearly 10% body weight in the first year compared with 5% weight loss in the placebo group, and fasting LDL cholesterol and insulin levels improved.[20] Other studies showed improvement in glucose metabolism and a reduction in high blood pressure.[21,22]

Side effects: Common side effects include oil-spotting, flatus with discharge, fecal urgency, and fecal incontinence. Serious adverse effects of Orlistat include hypersensitivity, anaphylaxis, angioedema, leukocytoclastic vasculitis, fat-soluble vitamin deficiency, hepatotoxicity, nephrotoxicity, and oxalate nephropathy.[19]

Black box warning: None.[19]

Contraindications: Patients with chronic malabsorption syndrome and cholestasis should not take Orlistat.[19]

Formulations: The trade name Xenical contains120 mg of active substance to be taken three times a day. The trade

name Alli is available over the counter and contains 60 mg of active drug to be taken three times a day in conjunction with a reduced-calorie and low-fat diet.[19]

Titration schedule: none.[19]

Monitoring: Monitor for side effects as indicated.[19]

Practical considerations: FDA approved Orlistat for weight loss and weight maintenance in 1999 as Xenical and in 2007 approved Alli as an over-the-counter medicine. Several attempts to decrease the inconvenient gastrointestinal side effects caused by Orlistat have been made without any success.[23]

43.2.6 Phentermine (Trade Name Adipex, Ionamin, Lomaira)

Indications: Phentermine is approved for short-term (a few weeks) weight loss as an adjunct to lifestyle changes in patients with a BMI of 30 kg/m^2 or greater or patients with a BMI of 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity.[24] Even though it is FDA approved for short-term use, there are reports to show that in practice, it is used for longer periods of time with acceptable side effects and efficacy.[25]

Mechanism: It is a centrally active adrenergic drug, a sympathomimetic amine that stimulates norepinephrine release in synaptic terminals. With Phentermine usage, patients can experience increased satiety and less hunger, craving, binging, and nighttime eating.[24]

Efficacy: A meta-analysis of nine randomized controlled trials showed that patients treated with Phentermine (15–30 mg/day) and lifestyle changes for 2 to 24 weeks lost an additional 3.6 kg compared with the lifestyle change group only.[26] Another study used Phentermine with lifestyle changes for the treatment of obesity for 156 weeks and showed a 6.1-kg additional weight loss compared with lifestyle changes only.[27]

Side effects: The most common side effects of Phentermine include dry mouth, headache, insomnia, irritability, nervousness, euphoria, palpitations, tachycardia, and elevated blood pressure. There have been a few case reports of primary pulmonary HTN and cardiac valvulopathy in patients taking Phentermine;[28] however, these probably represent the background in the general population, as this was not confirmed in controlled studies.[26,27] Drug abuse potential and addiction are reported as minimal;[29] however, it is still a Drug Enforcement Administration (DEA) Scheduled IV drug.

Black box warning: None.[24]

Contraindications: Phentermine is contraindicated in the pediatric population; pregnant and lactating patients; patients with uncontrolled HTN, arrhythmia, heart failure, hyperthyroidism, glaucoma, agitated states; patients with history of stroke, coronary artery disease, drug abuse, reactions to sympathomimetic amines; and within 14 days of treatment with a monoamine oxidase inhibitor (MAOI).[24]

Formulations: Phentermine is available as a 37.5 mg scored tablet, in 15 and 30 mg capsule form, and as an 8 mg tablet.[24,30,31] The lower dosage formulation can be taken up to three times a day and is used for patients who are sensitive to higher dosage. Therefore, this increases the options for a personalized treatment plan.

Titration schedule: Dosing should be individualized to obtain an adequate response with the lowest effective dose. Patients should avoid taking Phentermine before going to sleep to avoid sleep disturbance.[24]

Monitoring: Patients should be monitored for changes in heart rate and blood pressure.[24]

Practical considerations: The FDA approved Phentermine for short-term treatment of obesity in 1959, and it is now the most commonly prescribed obesity drug in the United States.[32] The popularity of Phentermine over the other drugs is most likely due to the long-term data,[33–35] the association with a rapid onset of appetite control, and improvement in patient attitude.[33–35] This is also the only drug approved for weight loss that can be found as a formulary, and consequently, at a relatively low price.

43.3 A Practical Approach to Pharmacological Management of Obesity: A Treatment Algorithm

Once it is determined that the patient meets the indications for using weight loss drugs (see earlier in the description of each drug), the management can be approached in a stepwise manner to maximize the rate of success.

43.3.1 Step 1. Pre-Treatment Discussion

Before initiating the pharmacological management of obesity, there are certain facts that need to be clearly discussed with the patient to correct popular myths about obesity and weight loss drugs.

Fact 1: Obesity is a serious condition, not a character flaw, and should be treated this way (https://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf). *Fact 2*: The FDA has approved five drugs for long-term management of obesity, and just like any other FDA approved drugs, weight loss drugs have risks that should be outweighed by the benefits when used in the management of a disease.[4–6,14,19] *Fact 3*: Weight loss drugs are approved to be used along with lifestyle changes for weight loss, and therefore, are not substitutes for but supplements to behavior change. They empower a person to adhere to the behavior changes implemented by decreasing appetite and craving and increasing satiety.[4–6,14,19] *Fact 4*: Since obesity is a chronic condition, weight loss drugs should be used long term for the management of obesity. Just like any other chronic disease, when drugs are discontinued, the disease comes back, i.e., weight loss is regained.[36] *Fact 5*: Few patients treated for obesity reach their goal weight, and almost no one reaches their ideal weight, with or without drugs.[37] However, weight loss improves comorbidities[1,10–12,15,16] and quality of life.[38] *Fact 6*: Patients must be able and willing to comply with

the medical regimen and lifestyle changes to improve their chances of success.[39] Therefore, a relevant motivation should be identified in discussion with the patient. It is important to note that improvement in health with weight loss is usually not a compelling motivator from a patient's standpoint, and if used as the only argument by a medical provider, it may be unsuccessful. A more careful discussion to identify relevant goals from the patient's point of view needs to be performed and agreed upon. For example, being able to play sports with the family, go dancing with friends without experiencing knee pain, or have improved sexual health may be more relevant for some patients compared with improved disease control, such as diabetes and hypertension.

43.3.2 Step 2. Medical Optimizations

Medical providers should obtain a comprehensive history and perform a comprehensive physical exam of the patients treated for excess adipose tissue. In particular, the history should include the lifestyle history and weight gain/loss history with identifications of concomitant events for changes in weight. The physical should include signs of obesity-related complications or causes for weight gain.

If the history and/or physical suggest a secondary cause for obesity, then patients should be screened for those conditions and treated if needed. If any new obesity complications are diagnosed, then they should be treated appropriately or referred to medical providers.

Medical providers should then carefully examine the drug reconciliation list and try as much as possible to replace any drugs promoting weight gain with drugs that are weight neutral or that may promote weight loss. If the provider treating obesity is not the prescribing provider of some of the medication for which change needs to be considered, then clear, justified recommendations should be made to the prescribing provider with appropriate follow-up. For example, in patients with type 2 diabetes, medical providers should consider switching weight-promoting medicine like TZDs or sulfonylurea with a weight-losing anti-diabetes drug like metformin, pramlintide, or GLP-1 agonists. For the treatment of hypertension (HTN), it may be worth considering either an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or a calcium channel blocker to avoid beta-blockers, which have a weight-gaining effect in most patients. For treatment of depression, medical providers should consider switching mirtazapine or tricarboxylic acid drugs with drugs that are associated with weight loss, like Bupropion. For women interested in contraception, medical providers should consider intrauterine devices or barrier methods rather than injectable or oral contraceptives that are associated with weight gain. For patients with rheumatoid arthritis or another chronic inflammatory disease, it is recommended to avoid (if possible) usage of corticosteroids, known to increase weight, and replace them with nonsteroidal anti-inflammatory drugs or disease-modifying antirheumatic drugs. For seizures, medical providers should consider the use of Topiramate and zonisamide instead of gabapentin or valproate to decrease the risk of weight gain and maintain the benefit.[40,41]

43.3.3 Step 3. Rule Out Pharmacotherapy Choices

Once the decision to use pharmacotherapy for weight loss has been made, and the patient has been medically optimized, medical providers need to identify what drug to start the treatment with. If the patient needs a short-term weight loss treatment, then Phentermine is the drug of choice.

If the patient needs long-term weight loss treatment, then the available drugs are Phentermine-Topiramate, Naltrexone-Bupropion, Semaglutide, Liraglutide, and Orlistat. We recommend a systematic approach that starts with an initial step to ruling out drug choices based on patient age, medical history, current pharmacological treatment, preference for medicine administration route, side effects, and medication cost.

For example, if the patient is 12 years old or younger, there are no FDA drugs approved for long-term weight loss. If the patient is between 12 and 18 years old, the only available choice is Orlistat, and therefore, the other four drugs are ruled out for use. Patients 18 years old or older have all the five drugs available for long-term weight loss treatment.[4–6,14,19]

The medical history relevant for this step is pregnancy, lactation, and medical comorbidities. Even though only Phentermine-Topiramate is labeled as a teratogen, none of the other drugs are approved for pregnant or lactating women due to lack of safety data.[4–6,14,19,24] The main contraindications based on the systems affected include the following. For head and neck, if the patient has glaucoma, then medical providers should not use Phentermine/Topiramate. For cardiovascular, if the patient has an unstable cardiac disease, then medical providers should not use Phentermine/Topiramate. For endocrine, if the patient has medullary thyroid carcinoma or MEN2, medical providers should not use Liraglutide or Semaglutide. For psychiatric, if the patient has bulimia or anorexia, medical providers should not use Naltrexone-Bupropion.[4–6,14,19,24]

The medication reconciliation list that the patient is taking at the time of the weight loss treatment is also important. Several weight loss drugs cannot be prescribed in combination with other drugs. For example, if the patient is taking a monoamine oxidase inhibitor, then medical providers should not prescribe Phentermine-Topiramate ER or Naltrexone/Bupropion. If the patient is on chronic opioid treatment, then medical providers should not prescribe Naltrexone-Bupropion. If the patient is taking warfarin, anti-epileptics, levothyroxine, or cyclosporine, medical providers should not prescribe Orlistat in order to avoid modified absorption of active substance.[4–6,14,19,24]

Patients' dislike for or inability to comply with certain administration routes and frequency is common and should be considered for improved compliance and effectiveness.

Liraglutide and Semaglutide are to be administered subcutaneously, which may not be accepted by some patients and therefore could be used to rule out drug choices. All the other drugs are administered orally. The frequency of administration may also represent an impediment for some patients and a reason to rule out some medication choices. Liraglutide is administered once a day, while Semaglutide is administered once a week. Phentermine-Topiramate is administered once daily. Naltrexone-Bupropion is administered twice daily. Orlistat is administered three times a day.[4–6,14,19,24]

Another important factor to rule out medication choices is the possible side effect profile. Patients should decide which risks they are willing to take. For example, in terms of cardiovascular risks, increased heart rate could be observed with Liraglutide, Semaglutide, Naltrexone-Bupropion, and Phentermine-Topiramate; and increased blood pressure could be caused by Naltrexone-Bupropion. For psychiatric risk, depression could be caused by Naltrexone-Bupropion. In terms of neurological risks, dizziness could be caused by Naltrexone-Bupropion and Phentermine-Topiramate; headache could be caused by Liraglutide, Semaglutide, and Naltrexone-Bupropion; insomnia could be caused by Naltrexone-Bupropion and Phentermine-Topiramate; inattention could be caused by Phentermine-Topiramate; seizures could be precipitated by Naltrexone-Bupropion, paresthesia by Phentermine-Topiramate, and metallic taste by Phentermine-Topiramate. Gastrointestinal symptoms and signs are the most common side effects: nausea may be caused by Liraglutide, Semaglutide, and Naltrexone-Bupropion; constipation may be caused by Liraglutide and Naltrexone-Bupropion; abdominal pain by Liraglutide and Semaglutide; pancreatitis by Liraglutide and Semaglutide; fecal urgency and oily stools by Orlistat. Disturbance in electrolytes may also happen, with decreased serum potassium observed in some patients taking Phentermine-Topiramate. For women of childbearing age, congenital malformation may be caused by Phentermine-Topiramate if taken in the first trimester of pregnancy.[4–6,14,19,24]

Cost is also a valid concern for patients, especially because most insurances do not yet cover weight loss drugs. The most inexpensive obesity drugs are Orlistat and Phentermine-Topiramate, so if this is a limiting factor for the patient, they may be a good choice to start with. Naltrexone-Bupropion price is mid-level, while the other drugs are reported as expensive without insurance.[40]

43.3.4 Step 4. Rule In Pharmacotherapy Choices

The next step in choosing the appropriate weight loss medication is to rule in pharmacotherapy choices so that the patient can have additional benefits, including concomitant improvement of other comorbidities, maximum effect on certain behaviors, and efficacy potential.

Patients' current comorbidities should be an important consideration when selecting a new drug. Weight loss by itself improves obesity-associated diseases, but as seen in the previous sections, weight loss drugs have benefits for other chronic diseases and therefore can be used to improve more than one condition. For example, if patients have migraines, medical providers should consider the use of Phentermine-Topiramate. If the patient has type 2 diabetes or prediabetes, medical providers should consider Liraglutide or Semaglutide. If the patient is smoking or has mild depression, medical providers should consider Naltrexone-Bupropion.

When taking the history of present illness, if the patient cites cravings as the major contributor to excess food intake, then Phentermine-Topiramate or Naltrexone-Bupropion should be considered. When the patient reports dissatisfaction with not feeling full when following a calorie-restrictive diet, medical providers should consider Liraglutide or Semaglutide. All the other long-term weight loss drugs (except Orlistat) are helping the patient to have a lower appetite and consequently, adhere to a low-calorie diet.[4–6,14,19,24]

One of the most frequently asked questions from the patients is which medicine is most effective. This is different for each patient depending on the causes of excess weight gain. Currently, we know that the average weight loss caused by Semaglutide is 10–12%, by Phentermine-Topiramate 7–9%, by Liraglutide 5–6%, by Naltrexone-Bupropion 3–5%, and by Orlistat 2–3%. This is the starting point for a discussion about effectiveness, with the note that each patient is different and that all these percentages are caused by the weight loss drug in addition to lifestyle changes.[4–6,14,19,24,42]

43.3.5 Step 5. Prescribe Medicine Using the Recommended Titration Schedule; Monitor the Efficacy and the Possible Side Effects

When using Phentermine-Topiramate, Naltrexone-Bupropion, Liraglutide, and Semaglutide for the management of obesity, medical providers should follow the recommended titration schedule as mentioned in the previous section. Side effects should be carefully monitored, and if medication is not tolerated, medication should be either discontinued or kept at lower dosages.[4–6,14,19, 24]. As with any other symptom or sign, a detailed history should confirm that the presented complaint is not due to a different disease or drug but is indeed caused by the weight loss medication prescribed.

The weight of the patient should be carefully monitored also, with a minimal target of 4–5% weight loss in 12 weeks.[4–6,14,19,24] If this target is not achieved, then medical providers should consider choosing a different drug for the management of obesity, referral to bariatric surgery, or optimizing the lifestyle change intervention. The change in behavior could be hindered by multiple facts, including certain barriers, inappropriate goals, or aberrant eating behaviors. Some patients may need to attend a comprehensive behavior weight loss program or a very low-calorie diet program to successfully reach their goals.

43.3.6 Step 6. Concomitant Management of Chronic Comorbidities

As with any other intervention that is causing weight loss drugs, medical providers should monitor the progression of the diseases improved by the weight loss. For example, patients with type 2 diabetes undergoing concomitant treatment with drugs for weight loss should be advised to monitor their blood glucose more often and report any change in glucose patterns to the medical provider. This will ensure that changes in the diabetes medication can be made appropriately and on time. Patients with HTN should also be instructed to monitor their blood pressure every morning at home and report any change in pattern. Patients with hyperlipidemia should be monitored with fasting blood lipids after three months of the program so that an adaptation in the management plan can be made as needed. Patients may need a decrease or discontinuation of type 2 diabetes, HTN, or hyperlipidemia medication as weight loss is achieved.

If the medical provider prescribing weight loss drugs is not the medical provider managing the other obesity comorbidities, then written recommendations for increased follow-up and the possible need for management optimizations should be sent to the appropriate medical provider. Coordination of care between the medical providers is essential to ensure compliance and effectiveness of weight loss management.

43.4 PRACTICE CONSIDERATIONS BEFORE PRESCRIBING DRUGS FOR WEIGHT LOSS

43.4.1 Prepare Your Medical Providers for Prescribing Drugs for Weight Loss

Medical providers looking to start using pharmacotherapy for weight loss need to be aware of the following. Some drugs are DEA Schedule IV: Phentermine, and Phentermine-Topiramate. Therefore, medical providers should follow all the local guidelines for prescribing any drug that is scheduled IV as defined by the DEA. One drug (Phentermine-Topiramate) has a risk evaluation and mitigation strategy in place, and therefore, all prescribing medical providers and dispensing pharmacies need a special certification[5, 43] obtained from the Qsymia website. This is meant to prevent congenital effects, which can occur if Topiramate is taken in the first trimester of pregnancy. It is recommended that Qsymia can be prescribed to women of childbearing age only if they have either a) an intrauterine device; b) tubal ligation/hormonal contraception and a barrier method; or c) two barrier methods. Medical providers can also seek out comprehensive education in obesity medicine by conducting training and obtaining a certification from the American Board of Obesity Medicine (www.abom.org). However, this certification is not required for managing obesity with drugs for weight loss.

43.4.2 Prepare Your Practice for Introducing Pharmacological Management of Obesity

All the drugs approved by the FDA for short-term or long-term weight loss should be used as indicated, in addition to counseling and education for lifestyle changes. And as per obesity management guidelines,[1,2] the lifestyle changes should match the characteristics of comprehensive intensive lifestyle intervention. This is an important aspect that needs to be considered by clinicians, practice managers, and owners of primary care practices. Just offering the weight loss drugs without lifestyle change interventions may not result in the desired/studied weight loss effects.

Just like with any other interventions for treating patients with obesity, special attention must be given to the environment of the clinic. The furniture and the medical equipment have to be appropriate for the management of patients with excess weight. The staff must be trained in managing problems that are associated with excess weight.

43.5 FUTURE DIRECTIONS

As most patients want either to lose weight or maintain their weight, and obesity is associated with multiple comorbidities from various specialties, most medical providers should be prepared to treat patients with obesity. In some cases, for which pharmacotherapy is indicated, they will need to prescribe, monitor, and optimize their treatment with weight loss drugs. A lot of progress has been made in this direction. First, obesity was declared a disease by the American Medical Association (https://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf), which should increase the number of insurance companies covering obesity management with reimbursement of medical providers' time and reasonable co-pays for patients. Second, an Obesity Medicine certification has been developed and is available for any provider to complete to become experts in the clinical management of obesity (http://abom.org/). Third, obesity medicine competencies have been developed in order to target objectives for educational activities,[44] and ready-to-use peer-reviewed educational activities are published.[45,46] Therefore, we predict that the management of patients with obesity using FDA approved medicine for weight loss will increase in use and popularity.

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CLINICAL APPLICATIONS

1. Obesity is a chronic condition that requires lifelong treatment. Add obesity diagnosis for all patients that meet the criteria, and address during clinic visit as needed.
2. Use of pharmacologic treatment of obesity is indicated as an adjunct to lifestyle changes in adults with a BMI at or above 30 kg/m^2 or at or above 27

kg/m^2 in the presence of at least one weight-related comorbidity.

3. Selection of an obesity drug should be performed in a stepwise manner, considering the patient's preferences, resources, medical and social history, current and past medications, and behaviors targeted, as well as the characteristics of the obesity drug (including administration route and schedule, side effects, other benefits).
4. If a weight loss drug in conjunction with lifestyle management does not cause at least 5% weight loss in three months or if it causes non-tolerable side effects, then the drug should be discontinued, and an alternative approach should be discussed with the patient.

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44 Surgery for Severe Obesity

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KEY POINTS

- Metabolic and bariatric surgery is an effective treatment approach for patients with severe obesity (BMI ≥40 kg/m^2) or moderate obesity (BMI ≥35 kg/m^2) with a comorbidity.
- All patients who are considering weight loss surgery should undergo a comprehensive assessment by a multidisciplinary team.
- Patients should receive ongoing lifestyle counseling throughout the perioperative process and particular attention to preventing and treating nutritional deficiencies.

44.1 INTRODUCTION

Bariatric surgery has been endorsed as an acceptable weight loss option for patients with a BMI of ≥40 kg/m^2 (severe or class III obesity) or those with a BMI of ≥35 kg/m^2 who have comorbid conditions.[1,2] Currently, overall age-adjusted U.S. population prevalence rates for those with severe obesity (BMI of ≥40 kg/m^2) are 6.9% and 11.5% for men and women, respectively, and 13.8% for non-Hispanic black adults, the most vulnerable subgroup.[4] According to the American Society for Metabolic and Bariatric Surgery,[5] 256,000 bariatric surgeries were performed in the United States in 2019. Given the high prevalence rates for moderate-to-severe obesity and the increased availability of bariatric surgery, it is likely that healthcare professionals from all disciplines will encounter patients who have undergone a bariatric surgical procedure. Similarly, primary care professionals will be expected to monitor and manage their patients on a long-term basis. Many of the weight loss surgeries—most notably the combined restrictive-malabsorptive surgical procedure Roux-en-Y gastric bypass (RYGB), the malabsorptive biliopancreatic diversion (BPD), and biliopancreatic diversion with duodenal switch (BPDDS)—place patients at high risk for development of both macro- and micronutrient deficiencies unless they are properly counseled and supplemented. Since most of the deficiencies can be identified at a preclinical stage, early identification and treatment will prevent or reduce symptoms and deficiency syndromes. Although bariatric surgery does not cure obesity, it is considered a significant tool for weight loss and maintenance of weight loss. As such, patients are at risk to experience weight regain several years following surgery. This chapter will review the most commonly performed weight loss procedures, the importance of preoperative and postoperative management, identification and management of nutritional deficiencies that may occur following bariatric surgery, and factors associated with weight regain.

44.2 BARIATRIC SURGICAL PROCEDURES

Weight loss surgeries have traditionally been classified into three categories on the basis of anatomic changes: restrictive, restrictive-malabsorptive, and malabsorptive. However, the clinical benefits of bariatric surgery in achieving weight loss and alleviating metabolic comorbidities have been attributed largely to changes in the physiologic responses of gut hormones, bile acid metabolism, the microbiota, and adipose tissue metabolism.[6] Metabolic effects resulting from bypassing the foregut include altered responses of ghrelin, glucagon-like peptide 1, peptide YY3-36, and oxyntomodulin. Additional effects on food intake and body weight control may be attributed to changes in vagal signaling. The loss of fat mass, particularly visceral fat, is associated with multiple metabolic, adipokine, and inflammatory changes that include improved insulin sensitivity and glucose disposal; reduced free fatty acid flux; increased adiponectin levels; and decreased interleukin 6, tumor necrosis factor α, and high-sensitivity C-reactive protein levels. The surgical procedures commonly performed are shown in Figure 44.1.

Restrictive surgeries limit the amount of food that the stomach can hold and slow the rate of gastric emptying. The laparoscopic adjustable gastric banding (LAGB) is the prototype of this category. However, due to poor long-term weight loss response, the LAGB has fallen into disfavor and accounts for only 0.9% of all bariatric surgeries performed in 2019.[5] The most commonly performed procedure (accounting for 59.4% of all procedures) is the laparoscopic sleeve gastrectomy (LSG). In this procedure, the stomach is restricted by stapling and dividing it vertically and removing approximately 80% of the greater curvature, leaving a slim "banana-shaped" remnant stomach along the lesser curvature.

The restrictive, malabsorptive bypass procedure combines the elements of gastric restriction with limited macronutrient malabsorption, primarily of fat. In the RYGB procedure (accounting for 17.8% of all procedures), a 10- to 30-ml proximal gastric pouch is formed by surgically separating the stomach across the fundus. Outflow from the pouch is created by performing a narrow (10-mm) gastrojejunostomy. The distal end of the jejunum is then anastomosed 50 to 150 cm below the gastrojejunostomy.

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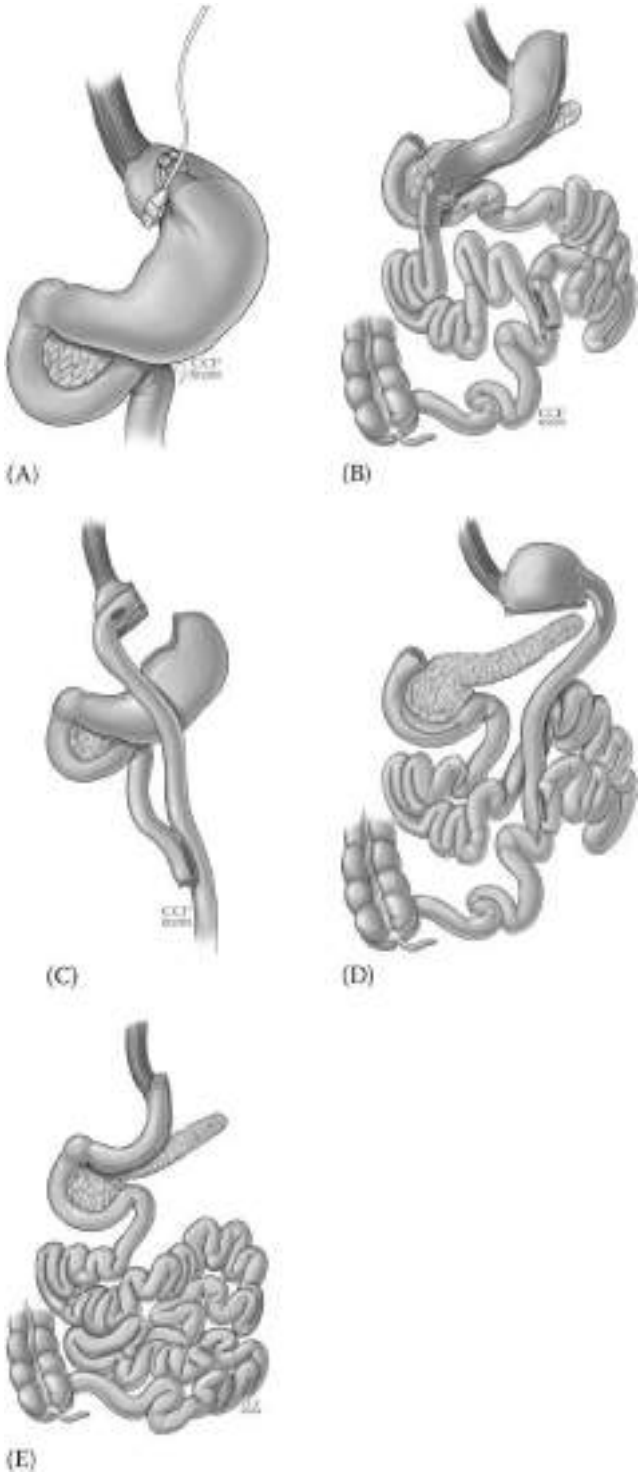


FIGURE 44.1 A. Laparoscopic Adjustable Gastric Banding (LAGB). B. Laparoscopic Sleeve Gastrectomy (LSG). C. The Roux-en-Y Gastric Bypass (RYGB). D. Biliopancreatic Diversion (BPD). E. Biliopancreatic Diversion with Duodenal Switch (BPDDS). (From Kushner, R. and Neff, L. Surgery for Severe Obesity. In Rippe, J.M. (ed), ***Lifestyle Medicine*** 3rd ed, CRC Press, Boca Raton, 2019. Reproduced by permission of Taylor & Francis Group.)

"Roux-en-Y" refers to the Y-shaped section of small intestine created by the surgery; the Y is created at the point where the pancreo-biliary conduit (afferent limb) and the Roux (efferent) limb are connected. RYGB may be performed with an open incision or laparoscopically. There are two malabsorptive procedures, which account for fewer than 1% of all procedures performed in the United States: the biliopancreatic diversion (BPD) and the biliopancreatic diversion with duodenal switch (BPDDS).

44.3 IMPORTANCE OF LIFESTYLE INTERVENTION

Since obesity is fundamentally a disorder of energy balance, all treatments must include attention to caloric intake (energy in) and physical activity (energy out). By altering gastrointestinal anatomy and physiology, weight loss surgery is a powerful tool to reduce caloric intake. Nonetheless, patients need counseling on diet and nutrition that is consistent with the specific surgical procedure (restrictive vs. malabsorptive) and with optimal health. They also need guidance on implementing dietary changes within the structure of their daily life. Similarly, patients benefit from education and advice about increasing daily physical activity and implementing an exercise routine.

44.4 PREPARING THE PATIENT FOR SURGERY

Several practice guidelines have been published regarding the nonsurgical medical and lifestyle support of patients undergoing bariatric surgery.[7–9] All patients who are considering weight loss surgery should undergo a comprehensive assessment by a multidisciplinary team of healthcare providers that includes a physician or advanced practice provider, registered dietitian, and mental health professional.[7] During the preoperative process, patients are typically instructed on healthy eating and physical activity patterns, behavioral strategies to implement the lifestyle changes, and the importance of stress reduction and social support for long-term success. Specific dietary and nutritional recommendations pertinent to the surgical procedures include use of protein supplements, consumption of multiple meals and snacks, and slowing the rate of eating. Patients are seen either individually or in small groups.

Although it is reasonable to encourage weight loss prior to surgery, the literature is conflicting regarding the benefit of mandating preoperative weight loss as a criterion to undergo surgery. The primary rationale for requiring routine preoperative weight loss is to decrease the short-term operative morbidity and mortality. Furthermore, the patient's motivation for and ability to adhere to the dietary restrictions considered essential for a successful surgical outcome can be assessed. While 5–10% of preoperative weight loss has been shown in some studies to reduce postoperative complications[10] and 30-day mortality[11] as well as improve one-year weight loss,[12] other studies have not

shown a benefit in longer-term weight loss outcomes.[13,14] An additional compelling reason to endorse preoperative weight loss is to optimize the operative field by reducing liver volume and visceral adipose tissue (VAT). A systematic review showed that preoperative treatment with a very low-calorie liquid diet (VLCD) for 9 to 12 weeks led to weight loss (−2.8 to −14.8 kg) and to liver reduction by 5% to 20% of the initial volume.[15] Based on the existing literature, there is a general agreement on the beneficial effects of recommending a modest loss in the immediate presurgical period.[16]

44.5 WEIGHT LOSS OUTCOMES AND IMPROVEMENT IN OBESITY-RELATED MEDICAL CONDITIONS

Several meta-analyses and systematic reviews of bariatric surgery outcomes have been conducted.[17–20] In general, weight loss is greatest with the malabsorptive procedures (BPD, BPDDS), followed by the restrictive-malabsorptive procedure (RYGB), and least with the restrictive procedures (LAGB, LSG). As compared with standard care, differences in BMI levels from baseline at year one are –11.3 kg/m^2 for BPD, −9.0 kg/m^2 for RYGB, −10.1 kg/m^2 for LGS, and −2.4 kg/m^2 for LAGB.[21] Mean weight loss at two to three years following a surgical procedure ranges from 20% to 34% of initial body weight, depending on the procedure. The trajectory of weight loss also differs between procedure types. Whereas the rate of weight loss is slower with LAGB, with maximal weight loss achieved after 2 or 3 years, maximal weight loss with RYGB and LSG is achieved at 12–18 months.

Significant improvement has been reported in multiple obesity-related comorbid conditions, including type 2 diabetes (T2D), hypertension, dyslipidemia, and obstructive sleep apnea.[22–30] One of the most significant clinical outcomes is the role of bariatric surgery in the treatment of patients with T2D. A substantial body of evidence from randomized controlled trials (RCTs) demonstrates that bariatric/metabolic surgery achieves superior glycemic control in patients with T2D compared with various medical and lifestyle interventions. The improvement in diabetes control appears to be due to both weight loss and weight loss–independent effects.[31] Based on these data, the Second Diabetes Surgery Summit (DSS-II) Consensus Conference published guidelines in 2016 that were endorsed by more than 50 other organizations interested in the treatment of diabetes.[3] According to the guidelines, metabolic surgery should be recommended to treat T2D in patients with class II obesity (BMI of 35.0 to 39.9 kg/m^2) when hyperglycemia is inadequately controlled with lifestyle and optimal medical therapy, and it should be similarly considered for those with class I obesity (BMI of 30.0 to 34.9 kg/m^2). The 2021 Standards of Care for Diabetes from the American Diabetes Association includes bariatric surgery in the treatment algorithm for T2D.[32]

44.6 NUTRITIONAL CARE

44.6.1 Dietary Changes after Bariatric Surgery

A variety of dietary changes occurs after bariatric surgery that can result in unbalanced diets and inadequate micronutrients and protein intake.[33] Most importantly, there is a significant and sustained reduction in caloric intake. Although portion sizes tend to increase gradually over time in postoperative patients, caloric intake is typically still reduced by 25% or more for years after surgery.[34,35] An analysis of the Swedish Obese Subjects (SOS) study, a prospective, matched (non-randomized), intervention trial of bariatric surgery, demonstrated the importance of early caloric restriction.[36] Study participants with greater reductions in energy and fat intake in the first six months after bariatric surgery maintained greater weight loss after ten years.

Food intolerances may occur and can lead to alterations in dietary patterns after bariatric surgery. Lactose intolerance can develop in patients who have undergone gastric bypass; as a result, nearly one-third of patients report avoiding milk after this procedure.[37] Dumping syndrome occurs in up to 76% of patients after RYGB and may lead patients to reduce their intake of concentrated sweets and fatty foods to avoid associated postprandial symptoms, such as abdominal cramping, nausea, diarrhea, light-headedness, sweating, and tachycardia.[38] Over 60% of patients report avoiding sweets and nearly 30% avoid fatty foods after RYGB surgery.[37] Other food intolerances include difficulty consuming whole meats, fresh fruits, and raw vegetables, presumably due to the phenomenon referred to as "plugging," when a food becomes lodged in the gastric pouch.

Regardless of the types of foods consumed, regurgitation or vomiting can occur when patients eat too quickly, fail to chew food thoroughly, or eat more than what the gastric pouch will hold. However, it should be noted that vomiting is not an intended consequence of bariatric surgery, and it should not be viewed as normal, particularly in the late postoperative period. Patients who have persistent vomiting or regurgitation after surgery should be evaluated for the presence of maladaptive eating behaviors as well as anatomical or functional issues such as stomal stenosis or ulceration, reflux, and gastric dysmotility.[7,39]

Patients with symptoms of dumping syndrome can usually be managed by dietary modification, including avoidance of concentrated sweets and simple sugars, consumption of small frequent meals, and inclusion of protein at every meal. Patients with symptoms suggestive of postprandial hypoglycemia that are not ameliorated by dietary modification should undergo evaluation for the presence of endogenous (or "post-bypass") hyperinsulinemic hypoglycemia.[7,40] Patients with more severe neuroglycopenic symptoms (such as confusion or loss of consciousness) should also undergo evaluation for this condition, which can occur after gastric bypass. For most patients with post-bypass hypoglycemia, dietary modification, including carbohydrate restriction to less than 30 grams per meal, can

significantly reduce the frequency and severity of symptoms.[41] However, when symptoms persist, pharmacologic therapies may be required.[42]

44.6.2 Recommended Dietary Patterns and Eating Behaviors

As a result of the reductions in gastric capacity and caloric intake after surgery, patients must take care to ensure that nutritional needs are met. Postoperative patients should be advised to consume small portions, have four to six small meals daily, and ensure an adequate intake of lean protein (60–120 grams/day), fruits and vegetables (more than five servings/day), and whole grains.[7] Patients should also eat slowly, chew thoroughly, avoid fatty foods, sweets, and sugar-sweetened beverages, and avoid ingestion of liquids within 30 minutes of meals. Unfortunately, many postoperative patients struggle to follow the recommended guidelines, particularly regarding fruit and vegetable consumption and avoidance of sweets and caloric beverages. For this reason, clinicians should routinely assess patients' dietary intake during postoperative visits and reinforce recommended dietary goals.

44.6.3 Prevention of Micronutrient Deficiencies after Bariatric Surgery

Patients who have undergone bariatric surgery should be counseled that they are at risk for the development of micronutrient deficiencies after surgery. After RYGB, the most common micronutrient deficiencies include those of vitamin B_{12}, vitamin D, calcium, and iron.[43–46] Folic acid deficiency has also been reported but is largely preventable with regular use of a standard multivitamin preparation. Sleeve gastrectomy has been reported to produce similar deficiencies as gastric bypass but at a somewhat lower frequency. As compared with RYGB, the BPDDS is much more likely to produce deficiencies of the fat-soluble vitamins, including vitamin A. Purely restrictive procedures such as LAGB are infrequently associated with specific nutritional deficiencies.

In most cases, micronutrient deficiencies can be prevented by regular vitamin and mineral supplementation along with appropriate clinical follow-up and routine biochemical surveillance. Expert guidelines are available regarding recommended vitamin and mineral supplementation after surgery and the frequency of laboratory screening for deficiency states.[7,43-45] Tables 44.1 and 44.2 summarize these recommendations. Patients who are found to have evidence of specific micronutrient deficiencies will need additional vitamin or mineral supplementation, as indicated.

44.7 PHYSICAL ACTIVITY

Among individuals who have lost weight with nonsurgical treatment approaches, physical activity clearly plays a vital role in long-term maintenance of weight loss.[47,48] Much less is known about the role of physical activity in weight control after bariatric surgery, but it is likely an important factor.

44.7.1 Physical Activity Levels after Bariatric Surgery

Numerous studies suggest that self-reported levels of physical activity increase significantly after bariatric surgery.[49]. However, there are few objective data regarding changes in

TABLE 44.1
Recommended Micronutrient Supplementation after Bariatric Surgery

Supplement	Dose and frequency
Vitamin B_1 (thiamine)	[a]12 mg daily
Folate (folic acid)	[a]400–800 µg daily800–1,000 µg daily for women of childbearing age
Calcium	[b]1,200–1,500 mg/day from all sources (after RYGB, SG, or LAGB)[b]1,800–2,400 mg/day from all sources (after BPD/DS)
Vitamin D (in calcium supplement or separate)	3,000 IU/day
Elemental iron	[a]18 mg daily for low risk patients40–60 mg/day for menstruating females
Vitamin B_{12}	350–500 µg/day orallyOr 500 µg every week intranasallyOr 1,000 µg/month parenterally (IM or SQ)
Zinc	[a]16–22 mg/d (after BDP/SD)[a]8–22 mg/d (after RYGB)[a]8–11 mg/d (after SG/LAGB)
Copper	[a]2 mg/d (after BPD/DS or RYGB)[a]1 mg/d (after SG or LAGB)
Vitamins A, E, and K	[a]Vitamin A 5,000 IU/D and vitamin K 90–120 µg/d (after LAGB)Vitamin A 5,000–10,000 IU/D and vitamin K 90–120 µg/d (after RYGB and SG)[a]Vitamin A 10,000 IU/d and vitamin K 300 µg/d (after DS)[a]Vitamin E 15 mg/d (after LAGB, SG, RYGB, and BPD/DS)

LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, BPDDS.
Patient subgroups at higher risk requiring additional supplementation are indicated.
[a]Obtained from multiple vitamin-mineral supplements.
[b]Calcium should be given in divided doses; calcium carbonate should be taken with meals; calcium citrate may be taken with or without meals.
Source: Adapted from the American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient. See Parrott, J. et al., *SOARD*, 13(5),727–741, 2017.

TABLE 44.2
Recommended Laboratory Tests and Frequency of Routine Biochemical Surveillance

Procedure	Recommended frequency of biochemical surveillance	Recommended laboratory tests
LAGB, RYGB, and SG	First year: every three to six months.Thereafter: annually	CBC, electrolytes, glucose, iron studies, ferritin, vitamin B_{12}, liver function, lipids, 25-hydroxyvitamin D**As needed:** intact PTH, thiamine, RBC folate, MMA, HCy
BPD/DS	First year: every 3 monthsThereafter: every 3–6 months	**Every 3–6 months:** CBC, electrolytes, glucose, iron studies, ferritin, vitamin B_{12}, RBC folate, liver function, albumin, prealbumin, lipids**Every 6–12 months:** 25-hydroxyvitamin D, vitamin A, vitamin E, vitamin K, INR, intact PTH**Every 12 months:** urine N-telopeptide, metabolic stone evaluation (24-hour urine calcium, citrate, uric acid and oxalate), zinc, and selenium**AAs needed:** osteocalcin, carnitine, essential fatty acid chromatography

LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, BPDDS; CBC, complete blood count; PTH, parathyroid hormone; RBC, red blood cell; MMA, methylmalonic acid; HCy, homocysteine; INR, international normalized ratio.
Source: Adapted from the American Association of Clinical Endocrinologists/The Obesity Society/American Society for Metabolic and Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. See Mechanick, J.I. et al., *Obesity*, 28(4), 1–58, 2020.

physical activity levels in the postoperative period, and self-reported increases are likely to be overestimated.[50] The data suggest that only 6–24% of post–bariatric surgery patients meet national guidelines regarding minimal physical activity levels for general health promotion (i.e. ≥150 min/week of moderate-to-vigorous physical activity).[51,52]

Significant weight loss, such as that achieved after bariatric surgery, may enable patients with severe obesity to become more active. However, cognitive barriers to physical activity may persist after bariatric surgery and may influence patients' activity levels.[53] These barriers include reduced awareness of the health benefits of exercise, fear of injury, a lack of confidence in the ability to participate in physical activity, and self-consciousness or embarrassment. Treatment strategies that address these barriers may help patients become more physically active.

44.7.2 Benefits of Physical Activity Interventions in Postoperative Bariatric Surgery Patients

Several meta-analyses of randomized controlled studies have reviewed the effect of physical activity in bariatric surgery.[54–57] Using large databases, they concluded that exercise leads to increased improvement in functional capacity and physical fitness over surgery alone, along with improving cardiometabolic risk factors such as blood pressure. However, the amount of additional weight loss is modest compared with the 30% or more loss of initial weight after bariatric surgery itself.

44.7.3 Recommendations for Physical Activity after Bariatric Surgery

National guidelines suggest that for optimal weight control, most overweight individuals will need to accumulate at least 150–300 minutes of moderate physical activity per week, or 30–60 minutes most days of the week.[58] Data from the National Weight Control Registry indicate that walking is the preferred form of physical activity in this group of individuals.[59] Regular pedometer use may be a practical and helpful strategy for patients who have had bariatric surgery.[60] However, a RCT suggested that the provision of pedometers to bariatric surgery patients may be an ineffective strategy unless it is coupled with ongoing exercise counseling.[61]

44.8 BEHAVIORAL/PSYCHOLOGICAL CARE

Bariatric surgical patients experience a variety of psychosocial challenges in the postoperative period. Initially, patients must adjust to the postoperative diet and to their altered relationship with food. As weight loss progresses, patients must adapt to changes in their appearance and their interactions with others. Dramatic weight loss, however desirable to the patient, can lead to unexpected consequences, such as body image issues related to excess skin, unwanted sexual attention from others, and jealousy from friends and loved ones. As a result of these many challenges, mood disorders, disordered eating patterns, and substance abuse are common among postoperative patients.

44.8.1 Mood Disorders

Mood disorders are prevalent among candidates for bariatric surgery. For example, in one prospective study utilizing structured clinical interviews to assess mood pre- and postoperatively, clinical depression was present in approximately one-third, and anxiety was present in almost 20% of preoperative patients.[62] In this population, the prevalence of clinical depression decreased by over 50% in the three years following surgery, but the

prevalence of anxiety remained relatively stable. Other studies have reported significant improvements in depressive symptoms that persist for up to five years postoperatively.[63,64] Data from the large SOS study suggest that after dramatic improvements in both depression and anxiety in the first postoperative year, there may be some deterioration of mood over time.[65] Data from the Longitudinal Assessment of Bariatric Surgery (LABS) study, a prospective, observational study of patients undergoing bariatric surgery, have provided further information regarding the effect of weight loss surgery on psychiatric disorders.[66] At pre-surgery, 30% of patients met the diagnostic criteria for an Axis 1 disorder. The prevalence dropped to 17% and 18% at two and three years after surgery, respectively. The corresponding prevalence rates at baseline and at years two and three for any anxiety disorder were 17.2%, 12.3%, and 7.8%, respectively. A recent systematic review and meta-analysis concluded that bariatric surgery improved depression and anxiety symptoms following the first 24 months after surgery.[67,68]

It is important to note that some studies have yielded discrepant findings. Patients who have undergone bariatric surgery may be at an increased risk of suicide, particularly in the first three years after surgery.[69–72] In a large, retrospective cohort study, individuals who had undergone gastric bypass surgery were twice as likely to commit suicide as control subjects with obesity matched for sex, age, and baseline BMI.[70] Case studies suggest that patients who commit suicide after bariatric surgery often have a history of recurrent major depression, both before and after surgery, and that their depression persists even if they have excellent weight loss results.[71] These reports highlight the importance of continued attention to psychosocial health in the postoperative period, regardless of weight loss outcomes.

44.8.2 Disordered Eating

Data from the LABS study have provided information regarding the effect of weight loss surgery on eating pathology.[73] Following a cohort of 183 patients for up to three years postoperatively, investigators found that pathological eating behaviors and eating-related experiences are common prior to bariatric surgery and improve following surgery. For example, comparing pre-surgery and one year after, prevalence rates for bulimic episodes declined from 11.6% to 1.3%, loss of control eating declined from 18.3% to 6.2%, picking/nibbling diminished from 36.0% to 20.2%, and evening hyperphagia was reduced from 16.5% to 5.0%. Post-surgery eating-related variables associated with poor weight outcomes included loss of control eating, hunger, and the eating disorder examination global score (which combines several factors, such as restraint and shape/weight concerns). It is important to probe for eating pathology, since patients may not report these behaviors unless they are prompted by a clinician.

44.8.3 Alcohol Misuse

The concern about the potential for development of alcohol dependence or abuse in postoperative patients was previously raised as a possible "addiction transfer" or "cross addiction," whereby patients substitute alcohol for binge eating after surgery.[74,75] Although there is little support for this hypothesis, it does raise the question of whether patients who drink alcohol preoperatively are at increased risk for continued use, and what effect (if any) bariatric surgery may have on development of alcohol use disorder (AUD). In a sub-study of LABS, patients completed baseline and follow-up assessments of alcohol consumption using the Alcohol Use Disorders Identification Test (AUDIT), a ten-item test. After RYGB, there was an increase in the prevalence of AUD from baseline (pre-surgery) (6.6%) to year two (9.6%) and year seven (16.4%).[76,77] The five-year cumulative incidence of AUD treatment was 20.8%. Male sex, younger age, smoking, and any or regular alcohol consumption pre-surgery were associated with increased risk for developing AUD. In another comprehensive review of the literature,[76] a preoperative history of substance use (including alcohol) was a reliable predictor of postoperative use.

The absorption and metabolism of alcohol may be altered after bariatric surgery, and as a result, postoperative patients may be more susceptible to the intoxicating effects of alcohol.[77–82] Patients should therefore be counseled to exercise caution when consuming alcohol after surgery. In addition, clinicians who care for bariatric surgery patients should ask patients about alcohol intake after surgery and remain alert to the possible presence of AUD in this population.[83]

44.8.4 Psychological Counseling and Peer Support in the Postoperative Period

Data suggest that patients with postoperative depression experience poorer weight loss than those who are not depressed.[62] Similarly, postoperative patients who exhibit disordered eating patterns, such as grazing and loss of control over eating, have poorer weight loss and greater weight regain.[84,85] Patients who are found to have mood disorders, disordered eating behavior, or substance abuse after bariatric surgery should be offered expert psychological counseling and support. It is not known, however, whether such treatment improves weight loss or other outcomes.

44.9 COMPREHENSIVE LIFESTYLE INTERVENTIONS AFTER BARIATRIC SURGERY

There are limited data regarding the benefits of comprehensive lifestyle interventions in the postoperative period. Several systematic reviews and meta-analyses on behavioral and psychotherapeutic interventions in the bariatric surgical population have been published. In the review by Rudolf and Hilbert,[86] they identified 15 behavioral management

studies published prior to 2012. Eight provided cognitive behavioral therapy (CBT), and seven included group support attendance. Across all the behavioral studies, patients in the treatment groups showed greater weight loss than patients in the control groups; however, differences did not reach significance in any samples. For the group support studies, the majority found greater weight loss among those who attended support group meetings than in those who did not, though the difference was once again marginal.

In the systematic review and meta-analysis of RCTs involving lifestyle and nutritional interventions by Swierz et al.,[87] 22 studies were included for analysis. Due to inconsistency in data reporting, they concluded that there was insufficient evidence whether perioperative interventions improve long-term outcomes, and called for better research and reporting.

In the review by Beck et al.,[88] they identified nine studies investigating the effect of psychotherapeutic interventions and support groups on weight loss following bariatric surgery that were published prior to 2012. Psychotherapeutic treatment targets the psychological factors that have been associated with variability in post-surgical weight loss, including binge eating, depression, motivation, and coping skills. They concluded that both psychotherapeutic interventions and support groups provided a modest beneficial effect on post-surgical weight loss, with an overall effect size of 0.18. In a subsequent review by Kushner and Sorenson[89] in 2014, seven RCTs were identified investigating the efficacy of behavioral, dietary, or exercise counseling for postoperative weight loss. The authors concluded that the lifestyle interventions either had no effect or were only modestly effective in enhancing further weight loss and influencing lifestyle-related behaviors among post–bariatric surgery patients. Additional pilot studies using CBT,[90] CBT and dialectical behavioral therapy,[91] and acceptance-based therapy[92] have been published. However, enhancement of weight loss outcomes has been largely disappointing. Multiple factors appear to influence the varied outcome results, including patient selection, timing and intensity of the intervention, comprehensiveness of counseling provided, and selection of outcome measurements. Further studies will need to be conducted to identify the most suitable targets and patients for intervention.

44.10 WEIGHT REGAIN FOLLOWING BARIATRIC SURGERY

Although clinicians commonly see bariatric surgery patients regain some weight postoperatively, the prevalence and incidence of weight regain has not been well characterized. Follow-up data from the LABS study have continued to inform clinical care regarding various aspects of postoperative management, including postoperative weight loss trajectories, behavioral variables, and three-year weight change.[93,94] The underlying factors that influence weight regain following bariatric surgery are multifactorial and include endocrine/metabolic alterations, anatomic surgical failure, dietary indiscretion, mental health issues, and physical inactivity.[95,96] The extent and significance of these factors is currently uncertain and likely varies between individuals and the operative procedure performed. Using cross-sectional data, weight regain has been estimated to occur in 20–35% of patients, depending on the procedure performed and the duration of time following surgery.[39] The physiological and behavioral (diet and physical activity) causes are common to surgical and nonsurgical patients. Depending on the patient's age and gender, a through history should be performed that reviews all these reasons, followed by appropriate counseling. More recently, there has been interest in the use of pharmacotherapy to treat insufficient weight loss and weight regain following bariatric surgery.[97]

44.11 CONCLUSION

Bariatric surgery is an effective and acceptable treatment for individuals with severe obesity who are at risk for or have complications associated with obesity. Several surgical procedures are available, with variable risk and weight loss outcomes. However, regardless of the procedure performed, surgery is considered a tool that is adjunctive to choosing a healthy, calorie-controlled diet and engaging in daily physical activity. For patients who undergo restrictive-malabsorptive or malabsorptive operations, dietary supplementation is necessary to avoid nutritional deficiencies. Patients are at risk for weight regain following surgery due to several biopsychosocial factors. In order to maximize successful outcomes, all patients should be monitored and managed by a multidisciplinary team of healthcare providers knowledgeable in bariatric surgical care.

CLINICAL APPLICATIONS

- Bariatric surgery should be considered for patients with a BMI of ≥40 kg/m^2 or those with a BMI of ≥35 kg/m^2 who have comorbid conditions and have failed nonsurgical approaches.
- Preoperative assessment and postoperative management should be conducted by a multidisciplinary team of healthcare providers with attention to medical, dietary, physical activity, and mental health aspects of care.
- Since obesity is considered a chronic disease, patients who undergo bariatric surgery require long-term management, employing lifestyle behaviors and strategies conducive to maintaining a healthy body weight.

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Part VIII

Immunology and Infectious Disease



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45 Chronic Exercise and Immunity

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KEY POINTS

- Regular exercise training is linked to overall better health, which extends to improved outcomes related to the immune system.
- Exercise training may induce beneficial changes to resting immune function.
- Participation in regular exercise is encouraged for prevention of many inflammation-related diseases, especially cardiometabolic diseases.

45.1 INTRODUCTION

Exercise training influences numerous aspects of host defense and indices of immune function. The field of exercise and immune function continues to be an active area of research, and there are documented potential changes in immunity that are induced by regular exercise training. The objective of this chapter is to identify practical implications of chronic exercise that are applicable to both fitness exercisers and athletes. The influence of chronic exercise on innate and adaptive immunity will be reviewed, along with the effect of excessive exercise training on selected immune parameters and resistance to infection. We will also address the influence of moderate exercise training on inflammation, wound healing, and the efficacy of vaccines.

45.2 EFFECT OF CHRONIC EXERCISE ON LEUKOCYTE NUMBER AND FUNCTION

Leukocytes are circulating cells of the immune and lymphatic systems derived from bone marrow hematopoietic stem cells, which are collectively responsible for mounting an immune response. A physically active or regularly exercising person has a lower number of circulating leukocytes at rest, but it can be difficult to partition the specific effects of exercise on immunity from the associated health benefits of regular exercise.[1–4] Furthermore, regular exercise and physical activity can alter the phenotype and influence the function of specific subsets of leukocytes.[5,6] These changes potentially mediate the systemic anti-inflammatory effects of chronic exercise, as evidenced by lower levels of circulating markers of inflammation (interleukin [IL]-6 and C-reactive protein [CRP]). In this section, we will summarize current literature to support regular exercise training eliciting changes in the number, function, and phenotype of major leukocyte subsets.

45.3 EFFECT OF CHRONIC EXERCISE ON INNATE IMMUNITY

45.3.1 Monocytes and Tissue Macrophages

Monocytes are circulating cells that have both innate and adaptive immune functions.[7] Monocytes can respond to infection or tissue damage by traveling to the lymph nodes to become dendritic cells[8] or migrating to the site of insult, where they then differentiate into tissue-specific macrophages (e.g., Kupfer cells in liver, macrophages in adipose tissue). Antigen presentation and subsequent cytokine release help to coordinate the responses of the adaptive immune system. Although beneficial in an acute immune response, chronic low-grade activation of the monocyte/macrophage lineage is thought to contribute to the pathophysiology of numerous diseases.[9,10]

Several researchers highlight the role of chronic exercise–induced alterations in monocyte phenotype/inflammatory response as a possible mechanism underlying the anti-inflammatory effects of exercise. In both cross-sectional and longitudinal training studies, participants who regularly exercised had lower mitogen-stimulated, ex-vivo whole blood production of inflammatory cytokines.[11,12] Regular exercise improves cardiovascular disease markers and inflammation—specifically, a reduction in monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α).[13] Taken together, this emerging evidence supports the contention that regular exercise can improve inflammation and cardiovascular disease linked to monocyte/macrophage activation.

Major populations of circulating monocytes are phenotypically classified based on cell-surface expression of CD14 and CD16. CD14++CD16− cells are classical monocytes, which make up the largest proportion of the circulating monocyte population.[14] CD14+CD16+ monocytes are non-classical "inflammatory" monocytes—a subpopulation with a proclivity for production of pro-inflammatory cytokines. CD14++CD16+ monocytes are called intermediate monocytes, but a range of methodologies employed in measuring this subpopulation makes it difficult to compare the influence of exercise on this subset of intermediate monocytes. Circulating inflammatory monocyte percentage is elevated in patients with subclinical atherosclerosis and obesity,[15] and is higher in healthy adults with an elevated risk for cardiovascular disease.[16] These findings are significant, as inflammatory monocytes adhere robustly to activated endothelial cells[17] and may be precursors to CD16+

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macrophages found distributed throughout atherosclerotic lesions and adipose tissue.[18,19] Regular exercise training can reduce the circulating inflammatory monocyte population[6, 20,21] and induce a shift in adipose tissue monocyte expression away from the more inflammatory M1 macrophage phenotype and toward the anti-inflammatory M2 phenotype,[22] thus providing another potential mechanism by which exercise reduces inflammation.

There is strong evidence in support of the concept that regular exercise can reduce monocyte/macrophage inflammation, possibly through modulation of TLR4 expression and/or altering the phenotype of circulating monocyte subpopulations. However, more studies need to be conducted to clarify the effect of regular exercise on adipose tissue macrophage recruitment and activation. This body of work is clinically important, as activation of the monocyte/macrophage lineage is implicated in the pathophysiology of diseases such as diabetes and cardiovascular disease.

45.3.2 Natural Killer Cells

Natural killer (NK) cells are cytotoxic lymphocytes and a major constituent of the innate immune system. They protect against certain tumors and virally infected cells by releasing granules containing proteases and porins that induce apoptosis in the target cell. The results of NK cell exercise/physical activity studies are varied, with exercise reported to suppress,[23] increase,[24–27] or not change the number or cytotoxic activity of NK cells.[28–30] The differences reported between studies may be attributable to differences between recreationally trained individuals and athletes, the length of time a person has engaged in habitual exercise, and the specific NK measurement used. Given the cytotoxic role of NK cells, some groups of people may benefit from increased NK cell number and/or activity—such as cancer survivors. Numerous researchers have reported NK cell benefits related to exercise training in people with cancer, including preserving NK cell activity during (neo)adjuvant chemotherapy[31] and an increase in circulating NK cells.[32] The benefits of exercise training to improve immune function in cancer survivors need to be further investigated, especially regarding the specific exercise prescription required to elicit maximum benefits.

45.3.3 Neutrophils

Neutrophils are polymorphonuclear cells and are the most abundant leukocyte subtype. They are the first responders of the innate immune system and migrate to the site of infection or injury within minutes. In athletes, resting circulating neutrophil number is similar to that in sedentary individuals.[33, 34] A lack of difference in neutrophil count may not indicate neutrophil function, as exercise training programs in physically inactive adults increased neutrophil cell-surface CCR5[35] along with phagocytosis and oxidative burst.[36,37] Further, comparing mostly healthy people may not provide a comprehensive view of the exercise-related neutrophil benefits. For example, an exercise training program lowered neutrophil count in overweight women with multiple risk factors for cardiovascular disease,[38] and the decrease in neutrophil number was correlated with improvements in insulin sensitivity. Although regular exercise may be of benefit to neutrophil numbers and function, when the regular exercise is intense, such as many elite athletes perform, it may reduce neutrophil function.[39–41]

45.4 Effect of Chronic Exercise on Adaptive Immunity

45.4.1 T and B Lymphocytes

T and B cells are the primary circulating cells of the adaptive immune system. T cells are involved in cell-mediated immunity, and B cells are primarily responsible for producing antigen specific antibodies (humoral immunity). It is well accepted that T cells are susceptible to immunosenescence, aging-related changes in adaptive immunity, which is also believed to contribute to age-associated morbidity.[42] However, immunosenescence may be offset by moderate resistance exercise training.[43] Regular exercise may also impact the number, function, and ex-vivo proliferative response of T cell populations in older adults, and as such, may be an important modality for maintaining immune health as one grows older. For example, the ex-vivo lymphocyte proliferative response to mitogen (PHA) was significantly higher in older runners than in non-runners.[44,45] Koizumi et al. reported that exercise training increased the absolute numbers of T cells and T helper cells in older adults, and a six-month aerobic exercise training intervention increased T cell proliferation in response to mitogen.[30] However, other researchers have reported that ex-vivo lymphocyte responses are not affected by exercise interventions. As such, ex-vivo T cell proliferation did not change after 12 weeks of exercise training,[39] and a 12-month moderate resistance exercise program for elderly women did not alter circulating numbers of lymphocytes.[29] This lack of consensus on the effects of regular exercise should be interpreted with caution, as the variability in results may be due to the wide range of exercise intervention type, the T cell–related outcome studied, or possibly, the infection history of the participants. For example, participants who were seropositive for cytomegalovirus (CMV) had a higher acute aerobic exercise response to total lymphocytes, KLRG1+CD28−CD4+ and CD8+ T cells, and CD45RA+CCR7−CD8+ T cells, than CMV negative participants.[46,47]

45.4.2 Th1/Th2 Balance

CD4+ T helper cells can be divided into several distinct subpopulations, including Th1, Th2, Th17, and T regulatory (Tregs) cells. Specifically, Th1 cells are part of cell-mediated immunity and produce tumor necrosis factor (TNF) and interferon gamma (IFNγ); Th2 cells release IL-4, IL-5, and IL-10 and respond to parasites; Th17 produce IL-17 and

appear to play a prominent role in autoimmune disorders. Tregs also suppress the activity of other immune cells and maintain discrimination between self and non-self antigens during an immune response, thereby preventing autoimmune diseases. In some respects, the ratio of T cell subsets may be a better indicator of health than the absolute numbers. For example, the ratio of Thelper1/Thelper2 (Th1/Th2) cytokines is often used as an index of inflammatory signaling, and intensive exercise training induces a shift toward Th2 dominance.[48] A pronounced shift in cytokine production typical of the Th2 anti-inflammatory milieu could render the vigorous exerciser more susceptible to infection.[49,50] However, moderate training appears to induce a positive, subtle shift toward a Th2 cytokine profile, balancing the Th1/Th2 response and inducing the anti-inflammatory influences of regular exercise.[49]

Treg and Th17 cells are not well studied in an exercise training or physical activity context. In the limited research available, Yeh et al. reported an increased Treg function in both healthy middle-aged adults[51] and subjects with Type2 diabetes[52] after 12 weeks of Tai Chi training. In response to a strenuous acute aerobic exercise event, athletes had a decrease in absolute numbers of Treg and an increase in Th17 cells. Furthermore, there was a decrease in percent circulating Treg cells that remained depressed below pre-race levels ten days after the event.[53] Treg and Th17 cells both have a role in regulating inflammation and need further examination in a physical activity context.

45.5 EXERCISE TRAINING AND INFLAMMATION

Evidence for the role that inflammation plays in the development and exacerbation of chronic disease has grown substantially. Inflammation or inflammatory biomarkers are clearly linked to cardiovascular disease,[54] type 2 diabetes,[55] osteoporosis,[56] and several other chronic diseases not previously believed to have an inflammatory etiology.[57] Exercise can provide substantial benefits for the prevention and management of chronic diseases. There is growing evidence that exercise has anti-inflammatory effects, but it is not clear how much of the benefit of exercise is due to the contribution of an anti-inflammatory effect or to the other actions of exercise. Regardless of the relative contribution, inflammatory biomarkers are significantly lower in segments of the population with moderate to high levels of physical activity.[58] Not surprisingly, intervention studies provide less consistent support of an anti-inflammatory effect of exercise. Small participant numbers, different exercise modes and intensities, supervised versus unsupervised exercise, and different choice of biomarkers all likely contributed to these inconsistencies. Nevertheless, there is fairly strong intervention literature to support the observation that exercise training has anti-inflammatory effects in serum or circulating cells,[6,20,59], in muscle,[60,61] and to a lesser extent, in adipose tissue.[62,63] Regular exercise reduces inflammation-promoting nuclear factor kappaB (NFκB) and toll-like receptor (TLR) 4 expression in diabetic subjects.[64,65] Thus, it appears that the ability of exercise to ameliorate the symptoms of chronic disease may be linked, in part, to its anti-inflammatory effects.

It is unclear whether exercise training can exert an anti-inflammatory effect in the absence of changes in body fat.[63,66] The literature in this area is mixed, but there are several examples of exercise providing an independent anti-inflammatory effect. In one review by Beavers, Brinkley, and Nicklas[58] (2010), the authors identified 19 studies in which self-reported physical activity level was linked to biomarkers of inflammation and an additional 9 studies during which the fitness level was measured. These authors concluded that accounting for obesity "attenuated, but did not negate, the strength of the relationship between inflammatory biomarkers and physical activity." There are few studies in which an exercise intervention with and without body weight losses have been compared, and conflicting results of exercise studies in general underscore differences that may be attributed to type and intensity of exercise. The equivocal nature of prior research is supported by a recent weight loss intervention study in people with metabolic syndrome, where all participants were counseled for weight loss and were also randomized into one of five 12-week interventions: low-volume high-intensity interval training, single set resistance training, three sets of resistance training, whole-body electromyostimulation, or control (no additional intervention beyond the nutritional counseling). Although all five groups reduced their body weight by a similar amount, and all three exercise groups reduced their severity of metabolic syndrome, only the low-volume high-intensity group reduced inflammation, specifically CRP and IL-6.[67]

In summary, exercise has anti-inflammatory effects, but these effects may be dependent on the exercise prescription and health of the individual. It is possible that there is an intensity threshold, but evidence in support of low-intensity exercise exerting anti-inflammatory effects suggests the need for further study. Although some mechanisms remain to be determined, the anti-inflammatory effect of exercise has important health implications.

45.6 CLINICAL AND APPLIED OUTCOMES OF CHRONIC EXERCISE AND IMMUNITY

45.6.1 Excessive Training and Immunity

Excessive training, often referred to as "overtraining" or "overreaching," can result in a wide range of negative clinical signs and symptoms, including lethargy, fatigue, mood disturbances, underperformance, immune suppression, and poor healing of cuts and scratches. Resting immunity is not substantially different between athletes and healthy individuals, but it appears that intensive training could negatively affect several resting immune measures. Changes in NK cell activity and T cell function have been observed

after intensified training programs, but it is unclear whether the changes in the immune system induced by hard training are to blame for a higher incidence of infection in athletes.[30] Nevertheless, the collective toll of excessive training on the immune system would appear to render athletes more susceptible to infection.

45.5.2 Excessive Training: URS or URTI?

Several indices of immune function are suppressed by heavy exercise, and athletes who train hard are frequently reported to have an increased incidence of upper-respiratory symptoms (URS) related to upper-respiratory tract infection (URTI).[68] These and similar findings have led to the assertion that heavy exercise lowers immune defenses and increases URTI risk. Two important factors remain unclear in this regard. First, whether excessive training suppresses immune function to the extent possible to result in an increased susceptibility to infection has not been determined.[30] There is a general consensus that several immune parameters are depressed following prolonged or severe exercise, most notably and consistently mucosal immunoglobulin A (IgA), but it is not known whether the immune depression is causative of an increased incidence of URTI. Second, it is not clear whether the URTIs reported by athletes in the majority of studies are pathogen-based or a result of local airway irritation or inflammation.[69] Problematically, most of the studies in which the incidence of URTI has been assessed in conjunction with heavy training largely relied on self-report and a lack of the presence of an infectious pathogen in the sputum of athletes reporting symptoms of URTI.[69] However, most researchers also acknowledge that the ability to detect these pathogens in sputum is far from perfect.

No increase in the rate of infectious episodes was found in marathon runners when runners with a pre-race infection were removed from the cohort,[70] casting further doubt on the relationship between hard exercise and URTI. Although there is evidence that regular, modest exercise reduces the risk of URTI[39] and prolonged, intense, or excessive exercise training increases the risk of URTI,[68] there is considerable controversy in this area, which prevents us from making concrete conclusions about the links between hard exercise and illness. Logistically, excessive time and cost make it difficult to include quantitative cellular immune measures in large cohort studies of infection incidence and prevalence.

Mucosal secretion or the secretion rate of immunoglobulin A (Ig_A) is considered a first line of defense against infection. Ig_A secretion appears to be consistently lowered following repeated, hard exercise sessions. Ig_A has also been more strongly and consistently linked to infection risk in athletes than other measurable aspects of immunity.[50] There are some larger-scale studies in which salivary Ig_A has been measured and negatively correlated with URTI incidence.[71] Gleeson et al.[50] monitored 80 athletes for several months and identified a sub-group of "illness-prone" subjects who had higher training loads, higher levels of multi-antigen-stimulated anti-inflammatory cytokines—illustrating a Th2 dominant response—and lower salivary IgA secretion and flow rates. In addition, the highest quartile of IL-10 producers had higher training loads, higher production of inflammatory and anti-inflammatory cytokines, lower Ig_A, and higher URTI incidence than the lowest quartile. The authors suggested that IL-10 might be a useful predictor of infection risk in physically active individuals.[50] There is clearly an increase in URS associated with hard training, but further research is required to document what proportion of these illnesses are pathogen-based or are linked to airway inflammation/irritation.

A relatively new area of research is related to the relationship between the microbiome and health in athletes. Between-study variability in the types of supplements, doses, and subject populations in this new research area makes it difficult to define an optimal regime for intestinal microbiota health in an athlete. However, there is some evidence that altering gut microbiota may reduce infection risk or length of symptoms in athletes. Post-marathon, runners who received a probiotic for a month prior to the race had lower incidence and severity of URTI symptoms than those in a placebo group.[72] In a separate study, highly trained athletes who received a multi-species probiotic had a lower incidence of URTI, but no improvement in athletic performance, during the 12-week study period.[73] Other researchers have also found a decrease in URTI infection incidence and length of symptoms in athletes taking probiotics, but the benefit may be dependent on the type of probiotic.[74–76] Additionally, more work is needed to determine if a sex difference exists in the responses to probiotics.[77]

45.6.2.1 Wound Healing

Aging and chronic conditions are known to slow the rate at which wounds heal. The influence of exercise training or physical activity levels on wound healing have been studied in a relatively small number of investigations, but the limited available information is promising. A recent scoping review of exercise or physical activity as an adjunct treatment in people with venous leg ulcers acknowledges the small number of studies in this area, but there does appear to be potential for exercise to improve would healing. The most promising interventions were multimodal, such as combined resistance and range of motion exercises.[78] In an experimental wound healing study, Emery et al.[79] divided 28 healthy older adults into an exercise and a non-exercise group. The exercise group had a significantly improved healing rate compared with the non-exercise group. Although this research was limited by a small number of subjects, the exercise effect in Emery's study was substantial, with 55% of the subjects in the exercised group having complete healing at day four compared with 0% in the non-exercised group. More work is needed to determine if simple, cost-effective interventions such as exercise training can alter the rate at which wounds heal. However, the paucity of literature on the topic prevents us from making solid conclusions regarding practical strategies for clinicians or patients.

45.6.2.2 Exercise and Efficacy of Vaccines

Aging is associated with a decline in immune function[80] and an increase in susceptibility to infections,[81] and can also result in low-grade chronic inflammation.[82] Aging-related immunosenescence contributes to the increased incidence and severity of infectious disease among older adults, who experience a greater mortality rate from influenza infection and generally exhibit reduced vaccine efficacy compared with young adults.[83,84]

Exercise training may improve immune competence among older adults who have been administered an influenza vaccine. Several cross-sectional studies in which physically active older adults were compared with sedentary controls have shown a greater influenza vaccine respo nse.[44,85,86] A cross-sectional comparison of older physically active, moderately active, and sedentary groups showed that physical activity was associated with greater response to influenza immunization. The older physically active group developed greater flu-specific IgG and IgM titers two weeks post immunization compared with the moderate activity and sedentary groups.[86] Peripheral blood mononuclear cell proliferation in vitro was also lower in the sedentary group. These studies suggest that lifestyle factors, including regular exercise, may influence immune response to influenza immunization.

In a longitudinal study, Kohut et al. reported that a ten-month exercise intervention in older adults resulted in a greater increase in influenza specific antibody titer and IFN-γ production following flu vaccine.[87] Additionally, 144 sedentary older adults were randomized to either a ten-month aerobic training (n = 74) or a flexibility and balance program (n = 70).[30] The intervention resulted in a significant increase in seroprotection, determined by a hemagglutination Inhibition titer of >40, 24 weeks after vaccination (30–100%). These titer data are significant, as they suggest that an enhanced vaccine response following exercise training can be maintained over a period greater than the length of a typical flu season.

The mechanisms responsible for mediating the effects of exercise on vaccine efficacy are not fully understood, and more recent research seems to be focused on a single bout of exercise rather than a longitudinal exercise training program. However, given that immunosenescence in aging is associated with an elevation in the ratio of memory T cells to naive T cells, potentially reducing the ability of the adaptive immune system to respond to novel antigens, exercise training to improve immune function and overall health in older adults is critically important. Exercise training has been previously shown to reduce the memory:naive T cell ratio,[30] leading to the speculation that exercise may prolong antibody response, potentially by restoring the naive T cell level and subsequent ability to respond to novel antigen exposure.

The SARS-CoV-2 pandemic has increased general interest in immune response and also whether fitness levels or exercising prior to or after vaccination can influence vaccine effectiveness or side effects. Healthy adults who exercised regularly were randomized to either 90 minutes of walking/running or continuing their non-exercise daily routine after receiving their first dose of the Pfizer BNT162b vaccine.[88] All participants were instructed not to exercise on the day of their second vaccine. Two weeks after the first vaccine dose and one week after the second dose, serum anti-RBD IgG antibody was higher in the group that exercised. Interestingly, there was a negative relationship between age and serum anti-RBD IgG antibody. This is important to note, as some of the most impactful effects may be in groups with lower immunity. In a separate study,[89] immunocompromised adults who performed 4 sets of 8–12 exercises on the vaccinated arm prior to immunization with their third dose of Coronavirus vaccine did not have a difference in neutralizing antibody positivity compared with the control group. However, the differences in exercise type and timing—whole-body exercise after the vaccine versus one arm before the vaccine—make it difficult to draw conclusions from these findings, and more studies are needed before specific recommendations can be made about whether exercise can serve as a behavioral adjuvant to the COVID-19 vaccine.

45.7 SUMMARY

It is clear that regular exercise has the potential to alter indices of immune function. Regular exercise may offer some protection against URTI, provide anti-inflammatory actions, and enhance the response to vaccines. However, many unanswered questions remain. For example, excessive training (overtraining) has been linked to increased risk of URTI, but researchers have questioned the reliability of both self-report of URTI and the direct method to detect pathogens in sputum. There is also much research that needs to be conducted on the effects of exercise to restore immune function after a substantial health outcome, such as that observed with cancer treatments or moderate to severe SARS-CoV-2 infection.

The ability of exercise to improve the course of chronic disease via anti-inflammatory and other immune changes is an exciting avenue for researchers. These studies will help to close the gap between the myriad benefits of exercise training and the available mechanisms to explain the benefits. Despite the gaps in our knowledge, it is clear that athletes can train effectively without excessive illness and that fitness exercisers adapt in primarily positive immunological fashion to regular, moderate exercise.

CLINICAL APPLICATIONS

- Regular exercise shifts circulating T cells toward a more anti-inflammatory profile and reduces pro-inflammatory cell-surface receptors on monocytes.
- Excessive training may increase the risk of developing an URTI, possibly in part by alterations in salivary IgA secretion and flow rate.

- Participation in regular exercise may improve wound healing and response to vaccine.
- High inflammation is implicated in many diseases, and people who regularly exercise have lower pro-inflammatory immune cells. An anti-inflammatory effect of exercise training at least partially explains the lower chronic disease rate observed in people who regularly exercise.

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46 HIV and Exercise

Jason R. Jaggers and Gregory A. Hand

KEY POINTS

- Investigations have continuously reported significant physiological and psychological health improvements by modest changes in activity.
- Light to moderate intensity levels are sufficient to achieve short-term health benefits as long as the individual stays consistent with their exercise plan.
- There is no evidence to indicate that exercise performed at low, moderate, or high intensity will negatively impact immune function or disease progression in HIV-infected individuals.
- Future research is necessary to determine successful motivational and behavioral changing interventions aimed at increasing physical activity for this population.
- With an increased lifespan and aging population, incorporating resistance training as part of a weekly exercise prescription for people living with HIV/AIDS (PLWHA) over the age of 50 is strongly encouraged.

46.1 INTRODUCTION

Living with HIV has become more of a management of chronic conditions in recent years than the battle of opportunistic infections from a depleted immune system that it was in the first two decades of the epidemic. Even faster have been the changes in patient symptomatology. With rapid advances in medical science, the pharmacological regimens designed to block viral replication and prevent the spread of infection have quickly gone from a multi-pill daily routine to a single combo-pill. Many people can now live decades longer and well into old age, but they also must be more health conscious to offset negative consequences from antiretroviral therapy (ART) side effects.

Although the advances in ART have increased life expectancy, this is not without consequence. Early into treatment, the chief complaints are often psychological in nature, which over time either subside or become more tolerable. However studies have shown that there are many physiological consequences, like increased lipids and risk for cardiovascular disease (CVD) and diabetes.[1–3] On top of medication related side effects, there is still an ongoing social stigmatization that comes with living with HIV. Even researchers still struggle not only to recruit eligible participants for HIV specific studies but to maintain their participation throughout the study duration. This, in turn, makes it more difficult to determine solid results due to a lack of longitudinal clinical trials and interventions with large datasets.

Due to increased life expectancy and only slight reductions in new infections, we have also begun to experience increased prevalence rates and an aging HIV population who are living well into their senior years. Healthy lifestyle choices, like diet and exercise, have now become that much more important with this population. Exercise alone has shown to have positive impacts on health across all populations, regardless of disease or health status, for both psychological and physiological outcomes. Research from our laboratory and others has also demonstrated significant improvements to the health and quality of life for people living with HIV/AIDS (PLWHA).

46.2 SYMPTOMATOLOGY OF HIV INFECTION

46.2.1 Psychological Consequences

PLWHA are burdened with multiple psychosocial stressors at all stages of illness. Immediately upon diagnosis, patients must face life-changing issues such as managing the illness, affording appropriate healthcare, and the daily struggles that accompany living with the stigmatization of HIV. In addition to these personal stressors, various environmental factors could potentially exacerbate the levels of stress already experienced, such as living in a lower socioeconomic status, facing unemployment, reduced access to healthcare, and many others. The patients' ability to cope with these burdens ultimately depends on their psychological state, their social support network, and their stage of HIV disease. Many studies of various chronic diseases have investigated consequences of distress among patients and reported positive associations with mood disturbance, poor treatment adherence, and negative health outcomes.[4,5] Similar findings have been reported among HIV-related investigations.[6] Although distress has been identified as an important measure to manage mental health, and self-reported symptoms have become a common method used to indicate health status, the literature on self-reported symptom distress within the HIV population is scarce.

Generally, a level of distress is experienced when symptoms are present, and research has shown a negative impact of psychological distress on HIV disease progression.[7] Increases in symptom distress potentially have negative consequences for both physical and psychological health that have been recently discovered, with a growing body of evidence supporting the psychoneuroimmunology (PNI) framework, as discussed by McCain et al.[8] Recent investigations have begun

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to show consistent reports of psychological distress and disturbances impairing immune function[9] as well as cytokine-induced changes in neurotransmitter and neuroendocrine function, which have been shown to correlate with the onset of depression and/or fatigue.[10] The burden of frequent symptoms is known to negatively affect disease management and mental health.[11] Identifying factors that are associated with increased symptom distress may provide possible strategies to lessen the burden of HIV infection and related symptoms while improving treatment adherence. It is also important to note that now that life expectancy has improved for PLWHA, there has also been evidence to suggest that this population may experience other disturbances in mental functions at younger ages than the general population, such as cognitive decline or early onset dementia.

46.2.2 Physical Consequences

All clinical populations face a large variety of disease-related physical and psychological symptoms, but prevalence rates of self-reported symptoms are generally over 50% among PLWHA, ranging from a single symptom to multiple concurrent symptoms.[12–14] Common physical symptoms reported include diarrhea, loss of appetite, nausea, muscle weakness, peripheral neuropathy, fever, dry skin, and persistent cough. These are often experienced in conjunction with antiretroviral side effects for those placed on an ART regimen. As a result, the management of multiple symptoms has become a daily task for PLWHA in an effort to maintain an optimal quality of life[15,16] and ultimately leads to a chronic state of deconditioning resulting in functional aerobic impairment.

As was the case before the discovery of antiretrovirals, the association between the number of self-reported symptoms and disease status still allows the use of reported symptom frequency as an indicator of disease progression and health-related quality of life. This has been able to assist health professionals with monitoring how well a patient is responding to current ART regimens.[13,17] Symptoms lasting anywhere between a few days and a few weeks increase the burden of disease among individuals, often resulting in negative lifestyle habits. The side effects and symptoms of HIV infection often have many patients turning to self-medication either by altering their daily ART regimen or by seeking additional alternative treatments, which may include illegal narcotics. Although the discovery of ART has led to an increased lifespan and decreased reports of AIDS and AIDS related deaths, many scientists have reported a complex variety of symptoms and side effects associated with ART regimens, creating a metabolic syndrome effect.

46.3 ANTIRETROVIRAL THERAPY TREATMENT AND SIDE EFFECTS

The timing for initiating treatment varies depending on viral infection as well as the patient's primary healthcare provider, but generally, it is recommended that patients begin an antiretroviral regimen if asymptomatic but with a CD4 cell count <500 cells/μL,[18] which should be checked every three to four months, or symptomatic. For optimal results, treatment is suggested for asymptomatic patients with CD4 cell counts >500 cells/μL.[3,18] The timing for initiating treatment is widely debated, but there is strong evidence to indicate that PLWHA who are taking ART are less likely to transmit HIV onto others due to higher rates of undetectable viral loads. The reason some healthcare professionals may recommend waiting until a decline in CD4 cell count is due to the negative implications long-term use of ART can have on a person's health.

The majority of side effects associated with ART are physiological in nature and directly alter metabolic processes, resulting in increased circulating blood lipids, lipodystrophy, and insulin resistance, thus creating a metabolic syndrome. What was once a short-term muscle wasting disease for people living with HIV that ended in death over a period of several months has evolved into a chronic metabolic disorder, with primary causes of mortality no longer being AIDS related.

Symptoms and side effects from ART medications will vary depending upon specific antiretrovirals included in the patient's pharmacological regimen as well as the total number of antiretroviral medications included. For example, nucleoside reverse transcriptase inhibitors (NRTIs) are associated with lactic acidosis, hepatic steatosis, and lipodystrophy. Evidence has shown that lipodystrophy is more prevalent among individuals currently taking a combination of NRTIs and PIs (prolase inhibitors), both of which have known side effects of stripping metabolic function and disrupting adipocyte mitochondrial function. Other symptoms specific to the type of NRTI being taken include pancreatitis, nausea, diarrhea, headache, insomnia, peripheral neuropathy, fatigue, malaise, anemia, and many others. For a more extensive list of all symptoms and side effects, please refer to Bartlett et al., medical management of HIV infection.

Further caution is advised over the possibility of drug interactions; for example, the PI ritonavir has demonstrated interactions with analgesics, cardiac medications, lipid-lowering agents, antimycobacterials, calcium channel blockers, antihistamines, antidepressants, neuroleptics, psychotropics, and ergot alkaloids (vasoconstrictors). It has also become evident that when an individual begins an ART regimen, their risk of developing CVD or diabetes increases every year. A complementary treatment that may help address ART toxicities in viral related side effects is exercise training. Similar metabolic abnormalities within the general population respond positively to prescribe dosages of routine exercise designed to increase fitness. These exercise-induced changes include decreases in total cholesterol and triglycerides, decreased fat mass, increased lean tissue mass, decreased waist circumference, and increased insulin sensitivity.[19–21]

46.4 LIFESTYLE MEDICINE FOR MANAGING SIDE EFFECTS ASSOCIATED WITH HIV

In populations with a broad range of chronic diseases, there is a growing body of evidence showing that health benefits can be obtained by incorporating structured aerobic and resistance exercise into an individual's recovery and/or treatment plan. For those living with chronic conditions, aerobic combined with resistance exercises can have positive effects in alleviating symptoms associated with the diseases and side effects of the medical interventions. More recently, research has been indicating that a combination of aerobic and resistance training is most effective, but that also any form of progressive resistance training that the individual can tolerate will lead to improvements in overall quality of life and activities of daily living as PLWHA reach older age groups.[22]

Only in the last few years has an association been established between HIV and increased risk of chronic diseases such as CVD and diabetes.[1,23] As a result, there is limited evidence to make a definitive statement as to whether or not exercise is a beneficial alternative to pharmacological therapy for decreasing the risk of CVD among PLWHA. Although limited, the data that are available suggest that even modest amounts of routine exercise can yield both psychological and physiological health improvements that are known to reduce the risk of CVD within the general population. Table 46.1 provides an overview of the primary findings that have been discussed in greater detail from previous literature rev iews.[22,24,25] There follows a general overview of the main physiological benefits reported within the literature.

46.4.1 Cardiorespiratory Fitness (VO_{2peak})

Most exercise-related interventions measure cardiorespiratory fitness (CRF) as common practice prior to any low- or moderate-intensity intervention. As a result, there are substantial data consistently showing both functional aerobic impairment (FAI) and training adaptations that increase CRF in as little as six weeks.[26,27] FAI is defined as a peak VO_2 less than 25% of one's age-predicted VO_{2peak}. This aerobic impairment results in a reduced CRF level, which is known to be a significant indicator of various chronic conditions and all-cause mortality.[19–21] Even before the introduction of ART, a common consistency among exercise interventions has been significant FAI. Whether this is due to lifestyle factors or disease-related pathologies is not well understood. In a previous investigation from our laboratory, we have demonstrated significant improvements in VO_{2peak} and reductions in submaximal heart rate.[26,28] Hand et al. showed evidence of these findings, which suggests that PLWHA can reverse any indications of FAI even by meeting less than half of the Surgeon General's recommendation of 150 minutes per week. This study also demonstrated that there were additional cardiovascular adaptations, such as a reduced resting heart rate and a reduced heart rate at submaximal workloads, which is a cardiovascular adaptation known as training bradycardia. These findings have also been in agreement with others.[22,25]

TABLE 46.1
Summary of Clinical Exercise Interventions: Physiological and Psychological Changes

	Response to Exercise
Psychological	• ↓ Depressive symptoms[37] • ↓ Anxiety[37]
Physiological	• ↑ VO_{2peak}[22,24,26,27] • Significant increases between 2.40 and 3.71 mL/kg/min • ↑ Strength[22,29] • ↓ Fat mass and waist circumference[22,40] • ↓ Cortisol[29,40]
Immunological	• No change in CD4+[22]

46.4.2 Muscular Strength and Endurance

With an increased number of PLWHA getting older due to successful disease management, it is imperative that resistance training for muscular strength and endurance also be included in a routine exercise program. It is important to be mindful of preventing other chronic conditions associated with general aging in more elderly populations, such as sarcopenia and osteoporosis. If there are no underlying conditions or concerns to prevent them from doing so, PLWHA over the age of 50 should follow similar resistance training guidelines recommended for elderly populations. The general consensus within the literature findings has clearly shown that resistance training, alone and/or combined with aerobic training, will lead to improvements in muscular strength for both upper and lower body.[29]

46.4.3 Blood Lipids

Another variable of interest regarding CVD risk is the blood lipid panel. Although not as strong as CRF, evidence suggests a potential effect regarding improvements in blood lipids following routine exercise. Thoni et al. and Grinspoon both showed increases in HDL cholesterol following light- to moderate-intensity aerobic exercise.[30, 31] Thoni also reported decreases in cholesterol and triglycerides. However, there is still limited evidence to draw any formative conclusions regarding blood lipids and exercise training. One of the common side effects of ART is increased blood lipids and fat deposits. Future studies should look into the long-term protective effects exercise may have in regard to normalizing blood lipids panels for PLWHA taking ART.

46.4.4 Body Composition

As stated previously, an increase in central fat accumulation is a common side effect of various ART regimens.

Additionally, it is well known that an increased waist circumference is a strong indicator of CVD risk. Multiple investigations have reported significant improvements in body composition by decreasing fat mass, waist circumference, and/or body mass index, as well as increasing lean tissue mass (see Table 46.1). Dudgeon et al. confirmed these findings by showing significant decreases in trunk fat and total fat while also increasing lean tissue mass following a six-week combination aerobic and resistance training intervention.[28] Although still limited by the small sample sizes, this evidence appears strong enough to confirm that similar benefits in body composition (specifically, fat mass and lean tissue mass) to those commonly observed among general populations can be obtained by PLWHA.

46.4.5 Inflammation Markers

Promising evidence has been shown in research studies examining markers of inflammation following exercise training.[29] However, with only a few studies published at this time, no real evidence can suggest current exercise routines that would work to help reduce markers of inflammation. It is believed that such improvements could possibly be met with a long duration of routine moderate-intensity activity as part of one's daily lifestyle. Limited evidence would also suggest that higher-intensity exercise may lead to better improvements in inflammation, but it is still unclear whether or not PLWHA can safely tolerate a more vigorous workout regimen at the earlier stages of a new exercise prescription; this needs further investigation.

46.4.6 Immune System

No significant changes in CD4+ cell count have been reported in high- or moderate-intensity exercise groups.[22] Further, there have been no significant changes from baseline reported in CD8+ cell count, leukocytes, or lymphocytes following moderate- or high- intensity exercise.[32] Also, it was shown that patients with dyslipidemia and lipodystrophy had no significant changes in immunological variables after completing 12 weeks of moderate-intensity aerobic exercise.[33] Notably, there are no published reports of exercise-induced immunosuppression in PLWHA who participated in physical activity regimens designed to reduce the psychological or physiological symptomatology associated with HIV.

46.5 PSYCHOLOGICAL IMPROVEMENTS WITH EXERCISE

Early investigations conducted prior to widespread use of ART compared the effects of aerobic exercise on psychological components, such as depression and anxiety. Eight to 12 weeks of moderate-intensity aerobic exercise completed twice weekly for 45–60 minutes has shown significant reductions in anxiety and depression.[34] Other investigators reported significant improvements after only five weeks of aerobic exercise. Men who exercised for 45 minutes a day, 3 days a week, reduced anxiety and depression upon learning of their seropositive status.[35] As most of these investigations were performed before ART, the results are limited to symptoms specific to viral progression and not treatment.

In the era of widespread use of ART, there has only been one investigation utilizing aerobic exercise as the primary intervention for HIV-associated depressive symptoms. Like those investigations previously discussed, reductions in depressive symptoms and/or significant improvements in quality of life were shown.[36] Findings from this study suggest that 60 minutes of moderate-intensity (60–80% VO_{2peak}) aerobic exercise conducted 3 days a week can be used as a beneficial method for improving the psychological disturbances experienced by PLWHA. These findings have also been demonstrated in studies with combined aerobic and moderate-intensity exercise over the years, leading to published meta-analyses.[37,38] In a meta-analysis by Gomes-Neto and colleagues in 2021, following a review of 40 published research studies, it was shown that the majority of the literature indicated that the higher chance of beneficial outcomes in psychological well-being was similar to that of increased fitness (VO_{2max}) when combining aerobic and resistance exercise at a moderate intensity level on three or more days a week.[27]

Emerging areas of research have looked more closely at the impact of exercise on cognitive function and its role in helping to reduce the risk of developing dementia and possibly offset its progression with the general aging of the population. Now that we are beginning to see an aging HIV population, there are indications that we will also experience a higher prevalence of those with dementia and cognitive decline, similar to that in general elderly populations. It is important that similar research efforts in cognition and mental health be considered for PLWHA and further investigated.

46.6 RECOMMENDATIONS FOR EXERCISE

Current exercise training recommendations as described in *ACSM's Guidelines for Exercise Testing and Prescription* (11th edition) for PLWHA suggest a moderate-intensity aerobic and resistance training regimen.[39] This includes accumulating a total of 150 minutes of moderate-intensity physical activity a week, as well as 2 days of full body resistance training at approximately 60% of one repetition maximum. Regardless of disease status, it is strongly recommended that anyone living with HIV or AIDS receive medical clearance from their primary healthcare provider prior to beginning an exercise program. The scientific literature shows a much higher strength of evidence to support a combined moderate-intensity aerobic and resistance exercise prescription for long-term health benefits. Even though the majority of PLWHA have a reduced aerobic capacity, most of the standard physical fitness tests are applicable to this population and can be completed with little or no risk to the individual. Table 46.2 outlines potential HIV-associated

TABLE 46.2
HIV-Associated Changes to Exercise Testing

Disease Status	Response to Exercise
Asymptomatic	• Physiological parameters within normal limits (e.g. blood pressure, heart rate, VO_2) • Possible functional aerobic impairments due to sedentary lifestyle
Symptomatic	• Reduced aerobic capacity and muscular strength • Possibility of increased heart rate at rest and submaximal work rates • Increased difficulty in adhering to exercise prescription • ART related side effects
AIDS	• Drastically reduced aerobic capacity and muscular strength • Possible abnormal neuroendocrine responses at moderate- and/or high-intensity work rates

changes that may be observed during exercise testing and/or training according to disease state.

Ongoing investigations by Jaggers and colleagues have been studying community-based approaches to facilitating increases in daily physical activity. A recent nine-month home-based activity program used accelerometers to assess changes in activity from baseline. As indicated in the results, the average number of total minutes of daily moderate-intensity activity was approximately 90 minutes, suggesting that the majority of the participants were already meeting the physical activity recommendations. However, when looking at step counts, the daily average was only approximately 5,200 steps per day.[40] It is possible that with such a deconditioned population, physical activity prescribed by total minutes, as indicated by wearable activity monitors, may grossly overestimate the amount of activity that is being achieved for health benefits. Therefore, it may be a more realistic approach that recommendations for deconditioned populations such as this focus more on gradual increases in daily steps with the ultimate goal of 10,000 or more daily steps.

46.7 CONCLUSION

Evidence would suggest that PLWHA, regardless of disease status, can obtain similar short-term health benefits from routine physical activity to those reported within general populations. Research has shown significant improvements following moderate levels of routine exercise in as little as six weeks. It is also clear that across various populations, routine moderate-intensity physical activity reduces the risk of chronic disease and that many of these conditions have been established as major causes of morbidity and mortality among PLWHA. It is therefore imperative that healthcare professionals and researchers test various approaches to help PLWHA adopt healthy lifestyle choices for the rest of their lives.[41]

In regard to immunity, research among PLWHA has demonstrated that aerobic exercise performed at low, moderate, or high intensity does not negatively impact immune function or disease progression at any stage of HIV infection.[32–34] This clearly shows that aerobic exercise can be both safe and beneficial for this clinical population. However, it is recommended that if aerobic exercise is to be performed by this population, they do so at a low or moderate intensity level, as data are lacking to draw the conclusion that a high-intensity aerobic regimen will not have a negative impact on overall health or quality of life in this population. To our knowledge, only one investigation with a modest sample size examined the effects of a four-month high-intensity interval training protocol among PLWHA ≥50 years of age and found similar improvements to those previously discussed for moderate-intensity exercise interventions.[42] It was also shown to be safe, with no adverse events reported or impaired immune function.

Responses and adaptations to exercise training will vary depending on current fitness level, disease status, and whether or not that patient is currently on an ART regimen. Asymptomatic individuals generally respond in a manner similar to someone without HIV of the same body size, age, and gender. However, some may be more deconditioned due to psychological disturbances commonly associated with daily sedentary behavior, such as depression or anxiety, among others. Further, individuals with symptomatic status will generally be on a current ART regimen, which also puts them at an increased risk of CVD. Therefore, extra caution should be taken prior to beginning an exercise prescription.

Although exercise itself is not going to eliminate the burdens of healthcare costs, social stigmatization, or other daily stressors, it could potentially reduce the health consequences of chronic stress, improve quality of life, and possibly increase the reduced lifespan of PLWHA. Most of the negative side effects from both the virus itself and treatment-related toxicities, including impaired glucose tolerance, fatigue, increased blood lipid profile, chronic inflammation, anxiety, depression, circulating cortisol, and others, are known to improve with routine exercise in various populations. Additional evidence from longitudinal studies has clearly shown that modest increases in CRF can decrease the risk of all-cause mortality as well as the risk of most chronic diseases. Whether or not PLWHA would have a similar response to long-term exercise is unknown due to insufficient research. Further, there are no reported exercise-related interventions lasting longer than six months, making it impossible to determine the long-term effects on overall health and longevity. However, benefits observed in a short time frame, as reported by multiple investigations, would suggest long-term gains in the physical and psychological well-being of PLWHA who participate in routine physical activity.

CLINICAL APPLICATIONS

- Increase in daily physical activity and/or weekly exercise has been proven to have beneficial effects

for PLWHA with no indications of reductions in immunity or negative health outcomes.

- Chronic stress is a daily struggle for anyone managing a clinical condition with added stigmatization. Weekly exercise regimens have proven to reduce physiological and psychological stress, but more attention should also be given to additional methods of effective stress relieving practices in addition to exercise.
- Regardless of disease status, all individuals with HIV are at an increased risk for cardiovascular disease and therefore should seek consent from their primary care doctor prior to initiating a new exercise regimen. Individuals can safely begin with daily walks at a light intensity prior to receiving consent if no other health concerns are evident.
- For individuals in a deconditioned state of aerobic impairment, it is important to set practical goals, since all activity can take moderate or vigorous efforts. Gradual increases in daily step counts by a few hundred steps each day may be more suitable as opposed to 30 minutes of moderate-intensity activity.
- With an increased lifespan and aging population, incorporating resistance training as part of a weekly exercise prescription for PLWHA over the age of 50 is strongly encouraged to help maintain independence and a higher quality of life down the road.

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47 Exercise, Aging, and Immunity

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KEY POINTS

1. Aging is associated with impaired immune responses (immunosenescence) and increased inflammation (inflammaging), which are correlated with increased susceptibility to acute infections and chronic diseases.
2. Moderate-intensity cardiovascular exercise training improves immune responses and reduces inflammation in older adults.
3. The available evidence suggests that modulation of adipose tissue inflammation, alteration of the gut microbiome, stimulation of the parasympathetic nervous system, and other mechanisms may drive the effect of exercise on aging and immunity.

47.1 INTRODUCTION

The population of older individuals is expanding rapidly, with the U.S. population of adults over 65 years of age projected to nearly double by 2060.[1] Older individuals have altered immune status, including increased inflammation (termed "inflammaging"[2]) and impaired vaccine and anti-pathogen immune responses (termed "immunosenescence"[3]). Therapeutic strategies to reverse age-related immune impairments are being widely investigated, but few have been shown to be broadly efficacious. However, regular moderate cardiovascular exercise has been shown in a number of studies to improve immune function in older adults, both by potentiating immune responses and by reducing inflammation.

47.2 EXERCISE AND INFLAMMAGING

Aging increases localized and systemic inflammation associated with age-related diseases, a condition colloquially known as inflammaging.[2] Because of the association between age-related disease and inflammation, treatment strategies to reduce inflammation in older adults are of major interest. Large cohort studies such as NHANES III have demonstrated negative correlations between level of physical activity and circulating inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα),[4] suggesting a dose-dependent relationship between activity dose and inflammation reduction.

Further, numerous longitudinal studies have shown that an exercise training program reduces inflammation in older adults. Vieira *et al.*[5] demonstrated that ten months of aerobic exercise training reduced CRP levels in older adults, and this was closely associated with reductions in adiposity. Similarly, Kohut *et al.*[6] found that ten months of exercise reduced IL-6, CRP, and IL-18 in older adults, and Nicklas *et al.*[7] found that a combined aerobic and resistance exercise intervention for one year reduced circulating IL-6 (but not CRP) levels. A variety of additional training studies have corroborated these findings, as recently reviewed elsewhere.[8]

While many studies have shown positive effects of exercise, several have found no benefit from moderate exercise training on inflammation in older adults.[9] Published protocols in this area have varied widely in exercise training duration, exercise bout intensity, subject population, baseline inflammatory status, overall baseline health status, subject demographics, and numerous other factors that might impact results. As such, we currently have little understanding of the physiological determinants of the effect of exercise on inflammaging. Additionally, more work is needed to conclusively link exercise suppression of inflammaging to beneficial effects on age-related disease incidence or progression, as this is not yet well established.

47.3 ANTI-INFLAMMATORY MECHANISMS OF EXERCISE

Additionally, mechanisms by which exercise exerts its anti-inflammatory effect are not well understood. A variety of theories have been promulgated; here, we describe several of the most established.

Adipose Tissue: Adipose tissue is no longer considered an inert lipid storage organ but instead, is known as a metabolically active system, which produces numerous factors which regulate physiological responses. Excess adiposity is linked to age-related inflammatory burden, suggesting age-associated increases in obesity as a primary driver of inflammaging. Wu *et al.* demonstrated increased gene expression of a variety of pro-inflammatory cytokines in aged mice compared with younger mice.[10] Numerous other studies have shown links between adiposity and inflammation, as comprehensively reviewed elsewhere.[11] Given the well-known effect of exercise on reducing adiposity, it has naturally been hypothesized that exercise training may also reduce adipose tissue–associated inflammation during aging.

Vieira *et al.* have previously demonstrated that moderate exercise training reduces adipose tissue inflammation

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in obese mice,[12] and this has been corroborated in aged mice by Yoon *et al.*[13] Likewise, a training study in older adults found similar exercise-mediated reductions in adipose tissue inflammation.[14] While the mechanism by which this occurs is unknown, exercise training promotes M2-like anti-inflammatory macrophages in adipose tissue and suppresses M1-like pro-inflammatory macrophages,[15] suggesting a plausible process by which inflammation is reduced in this system.

Cholinergic Anti-Inflammatory Pathway: The nervous system is known to be intimately involved in inflammatory regulation, and a substantial literature exists on this topic.[16,17] Importantly for exercise, stimulation of the efferent vagus nerve has been shown to reduce inflammation,[18] termed the cholinergic anti-inflammatory pathway. The vagus nerve controls heart rate responses during exercise, including heart rate variability and heart rate recovery, so it has been speculated that exercise-mediated stimulation of the vagus nerve may also suppress inflammatory responses. While there is little direct evidence to substantiate this at present, lower heart rate reserve is associated with decreased CRP during aging,[19] suggesting a possible link.

Gut Microbiota: The human gut is colonized by trillions of microbes, which exist more or less symbiotically with their host. Seminal research by Turnbaugh *et al.* showed that the composition of the microbiome is tightly linked to obesity, to the extent that transplanting microbiota from obese mice to lean mice caused weight gain and an obesity phenotype in the recipients.[20] Aging is also associated with microbiome changes,[21] as is the pathogenesis of a variety of age-related diseases.[22–24] Research into the links between exercise and the microbiome has therefore exploded in recent years. A cross-sectional study by Clarke *et al.*[25] demonstrated that higher fitness (in professional rugby players) was associated with increased diversity of gut microbes, which is generally considered a biomarker of a healthier microbiome. Later cross-sectional studies have directly shown an exercise-mediated effect on microbiome composition. Allen *et al.*[26] and Cronin *et al.*[27] both demonstrated in 2018 that short-term (six- to eight-week) exercise interventions modulated the microbiome in obese adults, and a variety of additional studies have since shown exercise to be efficacious in positively influencing the microbiome in both human participants and animal models.[28] Interestingly, the availability of fecal microbial transplants has also given rise to the possibility of transferring (some of) the beneficial effects of exercise between individuals. Support for this comes from Allen *et al.*,[29] who showed that transplant of microbiota from exercised mice reduced colitis symptoms in dextran sodium sulfate–treated gnotobiotic mice, and from Lai *et al.*,[30] who showed that transplant of microbiota from lean exercised mice improved metabolic profiles in sedentary obese mice. Gut microbiome–targeted therapeutic strategies have been proposed for the prevention and treatment of the symptoms of cognitive impairment.[31, 32] Other than physical exercise, administration of probiotics has been proposed to be a potent therapy. Buford *et al.*[33] showed that an orally delivered probiotic bacterium, *Lactobacillus paracasei*, modified to express angiotensin (1-7) benefits the gut-brain axis in older rats, including a reduction of neuro-inflammatory gene expression (COX2, IL-1β, and TNF-β) in the pre-frontal cortex.

Endocrine Mediators: Although somewhat speculative, a variety of endocrine mediators produced by skeletal muscle and other organs during exercise are known to have immunomodulatory effects and may reduce inflammaging. Contracting muscles (and other organs, including the liver) are known to produce immunoregulatory cytokines such as IL-6, IL-15, and growth differentiation factor-15 (GDF-15).[34,35] Exercise-derived IL-6 is thought to promote anti-inflammatory actions through stimulating cortisol and IL-10 release.[36] Likewise, GDF-15 is produced during exercise [35] and is a potent anti-inflammatory cytokine, which suppresses macrophage activation.[37] In addition to protein hormones, exercise-induced metabolites such as lactate and succinate have anti-inflammatory signaling properties[38] and may play a role in the anti-inflammatory effect of exercise. To date, these links remain speculative in the context of exercise, but endocrine crosstalk between metabolic organs and the immune system is a promising area for further research.

47.4 IMMUNOSENESCENCE

In addition to inflammaging, aging results in a generalized impairment in immune responses referred to as immunosenescence. This manifests in reduced vaccine efficacy and impaired anti-pathogen responses,[3] prominently illustrated by the substantially increased disease burden experienced by older adults during the coronavirus disease 2019 (COVID-19) pandemic.[39] Inflammaging, primarily but not exclusively a phenomenon of the innate immune system, is considered a facet of immunosenescence.[40] Additionally, profound dysregulation of the adaptive immune system occurs with aging.

Aging and Cell-Mediated Immunity: Cell-mediated immunity generally refers to antigen-specific activation of T lymphocytes (T cells), which both directly kill infected or transformed cells (CD8+ cytotoxic T cells [T_C]) and produce cytokines to activate other immune cells (CD4+ helper T cells [T_H]). Often included in this definition is the antigen non-specific activation of cell types such as macrophages, natural killer (NK) cells, and γδ T cells (among others), all of which mediate important immune responses during infection, cancer, sterile cellular damage, etc. Cell-mediated immunity is generally decreased during aging. Specifically, older adults have reductions in circulating naïve T cells and increased antigen-experienced memory and senescent T cells,[41,42] which is thought to serve to decrease the ability of the immune system to respond to novel pathogens. T cell proliferation, activation, and cytokine signaling are also decreased during aging.[41] To some degree, expansion of memory and senescent T cells and the parallel decrease in the naïve T cell pool are thought to occur due to the high

prevalence of latent herpesviruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV),[43] as a high proportion of aged individuals are seropositive for these pathogens, and an increased proportion of circulating T cells are antigen-specific for CMV or EBV. Aging is also associated with reduced T_H1 (pro-cytotoxic) and increased T_H2 (anti-inflammatory) cytokine production,[44–46] which is thought to skew T cell responses to a state less suited for antiviral immunity.

Aging and Humoral Immunity: Likewise, humoral (antibody-mediated) immunity is suppressed in older compared with younger adults. This is especially notable in vaccination,[47] where antibody responses may be sub-neutralizing, leading to decreased efficacy and increased risk of breakthrough infection. Antibodies are secreted by circulating B lymphocytes (B cells) in an antigen-specific manner, and aging is associated with reduced B cell number and function.[48] Older adults also have more rapid loss of protective antibody levels compared with younger individuals after vaccination[49] and thus may lose pathogen neutralizing ability prior to the end of, for example, the influenza season.

47.5 EXERCISE AND IMMUNOSENESCENCE

Given the multifaceted association between aging and immunosenescence, exercise has been widely investigated for its potential positive impact on immunity in this population. Exercise training has been established to reduce infection risk.[50,51] However, many studies have had mixed results, depending on the population studied, specific outcome measures, and overall study design.

Cell-Mediated Immunity: A variety of cross-sectional studies have shown increased T cell proliferative responses in older adults who report exercising regularly.[52–54] However, individuals who regularly exercise may also have overall healthier lifestyles, and cross-sectional results may reflect preventative rather than therapeutic effects of exercise training on these outcomes. As such, multiple longitudinal exercise studies have been undertaken to determine whether a prescribed exercise intervention can revert cell-mediated immune status to a more "youthful" state in older adults, with somewhat mixed efficacy. Shimizu *et al.*[55] found increased expression of the co-stimulatory receptor CD28 on circulating T cells in older adults who underwent a six-month exercise training program, which could reflect increased ability of these cells to produce immunoactivating cytokines upon antigen stimulation. However, a similar study by Kapasi *et al.*[56] found no effect of eight months of endurance training on co-receptor expression on T cells. Likewise, NK cell cytotoxic responses and T cell proliferation were not altered by a one-year exercise training regimen in older women,[57] but six months of aerobic exercise training in previously sedentary older adults did result in increased T cell proliferation and NK cell cytotoxic activity.[58] Higher aerobic fitness (as measured by VO_{2max}) is also associated with reduced circulating numbers of senescent T cells in older adults.[59]

In order to remove potential confounding factors related to lifestyle changes in these studies, several similar exercise training experiments have been performed in aged mice. Woods *et al.*[60] found increased naïve-to-memory CD4+ and CD8+ T cell ratios after four months of treadmill training in aged mice, and Kohut *et al.*[61] demonstrated increased T_H1-associated cytokine production after experimental herpes simplex virus-1 (HSV-1) infection in mice. Kruger *et al.*[62] found that a single acute bout of exercise caused apoptosis of highly differentiated T cells, suggesting a mechanism whereby antigen-experienced, late memory/"exhausted" cells[63, 64] may be removed to increase space for naïve populations.

Additionally, several studies have used a delayed-type hypersensitivity (DTH) model to assess T cell–mediated immunity responses in human subjects *in vivo*. Cross-sectionally, physically active older men have improved DTH responses compared with sedentary men,[65] and a 17-week aerobic but not resistance training program sustained DTH responses in older adults compared with a declining response in sedentary controls.[66] However, DTH responses are highly variable, and effect sizes in these studies have been relatively small, so these results must be interpreted cautiously. Given that, this human and mouse *in vitro* and human *in vivo* evidence suggests a potential for exercise to improve some aspects of cell-mediated immune function during aging, thereby potentiating responses especially to viral infection in this susceptible population.

Naïve T cells migrate from the thymus into the periphery, and aging is associated with thymic atrophy (involution).[67] Duggal *et al.* compared older adults who were lifelong cyclists with sedentary counterparts and found increased naïve T cell frequency and more recent thymic emigrant T cells in the physically active group.[68] Likewise, circulating levels of the cytokine IL-7, which is thymoprotective, were increased. This suggests that physical exercise may be protective against thymic atrophy during aging, which is a potential mechanism for reduced immunosenescence in this population.

Humoral Immunity: A variety of cross-sectional studies have shown that vaccine responses in older adults are increased when subjects report higher levels of physical activity. Keylock *et al.*[69] demonstrated increased influenza vaccine responses in highly fit active older adults compared with less active controls, as well as increased production of more highly potent IgG2 antibodies when these individuals were exposed to a tetanus toxoid booster vaccination. Several additional studies have found similar increases in influenza vaccine antibody responses in individuals with higher fitness levels or reported training loads.[54,70,71]

As with cell-mediated immunity, cross-sectional studies of antibody responses may be confounded by other healthy lifestyle factors, so several prospective training studies have also been undertaken in this population. Influenza vaccine–elicited antibody production was increased in older adults after a ten-month exercise training program compared with sedentary control subjects,[72] and a similar study [73] found

that ten months of training prolonged the duration of protective antibody levels in older adults (although it did not increase peak levels).

In addition to plasma antibody levels (IgG, IgM), exercise training also causes increases in salivary levels of IgA, although this is not consistent across all studies. A 6-month cycling intervention increased salivary IgA by 40% in older men and women,[74] and a 12-month combined resistance and aerobic training intervention increased salivary IgA levels in older men and women.[75] Conversely, a 16-week aerobic exercise intervention did not increase salivary IgA (but did increase plasma IgA, IgG, and IgM) in a similar population.[76] This suggests potential roles for exercise mode, intensity, and duration in determining changes in humoral immunity during interventions in the aged population.

Exercise and Immune Cell Redistribution: While mechanisms involved in these responses are not well defined, important progress has been made in recent years in characterizing the mobilization and redistribution of immune cell subsets via β2-adrenergic receptor signaling during acute exercise. Activation of this system preferentially mobilizes memory, highly differentiated, exhausted, and latent virus-infected lymphocyte subtypes,[77] possibly promoting their apoptosis [78] Additionally, exercise mobilizes effector cell subtypes that may promote enhanced immune responses.[79,80] While the links between these acute effects and the effects of chronic exercise training outlined earlier are not conclusive, it is possible to speculate that repeated exercise bouts mediate a more permanent shift in circulating immune cell phenotype that may underlie (some of) the beneficial effects of exercise training on the aging immune system.[77]

47.6 SUMMARY

During aging, exercise has anti-inflammatory and immunopotentiating roles that serve to limit aberrant inflammation and enhance immune responses in this critical expanding population. To date, we know little about the mechanisms by which exercise mediates these effects, although some progress has been made in defining exercise-induced metabolic, endocrine, nervous system, and microbiome changes that may play a role in modulating immunity in older adults. Additionally, variability of study results indicates that exercise intensity, dose, duration, and modality may be a determinant of the efficacy of immune modulation, and this is an area of important work in the future.

CLINICAL APPLICATIONS

- Aging is associated with "inflammaging," a chronic condition that is associated with increased age-related disease.
- Aging impairs the immune system, including by reducing innate and adaptive immune responses, a phenomenon referred to as "immunosenescence."
- Hallmarks of aging-related immunosenescence include poor vaccine efficacy and impaired defense against microbial infection.
- Regular, moderate-intensity exercise training may improve both inflammaging and immunosenescence.
- Changes in body composition, the gut microbiome, and exercise-associated endocrine mediators may be responsible for the anti-inflammatory and immune boosting effects of exercise in older adults.

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Part IX

Pulmonary Medicine



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48 Respiratory Symptoms

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KEY POINTS

- Dyspnea represents a spectrum of subjective symptoms as a result of the complicated multisystem pathophysiology that results in the sensation of breathlessness.
- Understanding the pathophysiologic mechanisms that result in dyspnea can guide the clinical evaluation and diagnostic testing in a patient with shortness of breath.
- The history and physical exam are critical in identifying causes of dyspnea and guide the appropriateness and necessity of further diagnostic testing.
- Dyspnea is often associated with a series of affective or emotional responses, which may alter behavior in a way that leads to greater breathing discomfort.
- Treatment of dyspnea is primarily dependent on treating the underlying disease process, although palliative interventions with both pharmacologic and non-pharmacologic interventions can provide symptomatic relief.
- Cough is clinically characterized as acute, subacute, or chronic, and treatment is predicated on the etiology of cough and symptomatic management.
- Hemoptysis is classified as massive (≥600 cc of blood over 24 hours) or non-massive.
- Wheezing is caused by turbulent flow due to narrowing of intra- and/or extrathoracic airways; intrathoracic airway narrowing results in expiratory wheezing and in severe cases of asthma, inspiratory wheezing, while extrathoracic narrowing causes inspiratory stridor.
- Snoring is of uncertain clinical significance, but a patient or bed partner complaining of snoring should prompt questions regarding signs or symptoms of obstructive sleep apnea.
- Apnea is defined as cessation of breathing for ≥10 seconds, while hypopnea is defined as a reduction of airflow for ≥10 seconds with a ≥4% decrease in oxygen saturation; an apnea hypopnea index of >5 is diagnostic of obstructive sleep apnea.
- Obstructive sleep apnea syndrome is the combination of an apnea hypopnea index of >5 and symptoms of day-time somnolence and fatigue.

48.1 RESPIRATORY SYMPTOMS

48.1.1 Introduction

Shortness of breath, cough, and wheezing are among the most common symptoms experienced by patients seeking medical care. As in most areas of medicine, the evaluation of patients with respiratory symptoms largely depends on a comprehensive and insightful history obtained by the healthcare provider. Information offered spontaneously by patients is the starting point in the evaluation of any problem, but knowledge of the pathophysiology and differential diagnoses underlying the symptoms allows the provider to probe further, to determine which areas of the physical examination require special attention, and ultimately, to narrow if not eliminate the radiographic and laboratory testing required to confirm the diagnosis. We must also remember that, as with pain, many patients do not spontaneously tell healthcare providers about breathing discomfort, and it is important to directly inquire about this symptom.

Often, there is confusion between respiratory symptoms and signs. For example, patients are described as being "short of breath" as part of the physical examination. In fact, symptoms can only be described by the patient. Healthcare providers may speculate that a patient is experiencing respiratory discomfort based on observing physical signs such as recruitment of accessory muscles of ventilation, tachypnea, or an inability to speak in full sentences, all of which are signs of underlying pathophysiology and the body's response to maintain adequate gas exchange. Nevertheless, *symptoms* characterize what patients are experiencing and can only come from their self-reported perceptions of their somatic experiences.

The timing of respiratory symptoms and conditions that precipitate or alleviate the discomfort can clarify the impact of the symptom on the patient. Understanding the "language of dyspnea," developed from descriptive research on patients with a variety of respiratory diseases, can help clinicians understand the significance of their patients' symptoms.

This chapter focuses on the physiologic and clinical significance of several common respiratory symptoms. The clinical utility of quantitative dyspnea scales, the multidimensional nature of breathing discomfort, and the consequences of dyspnea are briefly discussed. The role for and utility of pulmonary function tests (PFTs) is briefly reviewed, but a more complete description is beyond the

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scope of this discussion. Clinical and pathophysiologic details of specific disease states such as asthma and chronic obstructive pulmonary disease (COPD) will be addressed in other chapters. This chapter does cover how specific elements of the physical examination, in concert with reported symptoms, can narrow the differential diagnosis.

48.1.2 Objective Assessment of Respiratory Symptoms

Respiratory symptoms can be due to a variety of pathophysiological processes involving disparate organ systems. A general understanding of the use of PFTs is helpful in developing a preliminary, physiologically based approach to respiratory symptoms. We will also comment briefly on some of the common pitfalls associated with the use of pulse oximetry.

48.1.2.1 Objective Dyspnea Scales

There are several quantitative scoring systems designed to assess the severity and impact of dyspnea in patients with respiratory disease. Examples of such scales include the Medical Research Council (MRC) dyspnea questionnaire, the modified MRC (mMRC), the COPD assessment test (CAT), the oxygen cost diagram (OCD), the COPD Clinical Questionnaire (CCQ), the multidimensional dyspnea profile (MDP), and other scoring systems. These scales assess different components of the sensation of breathlessness.[1,2] The scoring systems demonstrate relatively similar performance with regard to assessing symptom severity in clinical practice, such that one scale is not clearly superior to another.[3] Assessing dyspnea severity using a quantitative scale can be useful to characterize baseline symptom burden, although following dyspnea scales in response to therapeutic interventions is of less certain clinical utility.[2]

The majority of available dyspnea scales assess patient-reported perceptions of functional disability attributable to dyspnea (e.g., MRC, mMRC, CAT) or more general perceptions of healthcare associated quality of life attributed to dyspnea (e.g., CCQ, OCD). As dyspnea manifests as a constellation of symptoms not solely defined by perceived functional limitation, multidimensional assessment using the MDP instrument has been increasingly used in clinical and research settings.[4] MDP measurements, as compared with other objective dyspnea scales, have demonstrated adequate sensitivity to detect changes in symptoms of dyspnea over time.[2] In addition, the MDP gives us insight into the relationship between the sensations of breathing discomfort and the affective or emotional responses associated with this frequently debilitating symptom. Anxiety, fear, and frustration are commonly associated with certain types of dyspnea, and these emotional responses may cause individuals to curtail activity, leading to cardiovascular deconditioning, more dyspnea, and even more drastic functional limitation.[5]

Quantitative dyspnea scales can be used for any patients with respiratory disease but may be of most use for patients with COPD as a component of determining the Global Initiative for Obstructive Lung Disease (GOLD) stage of disease severity, which has prognostic and therapeutic value for this patient population.[6]

48.1.2.2 Pulmonary Function Tests

Pulmonary function testing refers to maneuvers in which spirometry, lung volumes, inspiratory and expiratory pressures, and/or diffusion limitation of carbon monoxide (DLCO) are measured. Confusion regarding PFTs arises from imprecise use of the term "pulmonary function tests" in clinical practice to refer to measurements of spirometry alone. It is more precise to consider PFTs to include spirometry, lung volume, and DLCO measurements.

PFTs can provide objective data regarding a patient's specific respiratory impairment and can provide important insight into the cause of patients' respiratory symptoms. Not all respiratory symptoms are best assessed by PFTs, but several common symptoms are due to diseases that may be diagnosed by PFTs. For example, the diagnosis of COPD, which may affect 4–10% of adults in the United States,[7] is dependent on spirometric measurements. COPD is typically suspected based on clinical symptoms, but further evaluation by measuring spirometry confirms or excludes the actual diagnosis.

When obtaining PFTs, a trained respiratory therapist or technologist can influence the quality of data obtained; the instructions, prompts, and encouragement provided to the patient prior to and during the test can significantly affect the patient's respiratory maneuvers. Normal values for PFTs are determined from predictive equations developed from large descriptive studies and incorporate an individual patient's age, gender, and height.[8]

48.1.2.2.1 Spirometry

Spirometry refers to measurements of the flow and volume generated when a patient performs a forced vital capacity (FVC) exhalation; these tests are critical for assessment of airway resistance. To perform a FVC exhalation, the patient takes in as big a breath as possible to completely fill the lungs with air (to total lung capacity, or TLC) and then forcibly exhales as rapidly as possible until no more air can be emptied from the lungs (to the residual volume, or RV.) In addition to measuring the FVC, determining the volume of air the patient is able to exhale in one second (FEV1) is important in diagnosing and characterizing the severity of obstructive airways diseases. If a patient has increased airways resistance and is unable to generate high flows from TLC, the FEV1 relative to the FVC will be reduced.

Patients may develop increased airways resistance due to airway narrowing from airway inflammation, mucus accumulation, and/or smooth muscle hypertrophy (e.g., as a consequence of chronic asthma) or from loss of tethering of the airways leading to airway collapse during active exhalation (e.g., COPD). Increased airways resistance causes obstruction of airflow during exhalation, which results in a decreased FEV1 out of proportion to the FVC. Therefore,

the ratio of the FEV1 to the FVC (FEV1/FVC) will be reduced in such patients. In patients with severe airway resistance, expiratory time is insufficient to permit exhalation of a full vital capacity, and RV may be elevated. An elevated RV above 120% of the patient's predicted value (as determined by their age, sex, and height) is referred to as "air trapping."

Obstructive airways diseases are conditions that decrease the FEV1/FVC ratio. COPD and asthma are by far the most common causes of obstructive airways disease. Bronchiectasis, tracheobronchomalacia, sarcoidosis, and other esoteric processes are much less common causes. While a reduced FEV1, FVC, and a preserved (or increased) FEV1/FVC ratio suggest a restrictive pulmonary disease, lung volumes (particularly TLC) must be measured separately to confirm restrictive disease. Spirometry results alone can only suggest restrictive pathophysiology; lung volume measurements demonstrating a TLC of less than 80% predicted are necessary to diagnose restriction.

48.1.2.2.2 Lung Volume Testing

Lung volumes may be measured by one of two methods. Plethysmography refers to measuring lung volumes based on the change of pressure and volume of a known quantity of air in a closed container (a so-called "body box") to calculate lung volumes via Boyle's Law. Helium dilution refers to the measurement of lung volumes based on the differential exhaled helium concentration and the helium concentration in a closed, external container. Since helium is an inert gas that does not cross the alveolar–capillary basement membrane, the concentration of helium after the gas has equilibrated between the patient's lungs and the external container of helium provides a measurement of a patient's lung volumes. This technique is used to measure functional residual capacity (FRC), or relaxation volume at the end of a passive exhalation. Once this volume is known, other volumes (TLC and RV) can be determined with spirometric determinants of the change in volume as the patient goes through various maneuvers. Helium dilution may underestimate lung volumes in patients with poor ventilation (e.g., patients with large bullae) or patients with global hypoventilation (e.g., patients with severe COPD and air trapping).

As noted earlier, a TLC measurement below 80% of predicted is diagnostic of restrictive disease. When TLC and FRC are greater than the predicted value, one should consider reduced elastic recoil of the lung as a potential cause, most commonly due to emphysema. Specifically, a TLC of >120% of predicted indicates hyperinflation. Gas trapping and an elevated RV will commonly also be present in such patients.

48.1.2.2.3 Diffusion Limitation of Carbon Monoxide

The DLCO measures the transfer of carbon monoxide (CO) across the alveolar–capillary basement membrane. DLCO is considered a surrogate for oxygen transfer across the basement membrane and into the circulation. A patient performs the DLCO maneuver by inhaling air with a small, known concentration of CO to TLC and holding their breath for ten seconds to allow sufficient time for diffusion of CO into alveoli and for transfer of CO across the alveolar–capillary basement membrane. The amount of CO transferred into the blood stream is determined by the difference in the quantity of CO in inhaled air (which is known) minus the quantity of CO in exhaled air (which is measured).

The severity of the reduction is expressed as the percentage predicted. A DLCO 60–79% of predicted is consistent with a mild reduction in DLCO, 40–59% a moderate reduction, and <40% a severe reduction. The DLCO is reduced primarily when there is destruction of the alveolar–capillary interface (reduced surface area for diffusion) due to disease of the lung tissue, e.g., emphysema, or pulmonary vasculature, e.g., pulmonary arterial hypertension or chronic thromboembolic disease. Table 48.1 lists diseases associated with a decreased DLCO.

48.1.2.2.4 Pulse Oximetry

Assessment of oxygen saturation with a pulse oximeter is common in both inpatient and ambulatory clinical environments. Normal oxygen saturation does not mean that a patient's lungs are functioning appropriately. Patients with many cardiopulmonary conditions leading to dyspnea (e.g., asthma, pulmonary embolism, pneumonia, congestive heart failure [CHF]) may hyperventilate, leading to normal oxygen saturation with a low $PaCO_2$. Such hyperventilation can mask the presence of severe pulmonary disease. An accurate interpretation of the oxygen saturation must include an overall assessment of the patient's clinical status and/or an accompanying arterial blood gas. There are data suggesting that pulse oximetry, which is based on the wavelengths of light emitted by capillary blood in the finger nail, may be altered by racial differences in skin color.[9]

48.1.3 Dyspnea

48.1.3.1 Definition

The word *dyspnea* derives from the Greek term for difficult breathing, but has come to represent a more global set of sensations that can be grouped as "breathing discomfort." Dyspnea, or breathlessness, may be experienced by healthy individuals when exercising to the limits of their aerobic capacity, may represent primary pulmonary or cardiac disease, or may be a manifestation of a severe metabolic acidosis. In a study of more than 1,000 randomly selected adults, investigators discovered the presence of dyspnea in approximately 35% of adult patients without known, underlying cardiopulmonary pathophysiology.[10] Dyspnea in ambulatory patients has been associated with increased morbidity and possibly mortality as compared with patients without dyspnea;[10–12] similarly, dyspnea in hospitalized patients is also predictive of higher mortality and resource use.[13]

Given the frequency with which physicians encounter patients with dyspnea and the varied conditions that may lead to this symptom, having a clear understanding of the physiology and causes of dyspnea is critical in making a

TABLE 48.1
Causes of Decreased DLCO Categorized on the Basis of Lung Volume

	Causes of decreased DLCO
High lung volumes	• Advanced COPD • Bronchiectasis • Cystic fibrosis
Normal lung volumes	• Pulmonary vascular disease (e.g., pulmonary vasculitis or primary pulmonary hypertension) • Early pulmonary fibrosis • Anemia[a]
Low lung volumes	• Pulmonary fibrosis • Sarcoidosis • Congestive heart failure • Pneumonectomy[b]

[a] Anemia causes reduced DLCO by reducing hemoglobin binding sites for carbon monoxide; this will occur even in the presence of normal lungs and normal pulmonary vasculature.
[b] DLCO corrected for alveolar volume (DLCO/VA) should be normal, assuming the remaining lung tissue functions normally.

correct diagnosis. A summary of common cardiopulmonary conditions and the associated pathophysiological mechanisms that cause dyspnea is outlined in Table 48.2.

48.1.3.2 Physiology of Dyspnea

Dyspnea associated with respiratory disorders appears to arise due to a variety of physiologic mechanisms that involve stimulation of receptors in the upper airways, lungs, and chest wall as well as peripheral and central chemoreceptors (Figure 48.1). In addition, there are believed to be neural discharges, termed *corollary discharges*, between the motor and sensory cortex that are activated when ventilation is consciously increased. The physiology of cardiac dyspnea is less well understood, but likely involves many of these mechanisms as well as others unique to low cardiac output states.

TABLE 48.2
Relationship of Possible Mechanisms of Dyspnea to Selected Conditions

Asthma	Increased sense of effort Stimulation of irritant receptors in airways
Neuromuscular disease	Increased sense of effort
COPD	Increased sense of effort Stimulation of irritant receptors in airways Hypoxia Hypercapnia Dynamic airway compression
Pulmonary embolism	Stimulation of receptors in pulmonary vasculature or right atrium (?)
Congestive heart failure	Stimulation of J-receptors in the lung Stimulation of receptors in pulmonary vasculature (?) Hypoxia Stimulation of ergoreceptors (?)
Deconditioning	Stimulation of ergoreceptors (?)

Question marks indicate that the data in support of the listed mechanism are limited.

In the presence of increased mechanical load on the respiratory system, the motor cortex must increase the neural signals it sends to ventilatory muscles to overcome the load. These outgoing messages, or efferent signals, are associated with a simultaneous corollary discharge to the sensory cortex that is hypothesized to provide the individual with a sense of how much "effort" or "work" is being expended in the act of breathing.[14] Dyspnea associated with muscle weakness (e.g., myasthenia gravis, Guillain–Barre syndrome) is similarly attributable to this mechanism. Dyspnea also results when the respiratory system does not respond as expected to an elevated level of neural drive to breathe, often leading to a sensation of "air hunger" or "urge to breathe,"[15] discussed later, and the larger the discrepancy, the more intense the dyspnea experienced. This discrepancy between respiratory center output and the mechanical response of the system has been termed *efferent-afferent* or *neuromechanical dissociation*.[16–18]

Conditions resulting in a reflexive or automatic increase in the neural output from the brainstem respiratory control centers are also associated with breathing discomfort, generally described as a sense of "air hunger" or an increased "urge to breathe." Stimulation of peripheral chemoreceptors by hypoxia and hypercapnia and stimulation of central chemoreceptors by hypercapnia and metabolic acidosis is thought to produce dyspnea by this mechanism. Interestingly, inducing either hypoxia or hypercapnia in healthy volunteers results in similar levels of "air hunger" for each condition, demonstrating the importance of the corollary discharge from the brainstem in creating the sensation of dyspnea.[19] Hypoxemia, however is a relatively weak stimulus for ventilation and for dyspnea; most patients who are short of breath and hypoxemic have other derangements (e.g., increased airways resistance, hyperinflation, and pulmonary vascular disease) that contribute to the dyspnea. This is particularly evident when you encounter a patient with acute dyspnea and hypoxemia and you note that after administration of supplemental oxygen, there is relatively little change in the dyspnea. In patients with COVID-19 pneumonia, many people were surprised by individuals with relatively low intensity of dyspnea despite hypoxemia, overestimating the contribution of hypoxemia to dyspnea, particularly when a patient is able to hyperventilate, since hypocapnia reduces the drive to breathe and discomfort.[20] Stimulation of pulmonary mechano- or irritant receptors (e.g., from asthma or pulmonary embolism) may also result in an increase in ventilation and be responsible for part of the breathlessness in these conditions.

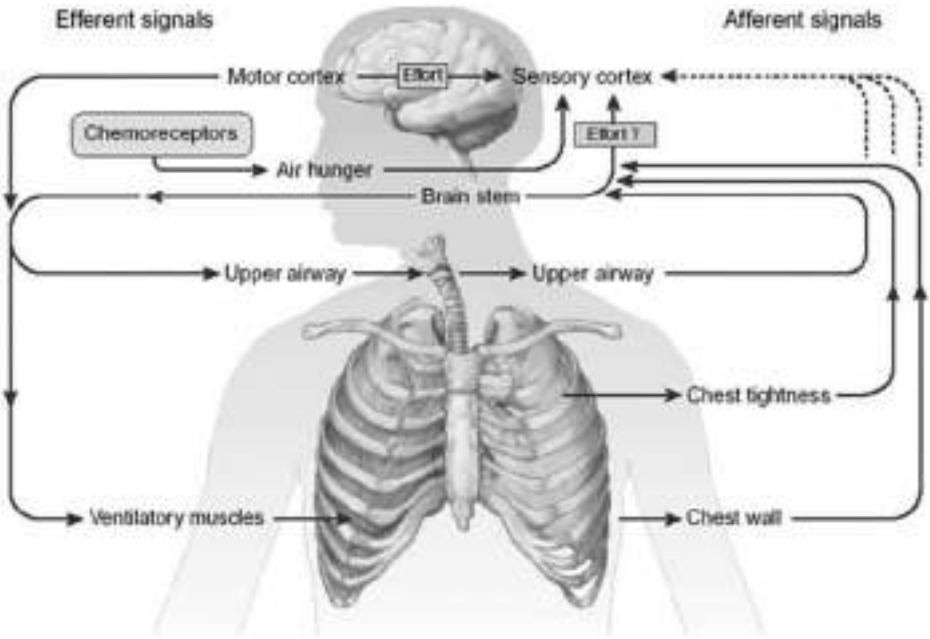


FIGURE 48.1 Physiologic mechanisms producing dyspnea. Respiratory symptoms included in the term "dyspnea" result from stimulation of a range of receptors throughout the respiratory system, as well as from corollary discharge thought to originate in the motor cortex when efferent neural discharges are sent to the ventilatory muscles. Qualitative phrases used to describe the sensations are based on research on and interviews with patients experiencing dyspnea. (From ***N. Engl. J. Med***. 333, 1547–1553, 1995. Copyright 1995 Massachusetts Medical Society. All rights reserved.)

Bronchoconstriction is associated with a sensation of chest tightness,[21–23] which is believed to arise from stimulation of pulmonary receptors by bronchoconstriction.[13] Studies of the possible palliative effects of inhaled furosemide demonstrate decreased dyspnea scores in subjects experiencing limited tidal volume excursion, acute hypercapnia, and resultant breathlessness.[24] The mechanism of action of inhaled furosemide likely involves stimulation of pulmonary stretch receptors, thereby creating a sensation that the lung is inflating more than it actually is in response to central efferent signaling, resulting in a decreased sensation of breathlessness. In addition, there is likely a psychological effect of the therapeutic intervention of delivering an inhaled aerosol that contributes to an expectation of relief of dyspnea with inhaled furosemide.[25]

Cardiac dyspnea may occur due to impaired systolic or diastolic function and resultant high left ventricular diastolic pressure. This leads to increases in pulmonary capillary wedge pressure and in some instances, transudation of fluid into the pulmonary interstitium and alveoli. As a result, the lung becomes less compliant, increasing the respiratory system mechanical load, and hypoxia may occur. Increased pulmonary vascular pressures and stimulation of pulmonary receptors by interstitial fluid may also directly lead to respiratory discomfort. Furthermore, low cardiac output states may lead to reduced blood flow to ventilatory muscles, resulting in muscle weakness and fatigue.[26] Also, congestive heart failure appears to alter respiratory control mechanisms, leading to increased levels of ventilation compared with control subjects for any given level of exercise.[27] Stimulation of the neural drive to breathe may lead to dyspnea. Finally, there appear to be receptors (ergoreceptors) in the peripheral muscles that are sensitive to increases in byproducts of anaerobic metabolism and may contribute to increased ventilation and breathing discomfort associated with low cardiac outputs.[28]

48.1.3.3 Qualities of Dyspnea

Do patients with CHF, COPD, pulmonary embolism, and asthma all experience the same sensations of respiratory discomfort? Can we differentiate distinct types of dyspnea by the questions we ask patients? Studies demonstrate that dyspnea, like pain, is actually multiple, qualitatively distinct sensations, and that attention to the "language of dyspnea" can provide insights into an individual patient's disease.

Using a questionnaire (Table 48.3) derived from interviews with patients and studies in which normal subjects were made breathless while performing a range of ventilatory tasks,[29] various cardiopulmonary conditions associated with dyspnea could be characterized by a unique set of verbal phrases.[22] These findings were confirmed in an investigation using a similar approach but with an expanded questionnaire.[23] Responses offered by patients when asked to describe their breathing discomfort have been shown to be reproducible over time.[25]

From these and related studies, a language of dyspnea has emerged (Table 48.4). Patients with bronchoconstriction commonly describe a sensation of "chest tightness." Increased mechanical loads (typical of airway obstruction), interstitial disease, and chest wall abnormalities

TABLE 48.3
Descriptors of Dyspnea

1. My breath does not go in all the way.
2. My breathing requires effort.
3. I feel that I am smothering.
4. I feel a hunger for more air.
5. My breathing is heavy.
6. I cannot take a deep breath.
7. I feel out of breath.
8. My chest feels tight.
9. My breathing requires more work.
10. I feel that I am suffocating.
11. I feel that my breath stops.
12. I am gasping for breath.
13. My chest is constricted.
14. I feel that my breathing is rapid.
15. My breathing is shallow.
16. I feel that I am breathing more.
17. I cannot get enough air.
18. My breath does not go out all the way.
19. My breathing requires more concentration.

TABLE 48.4
The Language of Dyspnea: Association of Qualitative Descriptors and Physiologic Mechanisms of Shortness of Breath

Qualitative Descriptors	Pathophysiology
Chest tightness or constriction	Bronchoconstriction, interstitial edema (asthma, myocardial ischemia)
Increased work or effort of breathing	Airway obstruction, neuromuscular disease, chest wall disease (COPD, moderate to severe asthma, myopathy, kyphoscoliosis)
Inability to get a deep breath	Hyperinflation (COPD, asthma)
Air hunger, need to breathe, urge to breathe	Increased drive to breathe (CHF, pulmonary embolism, moderate to severe airway obstruction)
Heavy breathing, rapid breathing, breathing more	Deconditioning

usually result in increased "effort of work" of breathing. Neuromuscular weakness produces a sensation of increased effort to breathe. Significant hyperinflation, as in severe COPD, may cause a sensation of an "inability to get a deep breath."[30] In experimental conditions, acute hypercapnia produces a discomfort characterized as "air hunger" or an increased urge to breathe.[31]. Air hunger occurs in diseases associated with an increased urge to breathe (e.g., severe asthma, pulmonary embolism, acute hypoxia, exercise in patients with underlying lung disease). Air hunger may include the sense of an inability to get a deep breath, seen with hyperinflation. Patients may express several of these sensations simultaneously, as many diseases are characterized by multiple pathophysiological derangements (e.g., asthma may result in chest tightness due to bronchoconstriction *and* increased effort of breathing due to hyperinflation and airway resistance).

Deconditioning, the inability to achieve maximal workloads with exertion because of reduced aerobic capacity of the heart and limb muscles, afflicts both healthy people and patients with cardiopulmonary diseases. It deserves special attention because deconditioning is a state that can be corrected with an exercise program.[32–34] Often, patients with underlying cardiopulmonary diseases are assumed to be limited by their disease when they are actually deconditioned. For example, when patients with asthma were asked why they had reduced exercise capacity, they stated that it was because of their asthma. When that same group was subjected to formal exercise testing, their primary exertional limit was cardiovascular deconditioning, not airway reactivity.[32] Patients with COPD, even those with severe airway obstruction (FEV1 <40% predicted), are often primarily limited by leg fatigue rather than by poor ventilatory reserve.[35] In the context of the "language of dyspnea," dyspnea associated with deconditioning has been characterized as "heavy breathing," "breathing more,"[23] or "huffing and puffing."

When questioning a patient with shortness of breath, it is best to inquire about the nature of the "breathing discomfort." This phrase is generic and allows one to elicit specific qualities of a patient's distress without introducing bias toward a particular sensation. At times, it may be helpful to show patients a dyspnea questionnaire and ask them to select up to three phrases that best describe their breathing discomfort. Patients may have different sensations (and different kinds of dyspnea due to different problems) under varying conditions (e.g., a patient with interstitial lung disease and superimposed airway reactivity, or a patient with asthma who also is deconditioned). It is also important to distinguish between dyspnea due to chest wall pain and breathing discomfort that is a primary sensation. For example, a patient with fractured ribs may have severe pain with inspiration and express a sensation of "inability to get a deep breath" or "air hunger" despite the absence of pulmonary or cardiovascular pathology.

48.1.3.4 Essentials of the History

48.1.3.4.1 Timing: Acute Versus Chronic Dyspnea

There are relatively few conditions that result in an abrupt onset of breathing discomfort (Table 48.5). These tend to be due to sudden changes in airway resistance, sudden hypoxemia, or sudden increases in pulmonary vascular pressures. With treatment, these conditions often improve as rapidly as they began. On occasion, dyspnea may develop acutely in a patient with a chronic pulmonary disease and limited pulmonary reserve from a sudden metabolic stress (e.g., a patient with severe COPD who develops an infection with a high fever and metabolic acidosis). The need to increase ventilation in the setting of a sudden metabolic stress to

TABLE 48.5
Acute Causes of Dyspnea

Bronchospasm
Acute asthma
Acute interstitial edema
Hypoxemia
Acute mucous plugging of airways
Pulmonary embolism
Pneumothorax
Increases in Pulmonary Vascular Pressures
Myocardial ischemia
Pulmonary embolism
Sudden Increased Demand for Ventilation
Acute metabolic acidosis
Chest Wall Pathology
Trauma (e.g., rib fractures)

meet increased demands for oxygen consumption and/or carbon dioxide elimination may result in both increased work of breathing and an increased urge to breathe.

Chronic dyspnea tends to develop slowly over the course of weeks or months. Often, patients have difficulty pinpointing the exact onset of symptoms, or attribute symptoms to a respiratory infection, despite resolution of all systemic infectious symptoms except for chronic breathing discomfort. Not infrequently, the date that a patient gives up cigarette smoking is, in retrospect, consciously or unconsciously related to the onset of dyspnea. Causes of chronic dyspnea include COPD, fibrotic lung disease, pleural effusion, progressive chest wall deformities, chronic CHF, and recurrent pulmonary emboli, among others. The chronicity of these conditions may be masked by lifestyle changes. As walking upstairs becomes progressively difficult, a patient with COPD may move to a building with elevators or to the ground floor. Children are called upon to do shopping. Deconditioning becomes superimposed on the underlying cardiopulmonary disorder, making even routine tasks uncomfortable. Patients may present with seemingly new symptoms over the course of a few weeks; however, the reality is that the patient has a chronic condition and is only able to avoid recurring dyspnea because of avoidance of physical activity.

48.1.3.4.2 Timing: Night Versus Day

Nocturnal dyspnea, awakening in the middle of the night with acute respiratory distress, can be an extremely frightening experience for a patient. The majority of cases are due to one or more of three problems: bronchospasm, aspiration, and CHF.

Patients with asthma may have worsening symptoms at night because of a trough in the level of bronchodilator medications, triggering of bronchospasm by gastroesophageal reflux through a reflex mediated by the vagus nerve when acid enters the esophagus, and/or as a result of exposure to allergens localized to the bedroom. Nocturnal sensations are usually similar to day-time asthma attacks (e.g., chest tightness and increased effort to breathe), although the precipitating factors are generally different. At times, patients may cough without discernible wheezing. The association of symptoms with changes in the home environment (e.g., new carpeting or a new pet) may give clues to the precipitant.

Recurrent aspiration causing nocturnal dyspnea can be an elusive diagnosis. Reports of witnessed aspiration or gagging are rare. The presence of partially digested food on a patient's pillow is infrequently reported, but if present, is suggestive of regurgitation and aspiration. The diagnosis is usually suspected in a patient with a history of gastroesophageal reflux or hiatal hernia, infiltrates on chest imaging in dependent portions of the lung, and no history of asthma.

Nocturnal dyspnea characterized as a sense of air hunger or a suffocating feeling is most typical of CHF and is termed *paroxysmal nocturnal dyspnea* (PND). Clues to the diagnosis of PND include the presence of peripheral edema and relief of the respiratory discomfort shortly after assuming an upright position. Redistribution of peripheral edema fluid to the central circulation during the night with consequent increases in pulmonary vascular pressures in a patient with compromised left ventricular function is believed to be the pathophysiologic basis for PND. Acute myocardial ischemia at night may mimic PND but is unlikely to have a recurring pattern, may be associated with chest pain, and is less likely to be relieved by sitting upright.

One cause of dyspnea that never occurs while sleeping is hyperventilation syndrome. The primary clinical manifestations of hyperventilation syndrome are intermittent episodes of tachypnea and subjective discomfort characterized by air hunger or an urge to breathe. Despite taking large tidal volumes, patients perceive that they cannot get a deep breath. Patients with hyperventilation syndrome experience dyspnea during the day, but objective assessment reveals normal spirometry, normal DLCO, and normal chest imaging. While sleeping, these patients have normal breathing patterns and appear quite comfortable.

48.1.3.4.3 Position

Dyspnea that occurs with or is relieved by changes in position should prompt a consideration of abnormalities in the ventilatory pump (i.e., the muscles of ventilation and the configuration of the chest wall), focal lung abnormalities that lead to hypoxemia when blood flow is increased to that area, or redistribution of fluid into the central circulation in patients with a history of CHF.

Orthopnea is dyspnea that occurs in the recumbent position. The most common explanation is redistribution of blood pooled from dependent veins into the central circulation, leading to increased pulmonary vascular pressures in the setting of compromised cardiac function. However, given the very rapid onset and resolution of orthopnea with change in position, it is probably secondary to stimulation of intracardiac (possibly right atrial) or pulmonary vascular receptors rather than the development of interstitial

pulmonary edema. In very obese patients, or patients with a distended abdomen due to ascites, the large abdomen increases the work of breathing with positional changes, as it now requires more force to initiate an inspiration due to the weight of the abdomen on the chest wall.[36] Severe dyspnea when bending over (bendopnea), frequently described by the patient as shortness of breath when tying one's shoes, is common in these patients, as there is little room for the diaphragm to move downward during inspiration. Lying supine, which removes gravity as a factor in pulling the abdomen away from the diaphragm, worsens dyspnea in these individuals. Bendopnea has also been described with CHF, likely due to acute increases in intracardiac pressure.[37] Patients with cervical spinal cord injury, amyotrophic lateral sclerosis, or bilateral phrenic nerve paralysis, who lack active intercostal inspiratory muscles or diaphragm, may also suffer from orthopnea.

Arteriovenous malformations (AVMs) in the pulmonary circulation lead to shunting of blood from the right to the left side of the heart (i.e., the blood never passes through the pulmonary capillaries and is sent to the systemic circulation with a low oxygen saturation). Any position that increases the gravity-dependent flow of blood through an AVM can lead to worsening hypoxemia and dyspnea. Focal areas of atelectasis or pneumonia will lead to similar gas exchange derangements when the body position is such that blood flow to that region of lung is enhanced. Consequently, the guiding principle in these circumstances is "good lung down" when positioning a patient to maximize gas exchange and minimize dyspnea.

Platypnea describes the development of tachypnea and hyperventilation when the patient is in the upright position. It is a physical finding rather than a symptom, although the patient may also complain of associated breathing discomfort. The exact mechanism of platypnea is unclear, but it probably relates to pathology at the lung bases with stimulation of pulmonary receptors or worsening gas exchange when blood flow increases to these areas with the patient upright.

48.1.3.5 Palliative Management

Management of dyspnea primarily involves treating the underlying pathophysiologic process causing the patient's breathlessness, and a detailed review of different treatments for the variety of medical conditions that can cause dyspnea is beyond the scope of this chapter. However, despite appropriate medical management, severe and debilitating dyspnea may persist for some patients. In these cases, symptomatic management may be indicated to achieve some degree of palliation of dyspnea.

Palliative management of persistent and severe dyspnea has been assessed in different patient populations and diseases, and systemic opioids have consistently demonstrated efficacy in ameliorating dyspnea in patients with cancer, COPD, and interstitial lung disease.[38] Opioids act by agonizing central mu-receptors, decreasing cerebral responses to afferent neuronal signals, as well as inducing cerebral depression and neurosystemic analgesia. Inhaled opioids may provide targeted symptom relief for patients with dyspnea while decreasing the effects of somnolence; however, the available data do not demonstrate superiority of inhaled opioids as compared with systemic opioids.[39]

Non-pharmacologic interventions, such as developing coping strategies for managing the physical and psychological aspects of breathlessness, have demonstrated effectiveness in helping patients manage dyspnea. A significant proportion of patients with COPD, up to 40–50%, have clinical evidence of depression, and counseling and cognitive behavioral therapy can address both depression and dyspnea.[40] In addition, environmental interventions such as blowing cool air on a patient's face can significantly reduce the severity of dyspnea in normal subjects with induced breathlessness, indicating that this intervention is likely of benefit in dyspneic patients.[41]

Benzodiazepines induce drowsiness in patients with dyspnea refractory to medical treatment but do not clearly improve symptoms of breathlessness. Multiple randomized trials assessing the effects of benzodiazepines do not provide compelling evidence for or against benzodiazepines for the management of dyspnea.[42] As such, benzodiazepines should be reserved for patients with persistent dyspnea despite treatment with other palliative interventions and/or for patients with a significant component of anxiety contributing to or caused by dyspnea.

Finally, while supplemental oxygen is frequently prescribed to patients with severe dyspnea, the available evidence does not support this intervention for patients who are not hypoxemic.[43] Administration of humidified air and providing high-flow air may provide some palliative benefit, possibly by stimulating nasal receptors that reduce the drive to breathe, but supplemental oxygen, per se, does not improve dyspnea for patients who are not hypoxemic.[44]

48.1.4 Cough

48.1.4.1 Definition and Physiology

A cough is a sudden expiratory maneuver, associated with high intrathoracic pressures, intended to clear secretions and foreign material from the airways. An effective cough starts with a deep breath, which expands the lungs and chest wall to a point of elevated elastic recoil. This elastic recoils works in synchrony with optimally contracting expiratory muscles to produce high intrathoracic pressures against a closed glottis. The sound of the cough is associated with the sudden opening of the glottis and the subsequent explosive release of pressurized intrathoracic gas with vibration of the vocal cords. Vibration may help to loosen secretions from the larynx.

Impaired inspiratory or expiratory muscle function leads to weakened cough. Patients with vocal cord paralysis or tracheostomy are unable to seal the glottis and cannot generate sufficiently high intrathoracic pressures needed to effectively clear secretions. Such patients are at increased risk for lower respiratory infections and may complain of

TABLE 48.6
Selected Causes of Cough Stimulation

Anatomic location	*Mechanism of cough stimulation*
Larynx	Activation of epithelial irritant receptors
Trachea and large airways	Activation of epithelial irritant receptors
Lung parenchyma	Activation of stretch receptors Activation of C fibers
Pleural space	Activation of irritant receptors
Esophagus	Reflex mechanism in response to reflux of gastric acid
Tympanic membrane	Stimulation of irritant receptors in the external auditory canal

increased chest congestion. The triggers for cough are complex; selected examples are reviewed in Table 48.6.

48.1.4.2 Clinical Causes of Cough

The most common etiologies of cough are outlined in Table 48.7. The differential diagnosis for cough varies based on whether a patient has an acute, subacute, or chronic cough. The differential diagnosis for chronic cough is further subdivided based on whether the patient has a normal versus abnormal chest x-ray.

48.1.4.3 Acute Cough

Acute cough is a cough that has been present for less than three weeks.[39] The most common cause of acute cough is a respiratory infection; it is characterized by sputum production and may be accompanied by a "raw" substernal sensation. Chest congestion may also be present. Fever, malaise, and other systemic symptoms of a viral or, less likely, bacterial infection are likely to coexist.

Subclinical bronchospasm is another cause of acute (as well as chronic) cough. In patients with mild asthma, wheezing may not be present. Sudden exposures to allergens, cold air, or exercise may result in transient cough. A high index of suspicion, along with appropriate PFTs, including spirometry and possibly bronchoprovocation maneuvers, is needed to make this diagnosis.

Inhalation of toxic fumes (e.g., cleaning agents, smoke) can damage the airway epithelium and precipitate cough. Airway hyperreactivity may also result from such exposures. As with acute infections, a raw substernal sensation is often present. Dyspnea commonly accompanies inhalational exposures. Foreign body aspiration (e.g., a food particle or in children, a small toy) may not be recalled by the patient. Cough may occur immediately after aspiration, but in some cases can be delayed for hours or days, at which point airway inflammation is probably contributing to the cough. A focal wheeze is appreciated on examination of the chest in some cases, and post-obstructive pneumonia can develop if the foreign material occludes a sufficient diameter of the airway lumen.

TABLE 48.7
Common Clinical Causes of Cough

Acute Cough
- Respiratory infection, airway inflammation
- Bronchospasm

Inhalational injury
- Aspiration

Subacute Cough
- Infectious or post-infectious cough (*Bordella pertussis*)
- Sinus infection/inflammation resulting in post-nasal drip

Chronic Cough with Normal Chest X-ray
- Upper airway cough syndrome (post-nasal drip)
- Bronchospasm
- Gastroesophageal reflux
- Chronic bronchitis
- Bronchiectasis
- Endobronchial neoplasms

Chronic Cough with Abnormal Chest X-ray
- Interstitial lung disease
- Recurrent aspiration
- Endobronchial neoplasm
- Indolent infections (e.g., *Pneumocystis jerovici*, pneumonia, tuberculosis)

48.1.4.4 Subacute and Chronic Cough with Normal Chest X-Ray

Chronic cough is defined as a cough lasting for more than eight weeks, while subacute cough lasts three to eight weeks.[45] There is considerable overlap in causes of subacute and chronic cough, and they are generally considered together in this section. However, post-infectious etiologies are an important cause of subacute, but not chronic, cough. A history of recent airways or sinus infection should be sought in patients with subacute cough. Subacute cough and a normal pulmonary exam may be due to sinus infection and inflammation resulting in post-nasal drip. In the appropriate clinical scenario, sinus imaging and/or treatment with nasal decongestants and antibiotics for bacterial sinusitis may be warranted.[46]

Paroxysms of cough resulting in post-tussive emesis or, less frequently, cough that produces a "whooping" sound are clues to a potential diagnosis of *Bordella pertussis* infection. For patients with cough and these symptoms, *B. pertussis* infection should be considered the diagnosis barring clinical evidence of another cause being more likely.[46] Although infants are typically vaccinated against pertussis, immunity wanes over five to ten years. As such, adolescents and adults are at risk for developing infections from *B. pertussis*.[47] While early antibiotic treatment (macrolides are particularly effective) can reduce the severity and duration of cough due to *B. pertussis*, the efficacy of antibiotics after two weeks of symptoms is unclear. General consensus based on the available studies is that after four weeks of symptoms, it is not appropriate to provide antibiotics; rather, care should focus on symptom management.[45,48]

Chronic cough without significant dyspnea and with a normal chest x-ray is commonly seen by both primary care physicians and pulmonary specialists. This entity has been well studied,[46,49] and the vast majority of patients will have one or a combination of three findings: upper airway cough syndrome (UACS), asthma, and gastroesophageal reflux disease (GERD).

UACS includes the spectrum of rhinosinusal causes of post-nasal drip. From perennial rhinitis to the sequela of upper respiratory infections, UACS encompasses the breadth of diseases that result in posterior nasopharyngeal secretions descending to the larynx, causing an irritating feeling or "tickle" in the throat. Cough due to UACS may be nonproductive or result in small amounts of white sputum; however, UACS due to chronic sinus infections may result in purulent sputum. Typically, the cough worsens when patients assume a supine position to go to sleep because of both positional worsening of nasal drainage and a greater awareness of the "irritation" in the absence of typical distractions one encounters during the day. Not uncommonly, patients will not be aware of a "drip" per se, but when questioned about the source of the cough (i.e., where the cough seems to be originating), they will localize it to the throat rather than the chest. Frequent "throat clearing" may be a clue suggestive of UACS. Friends or family members may be more aware of frequent throat clearing than the patient, and frequent throat clearing may be observed during the interview. A history of allergies may be suggestive of UACS due to rhinitis, particularly if there is seasonal variation of cough frequency or severity. However, in most cases, patients are unaware of specific allergens, and skin testing may be necessary if symptoms persist despite treatment.

Hyperactive airways without wheezing can present as chronic cough; this has been termed *cough variant asthma.*[50] In a patient without a prior history of asthma, symptoms often follow a respiratory infection. Systemic infectious symptoms will clear over several weeks, but cough persists. In many cases, the cough will resolve spontaneously in 8 to 12 weeks, but it can continue indefinitely. Typically, the cough will be nonproductive or result in small amounts of clear to white sputum. In contrast to cough due to UACS, patients with cough variant asthma localize the origin of the cough to the chest. Exposure to cold air, exercise, smoke, and toxic fumes characteristically worsens cough arising from airway reactivity. Spirometry is often normal during routine evaluation, and the diagnosis may be made based on response to a therapeutic trial of bronchodilators or by bronchoprovocation tests. Patients with cough variant asthma are typically quite responsive to treatment and generally achieve symptom control more easily than patients with classic asthma symptoms.[50,51]

GERD completes the triad of common causes of chronic cough and a normal chest x-ray. GERD may produce cough on its own or exacerbate cough in a patient with airway reactivity. Cough due to GERD is typically nonproductive and localizes to the chest. A history of heartburn or reflux symptoms is helpful if present, but is frequently absent. "Waterbrash," the sudden sensation of a sour taste in the mouth, is typically associated with reflux of gastric contents. Treatment of cough due to GERD should focus on lifestyle modifications (e.g., raising the head of the bed at night, avoiding foods that dilate the lower esophageal sphincter, and avoiding eating shortly before lying down). In one study, proton pump inhibitors were no better than placebo in treating cough due to GERD,[52] but in a more recent investigation, up to 28% patients with chronic cough *and* symptoms of heartburn responded to treatment for reflux compared with 14% in individuals without heartburn.[53]

Other, less common causes of chronic cough with a normal chest x-ray include non-asthmatic eosinophilic bronchitis (NAEB), bronchiectasis, chronic bronchitis, and bronchial carcinoid. NAEB causes cough by allergic airway inflammation in response to an environmental stimulus. NAEB is associated with normal chest imaging and normal spirometry. NAEB is not associated with airway hyperresponsiveness in response to bronchoprovocation maneuvers such as a methacholine challenge, in contrast to chronic cough due to asthma. The definitive diagnosis of NAEB requires identification of eosinophils in sputum or bronchial washings, or bronchial mucosal biopsy demonstrating increased eosinophil concentrations.[54] Given that these diagnostic modalities are not clinically practical for most patients with cough, empiric treatment may be appropriate when NAEB is suspected. The best treatment for NAEB is identification and avoidance of a causative environmental stimulus. When that is not possible or not effective, empiric treatment with glucocorticoids can be attempted. Typically, patients with NAEB return to their premorbid baseline after treatment with glucocorticoids or avoidance of causative environmental stimuli.

Patients with bronchiectasis typically have a cough productive of purulent sputum, although upper lobe disease, which tends to drain well throughout the day, may be associated with a dry cough or scant secretions. Sputum may be occasionally streaked with blood. A history of prior pneumonia(s) is suggestive but not diagnostic of bronchiectasis. Bronchiectasis increases the risk of recurring respiratory infections associated with low-grade fever, worsening cough, and sputum production. Growth of *Pseudomonas aeruginosa* on repeated sputum cultures is very suggestive of bronchiectasis. Although chest x-ray is often normal, focal areas of fibrosis or fibrocystic disease may be present, and chest computerized tomography (CT) scan is quite sensitive in defining the extent of disease.

Chronic bronchitis is defined as a productive cough present for at least three months of the year for at least two years. Chronic bronchitis is due to chronic airway inflammation induced by cigarette smoking or other environmental irritants. The cough associated with chronic bronchitis is typically most pronounced early in the morning and tends to diminish as the day progresses. Patients localize the cough to the chest. Sputum is occasionally mixed with blood. Due to associated obstructive lung disease, these patients can have dyspnea on exertion.

Endobronchial neoplasms in central airways can produce cough and in the absence of significant airway obstruction leading to focal atelectasis, will usually have a normal chest x-ray. Although bronchogenic carcinoma can present in this manner, bronchial adenomas or carcinoid tumors are more likely. These tumors, which usually behave as low-grade malignancies with a small potential for distant metastases, may have a polypoid appearance that in some cases leads to a postural cough due to intermittent positional airway obstruction from the adenoma.

48.1.4.5 Chronic Cough with an Abnormal Chest X-Ray

Interstitial lung disease typically presents with the gradual onset of dyspnea on exertion, but nonproductive cough, particularly with a deep breath, may be the prominent (or only) symptom early in the disease. Patients localize the cough to the chest. In severe cases, cough can be quite debilitating and refractory to cough suppressants. Chest x-ray findings may be subtle in early disease; later in the clinical course, chest x-ray frequently demonstrates low lung volumes and reticular interstitial changes.[55] For patients with normal chest x-rays but suspected interstitial disease, high-resolution CT scans are a very sensitive tool for confirming the diagnosis.[56] The interview should include questions about the occupational history (e.g., exposure to inorganic or organic dusts), tobacco use, joint symptoms or peripheral skin nodules suggesting collagen-vascular disease (e.g., rheumatoid arthritis, systemic lupus erythematosus), and eye symptoms or lower extremity joint pain suggesting sarcoidosis. Patients with symptomatic interstitial fibrosis typically have a restrictive defect on spirometry and lung volume testing.

Bronchogenic carcinomas in the central airways may cause partial or complete obstruction of a segmental or lobar bronchus, leading to focal atelectasis on chest x-ray and chronic cough. The cough is typically nonproductive but may be associated with intermittent hemoptysis.

Although cough due to lower respiratory infections usually presents acutely, there are indolent infections that can present with a chronic cough and minimal systemic symptoms. PCP pneumonia (i.e., pneumonia caused by *Pneumocystis jerovici*) in patients with acquired immunodeficiency syndrome due to human immunodeficiency virus or other immunosuppressed states is characterized by a nonproductive cough and dyspnea on exertion over weeks to months. Similarly, early reactivation of *Mycobacterium tuberculosis* can present with cough, fatigue, and mild weight loss. Chest x-ray usually provides evidence of the underlying infection in these cases.

48.1.5 Hemoptysis

48.1.5.1 Definition and Physiology

Hemoptysis refers to coughing or expectoration of blood or blood-tinged sputum. As a general principle, the term is reserved for blood that originates in the lower respiratory tract (i.e., below the larynx). However, it may be difficult to determine whether blood is coming from the lungs versus the posterior nasopharynx or the gastrointestinal tract, especially if vomiting is associated with a paroxysm of cough. It is worth noting that the normal tracheobronchial tree should not bleed even in the presence of coagulopathy. Thus, hemoptysis in the setting of anticoagulation is considered a pathologic finding.

The four major sources of blood in the lower respiratory tract are airways, pulmonary parenchyma, pulmonary circulation, and bronchial circulation. Inflammation or irritation of airway epithelium (e.g., with acute pulmonary infections, chronic bronchitis, or foreign body aspiration) usually results in small volume hemoptysis, often mixed with sputum. Bleeding from the pulmonary parenchyma occurs with pulmonary infarction or contusion. In the presence of pulmonary AVMs or greatly elevated pulmonary venous and/or capillary vascular pressures (e.g., from mitral stenosis), bleeding may occur as well. Finally, the bronchial circulation may result in hemoptysis in patients with bronchiectasis or large intrapulmonary cavities.

Massive hemoptysis is generally defined as production of ≥600 mL of blood in 24 hours, although the precise volume qualifying as "massive" hemoptysis varies between authors and guidelines. Patients commonly overestimate the amount of blood they have expectorated because of concomitant anxiety associated with coughing up blood. Therefore, it is important to encourage the patient to be as explicit as possible when quantifying the amount of blood. One should show the patient, and witnesses to the episode(s), various-sized containers to assist them in estimating the quantity expectorated. While massive hemoptysis can occur from an endobronchial carcinoma, it is more commonly associated with erosions of bronchial vessels in large intrapulmonary cavities or with bronchiectasis.[57]

48.1.5.2 Etiology

There are six etiologic categories to be considered when evaluating a patient with hemoptysis (Table 48.8). Determining the reason for a patient's hemoptysis depends on the presence or absence of additional symptoms beyond hemoptysis itself.

Lower respiratory tract infections cause airway inflammation, which can result in epithelial injury and bleeding. This is most common with bacterial tracheobronchitis but can also occur with bacterial pneumonias. Typically,

TABLE 48.8
Etiologic Categories for Hemoptysis

Pulmonary infections
Neoplasms
Collagen-vascular and immunologic lung diseases
Cardiovascular diseases (including pulmonary vascular and valvular diseases)
Aspiration of foreign bodies
Chest trauma with pulmonary contusion

hemoptysis in the setting of an acute infection is small in volume (<50 mL) and resolves with improvement in the other symptoms (e.g., cough, fever, malaise). Bronchiectasis and chronic bronchitis predispose patients to acute infections and are associated with occasional episodes of blood-streaked sputum, typically in the presence of an acute infection. Bronchiectasis infrequently leads to massive hemoptysis.

Lung cancers, most commonly bronchogenic carcinoma, are a common cause of hemoptysis. Lung cancer should be especially considered in patients over age 40 with a significant smoking history and more than ten days of hemoptysis.[58] Patients with an extrathoracic malignancy that can metastasize to the lungs (e.g., renal cell carcinoma, breast carcinoma, or sarcoma) are at increased risk of hemoptysis due to cancer. Bleeding due to cancer usually occurs in the absence of other symptoms and presents as frank blood without sputum.

Hemoptysis in association with joint symptoms, rashes, dyspnea, and/or renal dysfunction suggests collagen-vascular disease as an etiology. Pulmonary-renal syndromes (e.g., systemic lupus erythematosus, granulomatosis with polyangiitis [previously referred to as Wegener's granulomatosis], and anti-glomerular basement membrane disease [previously referred to as Goodpasture syndrome]) may present with hemoptysis as part of the symptom complex. In most cases, hemoptysis is not an isolated finding.

AVMs, pulmonary emboli, pulmonary edema, and mitral stenosis are cardiovascular causes of hemoptysis. Pulmonary edema classically produces pink sputum, and lung biopsy reveals hemosiderin-laden macrophages consistent with pulmonary hemorrhage. Gross blood is uncommon in CHF without concomitant coagulopathy. Bleeding may occur as the first symptom of an AVM, and massive hemoptysis has been reported.[59] Hemoptysis from pulmonary emboli or mitral stenosis usually occurs with other symptoms such as dyspnea and chest discomfort.

Foreign body aspiration can lead to hemoptysis by causing either direct airway trauma or local inflammation. Pulmonary contusions result most commonly from blunt chest trauma and are associated with other injuries such as rib fractures, pneumothorax, and cardiac contusion. Hemoptysis in these settings is usually small in quantity.

48.1.6 Wheezing

48.1.6.1 Definition and Physiology

Wheezing is a sound that emanates from lower airways (i.e., below the larynx), resulting from turbulent flow. It is a "continuous" sound as compared with the intermittent or staccato sounds that accompany chest congestion with mucus in the airways (commonly called rhonchi). Wheezing may occur during expiration or inspiration, or throughout the respiratory cycle. It is both a symptom, a sound that patients report hearing with breathing, as well as a physical finding appreciated when one examines a patient.

TABLE 48.9
Common Causes of Wheezing

Primary airway reactivity (e.g., asthma)
Interstitial edema
Airway inflammation and mucous hypersecretion
Endobronchial obstruction (e.g., neoplasm or foreign body)
Vocal cord dysfunction

The sound is produced by turbulent flow through narrowed airways and in some cases, may reflect rapid oscillation of the airway walls.[60] There are multiple causes of airway narrowing (Table 48.9). Wheezing, a sound originating in the airways, should be distinguished from stridor, a primarily inspiratory sound. Stridor is qualitatively similar to wheezing, but it arises from the larynx and upper airways. During inspiration, transmural pressure across the *intrathoracic* airways favors expansion (due to negative pleural pressures). As such, inspiratory wheezing is relatively uncommon. In contrast, atmospheric pressure surrounding *extrathoracic* airways is greater than the negative pressure inside them; consequently, the extrathoracic airways tend to collapse during inspiration. Collapse of extrathoracic airways during inspiration accentuates any pre-existing airway narrowing. Thus, wheezing that worsens during inspiration is likely due to an obstruction in the extrathoracic airways, whereas wheezing that is more pronounced on expiration likely originates in the intrathoracic airways. When the intensity of wheezing is constant throughout both inspiration and expiration, a fixed obstruction is likely.

48.1.6.2 Etiology

The most common cause of wheezing is asthma, although asthma may occur in the absence of wheeze. Historical data suggestive of asthma include wheezing associated with exposure to inhaled allergens or irritants, cold air, and/or exercise. Decreased wheezing in response to inhaled bronchodilators also suggests asthma. Physical examination reveals diffuse expiratory wheezing when a patient is suffering acute asthmatic symptoms and is usually normal in the absence of symptoms. With acute symptoms, spirometry demonstrates an obstructive ventilatory defect with decreased FEV1 and reduced FEV1/FVC. In the absence of symptoms between asthma exacerbations, PFTs are typically normal. Airway hyperresponsiveness can be elicited by performing bronchoprovocation maneuvers such as a methacholine challenge, which is sensitive but not specific for diagnosing asthma.

Mucus hypersecretion due to infections and/or airway inflammation may also cause wheezing. Since lower respiratory tract infections can also produce transient airway hyperreactivity, it may be difficult to distinguish wheezing from infection and/or inflammation from asthma. Rapid improvement of wheezing after cough or with bronchopulmonary clearance, however, is more suggestive of mucus hypersecretion than asthma.

"Cardiac asthma," wheezing in association with increased pulmonary capillary pressures and interstitial edema, which compresses small airways, is another common cause of wheezing. Generally, there are other symptoms or signs of CHF in the history (orthopnea, PND) and physical examination (distended jugular veins, S_3 gallop, and peripheral edema). However, acute CHF secondary to myocardial ischemia may be difficult to distinguish from asthma in a patient with a history of airway reactivity.

Partial endobronchial obstruction can lead to focal or localized wheezing. The patient may not recognize the focal origin of the sound or be able to localize any internal sensations associated with the wheeze. Bronchogenic neoplasms, either carcinomas or adenomas, and aspirated foreign bodies can cause focal wheezing.

Expiratory wheezing may originate from the upper airways when laryngospasm is present. Termed paradoxical vocal cord dysfunction (PVD), this condition is due to adduction of the vocal cords during expiration; expiratory wheezing originating from the upper airways can be extremely difficult to distinguish from asthma by history alone. Frequently, PVD occurs in young women, often with a history of emotional and/or psychiatric difficulties. When paradoxical vocal cord movement occurs only in the setting of exertion, particularly strenuous exertion, it is referred to as exercise-induced laryngeal obstruction (EILO).[61] PVD and EILO are commonly treated as asthma for months or years before the diagnosis is recognized.[61,62] Clues to the diagnosis of PVD are a very rapid symptom onset, an association of psychological stress with wheezing, and inconsistent bronchodilator response. EILO is characterized by exertional expiratory wheezing and excessive breathlessness, symptom resolution with exercise cessation, and normal resting spirometry results. Fiberoptic laryngoscopy during an attack of either PVD or EILO can confirm the diagnosis by directly visualizing adduction of the vocal cords during expiration. Treatment is primarily speech therapy and psychological counseling to assist patients in understanding the cause and nature of their symptoms and to teach techniques to develop better vocal cord control.

Vocal cord swelling from infection, allergic reaction, or chemical or smoke inhalation narrows the upper airway, increases turbulent flow, and may lead to stridor. As inhalational injuries can damage both upper and lower airways, laryngeal edema and inspiratory wheezing may be associated with intrathoracic airway hyperresponsiveness and expiratory wheezing. Allergic reactions causing laryngeal edema can be differentiated from inhalational injuries both from the history and from an association with urticaria and angioedema.

48.1.7 Nocturnal Respiratory Symptoms: Snoring and Apnea

48.1.7.1 Definition and Physiology

The prevalence, clinical importance, and societal impact of nocturnal respiratory symptoms have increased markedly in the 21st century. The primary cause of the increased frequency and severity of nocturnal respiratory symptoms is likely the marked increase in obesity in the general population. In 2022, 2.5 billion adults were overweight (43% of the world population), of whom 890 million were obese.[63] In the United States, the National Health and Nutrition Examination Surveys have demonstrated progressive increases in obesity (defined as a body-mass index of ≥30 kg/m^2) since the 1960s. The importance of high quality sleep for general health is increasingly recognized, with calls for more patient education about this problem.[64]

Snoring is defined as noisy breathing during sleep and is very common in the general population. The prevalence of snoring varies between studies, ranging from 10% to 60%.[65] Loud snoring more commonly afflicts men than women.[66] The prevalence of snoring increases with age up to 50–60 years of age, after which prevalence decreases.[67]

Snoring occurs due to vibration of the soft palate and faucial pillars. The likelihood that snoring will occur is dependent upon the size of the airway, the tone of the soft tissue structures in the airway, and body position.

The clinical significance of snoring is uncertain. Generally, in the absence of observed or measured apneic episodes, snoring is considered to be benign. However, the decrease in the prevalence of snoring that occurs with advancing age (>50–60 years of age) may indicate a survivorship phenomenon.[65] It is unknown whether snoring indicates pathologically narrowed airways causing comorbid conditions and death, or whether snoring is simply a marker of comorbid conditions that ultimately cause morbidity and death. Regardless, when a patient (or a patient's bed partner) complains of snoring, a history of signs or symptoms of obstructive sleep apnea (OSA) syndrome should be performed.

Nocturnal apneas are defined as a cessation of airflow during sleep. The term "apnea" specifically describes a cessation of airflow for at least ten seconds; hypopnea is a transient reduction in airflow (a reduction in the respiratory rate and/or tidal volume) that lasts for at least ten seconds and is associated with a ≥4% decrease in oxygen saturation. Frequent nocturnal apneas and hypopneas may result in hypoventilation. The diagnostic criteria for clinically significant OSA is an average of >5 apneas and/or hypopneas per hour of sleep (the "apnea hypopnea index" [AHI]). Polysomnography (i.e., a "sleep study") must be performed to accurately measure the AHI.

The clinical syndrome of OSA is the combination of an AHI of ≥5 with day-time symptoms due to chronic nocturnal hypoventilation. Day-time symptoms associated with the OSA syndrome include fatigue, somnolence, and morning headache. These symptoms are common even in patients without nocturnal hypoventilation, but clinical suspicion of OSA syndrome is increased in patients with concomitant obesity, snoring, and/or comorbid conditions such as hypertension, coronary artery disease, and cerebrovascular disease. Cognitive issues (specifically difficulty concentrating), erectile dysfunction, enuresis, and depression

TABLE 48.10
Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

TABLE 48.11
Mechanisms of End-Organ Damage in the OSA Syndrome

Pathophysiologic mechanism	Systemic effects	End-organ consequences
Increased sympathetic tone due to apneas/hypopneas	Increased systemic vascular resistance	Hypertension Cardiovascular disease Cerebrovascular disease
Increased systemic inflammation due to intermittent hypoxemia	Accelerated atherosclerosis	Coronary artery disease Cerebrovascular disease Peripheral vascular disease
Systemic oxidative stress due to cyclical hypoxemia and re-oxygenation	Atherosclerotic changes Tissue ischemia	Cardiovascular disease Cerebrovascular disease
Endothelial dysfunction (uncertain mechanism)	Increased thrombogenesis	Coronary artery disease Cerebrovascular disease

Chronic nocturnal hypoventilation results in increased sympathetic tone during airway obstruction, which leads to increased systemic vascular resistance and hypertension. Intermittent hypoxemia results in increased systemic inflammation, which accelerates vascular atherosclerotic changes and increases the risk cerebrovascular and/or coronary artery disease.[38] Systemic oxidative stress is increased due to the nightly cycle of hypoxemia and re-oxygenation.[43] Endothelial dysfunction occurs, resulting in increased thrombosis, although the mechanism is speculative.

may also be associated with the OSA syndrome due to end-organ damage from the systemic consequences of chronic nocturnal hypoventilation and cyclical hypoxemia.

The severity of day-time somnolence can be assessed and quantified by the Epworth Sleepiness Scale (ESS).[68] The ESS asks patients to rank their sleepiness in eight scenarios, such as "sitting quietly after a lunch without alcohol" or "in a car, while stopped for a few minutes in traffic" (see Table 48.10)[68]. Patients with a high score (≥9) have increased day-time sleepiness, but the ESS has not been validated as an independent predictor of the OSA syndrome.

There are multiple pathophysiologic mechanisms in the OSA syndrome that account for the epidemiologic association between OSA and cardio- and cerebrovascular disease (see Table 48.11). Essential hypertension occurs in at least 50% of patients with the OSA syndrome.[69] Congestive heart failure, arrhythmias, coronary artery disease, myocardial infarction, and cerebrovascular disease, including stroke, are all associated with and likely due to systemic physiologic derangements caused by OSA.[70]

The "obesity-hypoventilation syndrome" (OHS) is the combination of chronic hypoventilation with chronic hypercapnia and obesity. Right ventricular dysfunction, due to elevated pulmonary arterial pressures and left heart dysfunction, is commonly present in patients with OHS.

Of note, certain cerebral pathologies, particularly abnormalities involving areas of non-voluntary respiratory control, may result in a rare condition called central sleep apnea syndrome. Central sleep apnea is not associated with obesity, while OSA and obesity are clearly directly correlated.

48.1.7.2 Etiology

While snoring can be a normal finding, it may be associated with the OSA syndrome. As noted previously, extrathoracic airways, including the hypopharynx, are prone to collapse during inspiration due to the combination of positive atmospheric pressure outside the airway and negative intraluminal pressure during inspiration. Snoring is more likely to occur in obese patients, as the hypopharynx is already narrowed from increased soft tissue fat. Conditions that reduce the muscle tone of the surrounding tissue (e.g., alcohol, sedative agents) further increase the risk of hypopharyngeal obstruction and snoring. Rapid eye movement (REM) sleep is associated with decreased muscle tone, and snoring occurs most commonly during this phase of sleep.

The tongue is a major component of the anterior wall of the hypopharynx, and movement of the tongue can contribute to upper airway obstruction. When the tongue falls posteriorly, obstruction is worsened. Given the lack of bony support to maintain hypopharyngeal patency, intact glossal and pharyngeal muscle tone is necessary to keep the airway from collapsing. Patients who sleep in the supine position are more likely to snore or develop more severe obstruction because of the propensity of the tongue to be pulled posteriorly by gravity.

Children with large tonsils or adenoids may present with snoring, although significant airway obstruction is unusual.

48.1.7.3 Essentials of the History

Snoring, unlike many symptoms, is much less likely to be reported by patients than by bed partners. It may be valuable to distinguish between nasal and mouth snoring, as nasal snoring is generally not considered indicative of a pathologic process. If possible, the healthcare provider should ascertain whether the patient has been observed to experience apneas, either central (when there is no evidence of airflow or chest wall movement) or obstructive (no airflow but preserved chest wall motion). Loud snoring or loud snorts (which may occur at the end of the obstructive episode) indicate intermittent airway obstructions. Additional questions are focused on day-time symptoms of the OSA syndrome as outlined previously.

The chronicity of snoring, changes in weight, and/or drug and alcohol use are also important components of the history. For example, a middle-aged, non-obese woman whose snoring dates back to adolescence and who has otherwise been clinically well is likely to have a benign condition. Alternatively, a middle-aged man with a 20-pound weight gain over the last year and six months of snoring should be questioned about symptoms of the OSA syndrome.

Definitive diagnosis of OSA requires the presence of associated day-time symptoms and an AHI of ≥5. AHI can only be measured by formal polysomnography, which requires a patient to spend a night in a sleep laboratory, although the accuracy of home sleep studies is being assessed. There is no role for PFTs or chest imaging in diagnosing OSA, although these studies may be helpful in searching for associated conditions.

48.1.8 Summary

Respiratory symptoms are extremely common in clinical practice. As the lungs and upper airways have fairly limited ways to respond to pathologic changes, the challenge for clinicians is to understand the nuances of descriptions of the sensations and the sounds that patients report, and to ask probing questions that elicit these subtle distinctions. Understanding the physiology underlying respiratory symptoms can help a healthcare provider perform a focused yet thorough history and physical exam, determine what further testing is needed, and recommend targeted and effective interventions. Additionally, and importantly, having a better understanding of the physiology of respiratory symptoms aids in diagnosis, often guides treatment decisions, and augments one's intellectual enjoyment when caring for patients with these symptoms.

CLINICAL APPLICATIONS

Respiratory symptom	History and physical exam determinations	Diagnostic studies

Dyspnea	• Employ a dyspnea questionnaire to characterize the nature and origin of the patient's dyspnea
	  • "Chest tightness"—bronchoconstriction
	  • "Effort/work of breathing"—mechanical load
	  • "Air hunger"—increased drive to breathe
	  • "Smothering," "suffocating,", "short of breath bending over"—congestive heart failure
	  • "Huffing and puffing," "heavy breathing"—cardiovascular deconditioning
	• Determine whether the dyspnea is acute or chronic in nature
	• Identify if a patient's dyspnea occurs primarily during the day or at night
	• Assess for a positional component to the patient's dyspnea
	• Observe for use of accessory muscles of ventilation
	• Note if patient has difficulty completing a full sentence before stopping to get a breath
	• Assess for psychogenic component to the patient's dyspnea (e.g., are they "not getting enough air" despite normal lung function?)
		• Pulse oximetry at rest and on exertion
		• Pulmonary function testing (for suspected airway-related causes of dyspnea)
		• Complete blood count (to assess for anemia)
		• Chest x-ray
		• Chest CT (if the chest x-ray is abnormal and/or if clinical suspicion is sufficiently high)
		• Transthoracic echocardiography (for suspected cardiac causes of dyspnea)
		• Cardiopulmonary exercise testing (for patients with unexplained dyspnea despite an otherwise thorough evaluation)

Cough	• Determine if cough is acute, subacute, or chronic • For acute or subacute cough, determine if there has been a recent airways or sinus infection • For chronic cough, differentiate between upper airway cough syndrome, GERD, and asthma • Determine if the patient can localize the source of irritation provoking the cough to the throat or deeper in the chest	• Chest x-ray • Spirometry (when bronchospasm is suspected) • Methacholine challenge (when bronchospasm is suspected) • Sinus imaging (when sinusitis is suspected) • Chest CT for patients with an abnormal chest x-ray
Hemoptysis	• Quantify the amount of blood expectorated to determine massive versus non-massive hemoptysis • Determine the origin of hemoptysis (upper respiratory tract, lower respiratory tract, or non-respiratory source)	• Chest x-ray • Chest CT angiogram • Flexible bronchoscopy

Respiratory symptom	History and physical exam determinations	Diagnostic studies
Wheezing	• Differentiate between pulmonary, cardiac, and laryngeal causes of wheezing • Differentiate between inspiratory and expiratory wheezing • Differentiate between intra- and extrathoracic wheezing	• Spirometry (for pulmonary causes of wheezing) • Methacholine challenge (for pulmonary causes of wheezing) • Transthoracic echocardiography (for cardiac causes of wheezing) • Flexible laryngoscopy (for laryngeal causes of wheezing)
Nocturnal snoring and apnea	• Direct observations of snoring and/or apneic episodes by bed partner • Epworth Sleepiness Scale	• Polysomnography ("sleep study")

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49 Asthma

Evan W. Jones and Stephen J. Krinzman

KEY POINTS

- Asthma is a heterogeneous, inflammatory disease of the airways characterized by intermittent symptoms including dyspnea, cough, chest tightness, and wheezing.
- Both nonpharmacologic and pharmacologic interventions are often necessary to achieve disease control.
- Inhaled corticosteroids are the mainstay of pharmacologic chronic controller therapy for asthma.
- It is essential to evaluate medication compliance prior to escalating pharmacologic therapy in a seemingly uncontrolled asthmatic.
- Asthma symptoms are impacted by multiple lifestyle factors, including exercise, occupation, obesity, stress, and pregnancy.

49.1 INTRODUCTION

Asthma is an inflammatory disease of the airways that affects all age groups. It is characterized by intermittent symptoms that commonly include dyspnea, cough, and wheezing. While nonspecific, these symptoms are suggestive of asthma when associated with airway hyperresponsiveness and variable airflow obstruction.

In 2019, an estimated 20 million adults in the United States, representing 8% of the population, had asthma.[1] The disease remains a large burden to the healthcare system, accounting for over 1.6 million emergency department visits in the United States in 2018.[1] It is a frequent cause of absenteeism from both school and work. In 2019, over 3,500 deaths in the United States were attributed to asthma.[1]

The prevention and treatment of asthma are dependent upon a variety of interventions, both pharmacologic and nonpharmacologic. The daily habits and activities of asthmatics play an important role in disease management. Alterations in lifestyle practices can make a substantial difference to the long-term health of the asthmatic patient.

49.2 CLINICAL FEATURES

Typical symptoms of asthma are dyspnea, cough, chest congestion and tightness, and wheezing. Asthma is a heterogeneous disease, and clinical presentation will vary between individuals. Additionally, each individual is likely to have symptoms that vary in frequency and severity over time. An asthmatic is often able to identify certain triggers that destabilize his or her asthma. Common triggers include exercise, viral infection, exposure to furry or feathered animals, and environmental allergens including pollen, dust, mold, and smoke. Changes of weather, emotions such as laughing or crying, and menses may destabilize the asthmatic. Ingestion of aspirin or other medications can result in symptoms.

The asthmatic will often have a normal physical examination when asymptomatic. However, when patients are having symptoms, the physical examination often reveals an increase in respiratory rate, a prolonged expiratory time, and wheezing. On forced expiration, wheezing is accentuated, and coughing generally occurs. During more severe attacks, the patient will often be diaphoretic, using the accessory muscles of ventilation, and unable to speak in full sentences.

Multiple schemes have been proposed to classify asthma severity.[2–5] The classifications of mild, moderate, and severe are often used, although the defining characteristics for each group are not universally agreed upon. Some organizations advise against the use of the term "mild" asthma, as this may incorrectly suggest that these patients do not require careful and active management of their disease.[5]

49.3 PATHOPHYSIOLOGY

The hallmarks of asthma pathophysiology are: 1) airflow obstruction that may change over time, 2) airway inflammation, and 3) hyperresponsiveness of the airways to stimuli.

49.3.1 Variable Airflow Obstruction

Increased airway resistance and airflow obstruction in asthma occur through three major mechanisms:

- Increased airway lumen debris
- Airway wall thickening from inflammation, edema, and over time, fibrosis
- Airway smooth muscle contraction[2]

Damaged epithelial cells detach from the mucosal surface of the asthmatic airways. Airway wall thickening occurs from an unimpeded inflammatory process. The effects of inflammation accumulate over time, leading to smooth muscle hypertrophy, epithelial basement membrane thickening, connective tissue deposition, and proliferation and hypertrophy of mucus-producing glands. All these factors contribute to progressive airflow obstruction, which

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is further decreased by the presence of thick mucus, ineffective mucociliary clearance, and edema in the bronchial walls. Episodic smooth muscle contraction further leads to the variability of symptoms.

49.3.2 Airway Inflammation

Multiple mechanisms produce airway inflammation, and they involve a variety of interactions between pro-inflammatory and inflammatory mediators. The asthmatic inflammatory cell matrix is made of eosinophils, activated T-helper type 2 lymphocytes, mast cells, neutrophils, and macrophages. Both immune and non-immune factors can activate the disease process. Exposure to a specific activating allergen causes the release of a variety of mediators via high-affinity immunoglobulin E (IgE) receptors found on bronchial mast cells, and low-affinity IgE receptors on macrophages and eosinophils. Lymphocytes control these processes. Both antibody-mediated and cell-mediated immune systems are involved. There are increased levels of pro-inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13. Chemical mediators from the activated cells can directly contract airway smooth muscle, stimulate mucus secretion, enhance vascular permeability, and promote airway edema. Furthermore, some mediators actually attract other inflammatory cells and activate them, further damaging the airway. Part of the inflammatory reaction causes a disruption of airway epithelial cell wall integrity, which allows increased permeability to inhaled allergens and other triggering substances, decreased mucociliary clearance of airway debris, and enhanced cholinergic-mediated airway hyperreactivity, and predisposes patients to bacterial and viral infections. The loss of epithelial integrity exposes nerve endings, which partially explains the enhanced cholinergic-mediated airway hyperreactivity found in asthma.

Inflammation can be acute or chronic. The acute inflammatory response involves early recruitment of cells to the airway. This is followed by an evolving inflammatory reaction as recruited and resident cells are activated and produce a complex pattern of inflammation. Chronic inflammation can lead to permanent airway damage.

49.3.3 Airway Hyperresponsiveness

Airway hyperresponsiveness is a hallmark of asthma. Airway inflammation induces airway hyperresponsiveness. This hyperresponsiveness, along with the inflammatory changes of the airways, contributes further to airflow obstruction. Certain triggers may not only activate, but also propagate, inflammation and drive airway responsiveness to a more severe state. The magnitude of airway hyperresponsiveness seems to correlate with the activity of airway inflammation. Furthermore, airway hyperresponsiveness seems to correlate with the clinical symptoms and signs of asthma.

Hyperresponsiveness is assessed by measuring airflow before and after the inhalation of increasing doses of methacholine or histamine (Figure 49.1).[6] Hyperresponsive airways will develop obstruction at lower cumulative doses than normal airways. This increased response is thought to be a protective mechanism against the detrimental effects of irritating inhalants. Airway hyperresponsiveness is not unique to asthma and can be found in other conditions affecting the airways, including some patients with chronic obstructive pulmonary disease. The treatment of asthma

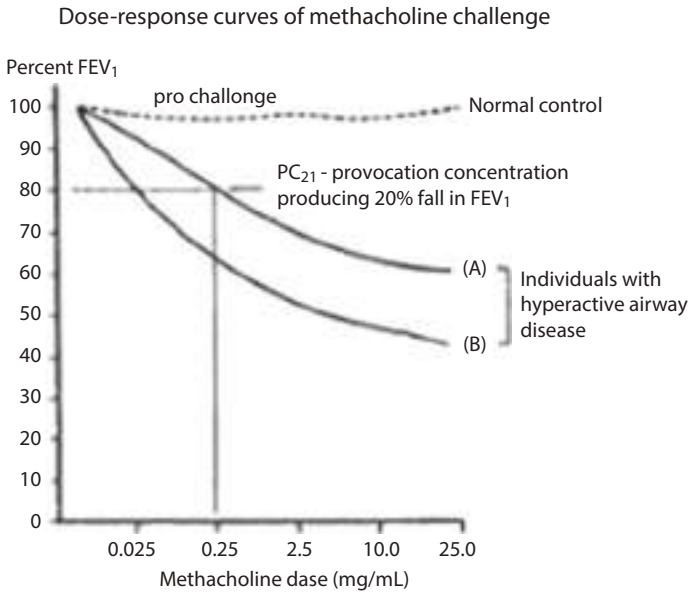


FIGURE 49.1 Asthmatics have hyperresponsive airways that are overly sensitive to immunologic or non-immunologic stimuli. Bronchial provocation testing can serve as a useful tool to measure the severity of bronchial hyperresponsiveness and is helpful to confirm the diagnosis of asthma.

by improving airway inflammation may diminish, but not eradicate, airway responsiveness, suggesting that additional factors are involved.

49.4 NON-PHARMACOLOGICAL MANAGEMENT

The management of asthma requires a comprehensive strategy that includes both pharmacologic and nonpharmacologic measures.[5] Effective management requires clear communication between the patient and medical provider. As an asthmatic's symptoms will vary over the course of time, so will the interventions necessary to achieve disease control.

The goals of asthma therapy are: (1) to prevent symptoms that interfere with quality of life; (2) to prevent exacerbations; (3) to avoid emergency department visits or hospitalizations; (4) to meet patient and family expectations for asthma care; and (5) to provide optimal pharmacotherapy with minimal adverse effects.[2] This section will focus on the nonpharmacologic management of asthma and strategies for longitudinal asthma care. The pharmacologic management of asthma will be reviewed in the following section.

49.4.1 Environmental Control

Environmental control measures, such as allergen avoidance, should always be included in asthma management strategies.[2] A comprehensive approach to control of allergen or irritant exposure is needed, since single measures for avoidance of allergens are generally not effective. Identifying the specific allergens and irritants causing symptoms for each individual is paramount. Common inhalant allergens include animal hair and dander, house dust mites, cockroaches, indoor and outdoor fungi, and tree, grass, and weed pollens. The NAEPP guidelines recommend environmental control at each step and have a questionnaire to help determine environmental and other factors that worsen asthma symptoms.[2,7] A history of likely sensitivity to seasonal allergens and positive skin testing or allergen immunoassay IgE blood testing can be helpful in identifying these allergens.[7]

When evaluating a patient with asthma, it is important to take a thorough history to identify triggering factors. Exposure to tobacco smoke should be avoided.[8,9] Most asthmatic patients should avoid beta-blocker therapies if possible. If these medications are essential for management of cardiovascular disease, there should be careful attention to any worsening of asthma symptoms.[10,11] Sulfite sensitive asthmatics should avoid foods and drinks that contain sulfite preservatives, such as shrimp, dried fruit, processed potatoes, sauerkraut, beer, and wine, all of which can cause exacerbations in a small percentage of asthmatics.[12] Asthmatics with a history of sensitivity to non-steroidal anti-inflammatory agents (NSAIDs) should strictly avoid these agents.[13,14]

49.4.2 Indoor Allergens

Major indoor allergens that are of particular importance include animal dander, dust mites, mold, and cockroaches. All warm-blooded pets can cause allergic reactions, with cats being a particularly strong trigger in sensitized individuals. While there is a popular notion that certain breeds of dogs and cats are "hypoallergenic" and less likely to cause allergic symptoms, no specific breed has ever been proven to have this quality. If there are pets in the home, and the person is sensitive to that animal, then removal of the pet should be encouraged, although it can take months for allergen levels to decrease.[2] Pets should be kept out of the bedroom, and all air ducts leading to the bedroom should be covered with a filter.[15]

House dust mite allergen is a major environmental factor in asthma.[2] House dust mites are universal in areas of high humidity, which include most of the United States. In addition to high humidity, mites depend upon human dander for survival. Dust mites thrive in mattresses, pillows, carpets, upholstered furniture, and soft toys. There are a variety of desirable control measures that should be considered in asthmatics with demonstrated dust mite sensitization.[2] Mattresses and pillows should be encased in allergen-impermeable covers. Bed sheets and blankets should be washed weekly in hot water, which must be >130 °F to kill mites. Indoor humidity should be maintained at less than 50%. Carpets, upholstered furniture, and stuffed animals should be removed as far as possible. Although there are a variety of chemical agents available for killing mites and denaturing the antigens, they are not as effective as the environmental control measures described here.

Molds are fungi that proliferate in humid environments, especially damp indoor environments. Creating a drier environment by fixing old water leaks and eliminating water sources reduces mold growth. Reducing indoor humidity to less than 50% substantially limits mold growth.

Asthma severity seems to increase with increasing levels of cockroach antigen. If cockroach infestation is present in the home, chemical control measures should be instituted to reduce the antigen load.[2] When chemical agents are used, the home should be well ventilated, and the patient should not return to the home until the odor has dissipated. Nonchemical strategies include keeping food out of bedrooms and storing food and garbage in closed containers.

A variety of measures can be taken to improve indoor air quality and reduce allergens, although the measures should not substitute for the strategies previously described. Vacuuming carpets twice a week using a vacuum equipped with a high-efficiency particulate air filter can reduce house dust accumulation. Ideally, the asthmatic should not be in the room when the vacuuming is occurring. Air conditioning and the use of a dehumidifier are helpful. Humidifiers and evaporative coolers are not recommended for use around dust mite–sensitive patients with asthma. High-efficiency particulate air filters and electrostatic precipitating filters

have been shown to reduce certain animal dander, mold spores, and the particulates from tobacco smoke.

49.4.3 Outdoor Allergens

A variety of tree, grass, and weed pollens, and seasonal spores, contribute to the outdoor allergens that affect many asthmatics. Avoidance, however, is challenging. Pollen sensitive asthmatics should use air conditioning when possible and keep windows closed. Pollen and spore counts are highest during the midday and afternoon at periods of brightest sunlight. Conducting outdoor activity shortly after sunrise or before sunset can result in reduced pollen exposure. Identifying the specific allergens that cause symptoms in an individual patient can help guide decisions about certain times of year when outdoor activity should be limited.

49.4.4 Allergy Testing and Immunotherapy

The two most common modalities used to identify the specific allergens affecting an individual are skin testing and in vitro immunoassay blood tests. Skin testing involves exposing the patient to a panel of allergen extract solutions and monitoring for a local cutaneous reaction to individual allergens. The discovery of IgE as the antibody responsible for allergic reactions has led to the development of immunoassay blood tests that can measure the level of allergen-specific IgE from a blood sample.[7] The total IgE level does not identify individuals with sensitization to specific aeroallergens and should not be used as a screening test for atopy.

Allergy skin testing is less expensive and more sensitive than in vitro immunoassay tests. It is also rapid, usually providing results within minutes. Skin testing is generally easy to perform and causes minimal patient discomfort. The results are dependent in part on the use of standardized extracts and the expertise of the tester. On the other hand, in vitro immunoassay tests do not require a specialized testing center and can be obtained anywhere phlebotomy is available. No allergen extracts are necessary, and they can be performed on patients who are taking medications that often suppress the skin test reaction (e.g., antihistamines and tricyclic antidepressants).

A positive allergy test from either methodology does not indicate to what extent the identified allergen is causing asthma symptoms. When a positive result is found with skin testing or an in vitro immunoassay, the clinician must look for clinical significance of the positive result in the context of the patient's medical history. When used in isolation, a positive allergy test alone only confirms exposure to an allergen, not that this exposure is clinically meaningful.

If the relationship between allergen exposure and asthma symptoms is clear, the allergen cannot be avoided by environmental control measures, and symptoms persist despite optimal pharmacologic therapy, then allergen immunotherapy can be considered.[2] Although available in both subcutaneous and sublingual preparations, current guidelines recommend that only subcutaneous immunotherapy be used in the treatment of asthma.[16] Immunotherapy should be administered in facilities with the ability to treat the possible serious adverse reactions that can occur.[17] It is unknown whether immunotherapy targeting multiple allergens simultaneously, versus a single allergen, impacts efficacy. Although multiple-allergen mixes are used for immunotherapy, only a few studies clearly support this practice.[18] Allergy immunotherapy is typically administered for three to five years.

There are controlled studies and a meta-analysis that support the use of immunotherapy in the treatment of asthma. Benefits include improved symptoms, decreased bronchial reactivity, and reduced medication use.[2,19–21] Immunotherapy is felt to reduce both the frequency and the severity of symptoms. Immunotherapy is most effective for some types of seasonal pollens (tree, grass, weed) and house dust mites, and also has some utility in pet allergy.[19–21] The success of immunotherapy is dependent upon identifying the correct target allergen(s).

There are risks associated with immunotherapy.[17] The most common is a local reaction at the site of injection, which can include swelling, erythema, and pruritus. This type of reaction is usually short-lived and can be minimized by using topical anti-inflammatory therapy or an oral antihistamine. The most serious adverse reaction is anaphylaxis. Therefore, immunotherapy should be performed in the presence of a physician experienced in treating anaphylaxis. Sufficient time should be allowed for anaphylaxis to occur, so an observation period of 15 to 30 minutes after each injection is required. Less serious reactions include nasal congestion and sneezing, worsened asthma symptoms, difficulty swallowing and talking because of a tongue or larynx edema, and lightheadedness. Because of the increased risk in severe asthmatics of adverse reactions to immunotherapy, including anaphylaxis and severe asthma exacerbations, and with the advent of effective biological agents that are safe and highly effective in severe asthma, biological therapies, when available, may be preferred over subcutaneous immunotherapy in most severe asthmatics. Immunotherapy could be considered when there is strong evidence of a specific allergic trigger, as in a cat allergic asthmatic who cannot avoid household cat exposures.

49.4.5 Asthma Action Plans

The NAEPP guidelines recommend a written asthma action plan for all asthmatics, based on signs and symptoms, changes in peak expiratory flow rate (PEFR), or both.[2] Written asthma action plans may be particularly helpful for those with poorly controlled asthma, moderate-to-severe persistent asthma, or a history of severe exacerbations. Action plans are useful in clarifying the roles of the medications and the medication plan, especially in less knowledgeable patients, and for adjusting treatment according to changes in symptoms and PEFR as needed. The more chronic and severe the asthma, the greater is the importance of a written asthma action plan.

49.4.6 Management According to Asthma Severity and Control

Multiple schemes have been developed to guide both the initial medication regimen at the time of asthma diagnosis as well as adjustments to pharmacologic therapy over time depending on the degree of asthma control. The two most commonly cited are from the NAEPP and the Global Initiative for Asthma (GINA).[2,5,16] Both schemes suggest an initial regimen according to disease severity at the time of diagnosis as well as stepwise adjustments over time depending on the ongoing degree of asthma control. Despite much overlap, there is variability between the two guidelines. Each guideline also provides multiple acceptable regimens at each step in the process. This highlights the need for an individualized management strategy for each patient depending on their specific modifiable risk factors, comorbidities, and overall preferences and goals. Clear and thoughtful communication between the provider and patient, and attention to medication compliance, are paramount throughout this process.

49.4.7 Monitoring Disease Activity

Periodic assessment and ongoing monitoring are necessary to achieve and maintain asthma control. Variables that require monitoring include daytime and nocturnal symptoms, amount of interference in daily activities due to asthma symptoms, quick-relief medication use for acute symptom relief, and measurement of airflow obstruction by spirometry and PEFR.[2] Both physician assessment and patient self-monitoring are part of the process.

Measurements of airflow are not necessarily related to asthma symptoms but do provide an objective measure to evaluate asthma control. Spirometry is recommended at least every one to two years, and especially at initial assessment, after treatment has stabilized symptoms and PEFR, and during periods of progressive or prolonged worsening of symptoms.[2,22] Spirometry is performed by taking a full breath and forcefully exhaling air from the lungs through a spirometer until all airflow has ceased.[23,24] As shown in Figure 49.2, airflow obstruction is shown by a decrease in the forced expiratory volumes, including the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1), and a decreased FEV1/FVC ratio. The normal, or predicted, ranges for these values are based on databases matched to the patient by parameters including age, height, and gender.

Measurements of the FVC and FEV1 are generally taken before and after inhalation of a quick-acting bronchodilator. The asthmatic typically shows significant improvement in these airflows following quick-acting bronchodilator treatment, indicating reversible obstructive airway disease. Significant improvement is defined as a post-bronchodilator increase in either FVC or FEV1 by at least 12%, and having a minimum absolute increase of 200 mL in the same parameter, compared with pre-bronchodilator measurements. The asthmatic can also independently measure airflow from the large airways using PEFR. The patient should determine a personal baseline PEFR. PEFR monitoring can be considered in asthmatics who have a history of frequent or severe exacerbations, who are poor perceivers of airflow obstruction or worsening asthma, or who have moderate-to-severe persistent asthma.[2]

The airflow obstruction of asthma waxes and wanes with variations in the degree of inflammation and smooth muscle constriction. There are alterations in FEV1 and PEFR with these changes (Figure 49.2). Over time, there will be variable needs for the use of medication to relieve symptoms. As asthma becomes better controlled with therapeutic interventions, overall airflow improves, and variability in airflow decreases. This results in a decreased need for quick-relief medication use to relieve acute symptoms and hopefully to an overall improvement in quality of life.

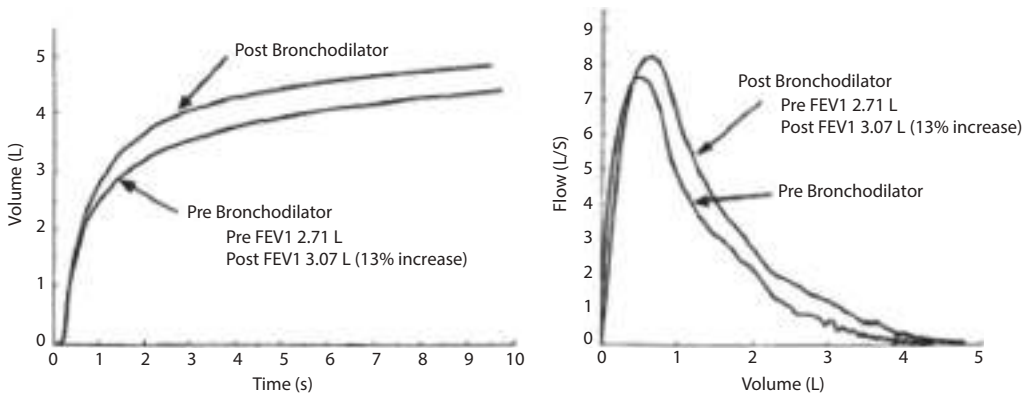


FIGURE 49.2 Spirometry pre-/post-bronchodilator in the asthmatic. Administration of an inhaled bronchodilator improves airflow significantly. The left panel depicts the volume-time curve and shows improvement in FEV1. The right panel shows the flow-volume curve and improvement in peak expiratory flow over exhaled lung volume. The dependent portion of the curve is also curvilinear (not straight), consistently with airflow obstruction.

Improved quality of life measures include better sleep at night, and improved resistance to asthma exacerbation during exposure to environmental challenges such as exercise or cigarette smoke. It is important to teach patients to recognize symptom patterns that indicate inadequate asthma control.

While spirometry and PEFR both help gauge asthma control based on the degree of airflow obstruction, it would be advantageous to have more directly measured biomarkers of airway inflammation. At the present time, however, although biomarkers can be helpful in establishing an asthmatic individual's inflammatory and immunologic phenotypes, and guide selection of biological agents, none have been found to be helpful in choosing or titrating conventional asthma therapies. The two most commonly employed biomarkers are fraction of exhaled nitric oxide (FENO) and peripheral eosinophil counts.[25]

Nitric oxide is produced by inflammatory cells and other cells in the airway. The FENO, which is easily measured with handheld devices, correlates with airway eosinophilia and is elevated in non-smokers with eosinophilic asthma, but it is also elevated in other illnesses such as allergic rhinitis, non-asthmatic eosinophilic bronchitis, and hypersensitivity pneumonitis.[5] In adult asthmatics, FENO-guided treatment did not show a reduction in exacerbations as compared with guideline-based treatment.[5,26] Accordingly, guidelines for severe asthma do not recommend using FENO for guiding therapy in adults, given the increased cost of care with an uncertain benefit.[4]

49.4.8 Bronchial Thermoplasty

Bronchial thermoplasty has been investigated as an additional therapeutic modality in poorly controlled asthma. The airways of chronic asthmatics are narrowed by increased wall thickness due to several mechanisms, including airway smooth muscle hypertrophy. Bronchial thermoplasty is a technique that delivers radiofrequency wave generated heat to the walls of airways to reduce airway smooth muscle hypertrophy and contractility.[27] The airways distal to the main stem bronchi are treated in a systematic manner during three separate bronchoscopies spaced about three weeks apart.

The benefits of thermoplasty remain uncertain. A systematic review and meta-analysis of 3 trials with a total of 429 patients found that overall, bronchial thermoplasty did not produce a clinically significant improvement in asthma symptoms or quality of life, and did not improve pulmonary function.[28] Exacerbation rates were lower in two of the three trials, but with an increase in hospitalizations and exacerbations during the treatment period. The most recent NAEPP recommendations conditionally recommend against the routine use of bronchial thermoplasty, given the proven benefits are small, the risks are moderate, and the long-term outcomes

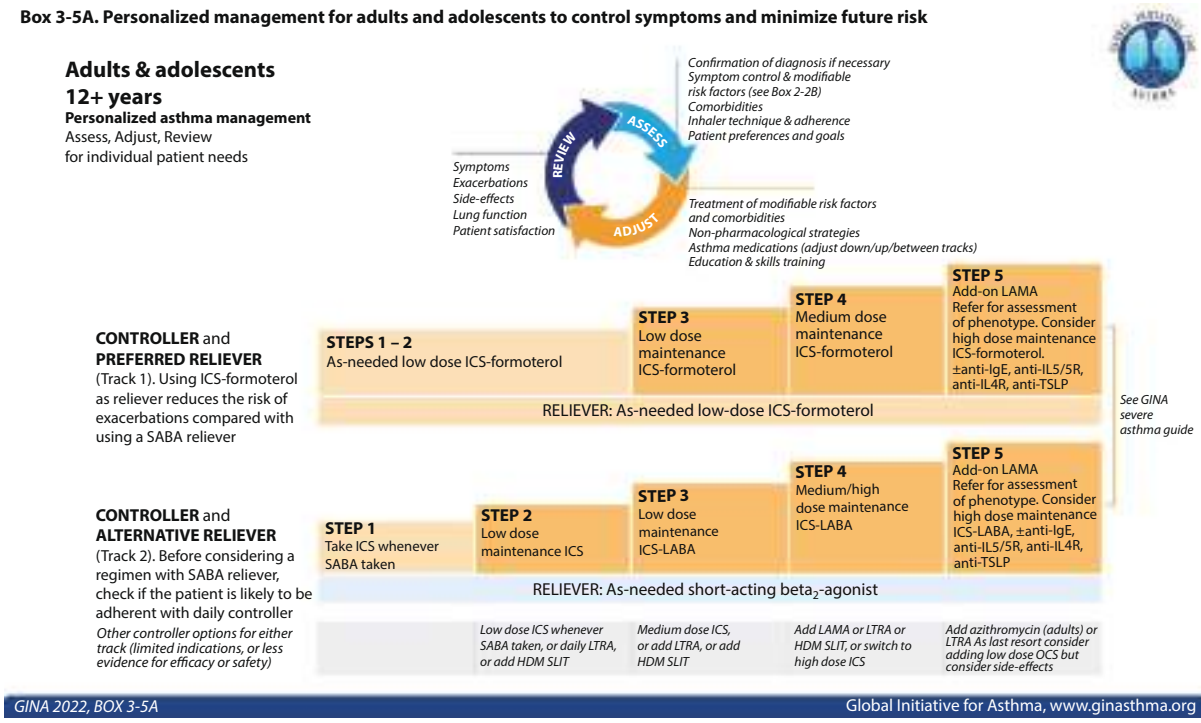


FIGURE 49.3 Personalized management strategies for asthma. HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta agonist; SLIT: sublingual immunotherapy. ***Source***: Adapted from 2022 GINA Main Report, Global Initiative for Asthma.

are uncertain. Furthermore, the efficacy and risks of thermoplasty need to be considered in comparison to an increasing number of effective alternative therapies for severe asthma, most notably biological agents. If pursued, bronchial thermoplasty should be performed in a clinical trial or registry study to enable the collection of long-term data.[16]

49.4.9 Other Issues in Long-Term Asthma Management

To enhance compliance with pharmacologic therapy, it is often helpful for patients to integrate medication administration into their lifestyle. For patients who are uncontrolled, or even controlled on their current regimen, it is important to determine if they are taking their medication as prescribed, especially inhaled corticosteroids. It is not uncommon to find that patients on a twice-daily regimen will remember the morning dose but forget the evening dose. To improve medication adherence, it may be prudent to change to a formulation that requires only once-daily administration. While mild asthma can often be effectively managed by general practitioners, there are multiple instances where referral to an asthma specialist for evaluation or co-management may be warranted.

49.5 PHARMACOLOGIC THERAPY

As noted earlier, multiple organizations have published guidelines for pharmacologic therapy in asthma. The two most commonly cited are the NAEPP and GINA. A detailed discussion of the specifics of the NAEPP and GINA management strategies is outside the scope of this publication. Also, each organization periodically updates its recommendations as new data becomes available. A provider should reference the recommendations directly from each organization to ensure that he or she remains up to date with the most current practices. That being said, there are some general strategies that are reasonable to review.

Pharmacologic therapy at the time of initial asthma diagnosis will vary depending on the severity of the patient's symptoms. Those with mild symptoms, such as less than twice per month, can often initially be managed with an as-needed rapid relief medication alone.[2,5,16] Patients with more frequent and severe symptoms at the time of diagnosis may benefit from an initial regimen including a chronic controller medication in addition to an as-needed quick-relief medication.[2,5,16]

After the initial diagnosis of asthma, evaluation of symptoms, exacerbation risk, quality of life considerations, and the need for medication adjustments should be assessed at regular intervals. How often this occurs will be different for each individual patient. When assessing the success of a medication adjustment, it is prudent to wait at least two weeks for a response to manifest, but reassessment should not be delayed more than three months.[5,16]

When asthma control is poor on optimal maintenance therapy, it is essential to review compliance. This cannot be accurately assessed from self report and requires a direct review of medication fill records from the pharmacy. This can now be performed directly with some electronic medical record systems. One of the most common pitfalls in asthma management is to escalate or add on therapies when the actual problem is non-compliance with the existing controller medication.

If asthma control is not optimal despite high dose inhaled steroids and a long-acting bronchodilator, with or without a long-acting muscarinic agent, it is important to review and identify extrinsic triggers, and re-check compliance with pharmacy record review. Addition of a leukotriene receptor antagonist can be considered, although the efficacy of these agents in severe asthma is uncertain and needs to be re-evaluated after instituting therapy. In asthmatics with poor control despite documented compliance with high dose inhaled steroids and long-acting bronchodilators, biological agents should be considered.[5,16] If not already pursued, at this point, the patient should be referred to an asthma specialist prior to initiating any additional therapies.

The pharmacologic treatment of asthma includes two broad categories of medications: bronchodilators that relax airway smooth muscle, and anti-inflammatory drugs that reduce the influx of inflammatory cells and the subsequent release of chemical mediators. Bronchodilators include short- and long-acting beta-2 receptor agonists (beta agonists), short- and long-acting muscarinic antagonists (anticholinergics), and methylxanthines. Anti-inflammatory agents include corticosteroids, leukotriene inhibitors, cromolyn, and monoclonal antibodies. The monoclonal antibodies available for the treatment of asthma are often collectively referred to as "biologics."

Pharmacologic therapy for asthma is administered through multiple routes. Inhalational therapy is the main route for bronchodilator administration, although the methylxanthines are administered orally or intravenously. Inhalational therapy can be administered via either an inhaler or a nebulizer. Inhalers can be further subdivided into metered-dose inhalers, dry powder inhalers, and soft-mist inhalers, all requiring a different technique to use properly. Anti-inflammatory administration route depends on the medication. Inhalation is the main route for corticosteroids used for chronic control, although systemic oral corticosteroids can be used in the chronic control of severe asthma, while oral or intravenous corticosteroids are used during acute exacerbations. Leukotriene inhibitors are administered orally. The currently available biologics are administered either via subcutaneous injection or intravenously, depending on the agent.

Medications are often characterized according to the manner in which they are used: rapid relief medications, or relievers, which are used to treat acute symptoms, and long-term chronic control medications, which are used to achieve and maintain control of chronic asthma.

49.5.1 Rapid Relief Medications

In order to achieve immediate relief of bronchoconstriction and the discomforting symptoms associated with asthma,

quick-relief medications, such as fast-acting/short-acting beta-2 agonists and anticholinergics, are employed. Short-acting beta-2 agonists relax airway smooth muscle within minutes and improve airflow. These agents are the drugs of choice for treating acute asthma symptoms and exacerbations.[2] They are also used for preventing exercise-induced bronchospasm.[2] The most commonly used fast-acting/short-acting beta-2 agonist is albuterol. Inhaled short-acting anticholinergic therapy, such as ipratropium bromide, can also be used as a bronchodilator in this setting, generally in combination with a beta agonist. Ipratropium bromide may provide some additional benefit during a moderate-to-severe asthma exacerbation, and it may also be considered as an alternative for those who absolutely cannot tolerate beta agonists.[2] These agents can be administered via an inhaler or nebulizer. Formoterol, a long-acting beta-2 agonist with a fast onset of action, alone or as part of a combination inhaler including an inhaled corticosteroid, can also be used in a quick-relief fashion in patients with mild to moderate asthma. Compared with using a short-acting bronchodilator alone, the combination of budesonide with formoterol used as a rescue inhaler significantly decreases exacerbations.[5,16] For patients with severe asthma, who are already likely to be on a maximal dose of an inhaled steroid and long-acting bronchodilator, using a combination of albuterol with an inhaled steroid as rescue inhaler also decreased exacerbations compared with albuterol alone.[29] Systemic corticosteroid therapy can speed the resolution of airflow obstruction and reduce the rate of relapse of treated severe asthma.[2]

The frequency at which quick-relief therapy is required for acute symptom control can serve as a marker of asthma stability. The more frequently these medications are necessary, the stronger the need for optimization of chronic controller therapy. Using a short-acting beta-2 agonist inhaler at the rate of one or more canisters per month has been associated with an increase in asthma morbidity and mortality.[30] It should be possible for 70–80% of chronic asthma patients in the United States to be controlled to a level of mild asthma with only intermittent symptoms, generally two or fewer mild episodes of symptoms per week. Therefore, if more than four puffs of a short-acting beta agonist are used weekly, then enhanced asthma control is necessary. A well-controlled asthmatic should only need one or two canisters of a short-acting bronchodilator per year, not counting the therapy that would be used to prevent exercise-induced bronchospasm.

49.5.2 Chronic Controller Medications

Corticosteroids are the most potent and effective anti-inflammatory medications available for the management of asthma. The inhaled form of these medications from an inhaler, or alternatively from a nebulizer in selected patients, is the first-line therapy for the long-term control of asthma. Corticosteroids reduce airway inflammation and airway hyperresponsiveness.[31–34] They also prevent bronchial wall remodeling, known to occur with chronic inflammation and to be responsible for the development of fixed airflow obstruction later in life. There are many different products and delivery devices for the administration of inhaled corticosteroids, and their inhalation doses vary.[2] The lowest daily dose of an inhaled corticosteroid should be used in order to control the disease. Systemic corticosteroids, administered orally or intravenously, are used during periods of acute destabilization and worsening of asthma. Long-term and chronic use of systemic corticosteroids should be avoided due to the numerous associated complications; however, some patients with severe chronic disease may require this therapy.

Antileukotrienes are another group of anti-inflammatory agents. These oral therapies block or inhibit the production of leukotrienes, which are by-products of the arachidonic acid–metabolic pathways and are potent bronchoconstrictors and inflammatory stimulants.[35] Leukotrienes are released from a variety of inflammatory cells, including lymphocytes, eosinophils, and mast cells, and not only induce bronchoconstriction but also increase vascular permeability, mucous secretion, and the abundance of other inflammatory cells. When these additional cells enter the airway, they are activated and release other powerful chemicals that propagate the inflammatory state.[35]

There are three antileukotriene agents currently available in the United States: montelukast and zafirlukast, which are leukotriene receptor blockers, and zileuton, a 5-lipoxygenase inhibitor. Leukotriene-pathway agents improve lung function, diminish asthma symptoms, and reduce the need for quick-relief medications.[36–39] Their efficacy has been shown in patients with mild-to-moderate asthma, and the improvements seen are modest in nature when compared with inhaled corticosteroid therapy.[40,41] These agents have been shown to reduce bronchoconstriction caused by exercise, aspirin, and inhaled allergen exposure.[37,42–45] Of note, very little is known as to whether these agents are helpful in severe asthma not controlled with high dose inhaled steroids and bronchodilators.

Theophylline, a methylxanthine compound, acts as a bronchodilator and may also improve asthma through certain anti-inflammatory effects and reductions in bronchial reactivity.[46,47] When theophylline is administered in a sustained-release oral therapy form, it has a long duration of action and can further control asthma when used in combination with inhaled corticosteroid therapy.[48,49] However, theophylline is now rarely used, because it has a narrow therapeutic margin of safety, multiple medication interactions, and overall weak bronchodilator effect.

The dosing of theophylline is titrated to a therapeutic level and also, importantly, to minimize the potential for drug toxicity. The target serum concentration has been recommended to be approximately 5–15 mg per liter.[2,50,51] Theophylline levels may be affected by several factors, including smoking, which decreases the level, and medical conditions that increase the level, such as heart failure, cor pulmonale, cirrhosis, hypoxia, hypothyroidism,

febrile illness, and pregnancy. Levels can also be affected by drugs that inhibit theophylline metabolism and hence increase levels (clarithromycin, ciprofloxacin) or drugs that enhance theophylline metabolism and decrease levels (rifampin, phenobarbital, phenytoin, carbamazepine). After the patient is on a stable dose of theophylline, drug levels should be checked at least once a year provided the patient has no changes in health or other medications.

49.5.3 Long-Acting Beta-2 Agonists

Inhaled long-acting beta agonist (LABA) medications are often used as add-on controller therapy to inhaled corticosteroids. Patients with moderate-to-severe asthma generally require at least two or three controller medications to optimize their pharmacologic therapy, and LABAs are generally next added following inhaled corticosteroids.[2,5,16] LABAs are generally not fast-acting but have a duration of action of at least 12 hours, far longer than that of the fast- and short-acting beta agonists used for the acute control of symptoms.[52] Formoterol is a unique LABA, as it is both fast- and long-acting, allowing use as both a quick-relief and a chronic controller medication. For ease of use, LABAs are commonly paired with inhaled corticosteroids into combination inhalers, where both medications are administered in a single puff. LABAs should not be prescribed separately from inhaled corticosteroids due to concerns of increased mortality in the absence of appropriate anti-inflammatory therapy.[5]

49.5.4 Long-Acting Muscarinic Antagonists

Initially studied in the treatment of chronic obstructive pulmonary disease, inhaled long-acting muscarinic antagonist (LAMA) medications also have a role as chronic controllers in asthma.[5,16] LAMAs moderately improve lung function and moderately increase time to severe exacerbation requiring corticosteroids.[53,54] In a meta-analysis from 2018, the addition of a LAMA to inhaled steroids resulted in lower asthma exacerbations but was no different from a LABA.[55] LABAs remain the preferred initial add-on agent to inhaled corticosteroids, but LAMAs can be substituted if LABAs cannot be used.[16] A LAMA can also be added to an existing inhaled corticosteroid and LABA regimen if the patient continues with suboptimal asthma control.[5,16]

49.5.5 Biologic Therapy

A patient with persistent suboptimal asthma control despite the combination of an inhaled corticosteroid and at least one other controller medication may be a candidate for monoclonal antibody therapy.[16] When used in asthma, these monoclonal antibodies are collectively termed "biologics." The first biologic approved for use in asthma was omalizumab in 2003. Since then, multiple new agents, with multiple different molecular targets, have been Food and Drug Administration (FDA) approved. Importantly, many asthmatics will meet criteria for more than one biologic. Currently there are no head-to-head trials comparing biologics, and it is unknown whether a patient may respond better to one medication or another. Despite this, algorithms to choose the best biologic for an individual have been proposed based on the best available information and expert opinion.[56–58]

Omalizumab is a recombinant humanized monoclonal IgG antibody that binds to circulating IgE antibodies. Subsequently, it prevents IgE binding to high-affinity receptors on mast cells, basophils, and other cells, leading to decreased mediator release from these cells.[2] It is used in patients with moderate-to-severe persistent allergic asthma and sensitivity to perennial allergens such as dust mites, animal dander, cockroaches, or molds.[59–62] Patients using omalizumab are able to reduce the dose of their inhaled corticosteroids and experience reduced frequency of exacerbations, including those requiring hospitalization.[59,63–70] However, in patients already on therapy for asthma, omalizumab does not improve spirometry.[62,70] There is also little to no effect on bronchial hyperresponsiveness, but it does decrease some airway inflammatory markers.[64,65,71,72] In rare circumstances, it has been used in occupational asthma with beneficial effects.[73,74]

Omalizumab is administered via subcutaneous injection every two to four weeks, with dosage and frequency determined by both body weight and IgE level. Treatment will affect the accuracy of most allergen-specific assays. Adverse effects include anaphylaxis and local injection site reactions.[75] Anaphylaxis is rare and has been reported as any combination of bronchospasm, angioedema of throat or tongue, hypotension, syncope, and/or urticaria. Of the patients who develop anaphylaxis, approximately 40% do so after the first dose and 20% after the second dose.[63] A Joint Task Force Report on omalizumab-associated anaphylaxis has made safety and management recommendations.[76]

There are currently two anti-IL-5 monoclonal antibodies available, mepolizumab and reslizumab. IL-5 is the major cytokine involved in the production and survival of eosinophils. While the mechanism of action of these agents is not fully understood, they do reduce the production and survival of eosinophils. This results in lower blood and sputum eosinophil counts, which is thought to reduce airway inflammation.[77]

Mepolizumab is administered as a subcutaneous injection at a fixed dose of 100 mg every four weeks. It has been shown to provide a corticosteroid-sparing effect and reduces asthma exacerbations by greater than 50% and exacerbations requiring emergency department care or inpatient hospitalization by greater than 60%.[77–79] Mepolizumab may increase the risk for herpes zoster infection; it is therefore important to determine if the patient has had the chicken pox or the varicella vaccine. The safety of mepolizumab during pregnancy is unknown. Mepolizumab may cause allergic hypersensitivity reactions, including anaphylaxis. The most common side effects of mepolizumab include headache, injection site reactions (pain, redness, swelling, itching, or burning), back pain, and weakness/fatigue.

Reslizumab is administered as an intravenous infusion over 20–50 minutes at a dose of 3 mg/kg every 4 weeks. It has been shown to reduce asthma exacerbations by approximately 50% and improves airway function.[80, 81] The most important side effect is anaphylaxis.

Benralizumab is a monoclonal antibody that binds to the IL-5 receptor alpha present on eosinophils and basophils. It also leads to a reduction of eosinophils and basophils in blood and sputum through an antibody-dependent cell-mediated cytotoxicity.[78] It is administered as a subcutaneous injection of 30 mg every four weeks for the first three doses, followed by 30 mg every eight weeks. It has been shown to reduce exacerbations, improve FEV1, and improve asthma symptom scores.[82] As with multiple other biologics, the most important side effect is anaphylaxis.

Dupilumab is a monoclonal antibody that binds the IL-4 receptor alpha subunit. Blockade of this receptor inhibits the activity of not only IL-4 but also IL-13. It is administered by subcutaneous injection every two weeks, with multiple dosage schemes depending on disease severity. It has been shown to provide a corticosteroid-sparing effect, reduce exacerbations, and improve lung function.[83–87] The most common adverse effects are dermatologic injection site reactions as well as ocular surface disorders including conjunctivitis and pruritus.

The most recently FDA-approved biologic for the treatment of asthma is tezepelumab, a monoclonal antibody that binds thymic stromal lymphopoietin. Thymic stromal lymphopoietin is a cytokine derived from epithelial cells, and serum levels in asthmatics correlate with airway obstruction, asthma severity, and glucocorticoid resistance.[88] Tezepelumab is administered via subcutaneous injection at a fixed dose of 210 mg every four weeks. Studies have shown improved lung function, lower rates of asthma exacerbations, and improved health-related quality of life compared with placebo.[88,89] The most commonly reported adverse effects are arthralgias and hypersensitivity reactions, including rash and conjunctivitis.

There are no direct comparative trials of biological agents to inform precise recommendations on which of these drugs is most effective for a given patient. Several recent publications recommend using an assessment of relevant comorbidities, including specific allergic triggers, chronic sinusitis with nasal polyposis and eczema, along with biomarkers such as peripheral eosinophilia and FENO, to predict the optimal first choice agent.[56–58]

49.6 ASTHMA COMPLICATIONS

There are both acute and chronic complications of asthma. Acute asthma attacks are associated with a variety of complications, including pneumothorax, pneumomediastinum, cardiac arrhythmias, lung atelectasis, and respiratory failure. Rarely, death can occur. The young and elderly are at particular risk for death because the severity of their disease is often not appreciated or is ignored. Death from asthma can be sudden, possibly associated with laryngospasm.

TABLE 49.1
Factors Associated with Increased Risk of Asthma Exacerbations or Mortality

Severe airflow obstruction, as detected by spirometry
Two or more ED visits or hospitalizations for asthma in the past year
Past intubation or ICU admission, especially in past five years
Patients feeling in danger or frightened by their asthma
Patient characteristics: female, nonwhite, nonuse of ICS therapy, and current smoking
Psychosocial factors: depression, increased stress, socioeconomic factors
Attitudes and beliefs about taking medications

ED: emergency department; ICU: intensive care unit.

However, most asthmatic deaths are slow in evolution to the point of respiratory failure as a multitude of metabolic problems develop.[90] Table 49.1 shows the factors that have been implicated in asthma exacerbation and mortality.

Irreversible airflow obstruction can develop with long-term poorly controlled asthma.[91,92] Recurrent airway infections are subsequently associated with fixed airflow obstruction.[93] Allergic bronchopulmonary aspergillosis (ABPA), often with mucoid airway impaction and secondary bacterial infection, can occur in some long-term poorly controlled asthmatics. ABPA associated with asthma is characterized by recurrent episodes of severe asthma exacerbations.[94] Fever, chest pain, and hemoptysis can be associated with this condition, and mucus impaction causes transient infiltrates to develop on chest imaging. There are no universally accepted diagnostic criteria for ABPA, although usual findings include a positive skin prick test or elevated *Aspergillus fumigatus* specific IgE, elevated total IgE, blood eosinophilia, and serum precipitating *Aspergillus fumigatus* antibodies. This condition generally requires daily high dose inhaled corticosteroids and sometimes, oral corticosteroid therapy. The addition of anti-fungal medications is controversial, although the most recent guidelines from the Infectious Diseases Society of America recommend their use.[95]

49.7 LIFESTYLE CONSIDERATIONS

49.7.1 Exercise and Asthma

Exercise-induced asthma (EIA) or bronchoconstriction (EIB) is a transient airway narrowing and airflow obstruction that occurs during or after exercise.[6,96] Nearly 90% of persistent asthmatics have EIB, and patients with allergic rhinitis, or even relatives of asthmatics, can demonstrate this phenomenon. As with asthma, the common symptoms are cough, wheezing, chest tightness, shortness of breath, and what the patient describes as an inability to take in a full breath of air during or following exercise. Symptoms and airflow decline can start within minutes of initiating

exercise and usually improve within one hour of exercise cessation, even without medication use. EIB can seriously and adversely affect athletic performance if not recognized and controlled.

EIB is thought to be caused by the exchange of heat and water in the airways that occurs due to increased minute ventilation during exercise. The main factors affecting the severity of EIB are the amount of minute ventilation attained and sustained as well as the inspired air-water content and temperature. The high minute ventilation causes a cooling and drying effect on the airway.[6,96,97] It is thought that the drying of the airway causes an increase in surface osmolarity, which triggers the release of inflammatory mediators. This cooling and drying effect also sets the stage for the rapid rewarming of the airway that occurs with rest.

EIB can be diagnosed clinically in most patients and does not require special testing. In those where the diagnosis is uncertain, and particularly if other diagnostic tests or interventions for these symptoms have not been helpful, provoking protocols can be employed. After an exercise challenge, airflow is measured sequentially at 5, 15, and 30 minutes. The patient with EIB often has a reduction in airflow within this time period. When airflow falls, especially when associated with symptoms consistent with asthma, the diagnosis can be made. This evaluation can be done by a physician or by individuals such as trainers or coaches under the guidance of a physician. EIB is likely underdiagnosed among urban varsity athletes. In one study, it was reported that during screening for asthma and EIB, approximately 10% of 238 students had a history of treated asthma and that another 9% had unrecognized EIB during screening. This suggests the need for vigilance for the presence of EIB, especially when it affects activity tolerance or quality of life.[98]

It is important to distinguish exercise-induced asthma from poorly controlled asthma with reduced pulmonary function and from deconditioning. Patients with poorly controlled asthma or deconditioning will develop exercise intolerance with low levels of activity, such as climbing one flight of stairs, and usually have abnormal baseline spirometry to explain these symptoms. Patients with true EIB only develop asthma symptoms with high levels of sustained activity, such as running for several minutes. Symptoms include wheezing, coughing, and chest tightness, which may help distinguish EIB from the general fatigue that characterizes deconditioning.

Management and prevention of EIB can be accomplished by both nonpharmacologic and pharmacologic approaches. It is helpful to avoid exercising in extremes of temperature. When exercising in cold air, a mask or scarf covering the mouth may help reduce EIB.[99] A warm and moist environment can often be helpful in minimizing EIB. The use of an extended warm-up session and special breathing techniques that help minimize hyperventilation and promote relaxation can also help. There are reports that a warm-up period before exercise results in a refractory period or reduction in EIB in more than 50% of individuals for up to two hours.[97,100,101] The athlete should warm up slowly to loosen muscles and elevate heart rate. With the beginning of a light sweat, the athlete can exercise at, or close to, maximum exertion for up to five minutes and then take a rest. More accomplished athletes can continue this warm-up process recurrently for 30 to 40 minutes. Another strategy is to do brief bouts of exercise for two to three minutes followed by three to five minutes of rest. These repetitive exertional challenges should occur over a 30- or 40-minute period. It is important for the individual athlete to determine which warm-up protocol works best for him or her.

The post-exercise period is also important. The cool-down phase after a workout or competition should consist of taking deep, slow breaths. Cooling down in a warmer environment can be helpful.

Medications are often necessary to prevent EIB. Using inhaled beta agonists shortly before, during, or even after exercise can prevent or relieve asthma symptoms.[2] Inhaled beta agonists will prevent EIB in more than 80% of patients. Administering a short-acting inhaled beta agonist approximately 15 to 30 minutes before exercise provides protection for two to three hours. When symptoms break through, these medications can be safely administered by an inhaler. The inhaled long-acting beta-2 agonists (formoterol, salmeterol) can be helpful for controlling the frequent need for short-acting beta-2 agonists. Salmeterol has been shown to prevent EIB for 10 to 20 hours and is valuable for prolonged prevention when the athlete will be re-exposed to the exercise challenge over an extended time period.[102] Long-acting beta-2 agonists should not be used alone as daily prophylaxis of EIB, as the duration of effect is reduced and may be masking suboptimally controlled asthma.[2] Other therapies can be used in addition to beta agonists. If available, inhaled cromolyn can be taken approximately 30 minutes to 1 hour prior to exercise, often in addition to the pre-exercise use of short-acting beta agonists, for further control in those patients who fail single preventative therapy.[103] Administered in a single dose at least 2 hours before exercise, the leukotriene receptor antagonists can decrease EIB in more than half of patients for a period of 12 hours or more.[2,104]

Most EIB occurs in the chronic asthmatic, making control of chronic asthma that much more crucial. Inhaled corticosteroids can decrease airway responsiveness over the long term and decrease EIB. When chronic asthma is controlled, the frequency and severity of EIB are reduced.[105]

49.7.2 Occupational Asthma

It has been estimated that occupational factors account for approximately 9–15% of cases of asthma in adults of working age, including new-onset or recurrent disease.[106] A variety of substances in the workplace have been implicated in the development of asthma, including a large variety of animal proteins, flour and grain dust, wood dust, cotton dust, chemical compounds such as isocyanates and hydrides, metal salts, and even pharmaceuticals.[106] The workers

TABLE 49.2
Selected Causes of Allergic and Non-Allergic Occupational Asthma

High-Molecular-Weight Substance	Occupations
Animal protein	Laboratory workers
Papain	Brewers, lens workers
Wheat flour	Bakers, millers
Trypsin	Plastic/pharmaceutical workers
Soybean dust	Farmers, food workers
Vegetable gums	Printers, food workers
Low-Molecular-Weight Substance	**Occupations**
Platinum	Jewelers, refiners
Trimellitic anhydride	Plastic and epoxy resin workers
Phthalic anhydride	Plastic and epoxy resin workers
Isocyanates	Spray painters, foundry workers
Polyvinylchloride	Meat wrappers
Western red cedar	Carpenters

most commonly reported for occupational asthma include paint sprayers, bakers and pastry makers, animal handlers, nurses, chemical workers, welders, food processing workers, and timber workers.[106]

The causative agents of occupational asthma can be grouped into immunologic and non-immunologic (e.g., smoke, aerosols, fumes). Up to 90% of cases have been of the immunologic type. Some causative agents, such as toluene diisocyanate, can produce occupational asthma through both immunologic and non-immunologic mechanisms resulting from airway damage and sensitization. The immunologic agents can be divided into high- and low-molecular-weight substances (Table 49.2). The high-molecular-weight agents are complete sensitizing agents, while the low-molecular-weight agents need to combine with a protein to form a sensitizing agent. The high-molecular-weight agents are usually mediated through IgE.

It is important to recognize occupational asthma as soon as possible because the likelihood of complete resolution of symptoms decreases over time.[2] Occupational asthma is suspected when either the patient or clinician realizes a relationship between asthma symptoms and work exposure. There is often a time delay between exposure to the offending agent and the development of symptoms of occupational asthma. Many times, the patient will improve on days away from the workplace, particularly during vacations. Sometimes, coworkers have similar symptoms. Serial PEFR measurements at work and away from work can help diagnose occupational asthma.[106] There are some (not well standardized) allergens available for skin prick testing, and some immunoassays for agent specific IgE exist. Occupational asthma can usually be diagnosed without using specific bronchial provocation testing, although occasionally, a bronchial provocation challenge performed with a suspected allergen or irritant from the workplace can be helpful.[106]

The management of occupational asthma can be difficult, and the patient may require referral to an occupational asthma specialist. Diagnosing patients early and avoiding further exposure to the causative agent will give the best opportunity for a complete recovery. Often, the patient must avoid the triggering substance. If impossible, the patient should be moved to an area of low or occasional exposure with increased health monitoring. The use of respiratory protection by wearing a respirator mask can be helpful. Many times, the patient must completely avoid exposure to the irritating agent; therefore, a new job position may be necessary.

The outcome of any intervention for patients with confirmed occupational asthma depends on factors such as age and the type of agent.[106] Unfortunately, some patients will have persistent asthma despite the removal of the inciting substance.

Irritant-induced asthma is a subset of occupational asthma where exposure to an occupational irritant induces new-onset asthma in a patient without preexisting disease. A variety of chemicals, dust, and other particulates can sensitize the airways and induce chronic asthma.[107] This is different from work-exacerbated asthma, in which preexisting asthma exists and is worsened by workplace exposure, but the workplace agents do not actually initiate the disease process. The syndrome known as reactive airways dysfunction syndrome (RADS), an acute form of irritant-induced asthma, occurs when a single high-intensity exposure to a non-immunologic irritant causes asthma-like symptoms within minutes. In RADS, symptoms may last for years.

49.7.3 Medication-Induced Asthma

Aspirin-exacerbated respiratory disease, also known as Samter's Triad, is characterized by the presence of asthma, rhinosinusitis with nasal polyps, and aspirin sensitivity. The ingestion of aspirin in sensitive individuals may result in nasal congestion, eye irritation, facial flushing, and an asthma exacerbation, which usually occurs rapidly after ingestion and often within 30 minutes.[108] Approximately 4–20% of asthmatics are sensitive to aspirin and related compounds, especially NSAIDs.[109,110] Severe and even fatal asthma exacerbations have been associated with aspirin ingestion. In adult patients with severe persistent asthma who have nasal polyps, it is important to take a careful history to determine whether there is any evidence suggesting exacerbations of upper or lower airway symptoms after NSAID use. Even if no such history can be elicited, high risk patients, such as those with chronic sinusitis and nasal polyposis, should be counseled to maintain vigilance for NSAID induced exacerbations. If such a history does exist, the patient should be instructed to avoid all NSAID exposures. Acetaminophen, particularly in lower doses, is tolerated in the large majority of NSAID sensitive asthmatics. The COX-2 inhibitor celecoxib is also tolerated in most NSAID sensitive asthmatics, but because there is still some risk of this agent precipitating exacerbations, the first dose should be given in an observed setting.[2,13,111,112]

Nasal polyposis and chronic rhinosinusitis occur in nearly 90% of patients with aspirin sensitivity.[113] The prevalence of aspirin sensitivity increases with age and the severity of the asthma. There is no known familial predilection to aspirin sensitivity. It is not known to be associated with atopy. The mechanism seems to be related to altered arachidonic acid metabolism and to inhibition of the enzyme cyclo-oxygenase (COX-1), in which arachidonic acid metabolites are passed through the leukotriene pathway, resulting in increased production of the leukotrienes C4, D4, and E4 (the slow reacting substance of anaphylaxis).[114] Therefore, medications that interfere with leukotriene synthesis or leukotriene receptor antagonists are helpful in the management of aspirin-induced asthma. Patients are treated according to asthma guidelines, but usually, a leukotriene modifying agent is added, which may also diminish nasal symptoms.[42,43,115] The treatment of aspirin-induced asthma also includes either avoiding all NSAIDs that inhibit the COX-1 enzyme or performing aspirin desensitization and maintaining daily aspirin therapy.[2] The biological agent dupilumab can be highly effective in treating both sinus disease and asthma in patients with chronic sinusitis and nasal polyposis, and is an attractive therapeutic alternative to aspirin desensitization in these patients.

Tartrazine, or yellow food dye No. 5, can induce asthma symptoms in some individuals. This food coloring is found in a number of foods and in some medications.

Beta blockers, including a variety of eye drop preparations, can induce asthma symptoms.[2,10,11] The NAEPP guidelines suggest avoiding non-selective beta blockers, and ideally, beta-blocker therapy should be avoided altogether unless the medication is necessary for a cardiac or ophthalmologic condition.[116] However, many patients who have mild-to-moderate airflow obstruction are able to tolerate more cardioselective beta blockers, and the NAEPP recommends using them in patients with cardiac disorders after careful consideration.[2] Fortunately, there are satisfactory alternatives to beta blockers for most of these patients.

49.7.4 Obesity

Asthma is more common and more difficult to control in obese patients.[5, 117] Some obese patients with asthma have prominent respiratory symptoms and little eosinophilic inflammation. These symptoms need to be distinguished from those of obese patients who have respiratory symptoms due to deconditioning, chest restriction, and obstructive sleep apnea.[5,117] Because of the potential contributors to dyspnea and wheeze in obese patients, it is important to confirm the diagnosis of asthma with objective measurement of variable airflow obstruction. There are various strategies for weight reduction. However, as part of a lifestyle change, the addition of exercise twice a week or a weight loss program in obese asthmatics can improve asthma control, pulmonary function, and inflammatory markers.[118]

49.7.5 Stress

Asthma is not a psychosomatic illness. However, there is evidence that stress plays an important role in precipitating asthma exacerbations and may act as a risk factor for the increased prevalence of the disease.[119] Stress exacerbation of asthma may involve enhanced generation of pro-inflammatory cytokines, but more importantly, psychosocial factors associated with stress influence the asthmatic's personal sphere and often lead to a poor outcome.[120] Since emotional upset does contribute to the asthma symptom picture, a variety of psychological interventions may be necessary to enhance overall asthma care. In some cases, a patient may need help to distinguish between asthma flares and panic attacks.

Conflict that develops between the patient, the family, and the medical staff often interferes with appropriate asthma care. The poorly controlled chronic asthmatic can often despair, and his or her disease can have a significant negative effect on personal relationships, family life, and self-image. Enhanced asthma control, and careful discussion of these issues with the patient and family, can help the overall asthma care process. The asthmatic who needs psychosocial assistance should take advantage of appropriate professional counseling with a psychologist, psychiatrist, social worker, or other licensed practitioner.[2] There are a variety of psychologically oriented approaches to asthma care that can be helpful, including family counseling, educational seminars, and psychotherapy. Ignoring asthma symptoms and neglecting to use medication can seriously adversely affect overall asthma control. Asthma education is associated with enhanced personal confidence in the management of chronic asthma.[2]

49.7.6 Food Hypersensitivity

Food allergens may rarely precipitate asthma symptoms alone but more commonly are associated with extra-pulmonary involvement, such as skin and gastrointestinal signs and symptoms.[2,121]

49.7.7 Gastroesophageal Reflux

Gastroesophageal (GE) reflux results when the acidic, liquid contents of the stomach are regurgitated into the esophagus, causing irritation. The reflux material does not have to be aspirated into the lungs to induce asthma. Reflux of the acidic fluid into the esophagus likely destabilizes asthma by enhancing the cholinergic autonomic nervous system influence or microaspiration, or both. GE reflux should be suspected in patients with poorly controlled asthma, particularly those who have nocturnal symptom breakthroughs.[2] The strongest evidence supports a link between symptomatic reflux and asthma symptoms. Empiric treatment with a proton pump inhibitor in asthmatics without GE reflux symptoms did not improve asthma symptoms.[122] A patient who has a hiatal hernia is at particular risk for GE reflux.

Treatment of patients with symptomatic GE reflux has been associated with improvement in some aspects of their asthma.[123,124] If GE reflux symptoms are present, medical management includes (1) avoidance of eating food and drinking liquids within three hours prior to bedtime; (2) sleeping with the head of the bed elevated by using six- to eight-inch blocks; (3) eating smaller, and if necessary, more frequent meals; (4) using appropriate pharmacologic therapy such as H2 receptor blockers or proton pump inhibitors; (5) cessation of alcohol, cigarettes, and caffeinated foods.[2]

49.7.8 Pregnancy and Asthma

Asthma is the most common medical condition during pregnancy, occurring in 4–8% of pregnant women.[125] The risk of asthma exacerbation during pregnancy is higher, especially in the second trimester.[5,126] As a general rule, one-third of all pregnant asthma patients improve, one-third remain the same, and one-third have worsening disease during pregnancy.[2,5,127] However a patient's asthma changes during the first pregnancy, it is likely that similar symptoms will occur with subsequent pregnancies. Patients with more severe and difficult-to-control asthma generally have worse symptoms during pregnancy.

Asthma also has an effect on pregnancy complications.[128] Uncontrolled asthma is risky for the fetus. One large study showed that asthmatic patients had an increased risk of infant mortality, preterm birth, and low birth weight.[128] Those with more severe asthma have a higher risk of complications.[128] However, this study did not find an increased risk of congenital defects.[128] A mother whose asthma is well controlled and free of complications imposes no additional risk to the fetus.

The goals of asthma treatment during pregnancy are to prevent acute exacerbations and to optimize lung function, providing maximum benefit to the health of the mother and the fetus.[2,129] If asthma medications are necessary during pregnancy, one must keep in mind the benefit of keeping asthma under control against the small potential risk for adverse effects from medication. The majority of asthma medications that are used in practice present little to no risk during pregnancy, although prospective well-designed and well-controlled clinical trials do not exist for most medications.[130] In one study, inhaled corticosteroids, beta-2 agonists, theophylline, and montelukast were not associated with an increased frequency of fetal abnormalities.[5,130]

The medications used for the treatment of acute asthma exacerbations during pregnancy are the same as in nonpregnant adults. Allergy immunotherapy can be continued through pregnancy but should not be initiated or altered. The safety of biologics during pregnancy is unknown.[131] The initiation of biologic therapy during pregnancy is generally not recommended. The decision on whether to continue existing biologic therapy once pregnancy is established involves a detailed discussion between the patient and the medical provider. The risks of the medication to the fetus must be balanced with the risk of discontinuation resulting in suboptimal asthma control. Patients electing to continue existing biologic therapy during pregnancy are encouraged to participate in a pregnancy exposure registry.[131]

The FDA currently requires all medication labels to include narrative sections regarding use during pregnancy. The information required includes details regarding pregnancy exposure registries, risk summaries, clinical considerations, and data. They also have similar sections regarding medication use by people of reproductive potential and medication use while lactating. The obstetrician, asthma specialist, and primary care physician should work together to create the safest treatment regimen for the pregnant asthmatic patient.

CLINICAL APPLICATIONS

- A positive allergy test from either skin testing or immunoassay blood testing does not necessarily indicate that the identified allergen is causing symptoms. The clinician must look for clinical significance of the positive result in the context of the patient's medical history.
- The mainstay of chronic controller medications for asthma is inhaled corticosteroids. Chronic controller inhaler regimens should never consist of a LABA or LAMA without an accompanying inhaled corticosteroid.
- It is essential to assess medication compliance prior to escalating pharmacologic therapy for uncontrolled asthma.
- For uncontrolled asthma, the addition of a monoclonal antibody is often more appropriate than pursuing immunotherapy. Monoclonal antibodies are highly efficacious, easy to administer, and have favorable side effect profiles for most individuals.

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50 Occupational and Environmental Lung Diseases

Shaun Toomey, Sunkaru Touray, Emil Tigas, and Nicholas A. Smyrnios

50.1 WORK-RELATED ASTHMA

50.1.1 Epidemiology

Asthma affects about 8% of the adult U.S. population, and it is estimated that about 15–20% of patients with asthma have work-related asthma (WRA).[1] Work-related asthma is a chronic inflammatory lung disease characterized by the presence of reversible airway narrowing following exposure to airborne dust, gases, or fumes in the work environment. Work-exacerbated asthma (WEA) is a subset of WRA, which describes asthma that worsens in individuals with a pre-existing diagnosis of asthma occurring in the context of exposure to triggers in the work environment.[2] Work-related asthma is grouped into sensitizer-induced asthma (SIA) and irritant-induced asthma (IIA) based on the mechanism of disease.

SIA is an immune-mediated inflammatory reaction to compounds known to be sensitizers, of which there are over 200. Diisocyanates are the most common cause of SIA in many industrialized areas.[1] Other sensitizers include proteins, polysaccharides, animal dander, castor beans, latex, cobalt, and vegetable gum. SIA is caused by the activation of T-lymphocytes resulting in cytokine-mediated airway inflammation. IIA, on the other hand, is thought to be caused by a direct irritant effect of inhaled chemical compounds on the bronchial wall that results in the activation of inflammatory pathways that cause reversible airway obstruction. It is less common than SIA.

50.1.2 Clinical Presentation and Diagnosis

Sensitizer-induced symptoms are variable and can occur at any time during the workday or toward its end. Symptom remission or improvement typically occurs during weekends and holidays when the patient is away from the work environment. Making a confident diagnosis of WRA first requires establishing a diagnosis of asthma on the basis of a consistent history, associated with reversible airway obstruction on spirometry.[3] In patients without airway obstruction, bronchial hyperresponsiveness demonstrated on bronchial provocation testing with either methacholine or histamine supports the diagnosis. Chest imaging in the form of a chest x-ray is recommended to exclude parenchymal lung disease that may be causing symptoms.

Once a diagnosis of asthma is established, the next step involves demonstrating an objective association between work-environment exposures and worsening lung function as determined by an objective demonstration of airflow obstruction measured by peak expiratory flow rate (PEFR) or FEV1 (forced expiratory volume in one second) on spirometry. The recommended minimum monitoring period should be two weeks at and away from work during which asthma treatment should be kept constant. Worsening of symptoms during work that improves when the patient is away from work is consistent with a diagnosis of work-related asthma. In patients who are unable to continue employment due to symptom limitation, referral to specialized centers for bronchoprovocation testing using occupational inhalational agents is recommended.[4, 5]

50.1.3 Prevention and Treatment

Primary prevention of work-related asthma involves employee education, avoidance of exposure to sensitizing agents; and, where this is not possible, substitution of known sensitizing agents with non-sensitizers. Periodic medical surveillance using respiratory questionnaires with or without spirometry and immunologic tests are recommended secondary preventative measures.[4]

Pharmacotherapy is an adjunct to sensitizer and irritant avoidance in the treatment of work-related asthma and follows recommended guidelines, including the use of short-acting beta agonists (SABA) on an "as-needed basis" for symptom relief, with the addition of an inhaled corticosteroid (ICS) inhaler in moderate cases. An inhaled long-acting $beta_2$–adrenergic (LABA) bronchodilator can be added to the regimen as a "step-up" therapy in refractory moderate-severe cases. Oral steroids are used for severe acute exacerbations, while immunotherapy has been tried in a few small studies with variable efficacy.[6,7] Additional emerging therapies in the severe and difficult to treat allergic asthma population include the use of biologic agents. Omalizumab, an anti-IgE antibody, was shown in one small study of work-related asthma to improve asthma control and corticosteroid use.[8]

50.1.4 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterized by irreversible airway obstruction.[9–11] Smoking is the most important risk factor, with more than two-thirds of COPD cases linked

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to the long-term effects of cigarette smoking.[12] Another important risk factor is biomass smoke exposure, which has been shown to be a risk factor for the development of COPD independent of smoking status.[13] This is an important consideration in the assessment of obstructive lung disease in non-smokers.

50.1.5 Epidemiology

COPD affects about 10% of the general population, with a prevalence that increases with age and smoking.[10,11] Globally, 65 million people are affected, and COPD kills over 3 million people annually.[14,15] In the United States, it is the third most common cause of death, affecting about 16 million people and causing over 120,000 annual deaths.[16,17] Healthcare costs from COPD are estimated to be over $50 billion annually.[17]

50.1.6 Clinical Presentation and Diagnosis

A diagnosis of COPD should be considered in any patient presenting with a chronic cough, shortness of breath, and sputum production in the context of a smoking history and suspected or established biomass fuel exposure. The latter should be considered in patients originating from low- and middle-income countries in sub-Saharan Africa, parts of South America, and Asia.[18]

COPD is a heterogeneous disease with different phenotypes that include chronic bronchitis and emphysema. Chronic bronchitis manifests as a cough and sputum production on most days for three months in two consecutive years. Patients with an emphysema phenotype have an abnormal and permanent dilatation of airspaces distal to the terminal bronchioles. Emphysema is associated with the destruction of the alveolar walls. Symptoms common to these two major phenotypes include wheezing, fatigue, and loss of appetite.

Spirometry is required to make the diagnosis of COPD. A post-bronchodilator FEV1/FVC less than 0.70 confirms the presence of persistent airflow limitation and identifies the presence of COPD in patients with appropriate symptoms and predisposing risks.[11] Physical examination findings are nonspecific and rarely aid in the diagnosis except in advanced cases where chest wall deformities such a barrel-shaped chest may be present.[19] The disease course is variable, with extended periods of chronic daily symptoms punctuated by periods of acute exacerbations during which there is a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that necessitate a change in regular medication.[20]

Once a diagnosis of COPD is made, a combined assessment is performed to determine symptom burden, degree of airflow limitation, and the risk of acute exacerbation. To assess symptoms, the modified Medical Research Council (MMRC) or COPD assessment test (CAT) score should be used. Next, the FEV1 is used to classify the degree of airflow obstruction based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Finally, the number of acute exacerbations and hospitalizations in the preceding year is determined. Using these variables, presented in Figure 50.1, patients are categorized into one of four groups (A, B, C, and D). The GOLD criteria present a framework on which treatment is instituted.[11]

50.1.7 Prevention and Treatment

The therapeutic objectives in COPD management include symptom control, prevention of acute exacerbations, and improvement of exercise tolerance. This is usually achieved with a combination of non-pharmacologic and pharmacologic interventions.

50.1.8 Non-Pharmacologic Therapy

Smoking cessation is the most effective non-pharmacologic intervention in preventing COPD and slowing its

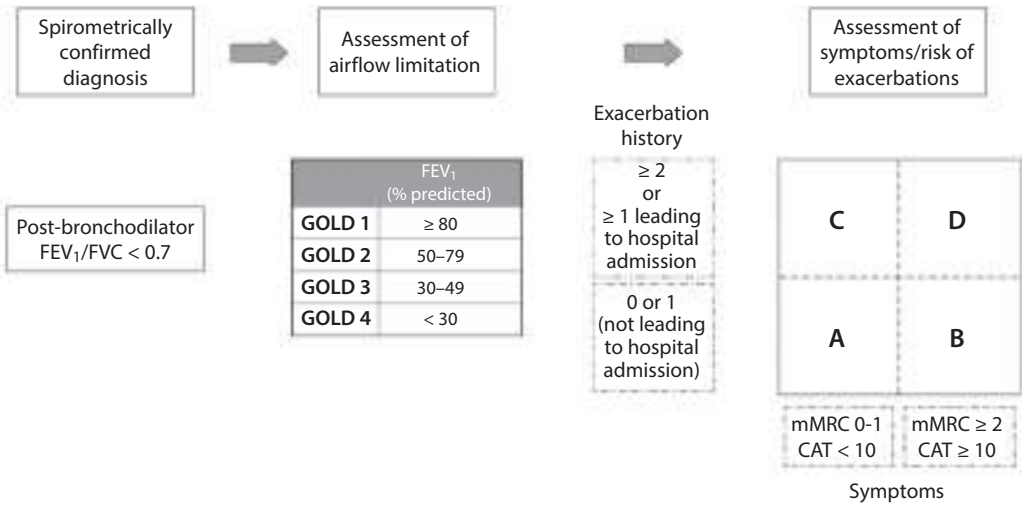


FIGURE 50.1 GOLD COPD assessment tool. (From Global Initiative for Chronic Obstructive Lung Disease, © 2021)

progression. All patients should be offered tobacco cessation counselling.

Assessing medication adherence and training in good inhaler technique are integral parts of patient education.[21,22] Pulmonary rehabilitation is a multidisciplinary program that aims to improve exercise capacity, reduce symptoms, and improve overall quality of life in patients across the spectrum of disease severity and has been shown to improve dyspnea, health status, and exercise tolerance.[21] It is therefore recommended that all patients with COPD be considered for pulmonary rehabilitation as part of a multimodality treatment regime.

Age-appropriate pneumococcal vaccination should be offered to all patients in accordance with established guidelines.[23]

50.1.9 Pharmacologic Therapy

Bronchodilators are the first-line pharmacologic drug class for symptom control and have been shown to improve lung aeration and exercise tolerance. In patients with low risk of acute exacerbation and fewer symptoms (Category A), the use of a short-acting beta agonist (SABA) alone or in combination with a short-acting muscarinic antagonist (SAMA) is appropriate for use as a reliever medication on an as-needed basis. For low-risk patients with high symptom scores (Category B) and high-risk patients (Categories C and D), maintenance therapy is indicated for symptom control. This involves the use of long-acting bronchodilators such as beta agonists (LABA) or a long-acting muscarinic antagonists (LAMA) singly or in combination. Patients in category D may also benefit from the addition of an inhaled corticosteroid (ICS). ICS use as monotherapy is discouraged, and evidence suggests a better outcome in patients on LAMA/LABA compared to an ICS/LABA, with a lower incidence of pneumonia in patients with moderate-to-severe COPD and higher dyspnea scores.[11, 24]

50.1.10 Asbestos-Related Lung Disease

Asbestos-related lung disease is a group of lung diseases caused by exposure to naturally occurring asbestos fibers. These fibers have desirable physical properties for industrial use, such as high tensile strength, flexibility, and resistance to chemical and thermal degradation, hence their prior extensive use in the construction, automotive, and textile industries.[25] Chrysotile (also known as white asbestos) is the most common and only type of asbestos currently used in manufacturing in the United States, while the more toxic amphibole fibers, including crocidolite, amosite, and tremolite are still used in parts of sub-Saharan Africa, South America, and Asia.[26] Asbestos fibers are highly carcinogenic and are known to cause lung cancer and malignant mesothelioma. Asbestos is considered one of the most important occupational carcinogens.[26]

50.1.10.1 Epidemiology

The use of asbestos has been banned in many developed countries. While there is no widespread ban in the United States, its use has been severely reduced. Therefore, exposure is limited to certain occupations such as asbestos removal, construction workers, car mechanics, and plumbers working on old homes and buildings where asbestos was used.[27] Global asbestos exposure is unknown, although it is estimated that worldwide over 40,000 people die of malignant mesothelioma each year.[26]

50.1.11 Clinical Presentation and Diagnosis

Individuals exposed to asbestos are mostly asymptomatic, and the latency period can be as long as 20–30 years between initial exposure and the development of the clinically apparent disease. In patients who develop clinical disease, benign asbestos pleural plaques are a common finding, the development of which suggests prior exposure and is reported to be prevalent in about 60–70% of individuals with an average cumulative exposure of about 32 years.[28, 29] The diagnosis is usually incidental and made during chest imaging for other reasons. Chest x-ray may show a diffuse pleural thickening in the lower portions of the chest, sparing the apices and costophrenic angles, which may be calcified in about 5–15% of cases.[30, 31] Chest CT has a higher sensitivity and specificity and can detect noncalcified pleural plaques.

Malignant pleural mesothelioma (MPM) is a dreaded consequence of asbestos exposure that typically occurs in older (median age 60) men. Patients with MPM present with nonspecific symptoms of dyspnea, cough, chest pain, and constitutional symptoms including fever, chills, night sweats, malaise, and weight loss. Pleural effusions may be present and are usually an exudate with an eosinophilic cellular profile. Unfortunately, thoracentesis has a low sensitivity for diagnosing MPM, hence a surgical pleural biopsy using a video-assisted thoracoscopic approach is the gold standard for diagnosis.[32] Treatment of MPM involves multimodality treatment, including surgery in patients who are good candidates for resection and chemoradiation therapy. In non-operable cases, chemotherapy, palliative radiation, and tunnelled pleural catheters have been employed for symptomatic relief.

Asbestos-associated pulmonary fibrosis (asbestosis) is a less common form of asbestos-related lung disease which may be difficult to distinguish from other causes of pulmonary fibrosis. Chest CT may show honeycombing and upper lobe involvement in advanced stages of the disease. The presence of pleural plaques suggests prior asbestos exposure and raises suspicion for asbestos-associated pulmonary fibrosis but is not confirmatory. Such patients should be referred to specialists familiar with asbestos-related lung disease for periodic monitoring of disease progression and the development of asbestos-associated malignancies.[33, 34]

While the carcinogenic properties of asbestos remain an important factor in the longitudinal monitoring of the exposed patients, routine screening for lung cancer in exposed individuals is not recommended in patients without smoking risk factors. Low dose chest CT (LDCT) monitoring has been recommended for lung cancer screening for patients considered at increased risk for based on age and smoking.[35] Low detection rates of malignancy in patients with asbestos exposure in the absence of smoking risk factors does not make screening LDCT a viable or beneficial option in this population.[36]

50.1.12 Silicosis

Silicosis is a fibrotic lung disease caused by inhalation of free crystalline silicon dioxide or silica and is recognized as one of the most important occupational diseases worldwide. Silicon dioxide or silica is the most abundant mineral and occurs in crystalline and amorphous forms.[37] The most common free crystalline forms of silica in workplaces are quartz, tridymite, and cristobalite.[37]

50.1.13 Epidemiology

Silica exposure is highest among individuals employed in construction work involving masonry, heavy construction, painting, and in iron and steel foundries. Metalworking occupations that involve sandblasting, grinding, or buffing of metal parts are also considered high-risk jobs.[37] Global disease burden is difficult to estimate due to lack of disease surveillance in lower-and middle-income countries; however, countries like China and South Africa have reported significant silica exposure, suggesting that the disease burden in these parts of the world may be high. In the United States, about 127,000 miners are reportedly exposed, with a higher rate of disease in African Americans compared to white workers with the same dust exposure.[38, 39]

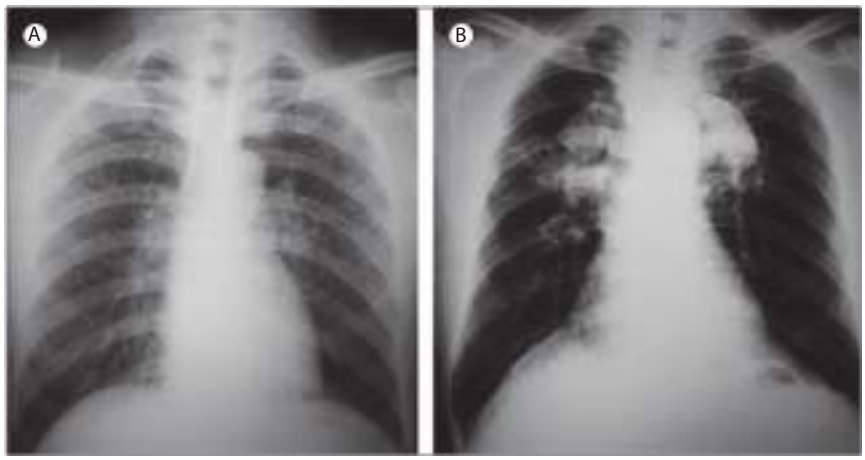
50.1.14 Clinical Presentation and Diagnosis

Acute silicosis is characterized by rapid onset of symptoms including dyspnea, cough, weight loss, fatigue, and sometimes pleuritic pain and fever following acute exposure to silica.[40] Lung examination may reveal crackles. Chest x-ray may be normal in the acute phase or may demonstrate bilateral consolidation and ground-glass infiltrates. Diagnosis of acute silicosis requires a high clinical index of suspicion and is contingent on establishing an occupational exposure to silica and the absence of other differentials.

Chronic silicosis is characterized by two clinical syndromes on two ends of a disease spectrum, namely, simple silicosis (SS) and progressive massive fibrosis (PMF). In simple silicosis, a chest x-ray may show upper lobe predominant ground-glass opacities; while in progressive massive fibrosis, there are mass-like areas of dense consolidation. Pulmonary function tests may reveal a mixed obstructive and restrictive ventilatory defect and a decreased diffusion capacity. Bronchoscopy may demonstrate a milky lipoproteinaceous bronchoalveolar lavage effluent, requiring the exclusion of other potential causes, including malignancy, pulmonary alveolar lipoproteinosis, and atypical infections such as *Pneumocystis jirovecii* and Norcardiosis. A diagnosis of silicosis can be established on the basis of a documented history of significant silica exposure, consistent chest imaging findings of diffuse nodular and patchy consolidative opacities, and supportive BAL findings in the absence of other causes (Figure 50.2).

50.1.15 Prevention and Treatment

The Occupational Safety and Health Administration (OSHA) recommends limiting exposure to silica using a combination of respiratory protection, medical surveillance, and good record-keeping. Half-face particulate respirators with N95 or better filters are considered appropriate



Chest radiographs of a patient with silicosis
Simple nodular silicosis (A) and progressive massive fibrosis (B).

FIGURE 50.2 Occupational environmental lung disease silicosis.

for silica at concentrations of 50 microgram/m3 or fewer; powered respirators are recommended for exposures above this limit.[41]

50.1.16 Berylliosis

Beryllium is a naturally occurring element that is extracted from ores and processed into metal, oxides, alloys, and composite materials used in the aerospace, automotive, and mining industries.[42] Berylliosis manifests as two clinical syndromes at opposite ends of a disease spectrum. Beryllium sensitization occurs in acutely exposed individuals, while chronic beryllium disease is an inflammatory lung disease affecting individuals who are chronically exposed to beryllium.

50.1.17 Epidemiology

It is estimated that about 134,000 current workers in government and private industry are potentially exposed to beryllium in the United States.[42]

50.2 CLINICAL PRESENTATION AND DIAGNOSIS

Acute exposure to beryllium presents with nonspecific respiratory symptoms, including cough, rhinorrhea, and dyspnea. This is associated with a delayed hypersensitivity reaction resulting in chronic granulomatous inflammation affecting the lungs, a condition known as beryllium sensitization (BeS). About 8% of individuals with BeS, may progress to chronic beryllium disease, characterized by progressive dyspnea, non-productive cough, fatigue, and exercise intolerance as lung tissues are destroyed by chronic granulomatous inflammation.[42] Patients may have constitutional symptoms, including fever, night sweats, and weight loss. Physical examination findings are nonspecific, although bibasilar crackles and digital clubbing may be present. Extrapulmonary manifestations are rare and include uveitis and cardiac conduction abnormalities.

Chest x-ray has a low sensitivity for diagnosing berylliosis in the acute setting, as it may be normal in BeS and early phases of chronic beryllium disease (CBD). Chest computed tomography has a higher sensitivity and may demonstrate hilar adenopathy, upper lobe predominant reticulonodular infiltration in a peribronchovascular pattern that is indistinguishable from sarcoidosis. It has been reported that about 6% of patients undergoing diagnostic evaluation for a clinical suspicion of sarcoidosis were ultimately diagnosed with berylliosis, highlighting the importance of a detailed occupational history to assess for exposure.[43–45] Pleural effusion is an uncommon manifestation of BeS and CBD. Pulmonary function tests may be normal in the early stages of the disease, while in advanced cases airflow obstruction, restriction, or a mixed pattern on spirometry may be present. A reduced diffusion capacity may also be present in advanced cases.

The diagnosis of beryllium sensitization is made on the basis of a positive blood beryllium lymphocyte proliferation test (BeLPT) in a patient with a history of beryllium exposure.

CBD is diagnosed when either blood or bronchoalveolar lavage fluid BeLPT is positive in a patient with a documented history of beryllium exposure. Other features supportive of the disease include consistent radiographic abnormalities and lung pathology demonstrating non-caseating granulomas with lymphocytic infiltration.

50.3 TREATMENT AND PREVENTION

Disease prevention involves the avoidance of inhalation and dermal exposures to beryllium by employing the use of personal protective equipment, administrative changes such as the exclusion of workers from specific areas to prevent nonessential contact, and regular screening of employees involved in activities with exposure to beryllium. Patients with respiratory symptoms suspicious for berylliosis should be referred to a pulmonologist for diagnostic evaluation and treatment, which generally consists of systemic corticosteroids. Inhaled corticosteroids have been shown to decrease respiratory symptoms and cough, but did not affect exercise capacity or spirometry in patients with mild disease.[46]

50.3.1 Coal Mine Dust Lung Disease

Coal mine dust lung disease (CMDLD) refers to a broad spectrum of lung diseases caused by exposure to coal mine dust. It includes disease entities such as coal workers' pneumoconiosis (CWP), progressive massive fibrosis (PMF), Caplan Syndrome, and Chronic obstructive pulmonary disease (COPD).[47, 48]

50.3.2 Epidemiology

Coal is the second largest energy source worldwide, accounting for over 25% of global energy supply and more than one-third of the fuel used to generate electricity. Consequently, the number of individuals exposed to coal particles is considerable, with China, the United States, and India being the top consumers accounting for over 70% of total global consumption. Coal production in the United States is largely concentrated in a few states, including Wyoming, West Virginia, Kentucky, Pennsylvania, and Texas, accounting for over 70% of production.[49] Most coal workers are men; therefore, CMDLD disproportionately affects men, with about 38% of coal miners showing radiographic features of interstitial lung disease. Diagnosis of CMDLD is made clinically on the basis of a combination of an appropriate exposure history, radiological or pathological findings consistent with the diagnosis, and a lack of alternative explanations for the patient's lung disease.[48]

50.4 CLINICAL PRESENTATION AND DIAGNOSIS

Coal workers' pneumoconiosis (CWP) is caused by the accumulation of coal dust in the lungs and classically presents as the occurrence of upper lobe predominant, small, rounded opacities.[48] Most cases are asymptomatic and are detected incidentally as part of surveillance programs or in the context of a diagnostic workup for other conditions.

Progressive massive fibrosis (PMF) is a progressive form of CMDLD found in miners with greater dust exposure. A study found PMF in about 63% of coal miners with a mean coal mining tenure of 27 years in Kentucky and Virginia.[50] It may present with dyspnea, cough, and the production of sputum that has been variably described as mucoid, mucopurulent, and rarely discolored as if mixed with black ink (melanoptysis). Clinical exam findings are nonspecific, and the average interval from a normal chest radiograph to massive fibrosis can be as long as 12 years.[51] Spirometry findings include a restrictive, obstructive, or mixed pattern of impairment, and a reduced DLCO depending on the severity of lung fibrosis.

An association between CWP and rheumatoid arthritis called Caplan syndrome, originally described by Anthony Caplan, describes the occurrence of multiple well-defined opacities on chest radiographs of rheumatoid arthritis patients.[52] CMDLD has also been associated with chronic obstructive pulmonary disease and other pulmonary infections which account for significant morbidity in patients with CWP.

50.5 PREVENTION AND TREATMENT

In the United States, environmental controls are mandated by federal law. Coal dust exposure can be minimized using ventilation systems, water sprays, and other dust capture devices as part of a continuous monitoring program. There is no specific medical therapy that has proven effective in reversing CMDLD. Management involves supportive care, periodic medical monitoring with periodic chest radiographs and spirometry.[47]

50.5.1 High-Altitude Illnesses

It is estimated that more than 30 million people each year travel to and from recreational areas with altitudes greater than 2,500 meters. This presents unique challenges for travellers to these areas, and therefore a good understanding of common problems that arise from exposure to high altitude is important to prevent the development of high-altitude illnesses.[53]

High-altitude illnesses (HAI) are a group of pulmonary and cerebral conditions that occur in the context of a rapid initial ascent to altitudes at a rate that exceeds the body's ability to acclimatize to changes in oxygen tension. The fraction of oxygen in inspired air is constant at 0.21 regardless of altitude, but for each unit change in altitude, there is a non-linear change in the barometric pressure of oxygen that affects the alveolar partial pressure and consequently, oxygen availability to tissues. The physiologic response to this change in oxygen tension is called acclimatization and is characterized by changes in the heart rate, respiratory rate, chemoreceptor sensitivity to hypoxia, and pulmonary vasoconstriction. These act in concert to restore normal oxygen levels in tissues, but when the rate of altitude change exceeds the body's homeostatic capacity, acute hypoxemia ensues, resulting in distinct clinical syndromes primarily affecting the lung and brain.

Risk factors for the development of HAI include pre-existing cardiopulmonary disease, heavy exertion at altitude, low-altitude residence before ascent, and obesity.[54]

50.5.2 Acute Mountain Sickness and High-Altitude Cerebral Edema

Acute mountain sickness (AMS) is the most common presentation of HAI that typically occurs about 6–12 hours after ascent to altitudes above 2,500 meters (8,000 feet). It is diagnosed when an unacclimatized traveller develops a headache, with one of the following symptoms: nausea, anorexia, vomiting, insomnia, dizziness, or fatigue. It occurs in about 10–40% of climbers at 3,000 meters, while more than 50% of climbers experienced symptoms at altitudes greater than 4,000 meters.[55]

High-altitude cerebral edema (HACE) is considered an end-stage form of acute mountain sickness and is characterized by the presence of ataxia and altered mental status in an unacclimatized climber and can occur in the absence of acute mountain sickness or pulmonary edema.

50.5.3 High-Altitude Pulmonary Edema

High-altitude pulmonary edema (HAPE) is a rare life-threatening form of noncardiogenic pulmonary edema that develops two to four days following rapid ascent above 2,500 meters (8,000 feet).

50.5.4 Prevention and Treatment

50.5.4.1 Controlled Ascent

Controlled exposure to hypobaric hypoxia remains the most effective non-pharmacologic means of preventing HAI. Gradual ascent that allows for acclimatization is the most effective preventive strategy. The ideal rate of ascent is variable, but it is generally recommended that at altitudes above 3,000 meters, daily ascent should not exceed 300–500 meters above the previous night with a rest day after every 1,000 meters (or every 2–3 days).[53–56]

50.5.4.2 Pharmacologic Therapies

The use of acetazolamide, a carbonic anhydrase inhibitor, has been shown to be effective in preventing HAI by inhibiting bicarbonate excretion in the kidneys. This results in an

increase in serum bicarbonate and a concomitant increase in minute ventilation. The benefit of acetazolamide for the prevention of AMS/HACE has been demonstrated in multiple trials, and it remains the primary pharmacologic agent of choice.[57, 58]

Dexamethasone, a systemic corticosteroid, has also been shown to have a benefit in HAI prevention and can be used as an alternative to acetazolamide in patients at moderate to high risk for development of HAI. Although dexamethasone does not facilitate acclimatation like acetazolamide, there are prospective trials that show benefit in HAI prevention[59, 60]. The exact mechanism of the benefits remain unclear, but reduced vascular permeability, anti-inflammatory/anti-oxidant effects, sympatholytic effects are thought to play a role[60]. Recommended dosing is 2mg every 6 hours or 4mg every 12 hours. Taper should be used if duration of therapy is greater than 10 days due to the risk of adrenal suppression.

Nifedipine, a calcium channel blocker, has been show to prevent HAPE in a small study and can be considered for HAPE prevention in travellers with a previous history of HAPE. Sildenafil and tadalafil, phosphodiesterase inhibitors, have also been described in prevention of HAPE but evidence remains limited[59, 60].

In patients who develop AMS, rest and descent to a lower altitude are recommended. The Lake Louise Scoring system is a screening tool that can detect AMS/HACE in high-altitude climbers. A score of 3–5 is consistent with AMS, while a score greater than 6 indicates severe AMS/HACE, and such patients should be treated with acetazolamide. The recommended dose is 125–250 mg twice a day. Common side effects include paresthesia, loss of appetite, and nausea. Because acetazolamide is sulfonamide, patients with sulfa allergies should not take this medication (Table 50.1).

50.5.5 Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (formerly extrinsic allergic alveolitis) is an immune-mediated inflammatory disease of the lung that occurs due to exposure to an inducing agent. Exposure typically occurs in an occupational or recreational setting, which has given rise to an extensive list of diseases, including farmer's lung, bird fancier's lung, and hot-tub lung. It is characterized by a lymphocytic inflammation of the lung due to the accumulation of activated T-lymphocytes in the lung tissues.

50.5.6 Epidemiology

The incidence of HP is about one per 100,000 in the United Kingdom, with a mean age of 57 and an almost equal sex distribution. Incidence in the United States is unknown.[61] In the United States, identified risk factors are quite extensive and include bird and hot-tub exposure, contaminated humidifiers, and exposure to mold or fungi in plants and water systems.[62, 63] Lung fibrosis on chest CT has been associated with poorer outcomes with about 25% of patients with fibrotic HP dying or requiring lung transplantation during a five-year follow-up period.[64]

50.6 CLINICAL PRESENTATION AND DIAGNOSIS

HP presents with intermittent dyspnea, wheezing, cough, and constitutional symptoms, including fevers, chills, and malaise with a temporal relationship to an antigen exposure.[65, 66]

Chest CT is crucial in the diagnostic evaluation of patients in whom a diagnosis of HP is being entertained.

TABLE 50.1
High-Altitude Illnesses and Definitions

Acute mountain sickness	**Headache and *at least one* of the following symptoms:** • gastrointestinal (anorexia, nausea, or vomiting) • fatigue or weakness • dizziness or lightheadedness • difficulty sleeping
High-altitude cerebral edema	The presence of a change in mental status and/or ataxia in a person with acute mountain sickness OR the presence of both mental status changes and ataxia in a person without acute mountain sickness
High-altitude pulmonary edema	The presence of *at least two* of the following symptoms: dyspnea at rest • cough • weakness or decreased exercise performance • chest tightness or congestion • AND *At least two* of the following signs: crackles or wheezing in at least one lung field • central cyanosis • tachypnea • tachycardia

Classical features include an upper lobe predominant centrilobular diffuse micronodular ground-glass opacification and mosaicism.[67, 68]

HP is classified into acute (inflammatory) HP, with a symptom duration less than six months and chronic (fibrotic) HP, with symptom duration greater than six months.[63] Chronic HP is characterized by fibrotic changes in high-resolution computed tomography images or lung biopsy and is associated with a poorer outcome.[63]

Diagnosis of HP requires a high index of suspicion in a patient presenting with typical symptoms and diagnostic imaging. Once the diagnosis is considered, a detailed history looking for potential exposure to an HP-inducing antigen is crucial, although these are identified in only about 50% of cases.[63, 66] A detailed occupational and social history should be obtained to identify any potential exposures in the work environment or during recreational activities.[69]

Pulmonary function tests and referral to a pulmonologist are recommended for further diagnostic evaluation, including bronchoscopy with bronchioalveolar lavage and/or lung biopsy. Specific IgGs have been employed as a screening tool, but these tests are performed only in a few specialized centers.

50.6.1 Treatment and Prevention

The cornerstone of HP treatment involves identification of the offending antigen and avoidance. However, given that an inducing agent remains unidentified in half of patients with HP, consideration of treatment with inflammatory suppression agents in symptomatic patients may be indicated. Prednisone has been used in this scenario while mycophenolate, rituximab, leflunomide and azathioprine have been used as second-line agents or in addition to prednisone to minimize systemic steroid dosing. Evidence for these regimens is limited to small studies and high-quality evidence is lacking.[70–72] Another option in patients with chronic and fibrosing HP would be anti-fibrotic agents such as pirfenidone and nintedanib. Use of these agents were initially described in patients with idiopathic pulmonary fibrosis (IPF) but their use is being expanded to non-IPF progressive fibrosing interstitial lung diseases. Nintedanib has been shown to slow the decline in lung function in this population.[73] Nintedanib may be favored over pirfenidone as one study showed that there is no benefit with pirfenidone therapy in patients with interstitial lung disease other than IPF [74]

50.7 LUNG TRANSPLANTATION IN OCCUPATIONAL LUNG DISEASE

Despite increased awareness of occupational lung disease and preventive measures through exposure control and monitoring programs, there is a subset of patients that progress to end stage lung disease where lung transplantation is the remaining therapeutic option. Lung transplantation has been performed in the USA for occupational lung diseases, most commonly for coal workers pneumoconiosis or silicosis. Metal pneumoconiosis, berylliosis and asbestosis are less common indications.[75]

CLINICAL APPLICATIONS

- A diagnosis of work-related asthma should be suspected in any patient with asthma that is difficult to control.
- COPD should be considered as a diagnosis in any patient with dyspnea from parts of the world where there is significant exposure to biomass fuel or coal mining (even among non-smokers).
- Employees involved in industries with exposure to silica, coal, asbestos, and beryllium should undergo periodic surveillance for pneumoconiosis using history, lung function testing, and chest imaging.
- Travelers to high altitudes should receive information on high-altitude illnesses and be counselled on how to prevent, recognize, and treat symptoms of these syndromes.

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51 Venous Thromboembolic Disease

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KEY POINTS

- Venous thromboembolism (VTE) is a common, morbid, and costly disease process with a multitude of risk factors.
- Risk factors for the development of venous thromboembolic disease are commonly present in combination rather than isolation.
- The role of modifiable risk factors for VTE, such as immobility, obesity, and smoking, is an area of growing interest.
- More study is needed to define the impact of modification of these risk factors with respect to VTE or VTE recurrence in individual patients,

51.1 VTE INTRODUCTION/OVERVIEW

Venous thromboembolic disease (VTE) in the form of deep venous thrombosis (DVT) and pulmonary embolism (PE) is a common, costly, and morbid problem encountered by both generalists and specialists in a variety of medical and surgical fields. As our understanding of the many risk factors for the development of VTE has grown, and as our approach to diagnosis and treatment has become more complex, it has become necessary to adopt an increasingly broad and multidisciplinary approach to the management of these patients; there is growing evidence that the principles of lifestyle medicine should become a central component of any comprehensive VTE management strategy.

Risk factor interaction is critical to the understanding of both VTE development and management. While it is true that many risk factors for the development of VTE have a non-modifiable genetic basis, or may exist because of an otherwise healthy or necessary exposure (e.g. oral contraceptive pills [OCP] use or surgical immobilization), others are a direct consequence of health or lifestyle choices. Application of the principles of lifestyle medicine can therefore reduce the overall risk of developing VTE due to their influence over several important risk factors that are synergistic, common, and *modifiable*. This concept of risk factor synergy acknowledges that the presence of *specific combinations* of individual factors engenders an overall risk that is potentially much greater than the sum of their individual contributions.[1] While the precise pathophysiological mechanisms underlying the interactions of these modifiable risk factors are not fully understood, we do know that adequate levels of physical activity, smart nutritional choices for maintenance of a healthy weight, and avoidance of cigarette smoking can play a prominent role in the overall management of patients at risk for, or who have developed, DVT and subsequent PE.

51.2 EPIDEMIOLOGY

Accurately assessing the true incidence of VTE disease is challenging due to the unknown number of asymptomatic DVTs or PEs that are suspected to occur each year. Asymptomatic PE alone is believed to complicate up to 50% of all confirmed cases of DVT.[2] In a retrospective study looking at 7,238 patients with 11,747 computed tomography (CT) examinations over a 5.5 year period, incidental (and unreported) PEs accounted for 54% of all PE events.[3] Estimates suggest a combined incidence rate of 1 in 1,000 people per year, with the rate of diagnosis of PE being approximately half of that of DVT (60 vs. 124/100,000).[1,4] Centers for Disease Control (CDC) data are in agreement, with up to 900,000 people affected each year in the United States.[5] As many as 80% of new cases of VTE will occur in the context of at least one, and often more than one, known risk factor.[6]

Based on updated analyses, VTE continues to disproportionately affect patients with malignancy despite broad application of best practices in prevention. In a 2021 systemic review and meta-analysis of 23 studies comprising a total of 12,977 patients, 4,200 (32.4%) incidental instances of VTE were observed.[7] In the last several years, COVID-19 infection has emerged as an important risk factor for the development of DVT and PE, and this remains an area of intense study. In a recent meta-analysis[8] of 66 studies involving 28,173 patients (19.4% of whom were intensive care unit patients), VTE prevalence was estimated at 14.1%. When asymptomatic ultrasound screening was utilized (14 of the 66 included studies), the prevalence of VTE was as high as 40%. More high-quality data are necessary to clarify the interactions between COVID-19 and more established risk factors for VTE.

The morbidity and mortality of VTE are difficult to quantify precisely and likely vary significantly with underlying patient comorbidities, characteristics of the VTE itself, as well as access to treatment.[9] PE is associated with most of the directly attributable mortality. Population data collected over the last several decades demonstrate an overall mortality rate of untreated PE as high as 30%, improving to 8% with prompt recognition and treatment. The highest mortality rates are observed in patients presenting in cardiogenic shock due to massive PE (up to 65%) or mobile

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thrombus within the atria (up to 27%). It is estimated that up to 100,000 deaths annually in the United States are due to complications of VTE.[10]

Both PE and DVT contribute to the morbidity and the societal costs associated with VTE. Much of that comes from the impact of chronic thromboembolic pulmonary hypertension, VTE recurrence, and peripheral vascular dysfunction due to damage to the valves in the deep leg veins. Using data obtained from nearly 27,000 U.S. cases of DVT and PE from 1997 to 2004, it has been estimated that average annual individual healthcare costs increase from approximately $7,000 pre-event to $17,500 and $25,000 after events of DVT and PE, respectively.[11] In this data set, the presence of post-thrombotic syndrome was also a strong driver of additional medical costs that extended far beyond the time of diagnosis and treatment. The relatively high pre-VTE annual medical expenditure in this cohort, compared with less than $1,000 in annual healthcare costs in age-matched, "healthy," controls, was thought to be due, in part, to pre-existing comorbid diseases in this population. The aggregate annual economic burden of VTE in the United States, including longitudinal cost of therapy and management of side effects, has been estimated to be between $7 billion and $10 billion per year.[10]

The costly, morbid, and frequently mortal nature of VTE is reason enough to explore all reasonable avenues of risk reduction and therapy optimization. As we will see later in this chapter, application of the principles of lifestyle medicine may represent an accessible, cost-effective, and efficacious adjunct to the growing technological arsenal of diagnosis and therapy.

51.3 PATHOPHYSIOLOGY

The development of VTE is dependent on the local interaction of venous stasis, vascular endothelial injury, and intrinsic hypercoagulability in the paradigm attributed to Virchow in 1856.[12] Though a detailed exploration of the hematological mechanisms of clot formation is beyond the scope of this text, there are several key ideas to understand as they pertain to the development of DVT and subsequent PE.

The risk of thrombosis can be thought of as proportional to the cumulative impact of multiple risk factors.[13] It has also been observed that while venous stasis is likely the most important contributor to DVT (and by extension PE), stasis in the complete absence of endothelial disruption or hypercoagulable state is likely insufficient for clot formation. While global stasis in the context of absent muscular contraction (such as during general anesthesia) has been linked to thrombosis, autopsy and physiological studies have also demonstrated that the local effect of eddy currents in venous sinuses adjacent to the valves of the large veins creates a microenvironment of relative hypoxia and increased viscosity, which further enhances the propensity to clot.[12,14] It has been theorized that this low–oxygen tension environment further contributes to clot formation, as it promotes the downregulation of antithrombotic proteins that are otherwise expressed in greater concentrations on the endothelial surface of such valves.[15] A similar imbalance in pro- and anticoagulants is also seen in locations of decreased endothelial cell surface to blood volume, such as the large femoral and iliac veins, and may explain the higher rates of clot formation in those areas.[16] The prothrombotic effect associated with inherited or acquired defects in expression of the constituents of the fibrinolytic and clotting pathways is magnified at such sites.[17]

51.4 EMBOLIZATION TO THE PULMONARY VASCULATURE

A perfect understanding of the frequency of embolization of these lower extremity clots is impossible, given the suspected frequency of asymptomatic DVT. Data derived predominantly from the surgical literature have provided some insight into features impacting the likelihood of progression, however.[18] While it is true that the development of de-novo thrombosis of the large veins in the periphery is dependent upon the factors noted earlier, the likelihood of subsequent embolization of these clots to the pulmonary vasculature has been linked only to the proximity of the clot to the central circulation.[19] These data also suggest that nearly all venous thrombotic events are asymptomatic until they reach the proximal veins (cephalad to the popliteal circulation).[20,21] In a consecutive series of 189 patients with clinically suspected lower extremity DVT, only 11% had distal calf DVT only, and more than 90% had continuous clot extension from the calf to the proximal veins.[18] It has been estimated that nearly half of the patients with symptomatic proximal DVT will have imaging evidence of pulmonary emboli at the time of diagnosis, and one-third will be diagnosed with concurrent PE, even in the absence of chest or respiratory symptoms.[22,23]

It should also be noted that the majority of these observations were made decades ago. With the now widespread use of multidetector CT scan, our ability to detect small PEs has significantly improved. Therefore, these older data may underestimate the frequency of embolization from proximal clots. It seems reasonable to conclude that the natural history of untreated DVT is one of eventual progression and ultimately, distal migration. The risk of such an event is believed to be highest immediately following the development of thrombosis, and this risk declines over a period of several months as the stabilization effects of partial resorption and endothelization of distal clot progress.[24]

51.5 RISK FACTORS

It is likely that truly idiopathic VTE or PE is rare, and the majority of VTE occurs in the context of at least one, and often multiple, risk factors.[25] The risk factors that predispose the patient to clot can be divided generally into two groups: inherited (e.g. genetic clotting disorders) or acquired (e.g. undergoing surgery).[26] Though these risk factors might

appear varied and unrelated, the final common pathway of clotting is the perturbation of the local vascular microenvironment such that some or all of Virchow's triad is satisfied.[27] There are several published data sets that enhance our understanding of both the relative *individual* strength of risk factors and the interplay of acquired and innate risks when present *concurrently*.[28]

Describing the effect of a single risk factor is straightforward: surgery with general anesthesia and the presence of malignancy are implicated in as many as one-third of all cases and are likely the most important single risk factors for the development of VTE.[25,29–31] Delineating the synergistic effects of multiple concurrent risk factors is more complex but more reflective of real patients and real risk. Using the example of surgery: in one of the largest (4,311 cases) case-control studies of VTE, it was observed that the combination of surgical immobility and non-malignant medical illness (including renal or liver disease, heart failure, and cerebrovascular accident [CVA]) increased the odds ratio (OR) for the development of VTE by 10.9 (95% confidence interval [CI] 4.2–28).[32] The addition of any of the inherited thrombophilias to that combination increased the OR to as high as 88. For the purposes of this text, we will focus primarily on the complex synergistic interaction between several pertinent lifestyle-related health choices: risk of immobility or a sedentary lifestyle, obesity, and smoking.

51.6 IMMOBILITY

Interest in the development of VTE due to prolonged non-surgical immobility has existed since it was first observed that there was a sixfold increase in the risk of fatal PE in patients who sat for prolonged periods of time in air raid shelters during the London Blitz of World War II.[33] More recently, it was reported that rates of incidence of distal DVT in patients requiring cast immobilization without surgery may be as high as 19% (35/188).[34] The risk associated with airline travel is likely the most intensely scrutinized, though it remains controversial. Estimates from prospectively obtained data sets indicate that the risk of DVT may be twice that of non-flyers.[35] On the other hand, the overall incidence of PE may be as low as 4.8 per million patients travelling more than 6,000 miles. However, these data may underestimate the true incidence of minimally symptomatic and non-embolizing distal clot for the reasons described earlier.[36] Of note, it has been suggested that it is not only the lack of movement while flying, but concurrent mild hypoxemia (cabin PaO_2 of 72 mmHg) that promotes coagulation.[37,38] As such, and given the frequency of multiple risk factors present in the same patients, it is challenging to quantitate the risk of immobility itself during activities such as airline travel.

Immobility not related to airline travel is less well-described but of increasing importance. As the modern office becomes more de-centralized, and Americans spend more and more time with their computers for both work and recreation, there has been an increase in individual case reports and case series describing the development of significant DVT related to elective, non-flight-related immobility.[39] In one of the largest series of its kind, 61 consecutive patients with VTE were surveyed and tested for underlying thrombophilia. Multiple risk factors were present in the majority of patients. Prolonged seated immobility was the second most common risk factor after a family medical history of thrombosis. This study defined "prolonged" as sitting a cumulative 8 hours in a 24-hour period (with at least 3 hours unbroken), 10 hours in a 24-hour period (with at least 2 hours unbroken) or 12 hours in a 24 hour period (with at least 1 hour of continuous sitting). Thirty-four percent of patients with a new diagnosis of DVT demonstrated this finding.[40] A follow-up case-control study attempted to describe the OR specifically associated with work-related immobility. Ninety-seven consecutive patients with radiographically confirmed VTE (both DVT and PE) were administered a questionnaire almost identical to that used in the Aldington case series. These patients were then matched to controls from the same center admitted over the same time period. Following univariate analysis, authors found that immobility due to work or recreation carried an OR of 2.2 (CI 1.0–5.0) for the development of VTE. While this is an important observation, the effect was modest, especially when compared with the effect of recent surgery or family history of VTE in this same data set (OR 70.6 and 5.7, respectively).[41] Interestingly, the total duration of hours spent sitting, irrespective of frequency or duration of breaks, had a direct relationship with an increasing risk of VTE.

51.7 OBESITY

In parallel with the rapid rise of the obesity epidemic in Americans, there has been increasing interest in understanding the role that obesity plays in the development of DVT and PE. Although obesity has been theorized for decades to exert a pro-coagulant effect, it is only in the last few decades that we have seen significant data in support of this association.[42–46] Several meta-analyses and large population cohort studies have supported the link between increasing body mass index (BMI) and the risk of VTE. The largest of these meta-analyses includes data from 21 case-control and cohort studies and represents 63,552 patients diagnosed with PE or DVT over the last 5 decades. Obesity, defined as BMI >30 kg/m^2, carried an OR of 1.84 (95% CI, 1.55 to 2.18; $I^2 = 69.2\%$; $P = 0.01$) for the development of VTE. The average BMI in the cohort of patients who developed VTE was 1.7 kg/m^2 higher than their matched controls.[47]

Though focused on a homogeneous population, data published in 2010 from the Copenhagen City Heart Study also found obesity to be an independent risk factor for the development of VTE.[48] Based on their evaluation of more than 360,000 patient-years and nearly 1,000 individual

cases of VTE, they observed that a BMI of 30 to 35 carried a hazard ratio (HR) of 1.65 (1.17–2.34, $P = 0.005$) for the development of DVT or PE. Their data set also suggested the possibility of graded risk with rising BMI, as the subset of patients with BMI over 35 kg/m^2 had a HR of 2.1 (1.39–3.16, $P < 0.001$). A similar trend was observed by Tsai et al. in the Longitudinal Investigation of Thromboembolism Etiology (LITE) study when they combined data from Atherosclerosis Risk in Communities (ARIC) (a prospective epidemiological study focused on four American communities) and the Cardiovascular Health Study (CHS).[49,50] These authors observed increasing HR for VTE proportional to rising quintile of BMI from <25 to >40.[42] Further understanding of this proportional risk requires additional study.

In addition to its independent impact on coagulation, obesity has also been associated with a magnified risk of DVT and PE, not only in certain populations (most notably women) but also in the context of other acquired and inherited risk factors. Data from both the all-female Nurses' Health Study and the Multiple Environmental and Genetic Assessment (MEGA) study show increased risk of VTE in obese female patients on OCPs.[51] Using subjects with a BMI <25 and no OCP use as a baseline, it was observed that patients on OCPs and a BMI between 25 and 30 had an OR of 11.63 (95% CI, 7.46–18.14) for the development of VTE. As BMI rose above 30, that OR similarly rose to 23.78 (95% CI 13.35–42.34).

The risk of VTE associated with obesity and the Factor V Leiden gene mutation was also demonstrated to be significant. Though the presence of this genetic abnormality was itself associated with an OR of 4.18 in normal weight patients (BMI <25), that OR rose to 5.77 and 7.86 at BMI levels of 25–30 and >30, respectively. The combined effect of obesity and prothrombin gene mutation was of a similar scale. Although it is unclear why obesity increases the risk of DVT and PE, investigators have recently shown that increasing levels of obesity correlate with increased levels of clotting factor VIII and activated protein C resistance, possibly due to the establishment of a chronic inflammatory state.[52]

In addition to its impact on the development of the first episode of VTE, obesity has also been observed to increase the risk of recurrence after treatment of an initial event. In a recent prospective study, investigators followed more than 1,000 patients for an average of 46 months following their first episode of unprovoked DVT and completion of anticoagulation therapy. They observed a recurrence rate of 9.3% in patients with normal BMI (<25 kg/m^2) and 16.7% (95% CI 11.0–22.3%) and 17.5% (95% CI 13.0–22.0%) among overweight and obese patients, respectively. The average BMI in those who suffered a recurrence at all in the 4 years of the study was 28.5 compared with 26.9 in those who were clot-free at the end of 46 months ($P = 0.01$).[53] These data suggest that efforts to reduce BMI through healthier lifestyle choices may have an impact on management of VTE.

51.8 SMOKING

Though smoking, and specifically cigarette smoking, has long been understood to be an independent risk factor for the development of arterial atherosclerotic disease, its role in the development of venous thromboembolic disease is less well understood. This controversy stems from conflicting data, to which a 2008 meta-analysis not supporting smoking as an independent risk factor for DVT or PE was central.[54]

In 2008, Ageno et al. collated more than 20 years of observational data regarding the overlap between VTE and traditional cardiovascular disease risk factors, finding that smoking carried a (non-significant) increased risk of 1.18 (95% CI 0.95 to 1.46).[54] Other small and more narrowly focused population-based studies also argued *against* smoking as an independent risk for VTE.[42,55,56] The largely retrospective data set generated by Ageno could not be evaluated in a way that controlled for the coexistence of other VTE risk factors such as age, increasing BMI, recent surgery, presence of concurrent malignancy, or diagnosed thrombophilia.[54] Six of the included studies were focused on the interplay of VTE and OCPs and thus, had a narrow population focus. The presence of VTE was not necessarily confirmed by accepted diagnostic practices such as CT or ultrasound, and no distinction was made between current and former smokers.

In contrast, Cheng et al. published a meta-analysis of 32 studies comprising 35,151 VTE events in 2013.[57] Studies lacking additional risk factor data or specific details regarding cigarette use were excluded from their analysis. They reported that after controlling for known VTE risk factors in a generalizable population, current smokers compared with never smokers had a statistically significant risk ratio (RR) of 1.23 (95% CI 1.14–1.33) for the development of VTE. They also reported that this risk increased by 10.2% (95% CI 8.6–11.8%) for every ten additional cigarettes per day or by 6.1% (95% CI 3.8–8.5%) for every additional ten pack years of smoking. Similar modest increases in the observed RR of VTE in smokers have been reported by several smaller studies.[51,58]

Mahmoodi et al. evaluated the role of cardiovascular disease (CVD) risk factors (such as smoking) in the development of VTE using only prospectively identified and definitively diagnosed cases of VTE.[59] The study demonstrated that while current smoking did carry a modestly increased HR of 1.19 (95% CI 1.08–1.32) for the development of VTE, this *overall* effect was attributed entirely to the effect observed in the subgroup of patients ultimately diagnosed with a provoked clot over the 4.7 to 19.7 years of follow-up (again highlighting the synergistic effect of multiple risk factors, qualitatively). Most recently, Gregson et al. analyzed data from the ERFC (731,728 participants) and UK biobank (421,537 participants) data sets with a median follow-up of 15.4 years. They showed current smoking to be associated with VTE in both data sets. The HRs were 1.38 (1.2–1.58) and 1.23 (1.08–1.40) in ERFC and UK biobank, respectively.[60]

The importance of smoking as a cofactor in the development of VTE is further supported by a body of evidence that demonstrates the synergistic effect of smoking in the context of known, non-lifestyle-related risk factors such as presence of a thrombophilic gene mutation or recent surgery.

Of the many genetic risk factors for VTE that have bene identified, the most well established are Factor V Leiden (FVL) and prothrombin gene mutations.[61] It has been estimated that up to 8% of patients with DVT will carry one of these mutations.[62] Though estimates vary , heterozygosity for these mutations has been associated with a statistically significant HR for VTE of approximately 2.6 for each locus individually and as high as 5.66 when found together.[63] It has also been observed that there is some degree of variability in the incidence of VTE in patients with known mutations, with many patients never developing VTE despite exposure to known, potent cofactors.[64] Hypothesizing that lifestyle choices (specifically smoking and obesity) may therefore exert an influence over the variable development of VTE in these patients, Severinsen et al. examined the dose–response impact of smoking on the development of VTE in patients with known FVL and prothrombin gene mutations.[65] Though the relatively small number of VTEs in the study group may have overestimated the effect of smoking, they reported a HR for VTE of 4.46 (95% CI 1.83–10.88) and 76.8 (95% CI 29.2–201.7) in patients with FVL and prothrombin gene mutation, respectively, who smoked more than 25 g of tobacco (slightly more than one pack of cigarettes) per day. Also of note, matched wild-type controls in this study who smoked less than 25 g/day of tobacco were not observed to have an increased risk for development of VTE.

It is well-established that the use of estrogen and combined OCPs is itself associated with an increased risk of VTE, which has historically ranged between two and four times that of matched controls.[66] Variability in the rates of VTE has in many large reviews and meta-analyses been attributed predominantly to differences in the progestin component of these medications.[67] Pomp, et al reported an OR of 8.79 (95% CI 5.73–13.49) in the subset of patient on OCPs who identified themselves as current smokers.[51] Further subgroup analysis of these data also demonstrated a direct, proportional increase in the risk of VTE with daily smoking, similar in magnitude to that effect observed by Cheng et al. Similarly, Traven et al. looked at the risk of VTE in females undergoing arthroscopy and anterior cruciate ligament (ACL) reconstruction. Obesity and smoking increased the risk of VTE in patients taking combined oral contraceptives, with an OR of 3.1 (1.99–4.65) and 4.3 (2.41–7.50), respectively.[68] Finally, data from the surgical literature suggest an association between marijuana use and VTE in trauma patients.[69,70] Causality, however, cannot be established, and more studies are required to further elucidate the link between these two entities.

We can conclude from these studies that while some CVD risk factors increase the risk of VTE, it is likely the synergistic effects of multiple risk factors (both acquired and inherited) that lead to the development of VTE.

51.9 DIAGNOSIS

The diagnosis of PE is dependent on the maintenance of a high degree of clinical suspicion, which is itself enhanced by an awareness of the common risk factors described earlier. While the clinical presentation can be variable, and that variability can be independent of the size or location of the clot, several large study populations have demonstrated a number of more commonly observed features.[23,44,71] These include dyspnea (present in nearly three-quarters of patients) and pleuritic chest pain (in two-thirds of patients). Tachypnea has been observed in half of patients presenting with PE. Cough and evidence of lower extremity DVT are present in nearly a quarter of patients at the time of diagnosis of PE. Rapidity of the onset of symptoms is seconds to minutes in more than 75% of cases.[24,44] High risk presentations characterized by refractory hypoxemia, obstructive shock, or cardiac arrest are comparatively rare but require a specific approach to initial management: while it has been observed that the duration of symptoms prior to diagnosis has a direct relationship with increasing size of clot burden, this relationship was not significantly associated with these high morbidity presentations.[72]

A large meta-analysis, which included more than 25,000 cases of PE, suggested that the clinical impression of physicians, based predominantly on consideration of these symptoms, may carry a sensitivity of 85% though understandably, a low specificity (51%) for the detection of PE.[71] Driven partly by these data, and in part by the need of enhanced focus on healthcare expenditure and resource utilization in the last several years, there has been increasing interest in a simple, standardized schema to identify very low-risk individuals.[73] The PERC rule (pulmonary embolism rule-out criteria, a set of eight clinical and patient features used to predict risk of PE on initial presentation) was developed as a tool to accomplish just that aim, demonstrating excellent performance.[74]

Laboratory tests can play an important role in risk stratification and in ruling out pulmonary embolism in patients who have a low pre-test probability based on clinical assessment or standardized scores (e.g. Wells) but are not strictly necessary for the diagnosis of PE. d-Dimer specifically has been studied extensively, and a negative test effectively rules out embolism and obviates the need for further testing in these low-risk groups.[75] An area of active research is the use of elevated and age-adjusted d-dimer thresholds. A recent randomized controlled trial (RCT) found that using different d-dimer thresholds combined with a validated algorithm (YEARDS) was non-inferior to conventional strategy while leading to a significant reduction in chest imaging.[76,77] Nonetheless, the performance, and therefore utility, of this test is degraded significantly in populations with a high prevalence of PE or with a medical history associated with elevated levels (hospitalized patients, the elderly, or those

with end-stage renal disease [ESRD]).[78] This is especially confounding given what has already been described regarding the increased risk of thrombosis in individuals with these features; many patients with these features but low to intermediate risk will undergo definitive testing, with understandably higher rates of negative studies.

The standard of care in diagnosing those with a high pre-test probability of PE is well established: modern studies support the use of CT scan protocoled for opacification of the pulmonary arteries. The performance characteristics of this test can vary with the pre-test probability of PE: PIOPED II data demonstrated a sensitivity and specificity of 90% and 96%, respectively, in patients with high suspicion for PE.[23] False negatives do occur across all groups, though as infrequently as 0.07% in high suspicion groups.[79] Technical challenges such as obesity, movement artifact, or incorrect contrast bolus timing can disproportionately reduce the accuracy of the test at the subsegmental level; interobserver variability among radiologists has been as high as 50% in such cases.[80] Finally, V/Q scans have a role in the diagnosis of PE in patients who otherwise cannot tolerate a contrasted CT scan of the chest. A systemic review and meta-analysis of 19 studies (6,393 examinations in 5,923 patients by Phillips et al.) found single photon emission computed tomography (SPECT) V/Q to be as effective as CT in diagnosing pulmonary embolism, and found both to be superior to planar V/Q.[81]

51.10 TREATMENT

The approach to treatment of VTE is dependent upon a variety of disease and patient factors that influence the choice of therapeutic agents and duration of anticoagulation therapy. These include the location of the clot (distal lower extremity vs. proximal lower extremity/pulmonary embolism), presence of hemodynamic instability, features of the underlying provocative risk factors, and vulnerability to serious adverse effects of treatment (i.e. bleeding risk).

Many of the recent investigations center around the use of direct oral anticoagulants (DOACs) (rivaroxaban, dabigatran, etc.) in the treatment of DVT and PE. Historically, vitamin K antagonists (such as warfarin), heparin infusions, or subcutaneous low molecular weight heparin injections were the standard of care. Though in some cases they remain as such, there is growing evidence to suggest that DOACs are safe and effective.[82–85]

The American College of Clinical Pharmacy (ACCP)'s *Antithrombotic Therapy for VTE Disease*, Second Update in 2021, is the most widely accepted standard for VTE management, and a highly condensed summary is included in the following. In patients with VTE but no malignancy:[86,87]

- Dabigatran, Rivaroxaban, Apixaban, Edoxaban are all recommended over warfarin.
- Dabigatran (150 mg twice daily) and Edoxaban (30 or 60 mg once daily) are preceded by a period of parenteral anticoagulant, usually a low molecular weight heparin, for *5–10 days*.
- Rivaroxaban (15 mg BID × 21 days, then 20 mg daily, all with food) and apixaban (10 mg BID × 10 days, then 5 mg BID) do not require initial Rx with low molecular weight heparin (LMWH).
- These recommendations are based on these factors:
  - Risk reduction for recurrent VTE appears to be similar to warfarin.
  - Risk reduction among these drugs appears to be similar.
  - Risk of intracranial bleeding appears to be less than warfarin.
  - Fatal bleeding is no higher than warfarin.
  - These medications are more convenient for patients and may lead to better compliance.
- If a choice is made to use warfarin, initial LMWH is used for a minimum of five days.
- If a heparin product is used, low molecular weight heparins are considered superior to unfractionated heparins in most cases.[88]

Duration of therapy is another extensively studied and debated issue in the treatment of VTE. The nature of underlying risk is of central importance to this decision. The key consideration in addressing duration of therapy is recurrence prevention, and data have shown that irrespective of the agent used in anticoagulation, there is an elevated risk of recurrence following discontinuation of treatment after 3, 6, or even 12 months.[89] The risk of recurrent VTE instead likely varies with the persistence of provocative risk factors: the largest data set available identifies presence of malignancy, age, BMI, and persistent neurological deficits as independent predictors of recurrence.[89] Conversely, the surgical literature demonstrates that isolated DVT following surgery is adequately treated with three months of anticoagulation, and treatment duration beyond this point confers no benefit in recurrence prevention.[90] Cohorts of patients with "unprovoked" thrombosis likely have a higher rate of recurrence than the general population, and as a reflection of that observation, consideration should be given to indefinite anticoagulation.[90]

It has not been demonstrated whether clots arising in the context only of the previously identified lifestyle related risk factors are more or less likely to recur following modification of the risk. While it is tempting to assume that weight loss, avoidance of prolonged periods of sitting, and smoking cessation would return baseline thrombosis risk to "normal" levels, this is unknown.

The following special situations may require tailored management strategies.

51.10.1 Massive PE

Hemodynamic instability acts as a critical branch point in all recommended treatment algorithms. Patients at high

risk of death presenting with obstructive shock should be considered for administration of thrombolytic therapies.[86,87] The potential benefit derived from thrombolysis is believed to be a continuum, varying directly with the patient's risk of imminent death from their VTE episode and inversely with their risk of major bleeding (most notably intracranial hemorrhage). The tipping point for potential benefit is hard to identify, however, due to the dearth of data precisely describing patient characteristics and outcomes after receiving thrombolysis. That being said, guidelines published by ACCP (2021)[87] and European Society of Cardiology/European Respiratory Society (ESC/ERS) (2019)[91] recommend full dose thrombolysis alongside anticoagulation for patients with hemodynamic instability.

Furthermore, studies have attempted to describe outcomes in patients with intermediate risk/sub-massive PE. The ESC/ERS guidelines propose a classification of patients with pulmonary embolism by early mortality risk. This model uses a combination of hemodynamic instability, clinical parameters of PE severity, right ventricular (RV) dysfunction, and cardiac enzymes to risk stratify patients. A recent study attempted to describe outcomes in "intermediate risk" patients (as defined by aggregate evidence of RV dysfunction but in the absence of true shock). Although more than 1,200 patients with acute PE and evidence of RV strain were randomized to receive tenecteplase and heparin (vs. heparin alone), no clear net benefit was identified due to the counterbalancing effect of increased bleeding (including intracranial bleeding).[92] Pending further data to suggest benefit and delineate the optimal target patient population, it is recommended that patients with intermediate risk PE receive anticoagulation as a first line therapy. Both ESC/ERS (2019) and ACCP (2021 update) guidelines recommend escalation to reperfusion therapy with thrombolysis in patients who fail to respond. Notably, ACCP guidelines recommend thrombolytic therapy in those who deteriorate but are not yet hypotensive, while ESC/ESR recommends it in those who develop hemodynamic instability.

The technical method of thrombolytic delivery has also been an area of research interest, and it has been hypothesized that PA catheter-directed thrombolysis (CDT) (versus peripheral vein infusion) would carry a lower risk of serious bleeding. Data are currently limited to mostly small trials with limited generalizability of results. Based on the current body of evidence, CDT leads to resolution of clot faster than heparin alone and is potentially associated with a lower risk of major bleeding compared with systemic infusions.[93,94] Catheter-directed therapy and systemic thrombolysis, however, have not been compared head to head in any trial to date. While recommendations may change as more evidence accumulates, current guidelines reflect this paucity of data and favor systemic therapy over CDT except in cases with simultaneously increased risk of mortality and bleeding.[87]

51.10.2 Distal DVT

Distal thrombosis of the extremities that has occurred with or without a potentially modifiable risk factor does not uniformly require anticoagulation. The decision to treat these patients with anticoagulation should be based on an evaluation of the patient's symptoms, risk of adverse bleeding events, and risk of recurrence or progression of clot conferred by their medical history. An approach to patients with distal DVT includes performing serial duplex ultrasounds of the lower extremities for a period of two weeks off anticoagulation.[87] An absence of symptoms or clot progression over this surveillance interval suggests that the patient is at low risk for embolization or clot propagation. Candidates most likely to benefit from such a treatment plan will have good cardiopulmonary reserve, small distal clot, and no concurrent PE.[95] Current guidelines recognize that shared decision-making may result in a higher value being placed on definitive therapy rather than a period of uncertainty, and this cohort of patients is likely at low risk of serious bleeding events with anticoagulation.[96]

51.10.3 Isolated Subsegmental PE

Isolated, asymptomatic, subsegmental pulmonary emboli detected by highly sensitive modalities (multidetector CT) do not always require anticoagulation. Patients with low risk of recurrent VTE can be managed with continued observation following a negative ultrasound evaluation of the proximal legs. This approach is based mostly on the expectation that a number of very small defects in the periphery on low or intermediate risk scans will be false positives, with the likelihood of a true positive rising sharply in the context of a persistent underlying risk factor (see earlier).[97,98] The presence of symptoms attributable to clot or the presence of residual lower extremity thrombosis should push patients and clinicians toward therapy. Furthermore, ACCP (2021) guidelines suggest anticoagulation in patients with imaging and clinical features highly suggestive of a true positive.[87]

51.10.4 Malignancy-Associated Thromboembolism

- Multiple studies and guidelines have come out since the publication of the previous version of this textbook that recommend either initiation of DOACs or LMWH in the treatment of malignancy-associated VTE. The 2021 update to the ACCP guidelines recommends an oral Xa inhibitor over LMWH for patients with malignancy-associated VTE. It places emphasis on apixaban or LMWH for patients with luminal gastrointestinal (GI) malignancies, given the higher risk of bleeding with other DOACs (edoxaban or rivaroxaban).[87] These recommendations are based on the following evidence. The Hokusai VTE Cancer investigators compared Edoxaban with LMWH Dalteparin, finding it to have a similar rate of recurrent VTE.

Major bleeding was studied as a secondary outcome and was higher in the edoxaban group with a HR of 1.77 (1.03–3.04).[99]

- The SELECT-D investigators compared Rivaroxaban with Dalteparin and demonstrated a lower rate of VTE recurrence in the Rivaroxaban group at six months (HR 0.43 [0.19–0.99]). More patients in the Rivaroxaban group experienced bleeding events in this study.[100]
- Apixaban was compared with Dalteparin in the ADAM VTE trial, with results showing a lower rate of VTE recurrence in the Apixaban group (0.7% vs. 6.3%) with a similar rate of bleeding events.[101]
- The Caravaggio investigators also compared Apixaban with Dalteparin and found similar rates of both recurrent VTE and major bleeding, suggesting non-inferiority.[102]
- The CASTA DIVA investigators compared Rivaroxaban with Dalteparin, showing it to be efficacious and safe but not reaching the statistical significance required for a non-inferiority assessment.[103]

CLINICAL APPLICATION

- Maintenance of a high clinical suspicion for DVT or PE must include an awareness of applicable risk factors, and a sedentary lifestyle, obesity, and smoking should be considered in the clinical assessment.
- The keys to diagnosing PE are maintenance of high clinical suspicion, application of serological testing in selected low-probability patients, and CT with contrast in patients with high pre-test probability.
- Direct oral anticoagulants have become the standard of care for most cases of DVT and hemodynamically stable PE.
- A number of special circumstances exist in the treatment of PE, which require a tailored approach to therapy.

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52 Influenza

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KEY POINTS

- Influenza is a highly contagious respiratory virus that infects the epithelial cells of the respiratory tract and is spread through contact with an infected person.
- Influenza viruses are constantly mutating to evade the immune response, which is the reason why people can be infected with influenza more than once and why it is necessary to update vaccine formulations annually.
- Laboratory testing for influenza virus is not required to make a clinical diagnosis of influenza, but testing may be useful in certain cases to help guide clinical management.
- Annual influenza vaccination can provide both individual and population protection from infection and is strongly recommended.
- Antiviral medications are available for chemoprophylaxis and treatment of influenza in select groups, but efficacy is variable, and antiviral resistance has been reported.

52.1 DEFINITION

Influenza is an infectious respiratory illness caused by the influenza virus, a highly contagious virus in the *Orthomyxoviridae* family. Influenza is a major source of economic burden worldwide and causes annual outbreaks with high rates of morbidity and mortality, particularly in certain populations who are at increased risk for complicated disease.

52.2 HISTORY OF INFLUENZA

The name "influenza" originated in 15th-century Italy, expressing the belief in the *influenza di stelle*, or "influence of the stars," on the appearance of an epidemic.[1] Influenza is now commonly referred to worldwide as "the flu" or simply "flu," a potentially misleading designation, as the word "flu" is frequently used by the general public to describe any febrile, viral illness, i.e. "stomach flu," despite having no association with the influenza virus. Influenza virus was first isolated in ferrets in 1933 and was later found to replicate in embryonic hen eggs, a discovery that enabled further characterization and study of the virus and ultimately led to the development of the first influenza vaccines in the late 1930s and 1940s. Prior to the 1930s, influenza epidemics can be identified throughout history by the characteristic signs and symptoms of the disease, seasonal variability, and severity of outbreaks. Influenza epidemics are believed to have occurred since at least the Middle Ages and possibly even earlier. One of the earliest reports of influenza-like illness came from the Greek physician Hippocrates, who described a highly contagious disease from northern Greece in 410 B.C. Most historians agree that the first recorded worldwide epidemic, or pandemic, caused by influenza occurred in 1580, originating in Russia and spreading across several major continents including Africa, Asia, and Europe over a period of six months until finally reaching the American continent. Historically, influenza pandemics occur at 10- to 50-year intervals. Over the past three centuries, there have been at least eight influenza pandemics, four in the 19th century, three in the 20th century, and one, so far, in the 21st century. The 1918–1919 influenza pandemic known as "Spanish Flu" was the deadliest outbreak of influenza in modern history, resulting in an estimated >50 million deaths worldwide, far surpassing the roughly 17 million people killed in combat during World War I.[1,2]

52.3 VIROLOGY OF INFLUENZA VIRUS

Influenza viruses are enveloped, negative-sense, single stranded RNA viruses belonging to the *Orthomyxoviridae* family. There are four types of influenza virus: Influenza A, B, C, and D. Influenza types A, B, and C are all known to cause symptomatic disease in humans; however, Influenza A virus (IAV) and influenza B virus (IBV) are responsible for annual epidemics. IAVs are the most virulent and associated with the highest rates of morbidity and mortality. IAVs have a broad host range, infecting humans as well as a variety of other mammals, including swine and horses, and numerous species of domestic and wild birds, with wild aquatic birds serving as the natural host/reservoir of IAVs. IAVs are major contributors to annual influenza epidemics and are the agents responsible for all known influenza pandemics. IBVs almost exclusively infect humans and cause milder disease compared with IAVs. While IBVs can cause annual epidemics, due to host limitations, they have never been associated with any pandemics. Influenza C viruses cause only mild illness, mostly in pediatric patients, and are not associated with annual epidemics. Influenza D viruses primarily infect cattle and are not known to infect humans.

Influenza virus particles are encased by a host-derived lipid envelope and can vary in appearance from spherical

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particles ranging in size from 80 to 120 nm in diameter to long filamentous-appearing particles. The genome is comprised of eight viral RNA gene segments encoding the eight essential viral proteins: RNA polymerase, the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), viral nucleoprotein (NP), matrix protein (M1) and membrane protein (M2), nonstructural protein (NS1), and nuclear export protein (NEP). The glycoproteins HA and NA project like spikes from the surface of the virion and facilitate viral entry and release, respectively. HA and NA also exhibit the most antigenic variability, making these proteins the primary targets of antibodies generated in response to natural infection and vaccination as well as the targets for certain antivirals. A total of 18 different HA subtypes and 11 NA subtypes have been identified. Of these, eight HA subtypes (H1, H2, H3, H5, H6, H7, H9, H10) and six NA subtypes (N1, N2, N6, N7, N8, N9) have been detected in humans.

All influenza virus isolates are uniquely named based on virus type (A, B, C, or D), host (if not of human origin) and geographic origin, isolate number, and year isolated. IAVs are also subtyped based on the major surface antigens HA and NA. For example, influenza A/Perth/16/2019 (H3N2) is a human IAV isolated in Perth in 2019, isolate number 16 containing HA subtype 3 and NA subtype 2. For simplicity, the name is often truncated to reflect only the HA and NA type (i.e. H3N2). Unlike IAVs, which can infect across different species, influenza B viruses are largely restricted to humans and are divided into two antigenically distinct lineages: B/Victoria/2/1987 and B/Yamagata/16/1988.

Influenza virus replicates in epithelial cells of the respiratory tract. Virus HA binds sialic acid residues on the host cell membrane, and the virus particle is internalized within an endosome. Acidification of the endosome induces a conformational change in viral HA enabling fusion of the viral and endosomal membranes and release of the viral genome into the cytoplasm. Before replicating, the negative-sense viral genome must be imported into the nucleus and transcribed into a complementary, positive-sense messenger RNA intermediate, which is then exported from the nucleus into the cytoplasm and translated into viral proteins. Viral transmembrane proteins HA, NA, and M2 are trafficked to and inserted into the host cell membrane. After additional rounds of replication, newly formed viral proteins are then packaged within endosomes in the cytoplasm and shuttled to the cell membrane, where budding of new virions occurs, incorporating the host plasma membrane containing viral transmembrane proteins. Viral replication destroys the host cell and activates the host inflammatory immune response, releasing immunomodulators such as pro-inflammatory cytokines and chemokines and recruiting additional immune cells. Although essential to virus elimination, an exaggerated or aberrant host inflammatory response can paradoxically result in severe disease.

52.4 GENETIC VARIATION

Infection with influenza virus does not confer complete, lifelong immunity against repeat infection. Influenza viruses continuously evolve and change their antigenicity to evade immune detection, thus enabling the virus to cause repeated infections throughout a person's lifetime. Much of influenza's virulency comes from its genetic variability and the ability of the virus to infect across multiple species. Genetic variability, particularly involving the surface glycoproteins HA and NA, which are the major antigenic determinants, results from two primary mechanisms known as antigenic drift and antigenic shift.

Antigenic drift is caused by point mutations within the RNA gene segments of HA and NA, which occur continuously as the virus replicates due to error-prone viral RNA polymerases. Over time, these small changes eventually result in antigenically distinct strains of the virus that are not fully recognized by the human immune system and cause symptomatic infection due to lack of pre-existing, cross-reactive antibodies. Antigenic drift is the evolutionary response of the virus to selective immunological pressure in a population over time, and along with waning humoral immunity, is responsible for annual influenza epidemics. Continuous surveillance of antigenic drift is essential for predicting flu outbreaks and is the basis for influenza vaccine generation. All human influenza virus types (A, B, and C) undergo antigenic drift.

Antigenic shift involves drastic changes in the viral genome from genetic reassortment, a process whereby genomic viral RNA is exchanged among viruses of the same type (i.e. two IAVs) that coinfect the same host cell. When a host is infected with at least two different strains of virus (typically a human strain and an animal strain), genetic reassortment between the two strains can lead to the emergence of a novel virus strain capable of infecting a species with little to no pre-existing immunity, causing widespread infection, and if the virus is easily transmissible from person to person, can result in a global pandemic. Antigenic shift occurs sporadically and is restricted to IAVs due to their unique ability to cross the species barrier. All influenza pandemics result from antigenic shift of IAVs. Additionally, antigenic shift can also occur via the direct infection of humans with an animal (usually avian) influenza strain. One example is the H5N1 "bird flu," which is known to cause sporadic infection in humans, usually in the setting of prolonged, close contact with infected birds. However, cases of person-to-person transmission are exceedingly rare and non-sustained, thus limiting the potential for H5N1 to become a pandemic threat.[3]

52.5 EPIDEMIOLOGY OF INFLUENZA

Influenza infections occur worldwide and are a major public health concern. In the United States, the annual attack rate is estimated at 5–20% but is often much higher in certain susceptible populations.[4] The major disease burden in

humans is due to seasonal epidemics of IAV and to a lesser extent, IBV strains. An epidemic is defined by a seasonal increase in influenza activity above a predicted baseline. Epidemics result from spread of a variant virus that has undergone antigenic changes differentiating it from previous strains to which some degree of pre-existing immunity in the form of cross-reactive antibodies exists within the population. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) perform year-round surveillance monitoring of influenza virus outbreaks and antigenic drift, which is crucial for predicting epidemics and formulating vaccines. Influenza outbreaks usually occur in the winter months, when conditions favor viral transmission. In temperate climates, the incidence of seasonal influenza typically increases in mid- to late fall and starts to decline by mid-spring. In tropical climates, influenza infections can occur intermittently throughout the year. Typically, influenza epidemics begins abruptly, peak within two to three weeks of onset, and last five to ten weeks. Approximately 10–20% of the population will become infected during an influenza outbreak.[5] The extent and severity of infection largely depend on the presence of pre-existing immunity within the population, which is determined by the presence of neutralizing antibodies from previous influenza infections and the degree of antibody cross-reactivity against the infecting virus strain. Children have the highest overall incidence of infection due to relative lack of pre-existing immunity. Host factors such as extremes of age, particularly adults over the age of 65 and children under 2 years old, and those with underlying medical conditions, especially cardiopulmonary disease, diabetes, and immunosuppression, cause higher risk for severe or complicated disease, hospitalization, or even death from influenza infection. In the United States, the CDC estimates that between 140,000 and 710,000 influenza-related hospitalizations and up to 52,000 deaths occur annually.[5]

Pandemic influenza occurs outside the usual influenza season, historically every 10–50 years. Criteria for pandemic influenza include the emergence of a novel IAV formed via genetic reassortment to which most of the population has little to no pre-existing immunity, which is capable of sustained person-to-person transmission, and which causes serious illness associated with high morbidity and mortality.[3] Since the start of the 20th century, there have been four major influenza pandemics: the H1N1 "Spanish Flu" in 1918, the H2N2 "Asian Flu" in 1957, the H3N2 "Hong Kong Flu" in 1968, and most recently, the H1N1pdm09 "Swine Flu" in 2009. Despite its name, the 1918 "Spanish Flu" was first detected in U.S. military camps during World War I and is estimated to have infected over 500 million people, or one-third of the global population, resulting in over 50 million deaths worldwide, making it the deadliest influenza outbreak in recorded history. During seasonal epidemics, death rates are highest in infants and elderly adults. An exception to this was the 2019–2020 influenza season, which resulted in the highest number of pediatric influenza deaths on record. However, during an influenza pandemic, the age distribution shifts, with higher mortality rates seen in healthy, young to middle-aged adults. The 1918 pandemic saw the highest mortality in young adults aged 20 to 40 years old. Similarly, high mortality was also seen in healthy young adults during the most recent H1N1 "Swine Flu" pandemic, which began in Mexico in February 2009 and rapidly spread across the globe at an unprecedented rate compared with prior pandemics. The CDC estimates that between April 2009 and February 2010, the H1N1 Swine Flu infected over 60 million people in the United States, with a predilection for infecting younger adults under the age of 25, resulting in approximately 265,000 hospitalizations and 12,000 deaths, with patients under age 65 accounting for an astonishing 90% of H1N1-related deaths.[6] The shift in age-related infection and mortality during the 2009 pandemic is believed to be the result of residual cross-protective immunity acquired from prior antigenically similar influenza infections earlier in life in older individuals. While pandemic influenza is rare, the limited number of prior pandemic events makes predicting future pandemics extremely challenging.

52.6 ECONOMIC IMPACT

The annual impact of influenza on the economy is substantial, though exceedingly difficult to accurately quantify. The CDC and the U.S. Department of Health and Human Services developed a model using epidemiological data to predict influenza-related health outcomes, which were then used to estimate the annual flu burden based on the 2003 U.S. population to evaluate the potential economic impact of annual influenza. Based on these data, the total annual economic burden of influenza on the U.S. economy was estimated at a staggering $87 billion, with direct medical costs amounting to $10.4 billion annually and estimated lost earnings due to illness and death from influenza totaling $16.3 billion annually.[7] More recently, an updated evaluation based on the 2015 U.S. population estimated the average total annual economic burden of influenza to be $11.2 billion, with direct medical costs estimated at $3.2 billion and indirect costs, including lost productivity, estimated at an average of $8 billion.[8] The cost discrepancies between these studies reflect just how challenging it is to measure the true economic burden of influenza. However, both studies clearly demonstrate the enormous financial impact of influenza.

52.7 PATHOPHYSIOLOGY OF INFLUENZA

Influenza is primarily spread from person to person via inhalation of large virus-laden respiratory droplets (≥5 μm in diameter) released into the air when an infected person coughs or sneezes within 6 feet or less of an uninfected person. Influenza can also be spread, albeit to a lesser extent, by smaller aerosolized droplets (<5 μm in diameter), which can remain airborne for minutes to hours and travel long distances, enabling virus transmission directly via inhalation

or indirectly by contact transmission, i.e. touching a surface contaminated with influenza virus and then touching the nose, mouth, or eyes. Transmission via fomites or hands contaminated with respiratory secretions can also occur; however, the virus only remains infectious on the hands for a short time (approximately 5 minutes), whereas virus deposited on non-porous surfaces can remain infectious for up to 48 hours.[9,10] Practical methods of limiting virus spread, such as frequent hand washing with soap and water and covering the nose and mouth when coughing or sneezing, remain crucial to preventing influenza transmission.

The main point of entry for influenza in humans is the mucosal surface of the respiratory tract. Once virus is deposited on the respiratory epithelium, the viral HA glycoprotein binds sialic acid residues on the host cell plasma membrane, triggering viral uptake into the cell via receptor-mediated endocytosis. Virus replication occurs within four hours of viral entry, resulting in either cell lysis or death by apoptosis, releasing newly formed infectious virions that subsequently infect and destroy adjacent cells. Following adult infection, virus is shed in respiratory secretions for about 24–48 hours prior to symptom onset and can be shed for up to 5–10 days with a peak of 1–3 days following the onset of symptoms.[11,12] The duration of virus shedding is prolonged in children and immunocompromised patients compared with healthy adults. Children may shed virus for several days prior to the onset of symptoms, likely due to a comparative lack of pre-existing immunity, whereas immunocompromised patients may continue to shed virus for months following initial infection.

52.8 CLINICAL ILLNESS

The incubation period for influenza is typically between one and four days, with an average of two days, and between three and four days among household contacts. Illness is usually heralded by the abrupt onset of fever and severe myalgias. While influenza infection may present with similar symptoms as other respiratory illnesses, systemic symptoms of influenza tend to be more severe, with prostration that is often out of proportion to the severity of other symptoms, which can help distinguish influenza infections. Fever is the most important physical finding and when present, can often be high, reaching up to 41 °C in the first 24 hours. Other systemic symptoms include generalized weakness, malaise, chills, headache, arthralgias, and nausea. Respiratory symptoms are typical and include non-productive cough, pharyngitis, nasal congestion, and rhinorrhea. Gastrointestinal (GI) symptoms such as vomiting and diarrhea may also be present but are generally more common in children. Infants and young children may present with febrile seizures. Adults over the age of 65 and immunosuppressed patients may present with milder, nonspecific symptoms such as weakness, confusion, anorexia, and malaise, with or without fever, and often in the absence of typical respiratory symptoms. Despite a milder initial presentation in the elderly population, infection can progress to severe and potentially life-threatening viral pneumonia. Findings on physical exam may include toxic appearance with facial flushing, conjunctival injection or watery eyes, clear nasal discharge, and hyperemic mucosa, including the posterior oropharynx; however, tonsillar purulence is uncommon. Occasionally, mild cervical lymphadenopathy may be appreciated. Lungs are generally clear, but approximately 25% of cases have diffuse rhonchi or rales on auscultation.[13]

In adults with uncomplicated infection, systemic symptoms usually last up to 7 days, with defervescence and improvement in respiratory symptoms after about 3 days; however, complete recovery may take up to 10 to 14 days, with longer recovery times associated with advanced age. On some occasions, patients may experience continued cough or malaise that persists for several weeks after acute infection. Since recovery from uncomplicated infection usually occurs within days, prolonged or ongoing symptoms may signal complications.

52.8.1 Pulmonary Complications

The most common and critical complication associated with influenza infection is pneumonia, which can manifest as primary viral pneumonia, secondary bacterial pneumonia, or combined viral and bacterial pneumonia. Complicated influenza infection classically presents with typical influenza symptoms followed by rapid respiratory decompensation.

Primary influenza virus–associated pneumonia was first officially described during the 1957 pandemic. Infection with certain influenza strains may be more likely to cause viral pneumonia than others. While primary viral pneumonia is a relatively rare complication of seasonal influenza infection, it can be rapidly fatal, especially in elderly patients. Primary influenza pneumonia results from direct viral infection of the lower respiratory tract. Symptoms include high fever and rapid onset of severe respiratory symptoms, including dry cough and dyspnea, often leading to respiratory distress with associated hypoxemia. Cyanosis may be evident on physical exam. Diffuse bilateral infiltrates are typically seen on chest imaging, and high virus titers can be readily detected in the sputum, notably in the absence of pathogenic bacteria on sputum culture. Mortality is high, with pathologic findings on autopsy revealing pulmonary edema, interstitial inflammation, necrotizing bronchitis, hyaline membrane formation, and alveolar hemorrhage.[14]

Pneumonia caused by secondary bacterial superinfection was first described during the 1918 pandemic as a biphasic illness and remains a significant cause of mortality associated with influenza infection. The development of secondary bacterial pneumonia is classically heralded by improvement and/or resolution of typical influenza symptoms, usually followed days later by rapid decompensation with recurrence of fever, new onset productive cough, worsening dyspnea, and consolidation on chest imaging. Blood counts may reveal a leukocytosis. and sputum cultures may

be positive for pathogenic bacteria. Influenza infection complicated by severe necrotizing staphylococcal pneumonia has been described in children and young adults and may appear as multiple cavitary lesions on chest imaging.[15] Bacterial species most commonly associated with influenza superinfection are *Staphylococcus aureus* (methicillin-sensitive and community-acquired methicillin-resistant strains), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae*.[16, 17]

Viral and bacterial coinfections are the most common influenza-associated pulmonary complications. Primary influenza pneumonia and secondary bacterial pneumonia occur most frequently in elderly patients >65 years old with underlying cardiopulmonary disease. Primary viral pneumonia is also more common in pregnant women and in young adults during pandemics and likely accounts for the increased mortality among young adults associated with pandemic influenza. Immunosuppressed patients, particularly with hematologic malignancy, recent solid organ transplantation, and HIV with low CD4+ count, are also at higher risk for influenza-related pulmonary complications.[18] Other pulmonary complications of influenza in children include laryngotracheobronchitis (croup), bronchiolitis, and bronchitis. In both adults and children with underlying chronic lung diseases such as asthma or chronic obstructive pulmonary disease (COPD), influenza infection can cause severe exacerbations associated with a decline in lung function, and increased risk of hospitalization and death.

52.8.2 Non-Pulmonary Complications

Although influenza primarily attacks the respiratory tract, other organ systems can also be affected with clinical manifestations that can vary based on the infecting virus type. Otitis media and sinusitis are relatively common complications of influenza infection, especially in children. During the 2014–2015 influenza season, several hundred cases of influenza-associated acute parotitis were reported in young males infected with influenza A (H3N2).[19] Myositis with elevated creatinine phosphokinase is also more common in children with influenza and can vary in severity from mild calf tenderness to problems ambulating. Myoglobinuria and rhabdomyolysis occur rarely but can result in prolonged renal failure.[20] Cardiac complications include myocarditis and pericarditis, and more commonly, exacerbation of underlying chronic disease in patients with pre-existing cardiac conditions.[21,22] Neurologic complications of influenza infection include encephalomyelitis, transverse myelitis, Guillain–Barre syndrome (GBS), aseptic meningitis, and encephalitis.[23,24] Reye's syndrome, an uncommon disease characterized by an acute and potentially life-threatening hepatic encephalopathy seen almost exclusively in children taking aspirin long term, has also been associated with influenza infection.[25] Reye's syndrome presents with nausea and vomiting followed by encephalopathy, seizures, coma, respiratory arrest, and even death. Laboratory results typically reveal transaminitis in the absence of elevated bilirubin and an elevated ammonia level. Cerebrospinal fluid studies are bland with no evidence of inflammation.[26] While the exact etiology of Reye's syndrome and the association with influenza infection remain unclear, the incidence of disease has decreased due to widespread warnings to avoid aspirin in children with acute respiratory symptoms.

52.9 Laboratory Diagnosis of Influenza

Diagnosis of influenza infection is often made clinically; however, the overlap in symptoms between influenza and other respiratory viruses can make accurate clinical diagnosis difficult. The sensitivity of clinical diagnosis ranges from 29% to 80% in healthy adults, with the likelihood of making an accurate clinical diagnosis largely dependent on the prevalence of influenza in the community as well as the clinical presentation/symptoms.[27–30] Fever and cough are the two most accurate symptomatic predictors of influenza infection, and rapid onset of these symptoms further supports the diagnosis. During seasonal epidemics when community influenza activity is high, the presence of fever plus either cough or sore throat in young to middle-aged adults can establish a clinical diagnosis of influenza with 77–90% accuracy.[27]

Laboratory tests for detecting influenza virus may be used to confirm the diagnosis, guide clinical management, or assist in surveillance efforts. Testing should be performed early in the disease course, ideally within the first 48–72 hours of symptoms when virus shedding is at its peak. Influenza can be detected in various respiratory specimens. Nasopharyngeal swabs are the most reliable and thus preferred specimen source, although nasopharyngeal washes or aspirates may also be used.[31] In patients with lower respiratory tract disease, endotracheal aspirates or bronchoalveolar lavage (BAL) specimens may be more sensitive in detecting influenza, especially in patients with influenza-associated pneumonia.[32] However, it is important to note that the respiratory specimen source(s) approved for different diagnostic tests may vary and should be considered when performing a specific test to prevent inaccurate results.

Influenza diagnostic tests include molecular assays such as reverse transcription polymerase chain reaction (RT-PCR) and other nucleic acid amplification tests, and antigen detection assays such viral culture, rapid influenza diagnostic tests (RIDTs), and immunofluorescence tests. Serologic testing for antibodies against influenza is virtually only used for research purposes and should not be used to influence clinical management. Viral culture and RT-PCR are considered the gold standard laboratory tests for diagnosing influenza. While influenza virus culture is highly specific (>95%) for influenza detection, it requires specific laboratory expertise and can take between three and seven days for results, precluding its use as an effective

diagnostic test, although it is useful for monitoring antigenic drift, detecting novel variants, and assessing response to antivirals.[33,34] Alternatively, RT-PCR is fast (results available within hours), can be performed in high volume, and is highly sensitive (>99%) and specific (>99%), making it the laboratory test of choice for diagnosing influenza. RT-PCR can determine the type and subtype of influenza virus and can also be multiplexed to detect and differentiate between influenza and other respiratory viruses. However, RT-PCR can be expensive and is subject to both higher false positive and false negative rates compared with viral culture due to specimen contamination and degradation, respectively.[35]

Rapid molecular assays are an alternative to traditional RT-PCR designed for rapid (within 15–30 mins), point-of-care detection of influenza A or B viral RNA, but unlike traditional RT-PCR, cannot distinguish between different IAV subtypes.[36] Antigen detection assays such as immunofluorescence and RIDTs are qualitative immunoassays that detect the presence of IAV or IBV antigens such as nucleoprotein (NP) in respiratory samples. Antigen detection tests provide rapid (<15 minutes to a few hours), inexpensive, point-of-care testing with high specificity but only moderate to low sensitivity (40–70%) making them good screening tests but limiting their diagnostic utility given their propensity for false negative results, often requiring follow-up confirmatory testing with a molecular assay. Rapid molecular assays have higher sensitivity (66–100%) and are thus recommended over rapid antigen tests.[37] It is important to note that treatment decisions should not be made exclusively based on laboratory tests, and the decision to treat should not be delayed for diagnostic testing, especially when the community prevalence of influenza is high.

52.10 PREVENTION

Vaccination is the most effective method for preventing influenza infection. Importantly, vaccination affords both individual and population protection from infection. Because children are very effective transmitters of influenza infection, and older adults may have a suboptimal response to vaccination, studies have proposed that vaccinating children may be more efficacious for preventing flu in the elderly than vaccinating the elderly population themselves.[38] Since influenza virus is primarily transmitted by inhaling virus-laden respiratory droplets, the cornerstone of infection prevention, aside from vaccination, is limiting exposure to infected persons, including avoiding close contact and maintaining a distance of at least 6 feet from people who are coughing or sneezing. Those who are sick with influenza or experiencing respiratory symptoms should avoid unnecessary close contact with other individuals or groups of individuals while symptomatic and attempt to limit the release of virus particles into the air by coughing or sneezing into a tissue or the crook of the arm. Other practical methods of prevention include washing hands with soap and water or alcohol-based hand sanitizers and avoiding contact with the face or eyes before washing hands, particularly during flu season and after contact with high-touch public areas such as door handles, and of course, after coughing or sneezing into the hands.

52.10.1 Vaccination

The immune response to both natural influenza virus infection and influenza vaccination is mediated by the humoral or B cell response. B cells generate antibodies primarily to the viral surface proteins HA and NA that can neutralize and eliminate the virus and protect against future infections. However, influenza virus is constantly undergoing antigenic drift to evade immune detection, and antigenic changes in HA or NA may result in incomplete immunity, whereby cross-reactive antibodies from a prior infection or immunization provide variable degrees of protection against the variant virus until new specific antibodies can be produced to clear the infection. Influenza vaccine formation relies on continuous surveillance of antigenic drift, particularly in HA, which is the main component of inactivated influenza vaccines. Vaccine composition is reviewed and updated annually based on surveillance and clinical and laboratory observations that enable prediction of the circulating strains most likely to cause human disease during a particular year. The Advisory Committee on Immunization Practices (ACIP) issues annually updated recommendations for influenza vaccination through the CDC.[39] The degree of protection afforded by influenza vaccination largely depends on community vaccination rates and how closely the predicted influenza virus strains represented in the vaccine match the actual influenza virus strains circulating during a particular year. Additionally, host factors such as age, immune function, and prior vaccination history can also impact the effectiveness of the influenza vaccine. Vaccine benefit is greatest among high-risk populations, specifically young children, adults over age 65, particularly with underlying comorbidities, and immunocompromised individuals. Vaccine-induced immunity develops within about two weeks in healthy adults, with peak antibody titers occurring after two to four months. Immunity typically lasts less than a year due to waning antibody levels and antigenic drift. Immunity may take longer to develop in children, particularly those who have not previously had an influenza vaccination. As a result, two doses of influenza vaccine are recommended for children aged six months to eight years who are influenza vaccine naïve. Studies have demonstrated the influenza vaccine to be up to 60% effective at preventing infection with influenza A and B.[40]

The ACIP recommends that all individuals aged six months or older who do not have any contraindications should receive an annual influenza vaccine.[39] Available types of influenza vaccines include inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), and live, attenuated influenza vaccine (LAIV). Influenza vaccines are formulated as either trivalent preparations, containing antigens from two strains of influenza A (H1N1 and H3N2) and one influenza B strain, or quadrivalent

preparations, containing an additional influenza B strain. IIVs are manufactured by growing virus either in embryonic chicken eggs or more recently, in cell culture, then inactivating the virus using ether or detergents. IIVs are administered by intramuscular injection. In recent influenza seasons, all available IIVs have been quadrivalent formulations, with both egg-based and cell culture–based vaccines available for individuals aged six months and older. Pregnant women should receive IIV during each pregnancy both to prevent severe infection of the mother while pregnant and to protect the baby during the first six months of life. Since inactivated vaccines are weakly immunogenic in elderly patients, a high-dose cell culture–based vaccine and an adjuvant-containing egg-based vaccine are specifically recommended for patients ≥65 years old.[39]

In 2013, a quadrivalent RIV was generated exclusively using recombinant DNA technology. Genetic recombination circumvents the use of the influenza virus and thus, the need for embryonic eggs, thereby shortening vaccine manufacturing time and enabling the use of RIVs in individuals with egg allergy. Currently, a quadrivalent RIV is approved for patients ≥18 years old.[39]

The first LAIV was introduced in the United States in 2003 as a trivalent formulation (LAIV3), which was later replaced by a quadrivalent LAIV (LAIV4) during the 2013–2014 flu season. In LAIVs, vaccine viruses are grown in embryonic chicken eggs and passaged at low temperature (25 °C), creating a cold-adapted, "attenuated" vaccine. LAIVs are administered intranasally and compared with inactivated vaccines, have been shown to induce a more broadly protective immune response in infants and children, with the distinct advantage of inducing mucosal immunity due to the ability of the vaccine virus to replicate in the nasopharyngeal mucosa. The ACIP adjusted its recommendation to include the use of LAIV4 during the 2018–2019 flu season.[41] Currently, a quadrivalent LAIV4 is approved for use in healthy individuals aged 2–49 years who have no contraindications; it has been shown to be effective in 90% of children.[39] Antiviral drugs may reduce the effectiveness of LAIVs and should be discontinued prior to LAIV administration (at least 2 days for oseltamivir and zanamivir, 5 days for peramivir, and 17 days for baloxavir) and avoided for at least 2 weeks following LAIV administration.[42]

Side effects of influenza vaccination are generally mild. Soreness at the injection site is common after intramuscular administration of IIVs or RIVs, particularly those that contain adjuvant, and can last for one or two days. Low-grade temperature elevations can also occur after vaccination; however, the occurrence is only slightly greater than with placebo. Nasal congestion and sore throat have been reported following LAIV administration. Absolute contraindications to influenza vaccination are rare, and the variety of vaccine formulations available has enabled more people to safely receive the vaccine who may have previously been contraindicated. A history of anaphylaxis to a vaccine component or following a prior dose of influenza vaccine is an absolute contraindication to receiving any influenza vaccine. Hypersensitivity to hen eggs is a contraindication to receiving influenza vaccines propagated in egg-based culture systems. Live, attenuated vaccines are contraindicated in pregnancy and relatively contraindicated in patients with immunodeficiency, as there are limited data on the safety of LAIV in this population. Although live attenuated vaccine virus can be transmitted to close contacts, this occurs infrequently and has not resulted in clinically severe illness. Regardless, LAIV administration is not recommended for those who have close contact with severely immunocompromised patients. A history of GBS within six weeks of influenza vaccination and moderate to severe acute illness, with or without fever, at time of vaccination are considered precautions, rather than contraindications, to influenza vaccination. Regarding GBS, it is worth noting that while GBS is known to occur, albeit rarely, after influenza infection, a clear link between inactivated influenza vaccination and GBS has never been identified even after years of vaccine safety monitoring.

52.10.2 Chemoprophylaxis

The antiviral medications oseltamivir, zanamivir, and baloxavir are approved for post-exposure chemoprophylaxis and are 70–90% effective at preventing influenza when initiated within 48 hours of exposure. Oseltamivir and zanamivir should be taken at the same time each day for a duration of seven days following most exposures or for ten days following exposure to a household contact. The new anti-influenza drug baloxavir is approved for post-exposure prophylaxis in persons 12 years of age and older and is given as a single oral dose based on body weight. In a multicenter, double-blind, randomized, placebo-controlled clinical trial, baloxavir demonstrated efficacy comparable to oseltamivir in preventing influenza infection after contact with an infected household member.[43] Antivirals are helpful adjuncts to vaccination to prevent influenza, although routine administration of antivirals for prophylaxis is not recommended, as this may promote antiviral resistance. Post-exposure prophylaxis is indicated for exposed, unvaccinated individuals at high risk for complications from influenza or for residents of long-term care facilities during an outbreak.

52.11 TREATMENT

The mainstay of treatment for uncomplicated influenza infection in low-risk individuals is supportive care. Adequate hydration should be maintained to replace insensible fluid losses from fever and increased respirations. Nonsteroidal anti-inflammatory drugs such as ibuprofen or aspirin (except in children or teenagers with influenza due to the risk of Reye's syndrome) can be used as antipyretics and for symptomatic relief of headaches, myalgias, etc. Most people with influenza infection generally do not require medical treatment or antiviral therapy. However, individuals at risk for severe or complicated disease, such

as the elderly, those with chronic cardiopulmonary disease or immunodeficiency, and pregnant women, who develop symptoms consistent with influenza should be evaluated for antiviral therapy by a medical professional as early as possible.

52.11.1 Antiviral Therapy

Three classes of antiviral drugs are approved for use against influenza in the United States: Adamantanes, neuraminidase inhibitors (NAIs), and the new class of anti-influenza drug, cap-dependent endonuclease inhibitor (CENI). Adamantanes, including amantadine and rimantadine, are an older class of antiviral drugs targeting the M2 ion channel of IAVs only and are no longer recommended for clinical use due to widespread resistance among circulating IAVs. The NAIs, oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), and the CENI baloxavir marboxil (Xofluza) are active against both IAVs and IBVs and are currently approved by the Food and Drug Administration (FDA) for treatment of influenza.[42]

NAIs target the enzymatic activity of NA by mimicking the binding of sialic acid in the active site of NA on influenza A and B viruses, preventing virus detachment from infected cells. NAIs are most effective against IAVs but demonstrate adequate effectiveness and efficacy against IBV strains as well. Oseltamivir is considered the drug of choice for treatment of influenza in most individuals. Early initiation of oseltamivir is associated with decreased duration and severity of influenza symptoms and has also been shown to significantly reduce the frequency of influenza-related secondary infections and exacerbation of underlying conditions.[44] Oseltamivir can be used to treat uncomplicated influenza infection up to 48 hours after the onset of symptoms in adults and children >2 weeks old and for chemoprophylaxis in adults and children >1 year old. It is administered orally as a prodrug absorbed by the gut, converted to the active metabolite in the liver, and excreted by the kidney. Standard dosing of oseltamivir for treatment of mild to moderate influenza infection in adults with normal renal function is 75 mg twice a day for five days. In individuals with renal impairment (creatinine clearance <60 mL/min), a reduction in the dose and/or dosing frequency of oseltamivir is recommended based on creatinine clearance. For individuals on hemodialysis, an initial 30 mg dose is recommended, followed by 30 mg after each dialysis session. The duration of therapy has also been extended in severely ill patients.[45] Oseltamivir is generally well tolerated with few side effects, the most common being GI upset, which can be abated when taken with food. It is also safe to use during pregnancy. Oseltamivir-resistant influenza A (H1N1) virus has been seen in individuals with no history of NAI use. However, most current circulating H1N1 strains remain sensitive to NAIs, although sporadic cases of oseltamivir resistance continue to be detected.

Zanamivir is administered via oral inhalation, with a standard dose of two inhalations twice a day, and is approved for treatment of uncomplicated influenza in individuals >7 years old within 48 hours of symptom onset and for chemoprophylaxis in individuals >5 years old. Zanamivir use can trigger bronchospasm in patients with underlying lung disease, such as asthma or COPD, and thus, is not recommended for use in these individuals. Zanamivir is also contraindicated in patients with milk protein allergy.

Peramivir is administered intravenously as a single 600 mg dose and is approved for influenza treatment in adults and children >2 years old within 48 hours of symptom onset. Dose reductions are recommended for individuals with renal failure with a creatinine clearance <50 mL/min, and additional doses have been used in patients with severe disease. Diarrhea has been reported with peramivir use. Peramivir is currently not approved for post-exposure prophylaxis.[46]

Studies of NAIs, usually oseltamivir, in healthy adults have consistently shown benefits, including reduced duration of illness, decreased risk of pneumonia and hospitalization, and reduced risk of mortality in hospitalized patients, with better outcomes strongly dependent on earlier antiviral administration (within the first 36 hours of illness).[44,46–51] Less is known about the benefits of early NAI use in high-risk or severely ill patients. One meta-analysis comparing oseltamivir use versus placebo in high-risk patients with underlying cardiopulmonary diseases found that oseltamivir use decreased the rate of pulmonary infections and hospitalizations by 28% and 52%, respectively, and reduced median duration of symptoms and disease severity compared with placebo.[52]

Baloxavir marboxil (Xofluza) is a new influenza antiviral medication approved for use by the FDA in 2018. Baloxavir is a CENI that prevents influenza replication by interfering with viral RNA transcription.[53] Baloxavir is given as a single-dose, weight-based oral regimen indicated for treatment of influenza or as post-exposure chemoprophylaxis in patients ≥12 years old.[43] As with NAIs, earlier administration (within 48 hours of symptoms) is associated with improved outcomes. While no significant adverse events have been associated with baloxavir use, taking this medication with dairy products, laxatives, or other products or supplements containing polyvalent cations (i.e. calcium, magnesium, iron, selenium, zinc) is not recommended, as it may decrease the efficacy of baloxavir by reducing the plasma concentration of the drug. Baloxavir is not currently recommended for patients who are pregnant or breastfeeding, for those with severe, progressive influenza infections, or in hospitalized influenza patients due to a paucity of data in these groups. Baloxavir and NAIs demonstrate similar activity against IAVs, although baloxavir has been shown to have improved activity against IBVs, significantly reducing the median duration of symptoms by over 24 hours in patients with IBV infection compared with oseltamivir.[54] The potential for combination therapy with NAIs and baloxavir is currently being investigated, although a recent randomized, double-blinded, placebo-controlled trial found no difference in time to clinical improvement in hospitalized

influenza patients who received combination therapy with an NAI and baloxavir compared with those who received NAI plus placebo.[55]

Early initiation of antiviral therapy (within 48 hours or less of illness onset) is recommended for patients with influenza or influenza-like symptoms with severe, progressive, or complicated illness, those at high risk for influenza-related complications, and those who require hospitalization.[56] Individuals at higher risk for severe or complicated influenza who should receive antivirals include children <2 years old and adults ≥65 years old, women who are pregnant or up to 2 weeks postpartum, patients with chronic pulmonary, cardiac, renal, or hepatic disease, hematologic disease including sickle cell, metabolic disorders (diabetes, obesity, body mass index [BMI] ≥40), neurologic, neurovascular, or neurodevelopmental conditions, immunocompromised patients (HIV/AIDS, chronic corticosteroids, chemotherapy), Alaska natives and American Indians, and residents of long-term care facilities.[57] Antiviral initiation in high-risk or hospitalized patients should not be delayed pending confirmatory testing results. While numerous studies have shown that antiviral initiation within 48 hours of illness onset is associated with the greatest clinical benefit, studies of high-risk and hospitalized patients with severe disease suggest potential benefits to antiviral therapy even when initiated after 48 hours of illness onset and when started up to 4 to 5 days after the onset of illness in patients hospitalized with influenza.[58,59] Antivirals can also be considered for treatment of influenza infection in previously healthy yet symptomatic patients who are not at high risk for complications, but only if initiation of treatment is less than 48 hours after symptom onset, as antiviral initiation later than 48 hours after symptom onset is unlikely to provide any clinical benefit in this population and may potentiate antiviral resistance. Factors to consider when selecting an antiviral include the indication for use (chemoprophylaxis or treatment), and the patient's age, weight, renal function, presence of chronic medical conditions, and current medications (to determine possible interactions).

52.12 INFLUENZA DURING THE SARS-COV-2 PANDEMIC

In 2019, the world was introduced to the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), to which a lack of pre-existing immunity resulted in a global pandemic on a scale that had not been seen since the influenza pandemic of 1918. Since the start of the SARS-CoV-2 pandemic, influenza activity worldwide has been at an all-time low even with increased influenza testing. In the United States, the 2020–2021 flu season saw such historically low influenza activity that the CDC was unable to provide information regarding the overall flu burden because stable estimates were impossible to ascertain. During the period from September 2020 to May 2021, only 0.2% of respiratory specimens tested by U.S. laboratories were positive for influenza compared with 26.2–30.3% of influenza-positive specimens during the previous three influenza seasons. This phenomenon is predominantly attributed to increased awareness and practice of infection prevention measures, such as physical distancing, including virtual learning, decreased global travel, self-quarantine practices, increased hand hygiene, and face mask use, among the public reducing influenza virus transmission.[60]

Influenza infection and SARS-CoV-2 infection cannot be distinguished by symptoms alone. Additionally, influenza and SARS-CoV-2 viruses can infect simultaneously, causing potentially deadly coinfections. While influenza and SARS-CoV-2 viruses are co-circulating, the CDC recommends that individuals with acute respiratory symptoms be tested for *both* influenza and SARS-CoV-2 infections, self-isolate while awaiting test results, and continue self-isolating if symptoms persist even with a negative test until symptoms abate due to the potential for false negative testing results, which depends on the type of test used and the community prevalence of both diseases. Various multiplex assays for simultaneous detection of influenza and SARS-CoV-2 viruses were approved for use by FDA Emergency Use Authorization (EUA) in December 2020.[37] Influenza vaccination remains as important as ever to prevent influenza infection as well as to prevent influenza and SARS-CoV-2 coinfections. The influenza vaccine does not protect against SARS-CoV-2 infection. However, several recent large cohort and retrospective studies have suggested potential protective effects of influenza vaccination on SARS-CoV-2 infection, including improved health outcomes and reduced risk of both severe SARS-CoV-2 infection and SARS-CoV-2 infection–related complications.[61–64] The influenza vaccine can be given simultaneously along with SARS-CoV-2 vaccines or boosters if administered at different anatomical sites. Antiviral therapies approved for influenza also have no activity against SARS-CoV-2 viruses and do not interact with any medications currently approved to treat SARS-CoV-2 infection. Given concern for coinfections, the CDC recommends early initiation of empiric antiviral treatment for influenza regardless of symptom duration for patients diagnosed with SARS-CoV-2 infection with respiratory illness who are hospitalized, have severe or progressive illness, or are at high risk for influenza complications.

52.13 SUMMARY

Influenza is a highly contagious respiratory disease caused by the influenza virus of the *Orthomyxoviridae* family. Influenza A and B virus types can cause repeated infection and seasonal epidemics in humans due to waning immunity and antigenic drift. Influenza A viruses can also undergo antigenic shift, creating a new virus subtype with the potential for causing widespread infection due to a lack of pre-existing immunity, which can ultimately lead to a global pandemic. IAVs are associated with the most severe infections and are responsible for all known influenza

pandemics. The symptoms and severity of influenza infection are determined by a combination of both virus and host factors and can range from mild upper respiratory symptoms to severe viral pneumonia. Pneumonia caused by bacterial superinfection is the most common complication of influenza infection; however, influenza can also cause a wide range of non-respiratory complications and lead to severe exacerbations of existing chronic diseases. Antiviral therapies are available for chemoprophylaxis and treatment of influenza and may be most beneficial in high-risk individuals, particularly when initiated early. While drug-resistant viruses have been detected, the clinical implications of these resistant strains are uncertain. Vaccination remains the cornerstone of influenza prevention. Despite a decline in seasonal influenza infections since the start of the SARS-CoV-2 pandemic, annual influenza vaccination remains as important as ever to prevent seasonal influenza and influenza coinfection with SARS-CoV-2.

CLINICAL APPLICATIONS

- Influenza infection is preventable through vaccination and interventions that reduce virus transmission, such as hand hygiene and avoiding close contact with those who may be sick with influenza.
- During seasonal outbreaks, when community influenza activity is high, an accurate clinical diagnosis of influenza can be made in the presence of typical symptoms (fever, cough, myalgias), and confirmatory laboratory testing is generally not indicated unless the diagnosis is in question (atypical presentation in elderly or immunocompromised individuals) or the results will impact clinical decision making (antiviral or antibacterial therapy).
- Supportive care (resting at home, adequate hydration, antipyretics) is the mainstay of treatment for uncomplicated influenza infection.
- Early initiation of influenza antiviral therapies is recommended for certain high-risk populations, and the decision to start antivirals in these populations should not be delayed pending results of diagnostic testing.

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53 Indoor Air Quality

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KEY POINTS

- Indoor smoking, elevated radon levels, and elevated carbon monoxide levels present significant health hazards.
- Humidity levels greater than 50% in your home can promote dust mite and mold growth.
- Mitigation of common allergens can improve quality of life for those with allergic asthma.
- Hookah and e-cigarette use remain prevalent and pose considerable risk.
- Home appliances including continuous/bilevel positive airway pressure (CPAP/BiPAP) devices need periodic cleaning and replacement of disposable components.

53.1 INTRODUCTION

Since humans take over 20,000 breaths daily, clean environmental air is essential. The relationship between health and air quality was recognized early in the fourth century BC by Hippocrates, the Father of Medicine. Indoor air quality is particularly important to humans, since we spend up to 90% of our time indoors.[1] Air quality in the United States is regulated by the federal government through the Environmental Protection Agency (EPA). In this chapter, we highlight some sources of potential morbidity of indoor air quality as it pertains to lung health.

One of the most important tasks of the clinician meeting a patient is taking a comprehensive history of environmental exposures both at work and in the home. The healthcare worker should ask about contemporary exposures as well as exposures in their childhood home or homes.[2] Household factors that may affect respiratory health include primary and secondhand smoke, radon levels, home water damage, heating, and ventilation, especially related to wood or coal, renovation history, the presence of a pool or hot tub, presence of pets, and specific hobbies including arts and crafts, do-it-yourself repair work, or gardening.

53.2 SECONDHAND SMOKE

The awareness of smoking and its adverse effects is widespread. Yet globally, smoking remains a prevalent lifestyle choice; in 2020, the WHO estimates that 22.3% of the global population use tobacco.[3] This number is only slightly lower in the United States, where 19% of adults are estimated to use any tobacco product.[4] As a result of such widespread individual use, secondhand smoke, or environmental tobacco smoke (ETS), is a common exposure and is itself a major public health problem. Approximately one nonsmoker dies from secondhand smoke exposure for every eight smokers who die from smoking.[5] Three publications serve as landmark summaries of the effects of ETS on human health. The U.S. Surgeon General's Report in 1986 and a report of the National Research Council described the health risks associated with passive smoking.[6] Lastly, the EPA released a report in 1992 that causally linked secondhand smoke exposure to lung cancer, effectively classifying ETS as a group A carcinogen.[7] While secondhand smoke has been referred to as ETS in the past, the term "secondhand smoke" better captures the involuntary nature of the exposure.

Secondhand smoke is composed of a mixture of both the smoke released from the burning end of a cigarette, labelled sidestream smoke, as well as smoke exhaled by the smoker themselves, labelled exhaled mainstream smoke. During cigarette burning, over 4,000 chemical compounds are created, which may be toxic and carcinogenic.[8] While sidestream and mainstream smoke contain similar compounds (Table 53.1), the concentration and the properties of these can vary significantly. Secondhand smoke can linger in the local indoor environment for about 1.5–2 hours, which may increase both the exposure period and entry into lung tissue and body cells.[9] Sidestream smoke composition does not vary significantly by tobacco product brand, but it remains as much as ten or more times more toxic than mainstream smoke.[10]

The term "thirdhand smoke" has been referred to as cigarette by-products that cling to a smoker's hair and clothing as well as to household fabrics, carpets, and surfaces even after secondhand smoke has cleared.[11] These invisible tobacco toxins pose danger to small children, who are especially susceptible when they come into contact with contaminated surfaces.[12]

Smoke exposure can be measured by testing either environments or body fluids for nicotine, cotinine (a breakdown by-product of nicotine), carbon monoxide, and other smoke-related chemicals.[11] Modern devices can perform active sampling of the environment, measuring nicotine, carbon monoxide, nitrogen oxides, polycyclic aromatic hydrocarbons, and general particulate matter on the scale of micrometers.[13,14] As expected, the measured exposure is directly related to exposure level, room size, and ventilation rate within that room.[14,15]

In June 2002, the International Agency for Research on Cancer (IARC) concluded that "involuntary smoking,

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TABLE 53.1
Carcinogens and Suspected Carcinogens in Secondhand Cigarette Smoke

Carcinogens	Suspected carcinogens
Arsenic	Acetaldehyde
Benzene	Acetone
Beryllium	Acrolein
1,3-Butadiene	Acrylonitrile
Cadmium	2-aminonaphthalene
Chromium	Ammonia
Ethylene oxide	Benzo[a]pyrene
Nickel	Butyraldehyde
Polonium-210	Carbon monoxide
Vinyl chloride	Catechol
	Cresol
	Crotonaldehyde and Formaldehyde
	Hydrogen cyanide
	Hydroquinone
	Isoprene
	Lead
	Methyl ethyl ketone (MEK)
	Nicotine
	Nitric oxide
	NNN, NNK, and NAT
	Phenol
	Propionaldehyde
	Pyridine
	Quinoline
	Resorcinol
	Styrene
	Toluene

exposure to secondhand smoke or 'environmental' tobacco smoke, is carcinogenic to humans." The IARC concluded further that there is a "statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from their spouse who smokes. The excess risk is on the order of 20% for women and 30% for men."[16]

In January 2005, the U.S. Public Health Service's National Toxicology Program issued its 11th report on carcinogens. This report unambiguously states: "environmental tobacco smoke is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between passive exposure to tobacco smoke and human lung cancer."[17] Some studies also support an association of ETS with cancers of the nasal sinus cavity, breast cancer, leukemia, lymphoma, and brain tumors in children.[18] Evidence of an increased cancer risk from ETS stems from studies examining nonsmoking spouses living with individuals who smoke cigarettes,[15,19,20] exposures of nonsmokers to ETS in occupational settings, and exposure to parents' smoking during childhood.[11] Many epidemiological studies, including large population-based case-control studies, demonstrate an increased risk of developing lung cancer following prolonged exposure to ETS. Lifelong nonsmokers living with smokers had, on average, a 24% higher chance of developing lung cancer than those living with nonsmokers. Those exposed to the heaviest smokers for the longest time had the highest risks.[20] Similarly, there is a growing body of evidence suggesting a higher risk of death from the association of secondhand smoke exposure and ischemic heart disease. Most of the data involves spousal smoke exposure and risk ratios that range between 20% and 30% and a twofold excess risk of cardiac death in this population.[21–23] There may be a confounding effect in these studies, as there may be an innate risk in the U.S. population to develop cardiovascular disease. In addition, there are pathophysiologic changes due to secondhand smoke that have not been fully elucidated. It is known that the elevation in serum carboxyhemoglobin levels decreases exercise tolerance in both healthy persons and individuals with ischemic heart disease.[24] Also, "time until angina" decreases with increasing concentrations of serum carboxyhemoglobin, as does the frequency of arrhythmias during exercise, vascular endothelium damage, lower high-density lipoprotein cholesterol levels, and increase in fibrinogen with associated fibrinogenesis.[24–26]

53.3 SECONDHAND SMOKE EXPOSURE IN CHILDREN

The Pro-Children Act of 1994 prohibits smoking in facilities that routinely provide federally funded services to children. Many state and local governments have passed laws prohibiting smoking in public facilities such as schools, hospitals, airports, bus terminals, parks and beaches, and private workplaces, including restaurants and bars. There is no doubt that the impact caused by secondhand smoke exposure raises the frequency and severity of respiratory illnesses and respiratory symptoms in children. In a 1993 report, the EPA estimated that between 150,000 and 300,000 annual cases of bronchitis and pneumonia in children could be attributed to secondhand smoke in the United States. Of these, between 7,000 and 15,000 will result in hospitalization. Secondhand smoke was also estimated to increase the rate of asthma exacerbations, with between 200,000 and 1,000,000 affected children.[5] In addition, secondhand smoke exposure increases the risk of sudden infant death syndrome (SIDS), and one survey found the risk of SIDS to be up to threefold in children exposed to active maternal smoking in utero and secondhand smoke exposure after birth.[27] Aside from the obvious medical implications, the economic burden associated with this increase in morbidity is responsible for a rise in healthcare costs likely to be in the millions, if not billions, of dollars. A recent study in Israel educated parents of 29 families to the dangers of tobacco smoke exposure to their children and showed a reduction in hair nicotine levels of the children, the number of cigarettes smoked by parents, and parent-reported child smoke exposure.[28] More education and research are needed to identify

opportunities for parents to reduce tobacco smoke exposure in their own children.

53.4 RADON

Radon-222 is a noble gas that is produced from the decay of uranium-238 and radium-226, which are naturally present in the earth's rock and soil. It decays with a half-life of 3.8 days. It can diffuse into the soil and air before decaying. The breakdown of radon-222 occurs by emission of an alpha particle, which produces radioactive progeny that include polonium-218 and polonium-214.[29,30] These are known as the "short-lived" progeny, and they, in turn, break down into "long-lived" progeny that include lead-210, which yields bismuth-210, which yields the stable isotopes polonium-210 and lead-206. This whole decay process takes hundreds of years. When inhaled into the lung, the alpha particles can damage cellular DNA and lead to mutagenesis in never-smoking lung cancer cases.[31]

Radon gas can seep into buildings through porous soil. The rate of diffusion is related to the pressure gradient created by the building structure across the soil, which in turn, is influenced by atmospheric pressure, wind flow over the structure, and the buoyancy of the air taking advantage of cracks or gaps in building foundations, floors, and walls, along with gaps along pipes, pumps, and drains. It can easily dissolve into and evaporate out of water. Therefore, water drawn from private wells in areas enriched with uranium can increase the exposure to radon. Inhaled radon poses a much higher risk for lung cancer than the ingested form from drinking water.[32,33]

Inhaled radon progeny have been linked to an increase in the risk of lung cancer in underground miners.[29] These progeny are the number one cause of lung cancer in never-smokers and the second-leading cause of lung cancer overall. The EPA estimates that radon exposure may account for over 21,000 lung cancer deaths each year, including 2,900 never-smokers, and the remaining deaths in smokers with radon exposure at concentrations as low as 2 pCi/L of air.[34] It is difficult to ascertain the exact amount, length, and degree of exposure needed to cause lung cancer. Most studies causally link the exposure of underground miners to uranium and lung cancer. A meta-analysis of 13 European case-control studies of uranium exposure showed an increased risk of lung cancer to smokers and recent former smokers, accounting for 2% of all cancer deaths in Europe, although it is difficult to accurately estimate the lifetime exposure to radon in these settings.[30]

The EPA recommends testing radon in homes and schools below the third floor, since toxic effects have not been reported in high-rise dwellings. A "do-it-yourself" kit may be easily acquired and left in place for 48 to 72 hours in the lowest floor and first-floor rooms without active ventilation or open doors. Long-term or 90-day trackers can better estimate year-round radon exposure and may be used when short-term devices yield a value higher than 4 pCi/L. If abnormal levels higher than 4 pCi/L are detected, interventions can include sealing gaps in the foundation or installing a ventilation or radon mitigation system that expels air to the outside environment and may require professional contractors.[34]

53.5 CARBON MONOXIDE

Carbon monoxide (CO) is an odorless gas, the by-product of the combustion of carbonaceous fuels. Sources of CO include unvented kerosene heaters, gas water or space heaters, leaking chimneys or furnaces, wood stoves, generators and any gas-powered equipment, automobile exhaust, and tobacco smoke.[35,36] Approximately 400 accidental deaths in the United States are attributed to accidental exposure to CO inhalation.[37,38] Interestingly, large storms and disasters have been associated with spikes in cases, as seen in Hurricane Rita in 2007 and again in New York city in 2012.[39,40] CO binds to hemoglobin with a high affinity, 200 times greater than oxygen, forming carboxyhemoglobin (COHb), which disrupts oxygen transport. Additionally, CO binds to heme proteins in myoglobin and cytochrome oxidase.[41] Tissues with the highest oxygen demands, including myocardium, brain, and exercising muscle, are first affected. The effects of CO are directly related to the level and duration of exposure. Initial symptoms include headache, fatigue, shortness of breath, nausea, dizziness, and tachycardia. At higher concentrations, cognitive impairment, loss of muscle coordination, coma, and death are possible. Symptom progression is illustrated in Table 53.2. Reductions in maximal oxygen consumption occur in normal young men with COHb levels near 5%.[42] Cardiovascular disease brings an even higher risk of morbidity with CO exposure.[50] A clear distinction should be made between angina and onset of cardiovascular disease as related to CO exposure, as moderate to severe CO exposures resulting in myocardial injury have shown morbidity and mortality implications.[43]

The average level of CO in homes without gas stoves is generally low, at 0.5 to 5 ppm. Levels near properly adjusted gas stoves vary between 5 and 15 ppm, but in poorly adjusted stoves, these levels can rise to 30 ppm or higher. At CO levels of 70 ppm, symptoms become more

TABLE 53.2
Carboxyhemoglobin Levels and Associated Symptoms

CO-Hb	Symptoms
10%	Dyspnea on exertion, forehead tightness, dilatation of cutaneous vessels
20%	Dyspnea on exertion, headache/throbbing temples
30%	Headache, irritability, altered judgment, fatigue, dizziness, vision changes
40–50%	Headache, confusion, syncope
60–70%	Coma, seizures, respiratory failure; death if prolonged exposure
80%	Rapidly fatal

noticeable, and at levels greater than 150–200 ppm, disorientation, unconsciousness, and death may occur.

CO levels can be monitored at home with a commercially available detector. The Consumer Product Safety Commission (CPSC) and the EPA recommend that a detector be located near the home sleeping area and on each level of the home.[44] They should not be directly above or beside burning appliances, as appliances may emit a small amount of CO upon start-up. A detector should not be placed within 15 ft of heating or cooking appliances or near very humid areas such as bathrooms.[45]

53.6 INDOOR MOLD

Mold is ubiquitous in the outside environment and plays an important role in breaking down organic matter such as trees and leaves. The abundance of mold enables easy transportation into the indoor environment, including homes, schools, and businesses, where it can raise concerns for long-term adverse health effects and worsening pre-existing lung disease. Approximately 100 molds have been identified as potentially harmful to human health, although only a few are commonly found in indoor environments. The molds most commonly found in the indoor environment include *Cladosporium*, *Alternaria*, *Epicoccum*, *Fusarium*, *Penicillium*, *Geotrichum*, *Rhodotorula*, *Chaetomium*, and *Aspergillus*.[46]

Molds are organisms with rigid cell walls that lack chlorophyll and vascular tissue. Molds are a subset of fungi and live on organic matter such as decaying plants and living animal tissue. By digesting materials deemed unusable by other organisms, molds can grow on home materials such as carpeting, drywall, ceiling tiles, and building materials made from organic matter. Molds thrive in a moisture rich environment and reproduce by germination of small particles called spores. Spores can grow, aerosolize, and be inhaled by or come in contact with humans in the environment. This was seen in the aftermath of hurricanes Katrina and Rita, when many homes had to be demolished due to excessive mold growth.[47]

A small subset of molds induce an immunoglobulin mediated antibody response in humans.[48] Illness brought on by molds can be classified into two types, infectious and noninfectious. Noninfectious types include allergic bronchopulmonary aspergillosis (ABPA), hypersensitivity pneumonitis, and worsening of pre-existing asthma. The most common symptoms of excessive indoor mold exposure include non-asthmatic cough, wheezing, headache, and sneezing. This can be exacerbated by energy-efficient homes, so-called tight homes, having closed ventilation systems with high indoor temperatures and humidity.[46] Exposure to mold or dampness during infancy increased the risk of asthma and rhinitis in a variety of cohorts, a risk that persisted into adolescence.[49,50]Infectious complications are less common. For example *Aspergillus* mold can be isolated in asymptomatic individuals, found in walled off cavitary lesions called aspergillomas, or in severe cases of infection, cause invasion of lung and blood vessels. However, this spectrum rarely causes disease in immunocompetent individuals and only becomes more common and more serious in the severely ill or immunocompromised.[51]

Preventing mold exposure involves identification and removal of both the mold and the moisture rich environment. Mold growth is readily identified in areas of prior water damage or high humidity by both visual identification and odors from the breakdown of organic matter. Mold can be successfully removed from hard non-porous surfaces with detergent and water, followed by complete drying. Porous areas, including ceiling tiles and carpets, should be disposed of, as the mold cannot be eliminated with cleaning alone.[52] Dead mold may cause health effects and must also be removed. Importantly, mold removal will not be complete until the moisture source is also eliminated.

53.7 ANIMAL DANDER

Animal dander is commonly associated with allergens from the skin cells of animals such as cats, dogs, and other furred pets. Cats and dogs seem to have the greatest risk of causing sensitization and the potential for causing health issues. Epidemiologic studies have shown that sensitization to dog and cat allergens is strongly associated with asthma.[53] Cats are well known to induce sensitization by a protein, Fel d1, which is found in the saliva and salivary glands. This protein is approximately 2.5 μm in diameter and is easily inhaled deep into the lower respiratory tract.[54,55] Because of its small size, up to 1 microgram of the Fel d1 protein may be inhaled per day, which is similar to the amount used in sublingual immunotherapy.[56] Even homes without cats can have high concentrations of up to 80 micrograms of Fel d1 per gram of dust/[54,57] Current evidence suggests that early exposure to animal dander in childhood reduces the likelihood of sensitization and subsequent development of asthma from both cats and dogs. It is important to tell patients that completely non-allergenic animals do not exist, but there are some breeds that are thought to be less allergenic.[58] Studies of Can r1 and r2, antigens released by dogs, found that these proteins were significantly higher in breeds promoted as hypoallergenic.[59,60] Reducing exposure to animal dander may be accomplished by using high-efficiency particulate air (HEPA) filters, frequent bathing of the animal, or removing the animal from the environment altogether.

53.8 DUST MITES

Dust mites, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are arthropods from the class Arachnida that colonize bedding, sofas, carpets, and any other woven material within the home. Dust mites are the most common allergen worldwide but are infrequently found at high altitude, in arid conditions, and in areas exposed to long, cold winters due to low humidity. Aside from causing allergic disease, dust mites

TABLE 53.3
Environmental Dust Mite Control Measures

- Use of impermeable mattress and pillow covers.
- Minimize reservoirs by frequent vacuuming and removal of stuffed animals from bedrooms.
- Remove carpeting from the bedroom.
- Decreasing the indoor humidity to less than 50%.
- Frequent washing of bedding, approximately every two weeks, in hot water.
- Removal of upholstered furniture.
- Avoidance of feathered and non-hypoallergenic pillows.
- Routine use of insecticides or allergen-denaturing agents is not recommended.

do not pose any other risk to human health. Mites, and the debris they produce, are microscopic, absorb moisture from the environment, and feed on dead animal and human skin cells. It is not the mite itself, but its fecal particles, that result in a strong allergic response in up to 26% of Americans.[61] Dust mite particles are large and heavy and when dispersed from their source only remain aerosolized for up to 15 minutes, settling very quickly.[62] This makes air purifiers such as HEPA filters ineffective with dust mite antigen removal. Although dust mites are found frequently in carpets and upholstered furniture, the most common sources are bed mattresses. Dust mite allergens can worsen pre-existing asthma but are not known to directly cause it. Table 53.3 shows control measures that can reduce dust mite allergen burden.

53.9 COCKROACHES

Cockroaches are common in the environment and play an important role in indoor air quality and the development of asthma, particularly in urban environments. While there are over 3,500 different species, the most common are the German species *Blatella germanica* and the American species *Periplaneta americana*. Antigenic particles Bla g1 and Bla g2, similar to those produced by dust mites, are found in fecal particles as well as secretions.[63] High levels of cockroach infestations are seen in densely populated areas, urban or inner-city communities, and areas of low socioeconomic status.[64] Children sensitized to cockroach antigen at high levels (>8 U/g) were more likely to develop asthma, have higher asthma morbidity, and require more office visits and hospitalizations due to asthma.[65] Matsui and colleagues outline a comprehensive review of disproportionate asthma mortality among inner-city residents where approximately half of the homes have cockroach allergen levels more than >8 U/g.[66]

Several techniques have been recommended to reduce cockroach exposure, including covering food, controlling humidity, improving indoor sanitation, and implementing both chemical and nonchemical extermination.[67] Although a difficult task, improving sanitation and reducing overcrowding may significantly minimize the development and severity of asthma in inner-city children.

53.10 MICE

Mice and the allergens they release pose a significant health risk for both urban and rural indoor air quality. Mus m 1 and Mus m 2 are the major allergens found in mice dander, hair, and urine.[68] These allergens are commonly found in inner-city urban environments and are highest in rooms where food products are stored, including the cafeteria or kitchen. Mouse allergens were found in 95% of homes in a large study of inner-city children with asthma.[69] The greatest predictor of high levels of mouse allergen exposure was the presence of visible droppings.[70] The impact of these allergens was noted by Sheehan et al., where children with pre-existing asthma in homes with high levels of mouse allergen had more missed school days due to asthma-related events.[71] Exposure to mouse allergen is associated with high rates of sensitization. Children sensitized to mouse allergen were found to have increased risk of developing asthma and higher rates of asthma-related morbidity.[72] Urban children with asthma in homes with a high bed mouse allergen concentration were shown to have an 87% higher probability of asthma-related healthcare use.[73]

Overall, mice have a significant impact on the lung health of the people exposed and sensitized to their allergen. The most effective way to limit their impact is to prevent or reduce the chance of exposure. The use of rodent-proof construction, improved sanitation, and population control using traps and chemicals may also reduce exposure.

53.11 WATER PIPE SMOKING (ALSO KNOWN AS HOOKAH)

Known by other names, including Shisha and Narghile, combustible water pipe smoking has occasionally been falsely touted as a "safe" alternative to smoking. It is not a new idea, with reports of use dating back to the fifteenth century in both the Middle East and Europe, and predates the use of cigarettes.[74] Hookah bars, some opened in response to laws limiting indoor tobacco use, are small cafés and clubs that rent hookahs and their respective materials.[74] These bars are often geographically located to market themselves to young adults aged 18–24. One study found that one in five boys and one in six girls aged 18 had used water pipe tobacco in the past year.[75]

Smoking is done through direct heating of tobacco, sometimes flavored with burning embers or charcoal. The smoke is drawn through a pipe to a mouthpiece to be inhaled. Not surprisingly, the limited existing evidence indicates that water pipe smoking carries the same or similar health risks as cigarette smoking. Links have been made to many of the same adverse health effects, including lung, oral, and bladder cancer, as well as coronary artery and heart disease.[76,77] Despite knowing the risks, almost 90% of beginning Hookah smokers thought that cigarette smoking was

more addictive.[78] Analysis of mainstream smoke from water pipes found that it contains significant amounts of nicotine, tar, and heavy metals.[78,79] Nicotine levels increased up to 250% and cotinine levels, a chemical marker of nicotine exposure, to 120% with just one water pipe session lasting 40 minutes.[79] Because water pipe smoking has a more prolonged inhalation time and exposure than a conventional cigarette, it has been estimated that one session can be equivalent to smoking 100 cigarettes within that time.[79]

Other risks are also seen with use of the heat sources that are used to light the tobacco, such as wood or charcoal. These substances alone, when ignited, put one at risk for exposure to smoke that contains heavy metals and carbon monoxide. These compounds are known to cause cancer and obstructive lung disease more commonly in developing countries that use fire to cook.

Continued research may determine the absolute long-term health risks of water pipe smoking. The current evidence supports that both direct exposure and secondhand smoke exposure are at least similar to that of cigarette smoking and does not support it as a "safe" alternative.[75]

53.12 ELECTRONIC CIGARETTES (ALSO KNOWN AS VAPING)

Similarly, somewhat based on the perception of their safety compared with combustibles, there has been an exponential growth in electronic cigarettes.[80] A variety of electronic products are available, such as e-cigars, e-pipes, e-hookah, vapes, pens, mods, and electronic nicotine delivery systems (ENDS).[81]

e-Cigarettes are now the most used tobacco product for youths. In 2021, 2.8% of middle school students and 11.3% of high school students had used e-cigarettes in the past 30 days.[82] Based on Centers for Disease Control (CDC) data in 2020, 3.7% of U.S. adults were current e-cigarette users, increasing by 0.5% in the last four years.[4]

e-Cigarettes consist of a mouthpiece, a cartridge, an atomizer, a battery, and an indicator light. Once activated, the battery-powered heating element aerosolizes and delivers to the lung a mixture of compounds, which includes propylene glycol, vegetable glycerins, flavorants, vitamin E, lecithin, solvents, sometimes adulterants, and the intended ingredient of nicotine or frequently, cannabinoids.[80,83] Each cartridge can contain 6 to 24 mg of addictive nicotine, with a real and sometimes even greater risk for e-cigarettes to become addictive.[80,84] With innumerable brands, flavors, and options from both shops and other less regulated sources, the actual ingredients and nicotine content have remained murky and unclear.

On a cellular level, ENDS may promote vascular endothelial dysfunction, increased inflammation, and oxidative stress. Impaired pulmonary immunity has been reported in animal studies.[85] Likewise, e-hookah, when compared with combustible hookah, increased larger arterial stiffening and showed an increase in inflammatory biomarkers of C-reactive protein, fibrinogen, and tumor necrosis factor.[86]

Clinically, e-cigarette use may cause bronchitic symptoms, especially in adolescents.[87] Propylene glycol and glycerol vapor are known upper airway irritants and the most common components of many e-cigarettes.[80,84] Clinically, numerous cases and even deaths from severe respiratory illness have been associated with vaping product use, leading to the novel term "e-cigarette vaping product associated lung injury" (EVALI).[88] Proposed definitions and largely supportive care management thereafter have been debated, but there is agreement that vaping proposes significant risk in these unfortunate cases.[83,88] Furthermore, the diverse nicotine derivatives, polycyclic aromatic hydrocarbons, heavy metals, and aldehydes have shown cytotoxic activity, the long-term implications of which are concerning but ultimately unknown.[89] Increased urinary excretion of known carcinogenic volatile organic compounds from adolescent e-cigarette users would support the worry of carcinogenic risk.[90] The California Department of Public Health, in fact, was among the first to issue an advisory for the potential of e-cigarettes to cause cancer and birth defects as well as other reproductive harm.[91]

Yet again, secondhand exposure to e-cigarette emissions and toxins, especially indoors, is not without risk, and as such, the German Cancer Research Center has even issued an advisory.[80] Thirdhand toxin exposure continues to be a risk, as possible transmission from residual airborne nicotine, indoor carbon dioxide, aldehydes, and other particulate matter may remain on indoor surfaces in a variety of vape shops and was strongly correlated with the number of active vapers per hour.[92]

53.13 CONTAMINATION OF HOME SHOWERHEADS, DISHWASHERS, AND CPAP DEVICES

Although showering is thought to cleanse us from bacteria and other organisms we encounter throughout our day, bacterial contamination of household showerheads with potential pathogens has been reported. Organisms that can cause pneumonia in humans, such as *Mycobacterium abscessus*, *Mycobacterium avium* complex (MAC), and *Legionella*, have been isolated from showerheads, raising concern for potential infection of immunocompromised patients even in their own homes. Unhooking and allowing the showerhead to dry did not reduce the risk of Legionella or MAC colonization.[93,94]

Home dishwashers may also be contaminated with organisms such as *Pseudomonas*, *Escherichia*, and *Acinetobacter*, which can also cause pneumonia in humans.[95] In addition to bacteria, in one study, 83% of dishwashers tested were positive for the presence of fungi. The most common sites of contamination were the side nozzles, doors, and drains. Hot aerosols from dishwashers released into kitchens were also found to contain human opportunistic yeast. The plumbing system supplying water to the home was the suspected site of dishwasher contamination.[96] While theoretically a risk to those who are immunocompromised, there have been no

scientifically tested regimens of clear benefit to rid dishwashers or showerheads of contamination.[96]

It is estimated that more than 18 million Americans carry the diagnosis of obstructive sleep apnea (OSA) and that untreated sleep apnea has cost implications with resultant workplace accidents, motor vehicle accidents, lost productivity, and comorbid diseases. It is therefore essential that patients with OSA be treated. Continuous/bilevel positive airway pressure (CPAP/BiPAP) is the therapy of first choice for patients with OSA and used as well for many other respiratory conditions. However, contamination of devices may lead to additional problems due to growth of bacteria in the humidifier chamber, contaminated tap water use, and inconsistent cleaning of the device, hoses, and filters. To prevent this contamination, distilled water, which is free from bacteria, is the safest type of water to use in the CPAP humidifier. It is recommended that nondisposable CPAP filters be cleaned and reused weekly and changed every six months, and that CPAP tubing should be cleaned with warm soapy water every week and changed every three months. It is also recommended that the cushions on a CPAP mask be replaced twice monthly and that a new mask should be obtained at least every six months.[97] Devices claiming to disinfect and sanitize CPAP machines via ozone gas or ultraviolet light have fallen out of favor following a warning that these cleaning devices are not in fact Food and Drug Administration (FDA) authorized.

53.14 SMART DEVICES THAT ANALYZE INDOOR AIR QUALITY

Smartphone technology, integration, and the internet of things allow the exciting development of smart devices for our homes, workplaces, and all public buildings. Individual tools such as smart thermostats can personalize temperature control on schedule or even autonomously. Sensors are available to monitor levels of common indoor air pollutants such as carbon dioxide, volatile organic compounds (VOC), and particulate matter, which is solid particles and liquid droplets found in the air.[98] Monitoring and integrated control of temperature and humidity could directly improve air quality while combining other comfort metrics such as lighting or acoustics, proposing complete control of the indoor environmental quality.[99] Smartphone applications for the management, display, and analysis of this data can then be personalized by users to specific targets or analysis from a public health perspective. Air quality monitoring or "e-nose" devices have been proposed to protect vulnerable groups from indoor hazards. Research will be necessary to see if smart devices will be helpful tools to improve immediate safety and long-term lung health.[100]

53.15 SUMMARY

This chapter has identified key elements of indoor air quality that significantly impact the health of individuals in the United States. We have emphasized the relationship between indoor air quality and health as it pertains to exposure to the many different agents in the home. Many individuals remain unaware of the potential detrimental effects associated with these exposures. These range from secondhand combustible or vape smoke to radon or even the family pet. Lung health is important to all ages, and it is crucial to target environmental exposures that may increase health risks, including asthma, allergic reactions, and lung cancer. The U.S. government, through various agencies, continues to monitor and provide guidelines, reports, and recommended testing for many of these agents. However, simple interventions that can promote lung health include not allowing smoking of any kind indoors; checking home radon levels; reducing conditions that promote mold growth, dust mites, and animal dander; monitoring carbon monoxide levels; and keeping home appliances clean and replacing worn parts. More research is needed to identify potentially new home contaminants and pollutants, and how best to monitor them and their potential respiratory health effects. Lifelong awareness among family members and housemates, elimination of potential indoor environmental hazards, and increased awareness by healthcare providers are essential to promote long-term lung health and wellness.

CLINICAL APPLICATIONS

- Keep pollution out of your home by not allowing smoking indoors, by checking for radon, and by protecting against carbon monoxide.
- Control humidity in your home to decrease dust mites and mold growth.
- Avoid e-cigarette and hookah use and educate adolescents to their potential dangers.
- Avoid adverse effects of pet exposure by using HEPA filters and bathing furred pets.
- Keep CPAP apparatus clean by changing masks, cleaning hoses and filters at prescribed intervals, and replacing disposable components.

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54 COVID-19

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KEY POINTS

- SARS-CoV-2 is a novel virus belonging to the *Coronavirus* family, which also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for major outbreaks in history.
- Human to human transmission of aerosolized viral particles is the route for community spread.
- Infection can be asymptomatic, or with mild flu-like symptoms, or present as severe pneumonia and multi-organ failure.
- Old age and certain comorbidities, such as obesity, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, chronic lung disease, malignancy, and underlying immunosuppression, have all been associated with progression to severe disease and increased mortality from COVID-19.
- Vaccination as well as early treatment with antiviral agents or monoclonal antibodies have been shown to significantly decrease the length of illness, severity, and mortality from COVID-19.

54.1 DEFINITION

Coronavirus disease 2019 (COVID-19) is an acute atypical respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified as an outbreak in Wuhan, China and later declared a pandemic by the World Health Organization on March 11, 2020.[1]

54.2 BACKGROUND OF CORONAVIRUS OUTBREAK

Coronaviruses (CoV) of zoonotic origins have been known to cause infections in humans, ranging from common colds to severe respiratory infections. Out of these, three have led to more severe disease and outbreaks. Severe acute respiratory syndrome coronavirus (SARS-CoV), originating from bats in Guangdong, China, was responsible for the respiratory disease outbreak in 2002–2004 with about a 10% case fatality rate.[2] Middle East respiratory syndrome coronavirus (MERS-CoV) from dromedary camels was first reported in Saudi Arabia in June 2012 and spread to 27 countries with a case fatality rate of 34.4%.[3] In December 2019, several cases of acute atypical respiratory infections were identified in Wuhan, China. The pathogen was rapidly identified as a novel coronavirus from the family *Coronaviridae* and was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), given its resemblance to SARS-CoV. The origin of COVID-19 outbreak is unclear currently. Human to human transmission is the route for community spread. As of September 2022, COVID-19 has been reported in 228 countries and is responsible for the death of more than 6 million people worldwide with an observed fatality rate up to 5.9% in some countries.[4,5]

54.3 STRUCTURE OF SARS-COV-2

The CoVs are enveloped, single-stranded RNA viruses with a multi-domain nucleocapsid. SARS-CoV-2 possesses four structural proteins, the N (nucleocapsid) that holds the RNA genome, the S (spike) protein that is involved in cellular attachment and viral host cell entry, the E (envelope), and the M (membrane) protein, which plays a key role in viral assembly.[6] The S protein is composed of two subunits: S1 assists with binding to the host cell receptor, and S2 is responsible for fusion of the host and viral cellular membranes.[1] The S1 unit is further divided into a receptor-binding domain (RBD), which binds to the human angiotensin-converting enzyme 2 (ACE2) receptor, and an amino terminal domain (NTD).[7] The two subunits of the spike protein require cleavage by cellular proteases to allow the activation of the S protein and subsequent attachment and fusion to the host membrane.[8]

54.4 GENETIC VARIATION

Constant mutations are part of natural viral evolution. Compared with DNA viruses, RNA viruses usually have higher mutation rates. Interestingly, CoVs have a lower rate of genomic mutations due to the presence of an exonuclease enzyme that decreases replication errors.[8] Most of the documented mutation in the SAR-CoV-2 virus has been identified in the spike protein, leading to a decreased immunologic vulnerability to neutralizing antibodies, whether vaccine-induced or therapeutic monoclonal antibodies, causing increased transmissibility rates and risk of reinfection.[8] Some of the most common mutations on the SARS-CoV-2 variant include D614G mutation, associated with increase in viral replication in the respiratory epithelium as well as greater infectivity, N501Y mutation, associated with higher affinity for the ACE2 receptor,[9] and the

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TABLE 54.1
Variants of Concern

Variant name	Initial identification	Mutations	Characteristics
B.1.1.7 (Alpha)	United Kingdom - 09/20	Spike mutations: RBD mutation N501Y, P681H; NTD deletions at 69-70 and 144 positionsNon-Spike mutations: D3L, R203K, and G204R	Able to antagonize innate immunity, which increase its transmissibilityHigh viral load in the upper airway50% increase in mortality compared with previous variants
P.1 (Gamma)	Brazil - 10/20	Spike mutations: RBD mutation N501Y, E484K, and K417TNTD mutations that interfere with the binding to neutralizing Ab	High infection rateAble to infect and cause disease in people with history of infection by prior variants
B.1.1.529 (Omicron)	South Africa and Botswana - 09/21	Highly mutated strain with amino acid changes in all four structural and in non-structural proteins	Increased transmissibilityReduction in neutralization by few monoclonal antibodiesLess severe disease
B.1.351 (Beta)	South Africa - 09/20	Spike mutations: RBD mutation N501Y, E484K, and K417NNTD deletions at 242-244 positions	50% more transmissible than other variants. Re-infections commonly seen
B.1.617.2 (Delta)	India - 3/21	Spike mutations: RBD mutations L452R, P681R, and T478KNTD deletions at 69-70 and 144 positions	Increased transmissibilityBNT162b[a] vaccine showed effectiveness of up to 85%, and AZD1222[b] vaccine was effective in 60% of cases

[a] Pfizer/BioNTech vaccine.
[b] AstraZeneca vaccine.
Table highlights common SARS-CoV-2 variant of concerns, critical mutations and other characteristics.[8–11]

E484K escape mutation, which is associated with reduced monoclonal antibody neutralization[8] (Table 54.1).

54.5 EPIDEMIOLOGY

SARS-CoV-2 has been a cause of major concern worldwide ever since it was first reported in December 2019 in China. As of September 2022, SARS-CoV-2 has been identified in 228 countries with 554 million cases and more than 6 million deaths.[5] COVID-19 was the third leading cause of death in 2020 in the United States, accounting for approximately 375.000 deaths.[12] As per the World Health Organization (WHO), the estimated case fatality globally is close to 2.2%, but this rate varies significantly between countries due to differences in socio-economic status, access to healthcare, resource limitation, capacity strain, varying comorbidities, age of the population, and severity of illness.

Patients with certain comorbidities are at a higher risk of developing severe disease and complications. Conditions associated with increased risk include age older than 60 years, obesity, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, chronic lung disease, smoking, neoplasia, and underlying immunosuppression. Both hospitalization and mortality rates were significantly higher in this select group compared with patients with no to low risk (45.4% vs. 7.6% and 19.5% vs. 1.6%, respectively). Male patients also were found to have an increased risk of severe disease and mortality compared with female patients.[13–16]

Although the racial disparities in COVID-19 outcomes have not been clearly identified, there is clear evidence that Black-American, Hispanic, and certain ethnic minority groups experienced a higher risk of infection and severe disease. Among these minorities, Hispanics had the highest mortality rate.[12,15,16,17]

54.6 ECONOMIC IMPACT

The total economic impact of the SARS-CoV-2 pandemic is unknown at this time, but history has shown that an event of this magnitude has long lasting effects on society. Several disease control strategies to limit the spread of infection, like "lockdowns," travel restrictions, and social distancing, have significant socio-economic impact resulting in economic fallout and unemployment rates. These strategies caused significant hardships within diverse sectors including education, the manufacturing and service industry, healthcare, and supply chains.[18] COVID-19 has also exposed the fragility of healthcare systems and the lack of disaster preparation strategies globally.[18]

54.7 PATHOPHYSIOLOGY OF SARS-COV-2

SARS-CoV-2 attaches to and penetrates host cells via the spike protein, which is formed by two subunits (S1 and S2) and a cleavage site. The S1 subunit is further divided into a receptor binding domain (RBD) and an amino terminal domain (NTD). RBD acts as a binding site for the human ACE2 receptor. The latter is found in abundance on respiratory epithelial cells, upper esophageal lining, myocardial cells, renal proximal tubular cells, bladder urothelial cells, endothelial cells, and ileal enterocytes.[19] The RBD domain

is also the target for neutralization by the host antibodies.[20] Attachment of virus to the ACE2 receptor leads to exposure of a cleavage site on the S2 subunit. This is cleaved by either the host transmembrane serine protease 2 or the cathepsins, leading to host–virus membrane fusion and viral RNA release into the host cell.[16,20,21]

Although SARS-CoV-2 can affect multiple organs, COVID-19 is mainly considered as a respiratory illness. The virus induced lung damage occurs in two phases, early and late. The early phase is characterized by rapid viral replication leading to direct tissue damage, whereas the late phase is dominated by an overwhelming response of the host immune system with deployment of neutrophils, monocytes, and T lymphocytes. This so-called cellular activation precedes the release of various cytokines—interleukin (IL) 1, IL 6, IL 8, and IL 12, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF).[16] In severe cases, the resultant overwhelming and uncontrolled systemic inflammatory response—the "Cytokine Storm"—leads to direct endothelial damage and subsequent microvascular and microthrombi deposition.[22,23]

Various other mechanisms leading to vascular permeability, such as dysregulation of the renin angiotensin system (RAS) and activation of the kallikrein-bradykinin pathway, have also been described. In the lungs, these manifest as COVID-19 pneumonia progressing to pulmonary edema and acute respiratory distress syndrome (ARDS). Besides the lungs, the overactivation of the immune system also leads to multi-organ dysfunction.

54.8 CLINICAL FEATURES

The clinical manifestations of COVID-19 range from asymptomatic to severe disease resulting in ARDS and multi-organ failure, as described earlier. The commonly reported symptoms of COVID-19 include:

- Fever
- Cough
- Shortness of breath
- Severe fatigue
- Anosmia
- Dysgeusia
- Nauseas
- Myalgias
- Diarrhea
- Anorexia

The clinical presentation of COVID-19 has been divided into five categories per the National Institute of Health:

- Asymptomatic or pre-symptomatic: Individuals with positive SARS-CoV-2 test without symptoms
- Mild disease: Patients with common COVID-19 symptoms without the shortness of breath and with normal chest radiographic findings
- Moderate disease: Patients with lower respiratory symptoms or with abnormal lung imaging but with oxygen saturation greater than 94% on room air
- Severe disease: Patients with oxygen saturation less than 94% on room air, a respiratory rate greater than 30 breaths per minute, ARDS, or lung infiltrates or pulmonary infiltrates of more than 50%
- Critical illness: Patients with respiratory failure, septic shock and/or multi-organ dysfunction

Other extrapulmonary manifestations of COVID-19 include:

- Cardiovascular: myocardial ischemia, myocarditis, arrhythmias, cardiomyopathy, cardiogenic shock
- Hematologic: lymphopenia, thrombocytopenia, leukopenia, leukocytosis, elevated inflammatory markers such as C-reactive protein (CRP)
- Renal: acute kidney injury, proteinuria, hematuria, electrolyte abnormalities, metabolic acidosis
- Central nervous system: stroke
- Gastrointestinal: transaminitis

54.9 DIAGNOSTIC TOOLS

Rapid and accurate screening is a vital step in the containment of SARS-CoV-2 virus, especially given its high contagiousness and virulence. A significant number of resources have been dedicated to the development of rapid and reliable diagnostic tests to detect SARS-CoV-2 in both symptomatic as well asymptomatic patients.[24]

The current available diagnostic tests can be divided into the following three main categories:

1. **Nucleic acid-base diagnosis**: Detection of genomic regions of the pathogen either via polymerase chain reaction (PCR) or by using hybridization probe.
   Reverse-Transcription–Polymerase Chain Reaction (RT-PCR) is currently considered the gold-standard for the diagnosis of COVID-19. Besides providing high diagnostic specificity, it also serves as a valuable tool for determining the prognosis of the disease and infectiousness using the cycle threshold (CT) value. A CT value is the actual number of cycles (or amplifications) needed for the PCR test to detect the virus.[25]

   The sensitivity of PCR is highly variable and is mainly affected by the sample type, reported technique, and initial viral burden of the sample. For example, the sensitivity is as low as 40% and 50% from a nasopharyngeal and sputum sample, respectively, but as high as 80–100% from bronchoalveolar fluid. Lately, there have been reports of higher sensitivity, up to 97%, from a self-collected salivary sample.[26,27]

Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) utilizes four to six primers for amplification at a constant temperature, leading to rapid analysis. It also provides high sensitivity and specificity in a timely manner, making it a useful point of care test.[24,28]

Transcription-mediated amplification utilizes a retroviral reverse transcriptase and RNA polymerase enzyme to amplify a specific region of the viral RNA. This technique has been successfully employed for multiple-pathogen detection.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) based tests can detect viral RNA in fewer steps compared with PCR tests.[29]

2. **Serological and immunological** tests identify viral proteins (or antigens) or antibodies against these antigens in a patient sample. These tests are cost-effective and provide rapid results but carry a lower sensitivity and specificity when compared with molecular tests. Ideal targets for serological assays are the viral structural proteins: the nucleocapsid (N) protein and the RBD domain of spike (S) protein. Both N and S proteins are highly expressed during an infection. Given high false positive and false negative rates, test results must be carefully interpreted in the context of patient symptoms.
3. **Imaging**: Lung imaging can be used as an additional test strategy to support COVID-19 diagnosis. It can also help in categorizing the severity of illness.

   Computerized Tomography (CT) Scan: The common radiological signs of COVID-19 pneumonia include multiple and bilateral peripheral pulmonary infiltrate with ground glass, lobular, and/or segmental areas of consolidation.

   Lung Ultrasound: The point of care ultrasound (POCUS) of the lung has become an important bedside tool for a rapid, safer, and cost-effective diagnosis. Recently, there have been several studies attesting to the use of POCUS with 85–97% sensitivity, 91% specificity, and 97% positive predictive value in detecting COVID-19 pneumonia.[24–30] (Table 54.2).

54.10 ANTIVIRAL THERAPY

The spectrum of medical therapies to treat COVID-19 continues to grow and evolve. Almost all available therapeutic options are investigational and used under the United States Food and Drug Administration (FDA) Emergency Use Authorization (EUA) policy. As of September 2022, Remdesivir is the only antiviral agent that has received FDA approval for use in adult and pediatric patients weighing at least 3 kilograms.[31]

COVID-19 therapeutics are broadly classified into:

1. Antiviral agents: target viral attachment and replication
2. Anti-inflammatory agents: suppress dysregulated inflammatory response to SARS-CoV-2

After an initial exposure to SARS-CoV-2, patients typically develop symptoms within five to six days. The virus then generates a diverse range of clinical manifestations, ranging from mild infection to severe disease accompanied by high mortality in certain individuals with risk factors for

TABLE 54.2
Characteristics of the Diagnostic Tests Most Used

Detection technique	Test type	Testing site	Processing time	Accuracy	Quantitative or qualitative	Detection time after infection
RT-PCR	Nucleic acid-based	Laboratory	4 h	High	Both	1–8 days
Isothermal nucleic acid amplification	Nucleic acid-based	Laboratory	>3 h	High	Both	1–8 days
CRISPR-based assays	Nucleic acid-based	Laboratory	1 h	High	Both	5–10 days
Nucleic acid sequencing	Nucleic acid-based	Laboratory	2 h	High	Both	5–10 days
ELISA	Antibody detection	Laboratory	2 h	High	Both	5–10 days
LFA	Rapid antigen detection	Point of care	10–30 min	High	Only qualitative	10 days
Luminescent immunoassay	IgM and IgG antibody detection in patient's serum	Laboratory	2–3 h	High	Both	5–10 days
Protein microarray	IgM and IgG antibody detection	Laboratory	20–30 min	Moderate	Both	5–10 days
Agglutination assay	Antibody detection	Point of care	10–30 min	Moderate	Only qualitative	5–10 days

RT-PCR: reverse transcription–polymerase chain reaction.; ELISA: Enzyme-linked immunosorbent assay; LFA: Lateral flow assay.[24]

disease progression. In patients with mild infection, the initial host immune response is capable of controlling the infection. But in severe disease, excessive immune response leads to organ damage, respiratory failure, or death. The viral load usually peaks in the first week of infection and declines thereafter, while the antibody response gradually increases and is often detectable by day 14.

There are two main processes that drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of the SARS-CoV-2 virus. Later in the clinical course, the disease appears to be driven by a dysregulated immune and inflammatory response to SARS-CoV-2 virus leading to pneumonia, subsequent respiratory failure, and multi-organ damage. Thus, the antiviral therapies would have the greatest effect early in the course of the disease, whereas the immunosuppressive/anti-inflammatory therapies (like dexamethasone, tocilizumab, baricitinib) are likely to be more beneficial in the later stages of COVID-19.

54.10.1 Remdesivir

Remdesivir is a broad-spectrum antiviral agent with activity against members of the filoviruses like the Ebola virus, Marburg virus, and Coronaviruses. It is a prodrug that inhibits viral RNA polymerases. It is currently available only in an intravenous (IV) formulation, although an oral prodrug of the Remdesivir parental nucleoside is under investigation at the time of this writing.[32]

High-risk patients with COVID-19 having mild symptoms and a normal oxygen saturation presenting within seven days from symptom onset would be eligible for a three-day Remdesivir course.

COVID-19 patients with hypoxia (oxygen saturation less than 94% on room air), or those requiring supplemental oxygen by means of non-invasive or mechanical ventilation, would be eligible for a five-day course instead.[33] The duration can be extended to ten days if there is no clinical improvement, especially for patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO), although the evidence is limited.

Patients on Remdesivir need monitoring of their liver function. Alanine aminotransferase (ALT) value more than ten times the upper normal limit is an absolute contraindication to Remdesivir use.[33] Remdesivir should be used with caution in patients with underlying renal insufficiency due to the cyclodextrin vehicle used in the intravenous formulation, which can accumulate in patients with renal failure and may be toxic.

The rationale for a five-day treatment course came from the ACTT-1 trial, which was a multinational, randomized, placebo-controlled trial of Remdesivir that included 1,062 patients with confirmed COVID-19 having evidence of lung involvement. Eighty-five percent had severe disease, and 27% were receiving invasive mechanical ventilation or ECMO at baseline. Remdesivir resulted in faster recovery, defined as discharge from the hospital or continued hospitalization without the need for supplemental oxygen. In a subgroup analysis, the reduced time to recovery as well as the mortality benefit was statistically significant only among patients who were on low-flow oxygen at baseline. Among the subset of patients on mechanical ventilation or ECMO, the time to recovery and mortality was comparable to those in the placebo arm. Overall, there was a trend toward a lower 29-day mortality that was not statistically significant.[33]

The PINETREE study[31] was a randomized placebo-controlled trial in non-hospitalized patients with COVID-19 who were at high risk of clinical progression and were within seven days of symptom onset. Non-hospitalized participants were randomized to receive three days of IV Remdesivir or placebo. The results showed 87% relative reduction in the risk of hospitalization or death compared with placebo in patients who received three consecutive days of IV Remdesivir.

In summary, the maximum benefit of Remdesivir is seen in patients receiving no, or only low, supplemental oxygen. Patients requiring high-flow oxygen, non-invasive or invasive ventilation, or ECMO have not been proven to benefit at this time.

54.10.2 Nirmatrelvir-Ritonavir (Paxlovid™)

Nirmatrelvir-Ritonavir belongs to the class of protease inhibitors. Nirmatrelvir is active against a specific SARS-CoV-2 protease that plays an essential role in viral replication. Ritonavir, on the other hand, is used in the combination as a pharmacokinetic boosting agent. It augments Nirmatrelvir to achieve target therapeutic ranges via cytochrome P450 3A4 inhibition. Both Nirmatrelvir and Ritonavir are co-packaged and commercially available as Paxlovid™.

In the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial,[34] co-administration of Nirmatrelvir and Ritonavir by mouth for five days, initiated as soon as possible and within five days of symptom onset, showed 88% reduction in the risk of hospitalization and death from COVID-19.

It is not recommended for use in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min and requires dose modification for patients with an eGFR between 30 and 60 mL/min. It is also not recommended in patients with severe hepatic impairment (i.e., Child-Pugh Class C). Paxlovid™ has significant drug–drug interactions, primarily due to the ritonavir component in the combination. Thus, an accurate medication reconciliation and review of drug–drug interactions must be performed.[35]

54.10.3 Molnupiravir

Molnupiravir is another oral antiviral agent used under FDA EUA in patients with mild to moderate COVID-19.[36] It is a ribonucleoside that has broad antiviral activity against RNA viruses, resulting in viral mutation. However, given

TABLE 54.3
Antiviral Agents Used in Patients with Mild to Moderate COVID-19

Drug	Route	Days from symptom onset	Dosing
Remdesivir	Intravenous	7	200 mg on day 1 and 100 mg on days 2 and 3
Monoclonal antibody	Intravenous	7	See Table 54.4
Nirmatrelvir-Ritonavir	Oral	5	eGFR ≥60 mL/min: 300–100 mg twice daily for 5 days eGFR ≥30 to <60 mL/min: 150–100 mg twice daily for 5 days eGFR <30 mL/min: contraindicated
Molnupiravir	Oral	5	800 mg twice daily for 5 days

the concerns of its mutagenic potential in human host cells, it is reserved as a second line therapy. It is also contraindicated for use in pregnant patients due to reports of fetal toxicity observed in animal studies. Likewise, sexually active men should refrain from sex or use barrier contraception while receiving molnupiravir and continue to do so for at least three months after the last dose (Table 54.3).

54.10.4 Monoclonal Antibody

A monoclonal antibody (mAb), as the name suggests, is produced by a single clone or cell line, and consists of identical antibody molecules targeting a particular protein. The monoclonal antibodies against SARS-CoV-2 are derived from immunization of humanized mice with the viral spike protein and tested for potency against the virus. The most potent antibodies are then selected and are put into a cell line for large-scale production.[35,37]

Anti-SARS-CoV-2 monoclonal antibodies binds to the RBD of the main spike protein of the virus and prevent viral attachment to the host cells. Multiple randomized trials of commercially available monoclonal antibodies have shown strong evidence of preventing hospitalization and severe outcomes, when administered early in the course of the infection, in patients with mild to moderate COVID-19.

Various formulations have been used for management of patients, primarily based on their effectiveness (or neutralization potential) against the predominant variants driving the pandemic at various points in time. Evolving mutations in the viral spike protein and eventual emergence of SARS-CoV-2 variants have rendered multiple commercially available products ineffective. For instance, the Regeneron® combination of casirivimab and imdevimab, which had demonstrated susceptibility against the Delta, Gamma, and Beta variants, lost its neutralization potential and effectiveness against the Omicron variant due to a critical mutation in its binding site on the RBD. As of September 2022, bebtelovimab is the only available monoclonal antibody that is approved under FDA EUA for use in COVID-19 patients due to its effectiveness against the predominant BA.4 and the BA.5 Omicron subvariants[38] (Table 54.4).

54.11 ANTI-INFLAMMATORY AGENTS

Anti-inflammatory agents are used in patients with severe and critical COVID-19 in whom the pathogenesis is predominantly guided by the dysregulated immune response to SARS-CoV-2 virus.

54.11.1 Dexamethasone

Dexamethasone is indicated in all patients with COVID-19 who have oxygen saturations less than or equal to 94% on room air or who are requiring supplemental oxygen,

TABLE 54.4
Anti-Spike Protein Monoclonal Antibodies

Monoclonal antibody	Dose	Variants neutralized	Variants escaping neutralization
Bamlanivimab-etesevimab	Intravenous 700–1,400 mg as a single dose	Alpha/B.1.1.7Delta/B.1.617.2	Beta/B.1.351Gamma/P.1Omicron/B.1.1.529 and all subvariants
Casirivimab-imdevimab	Intravenous 600–600 mg as a single dose	Alpha/B.1.1.7Beta/B.1.351Gamma/P.1Delta/B.1.617.2	Omicron/B.1.1.529 and all subvariants
Sotrovimab	Intravenous 500 mg as a single dose	Alpha/B.1.1.7Beta/B.1.351Gamma/P.1Delta/B.1.617.2Omicron/B.1.1.529	Omicron subvariants (BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4, BA.5)
Bebtelovimab[a]	Intravenous 175 mg as a single dose	Alpha/B.1.1.7Beta/B.1.351Gamma/P.1Delta/B.1.617.2Omicron/B.1.1.529 and all subvariants (BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4, BA.5)	None as of September 2022[38]

[a]As of September 2022, bebtelovimab is the only approved mAb for use in COVID-19.[38]

non-invasive ventilation, or mechanical ventilation. Results of the RECOVERY trial[39] showed survival benefit of dexamethasone among participants who required supplemental oxygen. In a subgroup analysis of patients with normal or baseline oxygen saturation, there was no evidence for benefit. In fact, there was a trend toward harm in participants who were not on supplemental oxygen.

54.11.2 Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor antibody. In an open-label trial of patients with suspected or confirmed COVID-19 with hypoxemia and CRP level ≥75 mg/L, adding one to two doses of tocilizumab to usual care reduced the 28-day mortality rate compared with usual care alone. Eighty-two percent of the trial participants were also using glucocorticoids, mainly dexamethasone, and the subgroup analysis suggested that they were more likely to benefit from tocilizumab than individuals who did not receive glucocorticoids.[40] Thus, Tocilizumab is recommended in patients with severe or critical COVID-19 requiring mechanical ventilation, ECMO, or high-flow oxygen. All eligible patients must be receiving adjunctive dexamethasone and should be within 24 hours of clinical deterioration. Tocilizumab is not recommended without concomitant dexamethasone use. Its use is not recommended in the case of elevated transaminases, thrombocytopenia (platelet counts less than 50,000), severe neutropenia (absolute neutrophil count less than 500), severe immunosuppression, or an active infection other than COVID-19, or in patients who are at a higher risk of bowel perforation.

54.11.3 Baricitinib

Baricitinib is a Janus Kinase (or JAK) inhibitor used for treatment of rheumatoid arthritis. In addition to immunomodulatory effects, it is thought to have potential antiviral effects by interfering with the viral entry. It is given at a dose of 1 to 4 mg orally once daily for up to 14 days, based on the eGFR. It is contraindicated for use in patients with eGFR lower than 15 mL/min and must be used with caution in patients with history of deep venous thrombosis and/or pulmonary embolism.[41] Like Tocilizumab, Baricitinib is indicated for use in patients requiring high-flow oxygen or non-invasive ventilation and for selected patients who are on low-flow oxygen but are progressing toward needing higher levels of respiratory support despite initiation of dexamethasone (Table 54.5).

TABLE 54.5
Drugs Used in the Management of Severe COVID-19

Drug	Route	Dose
Dexamethasone	Oral and intravenous	6 mg daily for 10 days
Remdesivir	Intravenous	Day 1: 200 mg once Days 2–5: 100 mg daily
Tocilizumab	Intravenous	Body weight <30 kg: 12 mg/kg once Body weight >30 kg: 8 mg/kg once (Maximum dose: 800 mg) If clinical improvement does not occur, a second dose may be considered ≥8 hours after the first dose
Baricitinib	Oral	1–4 mg once daily for 14 days based on age and renal functions

54.12 PREVENTION

51.12.1 Vaccination

The magnitude of the COVID-19 pandemic presented an unprecedented need for highly effective and safe vaccines against the SARS-CoV-2 virus. Traditionally, vaccine development is a long and complex process requiring years of research and testing. But, a global collaborative effort guided by expedited sequencing of SARS-CoV-2 and massive funding allowed the utilization of state-of-the-art technology to complete preclinical, phase 1 trials in less than a year's time and led to the approval and distribution of anti-SARS-CoV-2 vaccines in record time in human history.[42]

As of September 2022, there are five broad categories of available vaccines against SARS-CoV-2[43] (Table 54.6):

1. *Whole virus (live attenuated and inactivated) vaccine*: It utilizes either the complete SARS-CoV-2 virus or part of the virus to trigger an immune response from the host without causing the disease. Live attenuated vaccines stimulate both humoral and cellular immune responses, in contrast to an inactivated vaccine, which only induces a humoral response.
2. *Viral vector vaccine*: A non-SARS-CoV-2 modified virus (or vector) carrying a genomic sequence generates a viral antigen of interest (the spike protein in the case of SARS-CoV-2) using the host cell protein synthesis machinery.
3. *Protein subunit vaccine*: These vaccines use specific viral proteins (or antigens) to trigger an immune response in a host.
4. *Nucleic acid (DNA and RNA) vaccine*: RNA vaccines deploy the genetic code of a specific viral protein, most commonly as messenger RNA (mRNA), which uses the host cell protein synthesis machinery to translate into a protein (spike protein in the case of SARS-CoV-2). DNA vaccine uses a bacterial plasmid encoding the viral antigen of interest for the same purpose.
5. *Virus-like particles (VLP) vaccine*: Laboratory synthesized molecules mimicking viruses, VLP, are used for B and T cell activation in the host.

The immunological response to the current vaccines against the SARS-CoV-2 virus involves activation of T

TABLE 54.6
COVID Vaccines[49–55]

Type	Manufacturer	Dosing
mRNA vaccine	Monovalent (Pfizer, Moderna)	Two intramuscular doses given 3 to 8 weeks apart
	Bivalent - Original and Omicron BA.4/BA.5 (Pfizer, Moderna)	Single intramuscular booster dose
Viral vector vaccine	Johnson and Johnson (recombinant Adenovirus type 26 vector)	One intramuscular dose; used only in individuals who cannot receive other COVID-19 vaccines
	AstraZeneca (recombinant ChAdOx1 adenoviral vector)	Two intramuscular doses given 8 to 12 weeks apart
	Sputnik V (human Adenovirus type 5 and type 26 vector)	Two intramuscular doses given 3 weeks apart
Inactivated whole virus vaccine	Sinopharm (BBIBP-CorV)	Two intramuscular doses given 3–4 weeks apart
	Covaxin (BBV152)	Two intramuscular doses given 4 weeks apart
	CoronaVac	Two intramuscular doses given 2–4 weeks apart
Recombinant protein vaccines	NovaVax (SARS-CoV-2 recombinant spike protein nanoparticle vaccine)	Two intramuscular doses given 3 to 8 weeks apart

cells, allowing the production of cytokines and memory cells and providing an immune protection for up to six months post vaccination.[44] As of September 2022, a total of 12,659,951,094 vaccine doses have been administrated, with 63% of the global population fully vaccinated and 28.36% boosted. The vaccination rate varies significantly between countries and continents. Several countries in Africa, like Madagascar, the Republic of Congo, Mali, Senegal, and Sudan, have the lowest rates of vaccination in the world.[45]

54.12.2 Chemoprophylaxis

In December 2021, the FDA granted an EUA to EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for use as pre-exposure prophylaxis. Both tixagevimab and cilgavimab are long acting, anti-SARS-CoV-2 spike protein monoclonal antibodies that are used in selected high-risk COVID-19 negative patients who are unable to mount a good vaccine response due to their underlying disease condition or due to an immunosuppressive medication. A total of 300 mg of tixagevimab and 300 mg of cilgavimab are administered as two separate consecutive intramuscular injections for individuals weighing over 40 kg. A repeat dose of 300 mg of tixagevimab and 300 mg of cilgavimab can be given every six months.[46]

54.12.3 Best Practices in Infection Control

Since the beginning of the SARS-CoV-2 pandemic, several infection control strategies have been employed to slow down the community spread of this virus. These practices include:

- Physical distancing: maintaining a distance of about 6 feet away from others to avoid spread through droplets.
- Isolation: patients diagnosed with COVID-19 are recommended to stay at home.
- Frequent hand washing with alcohol-based gel or soap and water.
- Masking: the recommendation is to wear a mask that covers mouth, nose, and chin while indoors, particularly in poorly ventilated areas.

54.12.4 Lifestyle Implications

The association of certain risk factors with the severity of COVID-19, especially progression to critical illness and mortality, has been well established.

The non-modifiable high-risk factors include:

Age: Patients aged 65 and above are more likely to develop severe COVID-19 infection, have a higher rate of hospitalization, need for mechanical ventilation, and mortality compared with younger individuals.

Race and ethnicity: Some racial and ethnic minority groups have been associated with worse outcome, likely due to barriers to healthcare access.

Other risk factors with the potential for modification with lifestyle modification are:

- Cigarette smoking
- Obesity, especially with body mass index over 30
- Diabetes
- Cardiovascular disease, including hypertension and coronary disease

Smoking cessation is associated with reduced risk of cardiovascular and respiratory conditions. Patients with limited or no physical activity are likely to progress to severe COVID-19 compared with patients who are physically active.[47] Regular exercise also helps reduce the risk of chronic conditions such as diabetes and heart disease,

which are independent risk factors for severe COVID-19. Pre-infection higher hemoglobin A1C levels and poor blood pressure control are predictors of severe COVID-19.[48] Improving blood pressure and glycemic control has been shown to decrease the progression to severe infection and hospitalization.

54.13 SUMMARY

The SARS-CoV-2 pandemic has been the seventh deadliest pandemic in human history, claiming more than 6 million reported and 17 million unaccounted deaths. The outset of the pandemic was particularly challenging due to lack of evidence-based treatment options and spread of misinformation on the social platforms, making implementation of community-based infection control strategies more challenging. The silver lining was the unprecedented global collaboration, knowledge sharing, and application of cutting-edge technology that allowed the rapid development of treatment and vaccines. We have a lot more to offer than we did at the beginning of the pandemic. We now have highly effective vaccines and potent oral and intravenous treatment options that have helped prevent hospitalizations and lower mortality from COVID-19 and its complications.

CLINICAL APPLICATIONS

- The SARS-CoV-2 pandemic has been the seventh deadliest pandemic in human history, claiming more than 6 million reported and 17 million unaccounted deaths.
- Mutation of the viral spike protein is accountable for the various emerging SARS-CoV-2 variants as well as reduced affinity to the neutralizing antibodies (natural, vaccine induced, or therapeutic).
- Vaccination, community infection control strategies, and personal hygiene are cost-effective ways to control the spread of infection.
- Antiviral therapy is most effective if given early in the infection course and helps prevent hospitalization, severe outcomes, and death from COVID-19.

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Part X

Obstetrics, Gynecology, and Women's Health



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55 Preconception, Pregnancy, and Postpartum Care

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KEY POINTS

- Adopting healthy lifestyle behaviors *prior to conception* has the greatest potential impact on the health of future offspring.
- Well-balanced and predominantly plant diets prior to conception are associated with improved maternal health and pregnancy outcomes.
- Physical activity that is maintained during pregnancy reduces pregnancy complications and pregnancy-related symptoms and is associated with appropriate weight gain.
- Preconception optimization of a woman's mental health is associated with improved pregnancy outcomes and improved self-care and infant care postpartum.
- Adverse pregnancy outcomes increase the risk of cardiovascular and metabolic disease later in life and provide an opportunity for lifestyle interventions.
- Human milk is the optimal nutrition for infants and confers several maternal and neonatal benefits.

55.1 INTRODUCTION

Lifestyle behaviors of women during their reproductive years are central to their overall health as well as the health of future offspring. Broadly speaking, the reproductive years of women are a continuum of care between preconception, pregnancy, and postpartum or interpregnancy care. The goal during these years is to identify risks for the development of chronic diseases as well as to mitigate or reverse chronic diseases that have a negative impact on pregnancy, neonatal, and childhood outcomes. It is also important to optimize wellness in women who may not have overt disease but can benefit from enhanced nutrition, physical activity, and emotional wellness to enrich their reproductive health and overall well-being.

Chronic diseases are rising in younger women, increasing the risk of infertility and subfertility, adverse pregnancy outcomes, non-communicable diseases in children, and even maternal death. Additionally, pregnancy is considered a window into future health because adverse pregnancy outcomes signal increased health risks over a lifetime. Sadly, most women are not aware of the importance of optimizing their health during these pivotal years nor of the impact of lifestyle behaviors on their reproductive health. This underscores the importance of viewing every visit with a reproductive-age woman as a potential opportunity to educate her about the importance of achieving and maintaining healthy lifestyle behaviors.

This chapter reviews the principles of lifestyle medicine during the reproductive years that can enhance overall health and reduce pregnancy-related morbidity. Evidence-based strategies and practical recommendations are offered to assist women's healthcare providers in counseling their patients for optimal reproductive health and improvement of their health across their lifespan.

55.2 PRECONCEPTION HEALTH

Preconception and interpregnancy care are an integral part of the continuum of women's healthcare. The goal of preconception care (PCC) is to optimize the health of every woman to reduce pregnancy complications, improve the health of future offspring, and enhance the long-term health of the patient.

Addressing modifiable risk factors due to lifestyle prior to and between pregnancies is important for several reasons. Often, women present with infertility due to a chronic disease such as obesity, metabolic syndrome, diabetes, and renal disease. Reducing or reversing the effect of chronic disease has the potential to improve fertility and reduce the risk of adverse events during pregnancy. Additionally, pre-existing chronic diseases are increasing in younger women and account for nearly half of maternal deaths.[1,2] Chronic disease also has a reciprocal relationship with adverse pregnancy outcomes (APOs) such as preeclampsia, gestational diabetes, and spontaneous preterm birth (sPTB). Not only does chronic disease increase the risk of APOs, but APOs also increase the future risk of a variety of chronic diseases including cardiovascular disease (CVD).[3] There is also a growing body of evidence from the developmental origins of health and disease (DOHaD) theory that a variety of lifestyle factors during periconception and pregnancy has a multigenerational impact affecting the health of up to three generations.[4] These lifestyle behaviors result in epigenetic changes during pregnancy that are associated with an increase in non-communicable diseases (NCDs) in future offspring.[4,5] Consequently, it is essential to address lifestyle

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behaviors *prior to conception* to optimize both maternal and fetal outcomes.

55.2.1 Challenges and Opportunities for Preconception Care

Most patients do not deliberately seek out PCC because they do not perceive the risks that chronic disease poses to a potential pregnancy nor understand the purpose of PCC.[6,7] Another significant barrier to PCC is that nearly 50% of all pregnancies are unplanned.[8] This coupled with fragmented healthcare[9] and that nearly a quarter of women are not seen for an annual healthcare visit[10] pose significant challenges for providers.

It is important to keep in mind that preconception care is not limited to a single provider or patient visit. Rather, it is part of the continuum of reproductive-age women's healthcare that includes multiple stakeholders. With that in mind, primary care providers, specialists, and allied healthcare professionals should look for opportunities to initiate transforming conversations during *every* patient encounter with women during their reproductive years. Additionally, there is a need for a multidisciplinary team approach to PCC, including models of intensive lifestyle management tailored to the needs of reproductive-age women.

55.2.2 Developmental Origins of Health and Disease

The theory of DOHaD originated from studies of the offspring of pregnant women who were subjected to the Dutch Winter Hunger during World War II. During the Nazi occupation of 1944–1945, pregnant women were subjected to food rations amounting to <800 kcal per day.[11] Emerging evidence from multiple cohort studies shows an association between severe caloric restriction, or undernutrition, and the risk of chronic disease in the offspring decades later, including obesity, altered lipid profiles, and CVD.[5,11] However, the effects were mainly restricted to the offspring of mothers who were exposed to starvation during periconception and early pregnancy.[11,12] Children born to women exposed to the famine later during gestation were born smaller but were less likely to be obese later in life.[11]

It is now known that in utero exposure to modifiable risk factors including overnutrition and undernutrition, chronic disease, stress, substance use, and exposure to environmental toxins all play a role in the future health of the offspring.[4] Furthermore, the lifestyle behaviors of the mother during pregnancy appear to affect the health of future children up to three generations.[4]

Mounting evidence points to fetal programming in utero through alteration in methylation of the epigenome as the most plausible explanation for the increased risk of NCDs later in life. For example, hypomethylation of the insulin growth factor 2 (IGF2) gene occurred after exposure to periconception starvation during the Dutch famine, but not for fetuses exposed late in gestation.[13] This suggests that the most critical time for epigenetic dysregulation is during periconception and early gestation.[14] This underscores the importance of adopting healthy lifestyle behaviors *prior to conception*, which is likely to have the greatest impact on the future health of the developing fetus.[15]

55.2.3 Nutrition

Preconception nutrition primarily focuses on micronutrient deficiencies without taking into consideration the dietary patterns that lead to these deficiencies. In Western countries, nutrient shortfalls occur predominantly from an overconsumption of overly processed caloric-dense food.[16]

Micronutrient deficiencies of one or more nutrients occur in 41% of reproductive-age women.[17] Micronutrient deficiencies are problematic because they increase the risk of congenital anomalies and maternal anemia. The most common shortfall nutrients are potassium, magnesium, riboflavin, and choline, along with vitamins D and E.[18] These deficiencies are more common in women of color, those of lower socioeconomic status, and women with obesity.[17,18] Additionally, more than 90% of women do not meet the RDA of 25–28 grams of fiber daily[19] averaging only 12.6 grams/day of fiber.[18] This finding reflects the highly processed food consumed in the standard American diet.

Women should be encouraged to consume a high-fiber, plant predominant diet periconceptually to reduce the possibility of micronutrient deficiencies. This is because the more dietary fiber that is consumed, the greater the number of micronutrients and vitamins consumed, excluding B12 and vitamin D.[20]

Nutrients of concern for women considering a pregnancy include folate, choline, iodine, iron, and vitamin D. Folate deficiency increases the risk of neural tube defects (NTD), so it is important for reproductive-age women to meet the daily RDA of 400 micrograms per day of folate at least one month prior to conception.[21,22] This is because the neural tube closes six weeks from the last menstrual period—before many women realize they are pregnant. Women at higher risk for folate deficiency include those with diabetes, inflammatory bowel disease, obesity, or a history of bariatric surgery. These women often need a higher daily intake of folate to maintain an adequate level. Consideration should be given to adding a supplement of 600 micrograms of folate per day for "at-risk" patients, which is the RDA during pregnancy.[23]

Choline is an important nutrient due to its role in fetal brain development. The current RDA for choline for reproductive-age women is 425 mg/day.[21] However, a recent randomized controlled trial suggests a benefit to consuming a higher dose of choline of 450–1000 mg/day because it improved cognitive outcomes in children.[24]

Iodine deficiency has become more of a problem in developed nations due to the increased use of non-iodized salt. The RDA for iodine is 150 micrograms per day, which can be achieved through a quarter to a half teaspoon of iodized salt.[25] Women planning to become pregnant should

increase their iodine intake to 220–290 micrograms/day to account for fetal requirements.[26]

Reproductive-age women require higher amounts of iron due to menstruation. The RDA is 18 mg/day[23,27] in reproductive-age women and increases to 27 mg/day[23] during pregnancy. Women contemplating pregnancy should increase their consumption of iron. Alternatively, they can begin a prenatal vitamin which contains 27 mg of elemental iron.

Vitamin D insufficiency or deficiency is extremely common in reproductive-age women.[28] This is especially a concern for women of color, women with obesity, and those with limited exposure to the sun.[29] Deficient vitamin D is associated with poor immune function, decreased fecundity, an increase in the risk of some cancers, and an increased risk of APO.[30,31] Ideally, a vitamin D level should be assessed annually with supplementation as needed. The Endocrine Society recommends a minimum of 1500-2000 international units (IU) of vitamin D per day in women with a body mass index (BMI) <30.[28] Higher doses of 6000–10,000 IU per day are needed to maintain a normal level for women with a BMI >30 or those with malabsorption issues.[28]

Foods that are considered toxic or potentially harmful should be avoided, particularly for those desiring to become pregnant within a year. Processed meats are designated as a carcinogen and red meats as a probable carcinogen by the World Health Organization and effort should be made to eliminate them from one's diet.[32]

Caffeine consumption should be <300 mg/day or roughly three cups of coffee per day.[33] Higher doses potentially increase the risk of fetal loss.[33] Additionally, the use of non-nutritive sweeteners is associated with metabolic syndrome and higher BMIs.[34]

Exposure to methylmercury is of particular concern in reproductive-age women due to fetal neurotoxicity in utero. The consumption of fish should be limited to 8–12 ounces of fish per week while avoiding fish with the highest amounts of mercury.[35–37] However, since there is no safe level of mercury consumption, if possible, women should avoid or limit their consumption of fish. An alternative to fish consumption is taking a microalgae supplement.

55.2.4 Exercise

Regular physical activity in the preconception period is an important component of a pre-pregnancy wellness plan. Maximizing physical fitness prior to pregnancy improves baseline cardiopulmonary function, leading to better tolerance of the physiologic changes of pregnancy and fewer symptoms related to increasing cardiac and respiratory demands. Regular exercise before pregnancy is also associated with less pregnancy-related back pain and pelvic pain and with fewer work absences related to pregnancy symptoms.[38–42]

Despite the known benefits of intentional physical activity during pregnancy, pregnant women often face challenges to maintaining an exercise program when pregnant—such as pregnancy-related nausea, fatigue, musculoskeletal discomforts, and societal pressures to reduce their level of activity. It is therefore not surprising that most women reduce both the frequency and intensity of their baseline physical activity level once pregnant.[43–47] Women with a higher level of physical activity prior to pregnancy tend to maintain an above-average exercise level during pregnancy and are far more likely to meet recommended activity guidelines than those who did not exercise sufficiently prior to pregnancy.[43,48]

Pre-pregnancy physical activity is also associated with improved obstetric outcomes. Increasing levels of activity prior to pregnancy are associated with a progressively reduced risk of excessive gestational weight gain (EGWG).[49,50] Pre-pregnancy physical activity is associated with improved insulin sensitivity[51] and a 22–86% reduction in the risk of gestational diabetes (GDM), with the largest reduction in risk found with more vigorous and more total hours of activity per week.[52–58] Some studies suggest a similar reduction in the risk of hypertensive disorders of pregnancy, though these data have been inconsistent.[59, 60] Pre-pregnancy exercise has also been associated with improved labor outcomes, including slightly earlier onset of term labor, 30% shorter average labor duration, and fewer operative deliveries.[48] No consistent association has been found between pre-pregnancy physical activity and the rate of Cesarean delivery, nor with neonatal birth weight.[39,48,61–63]

55.2.5 Prevention of Adverse Pregnancy Outcomes

Optimizing modifiable risk factors prior to conception has the potential to significantly reduce the incidence of APO. It is important to convey the risks of a poor lifestyle to our patients because it increases the risk of maternal and fetal complications including preterm birth, maternal mortality, and lifelong risk for chronic diseases including CVD.

Addressing modifiable risk factors preconceptually can significantly reduce the risk of GDM. Strategies for preventing GDM include obtaining a BMI <30,[64] normal HgA1C,[65] reducing insulin sensitivity with a plant predominant diet,[66] and supplementation with vitamin D.[31]

Diets higher in animal protein and eggs[67, 68] along with processed grains, sugar, and fat all substantially increase the risk of GDM.[69] In comparison, women who are most adherent to the Dietary Approach to Stop Hypertension (DASH) diet or a Mediterranean (MED) diet reduced the risk of GDM by 34% and 25%, respectively.[70] This was recently confirmed in a large prospective study (n=1900) in which those most adherent to the MED diet during periconception had a significant reduction in risk for GDM.[71] Interestingly, there is a linear dose response between consumption of dietary fiber and reduced risk of GDM. In this study for each 10g of fiber/day consumed, there was a 26% reduction in the risk of GDM, which underscores the importance of high-fiber diets in reducing APO.[72]

Physical activity is known to improve insulin sensitivity and can substantially reduce the risk of GDM. Women who exercise prior to conception can reduce the risk of GDM with the greatest benefit seen in women doing vigorous exercise and who exercise longer.[52–55,57]

Sleep disordered breathing (SDB) is associated with an increased risk of adverse pregnancy outcomes. Facco and colleagues noted that SDB more than triples the risk of GDM when present in early pregnancy after controlling for BMI, age, and hypertension.[73] There is also a linear correlation between the severity of obstructive sleep apnea (OSA) and the incidence of GDM.[74] Identifying women with SDB prior to conception and treating to improve overall sleep is important for improving overall health and may reduce the risk of GDM.

Chronic stress from adverse childhood events (ACEs) has also been associated with an increased risk for APO. In patients with depression before pregnancy, three or four or more ACEs are associated with an increased risk of GDM compared with women with no ACEs or history of depression.[75] Specifically, physical abuse had the highest correlation for risk of GDM. The Nurses' Health Study (NHS) II also found that physical abuse in childhood was associated with a 42% higher risk for GDM.[76] Additionally, forced sexual activity was associated with a 30% higher risk for GDM.[76] These findings underscore the importance of evaluating women for a history of ACEs before pregnancy so that appropriate intervention can be given that has the potential to reduce the risk of APO.

Preterm birth is a significant public health problem due to the high rate of neonatal deaths and subsequent infant morbidity.[77] Modifiable risk factors include nutrition, substance use, smoking, stress, and chronic diseases including obesity.[78,79]

In a recent large prospective trial, the risk of both spontaneous and medically indicated PTB was significantly reduced with a BMI <25 (aRR 0.58), a high-quality diet (aRR 0.68), and low to moderate stress in preconception or early pregnancy (aRR 0.60).[79] There was also a synergistic effect for more than one low risk factor compared with none and the risk of PTB. This effect was greater in women with a medically indicated PTB (RR 0.45) than for sPTB (RR 0.82).[79] These data emphasize the importance of optimizing modifiable risk factors prior to pregnancy, especially in women with preexisting chronic disease.

Periconception nutrition is an important topic to discuss with patients with a history of preterm birth or chronic diseases that increase the risk of a medically indicated PTB. Dietary patterns at periconception that are like the standard American diet, high in sugar and fat, increase the risk of PTB by 50%.[80] By comparison, a recent prospective study consisting of a multiethnic cohort showed that adherence to a MED and DASH diet during periconception significantly reduced the risk of sPTB.[71] A recent systematic review also showed dietary patterns higher in whole plant food that also included seafood with decreased amounts of fried food and red meat lowers the risk of PTB.[81] Additionally, supplementation with vitamin D reduces the risk of PTB by half.[31]

Sleep is an important vital sign for preconception health yet is typically not assessed at preconception visits.[82] In a systematic review and meta-analysis both short sleep duration and poor sleep quality were associated with a 23% to 54% increased risk for PTB.[83] Another group at risk is women who work night shifts or variable shifts—both are associated with an increased risk for PTB.[84] There also appears to be a trend in risk for PTB with moderate to severe SDB.[85,86]

Chronic stress has also been linked to lower rates of conception[87] and increased risk of PTB and infant mortality.[88,89] Specifically, an ACE score of two or more doubles the risk of PTB[88,90] Ideally, ACE screening should take place prior to conception with referral to a trauma specialist.

Preeclampsia is a disorder specific to pregnancy with the new onset of hypertension, proteinuria, and other signs and symptoms after 20 weeks' gestation.[91] The pathophysiology includes endothelial dysfunction and oxidative stress in utero and is a marker for increased risk of hypertension postpartum and a three-fold increased risk of CVD in the future.[92,93] The estimated increase in cost is over US$2 billion annually due in large part to the higher number of medically indicated preterm births.[91] Modifiable risk factors for preeclampsia include obesity, nutrition, obstructive sleep apnea, chronic stress, diabetes, chronic hypertension, and gestational diabetes.[91]

Dietary patterns greatly influence the development of preeclampsia. The Western diet consisting of increased sodium intake, processed meats, and sugar-sweetened drinks increases the risk of preeclampsia by 20%.[94] However, the reverse is true in those consuming a diet higher in whole plant food and fish and lower in refined grains and meat.[94,95] For example, a MED-type diet in Norwegian women reduced the risk of hypertensive disease by 42%.[96] And a retrospective study of women who were part of a vegan community had a very low rate of preeclampsia (0.001%).[97] This suggests there is a correlation between increased consumption of fiber from plants and a decreased risk of preeclampsia. In fact, consuming more than 21 g/day of fiber reduces the risk of preeclampsia by 67% compared with those consuming less than 12 g/day.[98] This study also noted a linear dose response to fiber. For every 5 grams/day of dietary fiber consumed, there is a corresponding 14% decrease in the risk of preeclampsia.[98] A whole food plant-based vegan diet averages greater than 50–60 g/day of fiber, which may explain why the incidence of preeclampsia is lower in that group.[20,97] Additionally, supplementation with vitamin D reduces the risk of preeclampsia by half.[31]

SDB is strongly associated with the development of hypertensive disorders in pregnancy.[73,99] Screening for OSA prior to conception is important so the patient can be referred to a sleep specialist for diagnosis and treatment. OSA typically worsens during pregnancy[100] and intervention with continuous positive airway pressure (CPAP) can reduce SDB, which has the potential to reduce APO, although more investigation is needed.

Chronic stress determined by an ACE score also increases the risk for hypertensive disease in pregnancy. A high ACE score, defined as more than three, had 60% increased odds of developing a hypertensive disorder of pregnancy after controlling for confounding variables.[90] Since ACE scores correlate with the development of chronic diseases, it is important to evaluate women prior to conception and refer for appropriate services.

55.2.6 Optimizing Mental Health

Mental health and physical health are intricately connected. Mental illness and chronic disease are strong risk factors for each other and frequently co-exist, with lifestyle factors, healthcare disparities, and secondary effects of medical treatments driving much of this relationship.[101–103] Just as it is critical to manage chronic disease prior to pregnancy, mental health should be assessed and optimized prior to pregnancy. Uncontrolled preconception mood symptoms have been linked to reduced fertility,[104,105] reduced success of in-vitro fertilization,[106] adverse pregnancy outcomes, impaired maternal self-care, and increased substance use.[107,108] Women with pre-pregnancy psychosocial risk factors including mental health conditions, substance use, health disparities, and exposure to violence or self-harm have also been found to have infants with lower mean birthweight, increased risk of neonatal injury or hospitalization, and increased infant mortality.[109] Up to 6% of women experience intimate partner violence (IPV) in the year prior to pregnancy, placing them at increased risk of depression, anxiety, posttraumatic stress, suicidality, substance use, reproductive coercion, and unintended pregnancy, in addition to physical harm.[110,111]

Women should be screened for both mood disorders and IPV in the preconception period. Any evident psychiatric diagnoses or risk factors should be identified, addressed, and managed with a pregnancy-appropriate treatment plan. Patients should be offered reliable contraception and understand the goal of timing a pregnancy once both mental and physical health have been optimized. Women with known or suspected psychiatric diagnoses should be counseled about the need to balance the risks of untreated mental illness in pregnancy against the risks of treatment in pregnancy. Non-medical strategies such as dietary modification, exercise, mindfulness, cognitive-behavioral therapy, and support groups should be employed first to reduce or eliminate the need for medical therapy in pregnancy. When such strategies are insufficient, most psychotropic medications can be continued during pregnancy when beneficial for the health of the mother. Valproate, carbamazepine, lithium, and paroxetine carry increased risks compared with other alternatives, and should therefore be avoided in pregnancy unless no viable substitute exists. Women using antiepileptic medications should be counseled to begin a daily 4 mg folic acid supplement at least two months prior to conception.[107] Multiple exposures increase pregnancy risks, so generally women planning pregnancy should be managed with the fewest psychotropic medications necessary to adequately manage their symptoms. This principle also includes exposure to comorbid substance use, which should be avoided when attempting pregnancy. Any planned initiation, discontinuation, or changes in the treatment regimen should ideally be accomplished prior to pregnancy, with the goal of achieving a period of proven stability on a stable regimen prior to conception.

If IPV is identified prior to pregnancy, the patient should be connected with a trained professional to address her safety, issues of reproductive choice, and potential psychiatric consequences; ideally utilizing a trauma-informed treatment approach.[110,111] Healthy social relationships should be encouraged, as positive social connectedness prior to pregnancy has been linked to fewer unintended pregnancies, fewer mood symptoms, and better coping skills for women with prior pregnancy complications or losses.[112] It also reduces feelings of isolation and improves self-confidence in women with mental illness, who may doubt their ability to successfully manage pregnancy and parenting.[113]

55.2.7 Optimizing Chronic Disease

Preexisting chronic disease in women poses significant maternal and fetal risks to a future pregnancy by increasing APO, severe maternal morbidity (SMM), and maternal mortality. Nearly four out of ten reproductive-age women have one or more chronic diseases, yet they are typically not aware of their risks, nor the importance of optimizing or reversing chronic disease via lifestyle changes, before trying to conceive.[114,115] Mitigating these risks is a crucial step toward reducing maternal morbidity and mortality due to chronic diseases from an unhealthy lifestyle.

Preconception counseling ideally should be integrated into *every* patient visit since nearly half of all pregnancies are unplanned. Another option for women with chronic disease who are contemplating pregnancy is to schedule a preconception consultation with a maternal-fetal specialist who can discuss specific pregnancy-related risks and contraindications for pregnancy. The goal of preconception counseling is to review maternal and fetal risks, advise on optimizing lifestyle behaviors to mitigate or reverse chronic disease, eliminate or avoid medication, avoid exposure to known toxins or recreational substances, and discuss preconception goals. An overview of maternal and fetal risks associated with the most common chronic diseases in reproductive-age women is outlined in Table 55.1.[116–118]

When feasible, lifestyle change should be employed to avoid or minimize medication exposures during the reproductive years. For women requiring ongoing medical therapy, some general principles should be followed: (1) medications with the best safety data for pregnancy should be selected; (2) known teratogens should be avoided unless no alternative exists; (3) anyone using a known teratogen during the reproductive years should be counseled about avoiding unintended pregnancy, intentional pregnancy planning with risk-mitigation measures,

TABLE 55.1
Preconception Counseling for Women with Chronic Disease[116–118]

Chronic Disease	Maternal Risks	Fetal Risks	Childhood Risks
Obesity	Infertility, miscarriage	Fetal anomalies	Childhood adiposity
	Nutritional deficiencies	(e.g. NTD, CHD)	Metabolic syndrome
	Cardiac dysfunction	Macrosomia	Developmental delay
	Obstructive sleep apnea	Birth trauma	ASD, ADHD
	Preeclampsia	Stillbirth	
	Gestational hypertension		
	Gestational diabetes		
	Failed induction of labor		
	Cesarean delivery		
	Endometritis		
	Postpartum hemorrhage		
	Venous thromboembolism		
	Maternal death		
Chronic HTN	Preeclampsia	Congenital anomalies	
	Cerebrovascular accident	Growth restriction	
	Renal failure	Preterm birth	
	Myocardial infarction		
	Gestational diabetes		
	Cesarean delivery		
	Placental abruption		
	Postpartum hemorrhage		
	Maternal death		
Diabetes	Preeclampsia	Miscarriage	ASD
	Cerebrovascular accident	Congenital anomalies	
	Myocardial infarction	Growth restriction	
	Pyelonephritis	Macrosomia	
	Urinary tract infections	Preterm delivery	
	Renal failure	Stillbirth	
	Cesarean delivery	Birth trauma	
	Maternal death	Hyperbilirubinemia	
	DKA	RDS	

NTD, neural tube defect;
CHD, congenital heart defect;
ASD, autism spectrum disorder;
ADHD, attention deficit hyperactivity disorder;
HTN, hypertension;
RDS, respiratory distress syndrome;
DKA, diabetic ketoacidosis.

and vigilance for early pregnancy; (4) if a medical regimen will be modified for pregnancy, a patient should ideally be switched to and stabilized on their new regimen prior to attempting pregnancy; and (5) a preconception plan should be developed for how to manage medications once pregnancy is suspected. With a few exceptions, prescribed medications should not be reflexively discontinued on the diagnosis of pregnancy, as doing so places the mother and her pregnancy at risk of uncontrolled disease. Outside of known teratogens, most medications are neither completely safe nor unsafe for pregnancy, as each agent has an individual safety profile influenced by dose, exposure timing, and genetic and environmental influences.[119] Patients should be involved in making a shared decision about treatment in pregnancy based on the potential risks and benefits.

An overview of preconception goals for the most common chronic diseases in women is outlined in Table 55.2.[64,120]

55.3 PREGNANCY

Pregnancy is an opportunity to improve the lifestyle of women and make a multigenerational impact on the future health of their offspring. It is also a time in which underlying disease can be unmasked, especially diabetes and

TABLE 55.2
Preconception Goals and Recommendations[64,120]

Chronic Disease	Recommendations	Goals
Obesity	Counsel on maternal and fetal risks	BMI <25
	Whole food plant-based diet	
	Screen for obstructive sleep apnea	
	Diabetes screen	
Pregestational diabetes	Counsel on maternal and fetal risks	Serum Cr <1.5 mg/dl
	Whole food plant-based diet	Total urine protein < 3g
	24-hour urine for protein and Cr Cl	BMI <25
	Retinal exam	HgA1c <6
	ECG	
Chronic hypertension	Counsel on maternal and fetal risks	Avoid ACE inhibitors
	Plant predominant diet	Avoid ARBs and statins
	Consider screening for cardiac	BP <120/80 mmHg
	dysfunction and renal disease	BMI <25

BMI, body mass index;
Cr, creatinine;
Cr Cl, creatinine clearance;
ECG, electrocardiogram;
ACE, angiotensin-converting enzyme;
ARBs, angiotensin receptor blockers;
BP, Blood pressure.

CVD. Thus, early identification of CVD risk factors with lifestyle intervention has the potential to positively impact both maternal and fetal outcomes.

55.3.1 Maternal Morbidity and Mortality

Over the last few decades, there has been a shift away from pregnancy-related maternal mortality such as postpartum hemorrhage to lifestyle-related mortality secondary to NCDs. Chronic diseases are now the underlying cause for almost half of all maternal mortality in the United States with rates three times higher in African American women.[1] CVD is the single leading cause of maternal death (33%) with another 14% due to non-cardiovascular medical conditions.[2]

More than 60% of women have one or more CVD risk factors during pregnancy, placing them at greater risk for APO and SMM.[121] There is also a linear correlation between the number of CVD risk factors (BMI >25, smoking, hypertension, diabetes) entering pregnancy and the relative risk of ICU admission, preterm birth, and fetal death with the greatest risk occurring in women with hypertension and diabetes.[121] Furthermore, SMM is directly correlated to the number of comorbidities with nearly a nine-fold increased risk for women with three or more chronic diseases compared with women with none.[122] These data underscore the importance of counseling patients toward a healthier lifestyle to reduce maternal morbidity and mortality from chronic diseases.

55.3.2 Nutrition

In general, dietary advice in pregnancy has focused on macronutrient and micronutrient requirements without regard to the dietary patterns that best meet those requirements. Sadly, nearly half of all pregnant women are deficient in one or more micronutrients in the United States, primarily due to overconsumption of processed food.[16,17] Non-Hispanic blacks and women with obesity and lower socioeconomic status have the highest rate of micronutrient deficiency.[17] And women who have malabsorption issues, underwent bariatric surgery, smoke, abuse substances, or have multiple gestations are at greater risk for micronutrient deficiencies.

A recent National Health and Nutrition Examination Survey (NHANES) showed that despite meeting the recommended number of macronutrients, pregnant women overconsumed salt (3.6 g/day), sugar (21 tsp/day), and saturated fat, with an average consumption of only 17.3 g/day of fiber.[123] The NHANES study also revealed several shortfall nutrients including folate, calcium, iron, magnesium, choline, and potassium, along with vitamins A, C, D, E, K, and B6.[123] These data reflect the calorie-dense, low-fiber intake from the standard American diet which is high in processed food and animal products.

Most pregnant women are also deficient in vitamin D. Vitamin D supplementation has been shown to halve the risk of a low birth weight neonate, preeclampsia, and GDM.[31] It can also improve bone mineralization in offspring.[124] Considering these benefits, it is prudent to assess a vitamin D level during pregnancy and supplement using current guidelines.[28]

Current recommendations for caloric intake during pregnancy are 2000 to 2200 kcal/day, which includes a 340 kcal/day and 450 kcal/day increase in the second and third trimesters, respectively.[23] The recommended daily macronutrient intake consists of 71 g protein a day (1.1 g/kg/day), 175 g of carbohydrates, and 20–35% fat.[23] Most micronutrient requirements during pregnancy are slightly higher when compared with preconception with the exception of iron (27 g/day), folate (600 µg/day), and iodine (220 µg/day).[23]Additionally, women should consume 28/34/36 g/day of dietary fiber during the first, second, and third trimesters, respectively.[19]

Nutrition counseling during pregnancy should emphasize nutrient-dense, fiber-rich plant predominant dietary patterns. A well-balanced vegetarian diet is considered safe during pregnancy and provides additional health benefits.[125]

Many providers are reluctant to endorse diets that are predominantly plant based out of concern for macro- or micronutrient shortfalls. In fact, whole food plant predominant diets meet or exceed the current DGA recommendations for micronutrients (except B12) and protein and provide more than 60 g/day of fiber.[20]

Ketogenic and low carbohydrate diets should be avoided as they lead to micronutrient deficiencies and hyperlipidemia during pregnancy.[126] Low carbohydrate diets are also associated with a higher risk of GDM,[127] and infants with an NTD, including those taking folate supplements.[128]

55.3.3 Exercise

Physical activity during pregnancy is beneficial to both the mother and fetus, as it is associated with reduced risks of excessive gestational weight gain, GDM, diabetic hyperglycemia, hypertensive disorders of pregnancy, mood disorders, preterm delivery, low birth weight, and operative and Cesarean deliveries.[47,129,130] The American College of Obstetrics and Gynecology and US Department of Public Health and Human Services guidelines for physical activity in pregnancy recommend at least 150 minutes per week of moderate-intensity aerobic activity,[47,131] a minimum standard not met by the majority of pregnant women.[132–134]

Physical activity during uncomplicated pregnancies is safe, with no associated risk of miscarriage, congenital anomalies, fetal growth abnormalities, preterm delivery, perinatal mortality, or hyperthermia.[47,130,135] Injuries from exercise during pregnancy are uncommon, with the majority related to falls.[136] Exercise techniques should account for mechanical changes such as a shifted center of gravity, and supine positioning should be avoided beyond 20 weeks of gestation to prevent aortocaval compression and hypotension. Women should wear loose-fitting clothing, ensure adequate hydration and caloric intake, and avoid high heat and humidity while exercising. Exercise should be done cautiously or avoided in women with cardiopulmonary disease, severe malnutrition, or obstetrical complications.[47,137–139]

A prescription for exercise in pregnancy should include guidelines for the frequency, intensity, type, and time (duration) of activity. These can be summarized using the pneumonic **FITT**.

(1) **F**requency: A minimum of 150 minutes of moderate-intensity exercise per week throughout pregnancy, ideally spread over four to seven days per week. For women who have been sedentary previously, they may initiate an exercise program two to three days per week and gradually increase to the goal activity frequency.[47,137]

(2) **I**ntensity: Moderate-intensity exercise, which is typically defined by a maternal heart rate no more than 60–80% of the age-predicted maximum heart rate but may also be defined by a perceived exertion scale or a "talk test" in which a woman can carry on a conversation while exercising.[47,140,141]Women who do regular vigorous-intensity exercise prior to pregnancy may continue these activities during pregnancy. Studies of fetal status during vigorous activity have been reassuring, though it is unclear if there is an absolute level of intensity or exercise duration beyond which fetal risk may occur. Elite athletes may warrant individualized counseling and close supervision, especially with frequent and prolonged duration of activity, or intensities exceeding 90% of their maximum heart rate.[142]

(3) **T**ype: Examples of safe activities in pregnancy include walking, stationary cycling, dancing, resistance work, stretching, and water aerobics. Exercises that should be avoided during pregnancy include scuba diving, contact sports, and activities with a high risk of abdominal trauma, imbalance, or falls.[47,143,144]

(4) **T**ime: The goal duration of exercise should be at least 20–30 minutes and up to 60 minutes per session.[145] Women new to exercise may begin with 10–20 minutes and gradually increase the duration of activity as tolerated.[146]

53.3.4 Emotional Wellness

Mental health conditions are common in pregnancy and are associated with increased risks, particularly when uncontrolled.[147] Women may carry psychiatric diagnoses such as depression or anxiety; may experience situational stress, pregnancy-specific anxiety, social stressors, and IPV while pregnant; or may experience long-term impacts from chronic stressors related to ACEs, societal marginalization, or trauma. Any number of these mental health and stress-related exposures may increase risks of unintended pregnancy, inadequate prenatal care, substance use, excessive or insufficient gestational weight gain, hypertensive disorders, and preterm birth.[148–155] All women should be screened in pregnancy for depression, anxiety, IPV, and psychosocial stressors using a validated screening instrument for each assessment. Specific screening tools should be adopted by each provider or practice and then incorporated into routine care in a consistent fashion.[156,157] Validated ACE questionnaires are also available to screen for adverse childhood experiences.[158]

Women with mental health conditions or significant stressors in pregnancy should be offered a multimodal approach to management, with lifestyle interventions first-line and ancillary or pharmacologic interventions as needed. Mood symptoms are more common with increased consumption of a Western-style diet pattern, processed and fast foods, added sugars, solid fats, and alcohol; in turn, symptoms tend to be reduced with consumption of more whole unprocessed and nutrient-dense foods.[159–161] Consumption of adequate macro- and micronutrient precursors and increased antioxidants and flavonoids in plant foods may prevent common nutritional deficiencies in pregnancy and reduce inflammation, both factors independently

related to mood disorders.[159,161,162] Aside from nutritional interventions, improved control of mood symptoms can be achieved with interventions such as improved sleep duration and quality, regular physical activity, mindfulness exercises, and social support. In women without an intrinsic support system or for those exposed to IPV, an unstable living situation, or prior trauma, referral for psychobehavioral interventions, trauma-informed care, social work services, or support through community partners may improve their emotional wellness and self-efficacy.[163]

55.3.5 Prevention of Adverse Pregnancy Outcomes

Gestational diabetes occurs in approximately 6% of pregnancies and contributes to increased risks of preeclampsia, macrosomia, birth trauma, Cesarean delivery, and neonatal complications.[78] GDM is more common among women who consume Western or high-protein diets,[164,165] while consumption of whole unprocessed foods and Mediterranean-style diets are associated with reduced risk.[165–167] Once diagnosed, dietary changes are the first line to manage maternal hyperglycemia. The American Diabetes Association (ADA) GDM diet, which advises a dietary composition of 40% carbohydrates, 20% protein, and 40% fat, is commonly recommended.[168] However, increased dietary fat is known to be detrimental to insulin sensitivity, and emerging data have shown that women started on the DASH diet or other diets higher in complex carbohydrates and lower in fat have improved glycemic control, lower insulin needs, and reduced macrosomia compared with those on the ADA diet.[169,170] Exercise is considered an adjunctive treatment for GDM, as it has been found to reduce maternal blood glucose levels and fetal hyperinsulinemia, and to support appropriate maternal and fetal weight gain.[129] Sleep deprivation should be avoided, as it interferes with glucose metabolism.[171] In addition, patients with OSA have an increased incidence and severity of GDM that correlates with the severity of the disorder[74,172] and management of OSA may improve insulin resistance and blood glucose control.[173,174]

Hypertensive disorders of pregnancy (HDP) affect 3–10% of all pregnancies and are responsible for a significant portion of iatrogenic preterm births, maternal morbidity, and mortality.[91] Western dietary patterns significantly increase the risk of preeclampsia,[96, 175] while Mediterranean diets and those with higher consumption of fruits, vegetables, whole grains, nuts, legumes, and fish are associated with reduced risk.[95,96] There is a strong dose-dependent reduction in the risk of preeclampsia with progressively increased daily fiber intake during pregnancy.[98] Other modifiable risk factors for HDP are low levels of physical activity and disrupted sleep, both of which are associated with an increased risk.[47,129] In patients with OSA, there is a cascade of sympathetic activation, endothelial dysfunction, altered vascular resistance, and impaired placental perfusion which is known to dramatically raise the risk of HDP.[172,176,177] Significant OSA typically requires treatment with overnight CPAP, an intervention that may reduce the likelihood of progression to preeclampsia and improve overnight blood pressure in women already diagnosed with preeclampsia.[178,179]

Preterm birth is the single most significant cause of neonatal morbidity and mortality, occurring in 10–12% of pregnancies but with notable racial and ethnic disparities.[180] One large prospective cohort study suggested the DASH diet may reduce the incidence of preterm birth by 42%, while those consuming a high percentage of processed meat, dairy, and fried and fast foods had a 53% increase in the incidence of preterm birth.[181] Other studies have demonstrated a reduction in the risk of preterm birth with adherence to Mediterranean and simple vegetarian dietary patterns.[182,183] Supplementation with omega-3 polyunsaturated fatty acids has been associated with a reduction in preterm birth in a systematic review, however, the benefit appears most substantial in women with low omega-3 consumption.[184] Some data suggest regular physical activity in pregnancy reduces the risk of preterm birth, though this impact may be stronger in overweight or obese women compared with normal-weight women.[185,186] Although OSA has been associated with an increased risk of preterm birth,[172,177,187] it is not clear if this is a direct effect or a consequence of maternal complications requiring preterm delivery.

55.4 POSTPARTUM AND LACTATION

55.4.1 Introduction

The postpartum period is a critical time of mental and physical recovery following pregnancy. Referring to the first 12 weeks postpartum as the "fourth trimester" reflects the continuum of fetal to infant development and the maternal changes that must occur to conclude a pregnancy.[188] The postpartum period carries an increased risk of maternal health complications, mood disorders, and maternal mortality; with a disproportionate number of maternal deaths occurring in women of color.[188–190] Yet, historically, the postpartum period is given little medical attention and is often devoid of adequate social and mental health support services. Shifting away from a single-visit model to a more holistic postpartum care model—one which incorporates recommendations known to improve postpartum recovery, supports the transition to parenthood, and provides risk prevention strategies—is expected to improve both short- and long-term postpartum outcomes.

55.4.2 Nutrition

Pregnancy demands increased nutritional requirements and may deplete maternal essential nutrient stores, impairing postpartum recovery and increasing the risk of mood disorders.[159,191] The largest and longest-lasting impact is on folate and iron levels, but reduced circulating levels of vitamins A, B6, B12, calcium, and zinc are also typical in the postpartum

period.[192] Postpartum caloric requirements are equivalent to those in non-pregnant individuals, but with lactation, there is an additional caloric requirement of 300–700 kcal/day necessary to maintain an isocaloric state.[19,193] In addition, a modest (100–200 kcal) caloric deficit is recommended to support early postpartum weight loss.[19] Specific caloric and nutrient recommendations for an individual patient may be calculated based on various factors (age, sex, height, weight, activity level, pregnancy or lactation status) using the USDA Dietary Reference Intake (DRI) calculator (www.nal.usda.gov/fnic/dri-calculator/index.php).[194]

Postpartum weight retention (PPWR) is the retention of gestational weight for one year or more following pregnancy. Women who lose all gestational weight by 6–12 months postpartum weigh significantly less ten years later, on average, than those who retain weight beyond one year postpartum.[195] Beyond 18 months, many women are moving into the preconception phase of their next pregnancy, and weight retained from a prior pregnancy increases their new baseline pregnancy weight. A cycle of weight gain and incomplete gestational weight loss with each pregnancy increases the risk of future pregnancy complications and later life health risks,[64,196] and pregnancy has been noted as a primary trigger for weight gain in 75% of obese women.[197] The primary driver of postpartum weight loss is nutrition. Although interventions such as physical activity, stress reduction, and adequate sleep are important for postpartum recovery and may augment weight loss, any successful postpartum weight loss program must contain a nutritional component to be effective.[64,197,198]A summary of recommendations is found in Table 55.3.[64,196,198–206]

In addition to repleting micronutrient stores, boosting satiety, and supporting gestational weight loss, consumption of a nutrient-dense diet in the postpartum period can support other healthy lifestyle behaviors. Adequate nutrient intake improves energy for physical activity, improves post-exercise recovery, promotes better sleep quality and regulation of melatonin levels, and reduces constipation.[198,207,208] Postpartum nutrition also plays a role in postpartum mental health, given the role of dietary nutrients in neurotransmitter production as well as the strong correlation between chronic diet-related diseases and mental health.[159,191]

55.4.3 Exercise

Physical activity may be resumed gradually in the postpartum period, and in most cases may be safely back to a pre-pregnancy frequency and intensity by four to six weeks postpartum.[47,198] At that point, women should aim to meet general adult activity guidelines of at least 150 minutes of moderate physical activity or 75 minutes of vigorous activity per week, as well as resistance training.[131] Exercise programs that can be done at home or those tailored to new parents may be beneficial and easier to maintain.[207,209] As an isolated intervention, postpartum physical activity is not highly effective for PPWR; but it has been shown to enhance the effectiveness of dietary interventions for postpartum weight loss.[198,207,210] It also has beneficial effects on cardiovascular and physical fitness, postpartum stress and mood symptoms, and sleep quality.[198,207,209]

55.4.4 Sleep

Obtaining sufficient sleep in the postpartum period is likely the most recognized challenge new parents face. Infant sleep patterns and overnight care lead to frequent parental sleep disruptions, short sleep duration, and poor sleep quality.[208,211,212] Impaired sleep is associated with increased postpartum mood symptoms, reduced physical activity, and more difficulty with self-care, meal preparation, relationships, and parenting.[196,208,211,213–215] Women who sleep less than five hours per night have a three-fold higher risk of PPWR at six months postpartum compared with those with a longer sleep duration.[196,211]

Cognitive behavioral therapy (CBT) focused on sleep hygiene can be an effective intervention to improve postpartum sleep.[213] Other interventions known to promote sleep quality and melatonin regulation include stress reduction techniques, exercise, sufficient intake of polyunsaturated and omega-3 fatty acids, creation of a conducive sleep environment, and modification of infant sleep routines.[208,209,213]

55.4.5 Postpartum Depression and Mental Health

Mood symptoms in the postpartum period are extremely common. Postpartum blues is a self-limited condition affecting up to 80% of women in the early postpartum period, usually resolving within two weeks without treatment.[216] Postpartum depression, on the other hand, is a major depressive episode lasting two weeks or more, seen in 10–20% of women in the postpartum period. Symptoms may be disabling and long-lasting, and often require both supportive and pharmacologic treatment.[216,217] Postpartum psychosis is rare, occurring in only 0.1% of postpartum women, but is the most potentially dangerous postpartum mood disorder and typically requires psychiatric hospitalization.[217] Postpartum depression and psychosis are associated with negative maternal and offspring outcomes[217] and warrant standardized screening and intervention. Suicidal ideation, homicidal ideation, or acute psychosis should be managed as psychiatric emergencies.[156,218] A less but increasingly recognized postpartum psychological complication is PTSD, which occurs in 1.5–7% of women, often resulting from a perception of vulnerability, danger, or trauma during the labor and delivery process – though this perception is not necessarily concordant with the actual circumstance or outcome.[219–222] PPD and PTSD frequently co-exist and effective treatment needs to address both conditions.[221]

Interventions known to be beneficial for postpartum mood disorders include simple screening and recognition, CBT, trauma-informed psychotherapy, and psychotropic medications when needed.[156,220,221,223] Healthy dietary patterns including whole and nutrient-dense foods are

TABLE 55.3

Summary of Postpartum Lifestyle Recommendations[64,196,198–206]

Nutrition Recommendations

Adequate caloric intake
- Non-lactating: 1200–1800 kcal/day
- Lactating: 1500–2300 kcal/day
  - 0–6 months: 500–700 kcal additional, target 300–500 kcal to account for modest calorie deficit/weight loss
  - 6–12 months: 300–400 kcal additional, assumes weight stability
- Use DRI calculator for individual needs
- Strict calorie counting not necessary
- Encourage portion awareness

Replenish micronutrients
- Aim for a healthy dietary pattern of whole nutrient-dense foods rather than focus on consuming specific nutrients
- Consume antioxidants and flavonoids from whole plant foods

Choose a healthy dietary pattern
- Whole food, plant-based diet
- DASH diet
- Avoid extreme carbohydrate restriction

Reduce dietary fat
- Consume ≤30% kcal from fat
- Most/all consumed fats should be polyunsaturated and omega-3 fatty acids
- Minimize intake of saturated fats
- Avoid all intake of trans fats

Increase consumption
- Whole grains (should be most or all of carbohydrates consumed)
- Fruits, vegetables, legumes, nuts, seeds
- Total and soluble fiber

Minimize or avoid
- Energy-dense foods (snack foods, fast foods, processed foods)
- Added sugars, added fats, high glycemic-load
- Red and processed meats
- Alcohol

Increase fluid intake, especially if lactating
- Primarily water
- Avoid sugar-sweetened beverages

Supplementation

Lactation
- Prenatal or multivitamin daily
- Vitamin D 1400 IU/day (4000–6000 IU/day if not supplementing infant)

Plant-based diet
- Vitamin B12 at least 2000 μg/week

Other Recommendations

Physical activity
- Minimum of 150 min/week moderate intensity or 75 min/week vigorous intensity
- Resistance training

Address mental well-being
- Manage postpartum mood disorders
- Provide strategies for stress reduction

Address sleep impairment
- Ideally target seven to nine hours per night, no fewer than five hours

Avoid smoking or substance use

Weight loss
- Target loss of gestational weight by 6–12 months postpartum
- Attempt to normalize BMI if elevated

Encourage lactation
- Aim for at least 12 months
- Exclusive for first six months if feasible

Arrange follow-up care
- GDM: GTT 4–12 weeks postpartum
- Transition from OB care to primary care
- Periodic screenings as indicated if history of APO (BP, glucose, lipids, BMI)

For all lifestyle interventions
- Start within six months of delivery
- Provide specific, actionable advice
- Intervention led by healthcare team if available
- Consider RD referral if available
- Primarily home-based interventions preferred
- Incorporate patient self-monitoring
- Involve the whole family

DRI, dietary reference intake;
DASH: Dietary Approaches to Stop Hypertension;
BMI, body mass index;
GDM, gestational diabetes;

associated with fewer symptoms of postpartum depression.[159,191] Increased mood symptoms are seen with the consumption of a Western-style dietary pattern with increased intake of processed foods, fast foods, added sugars, solid fats, and alcohol, as well as with extreme carbohydrate restriction.[159,191]

55.4.6 Adverse Pregnancy Outcomes and Long-Term Health

The postpartum period represents an opportunity to address the implications of any recent APO. Women should be counseled that APOs act as a window into their future health, as these outcomes often reveal latent disease risks that manifest clinically under the physiologic stress test of pregnancy.[64,195,197,206,224,225]

The risk of developing preeclampsia in pregnancy is strongly associated with classic cardiovascular risk indicators such as hypertension, elevated BMI, diabetes, and abnormal lipid levels; in turn, preeclampsia itself has been identified as an independent cardiovascular risk indicator. Patients with a history of preeclampsia during pregnancy are at increased risk of cardiometabolic disease, renal disease, premature cardiac death, and all-cause mortality

later in life when compared with women without this history.[197,206,224–231] These risks are highest with a history of severe, early-onset, or recurrent disease.[197,206,225,226,231,232] The cardiovascular risk is also increased with a history of other APOs, such as gestational hypertension, GDM, placental abruption, preterm birth, fetal overgrowth or undergrowth, and stillbirth; particularly when they exist in combination.[3,196,197,206,229–231] Many APOs are rooted in placental dysfunction, inflammation, and endothelial activation,[206,233] with an underlying vascular pathology similar to that seen in cardiovascular disease and supporting the closely interconnected nature of APO and cardiovascular disorders.[206,224,233] Patients with a history of GDM also have a dramatically increased risk of developing type 2 diabetes, with 5–10% of affected women meeting diagnostic criteria for type 2 diabetes immediately postpartum and 50% by ten years after delivery.[188,195,234] The risk of type 2 diabetes is also increased with a history of delivering a macrosomic infant, regardless of GDM status.[195,229,230]

Because of the associations with future chronic disease, women with a history of APO should be counseled about these risks, undergo periodic health screenings as indicated given their elevated risks, and be encouraged to consider lifestyle interventions that may not only reduce progression to clinically apparent cardiometabolic disease later in life, but also reduce the recurrence of APOs in any future pregnancy. Although news of their increased risks may be sobering to many patients, it is important to stress that the risks predicted by APOs are modifiable with lifestyle intervention. The unique preview of future health risks that pregnancy provides should be viewed as an opportunity for early intervention and as a motivating factor for change. A summary of recommendations may be found in Table 55.3.

55.4.7 Breastfeeding

Human milk is the preferred and physiologic source of nutrition for human infants.[235] The World Health Organization, Centers for Disease Control and Prevention, and American Academy of Pediatrics (AAP) recommend exclusive breastfeeding for the first six months of life, then continuing with the addition of complementary foods through one to two years of life.[235–237]

Human milk contains fats, carbohydrates, proteins, vitamins, and antibodies in a composition specific to the needs of human infants. This includes a higher whey-to-casein ratio, higher lactose content, and much lower protein content than most animal milks.[238] It is also a dynamic substance, providing a higher nutrient density during periods of rapid infant growth. The nutritional content of milk reflects the nutritional status of the mother for some nutrients, such as the content and type of fatty acids, the content of certain micronutrients (vitamins A, B1, B2, B6, B12, D, folate, iodine, selenium, choline), and of other substances such as insulin, environmental chemicals, heavy metals, and toxins.[239,240] Nutrients not significantly impacted by maternal diet include the total carbohydrate and protein content and other micronutrients (vitamins C and E, calcium, phosphorous, magnesium). Human milk is a poor source of iron, zinc, copper, and vitamin K regardless of maternal diet.[239] However, the only supplement routinely recommended for exclusively breastfed newborns is vitamin D, as all other micronutrients, including iron, are considered in sufficient supply until complementary foods are introduced around six months of age. The AAP and US Dietary Guidelines for Americans recommend infant supplementation of vitamin D 400 IU per day.[19] Although the RDA of vitamin D for lactating women is 600 IU per day, women are expected to benefit from increased supplementation of 1400 IU per day during lactation.[19,28] In addition, women who prefer to satisfy infant vitamin D requirements without supplementing their infant directly may consider high-dose vitamin D supplementation of 4000–6000 IU per day, a dose found to be safe and sufficient to enrich breastmilk adequately for infant vitamin D needs.[19,28]

There are a variety of maternal and infant benefits to breastfeeding beyond the simple provision of nutritional needs. Maternal benefits of breastfeeding include the additional caloric expenditure, which may facilitate postpartum weight loss, and reduced risks for later life type 2 diabetes, metabolic syndrome, hypertension, cardiovascular disease, and certain cancers.[64, 241] Lactation also facilitates maternal-infant bonding, reduces maternal stress, improves sleep quality, and supports natural family planning.[64,212,242] Infants fed human milk have a significant reduction in sudden infant death syndrome and develop a more favorable gut microbiome, which has been associated with improved gastrointestinal function and fewer gastrointestinal infections.[241,243–249] They also benefit from a reduction in respiratory, ear and throat infections, asthma, and atopic disease.[243] Breastfeeding promotes training of neonatal hunger and fullness cues, reducing infant and childhood overeating.[250,251] Infants fed human milk also have a lower risk of childhood leukemia,[252] improved neurocognitive development in childhood,[253,254] and reduced risks of both type 1 and type 2 diabetes and adulthood obesity.[231,241,253–255] Concerns about imperfect maternal nutrition or everyday environmental exposures should not be considered a reason to avoid or cease lactation – human milk remains the most nutritive and beneficial infant food even with a less-than-ideal diet.

Successful and sustained lactation relies not just on maternal will, but on practical needs such as social acceptance, lactation support, adequate parental leave, protected time and space for expressing breastmilk at work, and legal protections. Prenatal breastfeeding education, skin-to-skin contact at birth, infant rooming-in with the mother after delivery, and hospital policies and education supporting lactation have been shown to improve lactation initiation and continuation rates and reduce disparities.[256] Consultation with an International Board-Certified lactation consultant should be offered for any breastfeeding difficulties or maternal-infant separation. Community policies and legal protections supporting a woman's right to time and space

to lactate outside of the home should be supported by medical professionals and policymakers. Recommendations for unnecessary cessation of lactation – for example, advice to "pump and dump" after surgery or medication use – should be avoided unless supported by medical evidence. There are very few true medical contraindications to lactation, and disruption should not be advised unless a known medical contraindication exists.

55.5 CONCLUSION

Lifestyle behaviors of reproductive-age women play a significant role in the health of pregnancy and the future health of the child. Consequently, women's healthcare providers play a key role in addressing modifiable risk factors before, during, and interpregnancy. It is also important to form partnerships with other lifestyle medicine providers including dieticians, health coaches, primary care, and specialists to provide a multidisciplinary model of care that is seamless during her reproductive years.

The postpartum period represents a unique opportunity to identify and address future health risks, motivate change, and set the stage for improved outcomes in future pregnancies and later in life. Lifestyle interventions during this period are beneficial not only to the postpartum woman but also to her offspring and to the entire family unit.

CLINICAL APPLICATIONS

- Preconception goals ideally include a BMI <25, HgA1c <6.0, nutrient-dense diet with a minimum of 25 g/day of fiber, reduction or elimination of medications, and if applicable reversal of chronic disease.
- Well-balanced whole food plant-based diets are safe in pregnancy and include adequate calorie, protein, and fiber intake. Pregnant women should consume 28/34/36 g/day of dietary fiber during the first, second, and third trimesters, respectively.
- Reproductive-age women should have a vitamin D level checked annually with a goal of 40–60 ng/dl.
- Diverse plant-based diets provide all the necessary micronutrients with the exception of vitamin B12. Women consuming an entirely plant-based diet in pregnancy should intentionally consume B12-fortified foods four times per day or take a vitamin B12 supplement containing 50 µg daily or 2000 µg weekly.
- Women before, during, and after pregnancy should be advised to perform a minimum of 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise, spread over four to seven days each week. Return to a baseline activity level should be possible for most women by four to six weeks postpartum.
- Lactation should be stimulated as soon as possible after birth. When possible, human milk should be provided as the exclusive source of infant nutrition for six months and continued along with other foods through 12 months or more. If not possible, the provision of any amount of human milk for any length of time is beneficial and encouraged.
- Adverse pregnancy outcomes should be managed as cardiovascular risk factors from the standpoint of future health screenings and risk assessment.

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56 Menstrual Health and Menopause

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KEY POINTS

- Polycystic ovarian syndrome (PCOS), and its associated insulin resistance, can cause significant abnormal uterine bleeding (AUB).
- Advanced glycation end products (AGEs) and oxidative stress have been implicated in PCOS.
- Lifestyle, particularly diet and exercise, can be used to manage or reverse PCOS.
- Later age at menopause is largely associated with improved health outcomes and can be impacted by certain lifestyle factors.
- Menopausal symptoms can often be ameliorated with dietary changes.

56.1 LIFESTYLE-RELATED MENSTRUAL DISORDERS

Polycystic ovarian syndrome (PCOS) is a constellation of obesity, insulin resistance, and oligo-ovulation, or anovulation, which can result in infertility, menstrual dysfunction, and hirsutism. It impacts approximately 10% of women of reproductive age and 40% and 85% of women with PCOS are overweight or obese. As women become obese, insulin resistance leads to elevated levels of circulating insulin which suppresses the synthesis of sex hormone-binding globulin (SHBG). This leads to a rise in free androgens that interfere with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion at the level of the pituitary. As such, multiple small follicles accumulate in the ovary, but none are capable of growing to a size that would trigger ovulation. This leads to infrequent ovulation characteristic of PCOS with heavy, irregular uterine bleeding.[1]

Chronic inflammation and oxidative stress have also been incriminated in the pathophysiology of PCOS. The role of advanced glycation end products (AGEs) is becoming more prominent as well. Elevated concentrations of AGEs, or glycotoxins, which exert their effects through interaction with specific AGE receptors (RAGE), have been implicated in cellular and tissue damage. Women with PCOS have almost twice the circulating AGE levels in their bloodstream and more than three times the expression of RAGE. This is true for both obese women with PCOS as well as for lean, non-insulin-resistant women with PCOS. PCOS ovaries have higher levels of AGEs within the ovary itself and have a stronger expression of RAGE, contributing to the development of PCOS and its associated abnormal uterine bleeding (AUB).[2–5]

56.2 TREATMENT

Conventional treatment for PCOS is tailored to the woman's immediate reproductive desires. For those women trying only to control the symptoms of PCOS, such as irregular bleeding, hirsutism, and acne, oral contraceptive pills are often first-line therapy. Oral contraceptives are effective for symptom amelioration, as they lower total testosterone levels and increase SHBG, however, they can have a negative impact on lipid profiles.[6] However, the two primary causative agents in PCOS are insulin resistance and AGE-induced oxidative stress, which are best addressed through diet and lifestyle changes.

A study done by Barnard and colleagues showed that SHBG is increased by 16% when women consume a low-fat plant-based diet, which could lead to improved ovulatory function.[7] Likewise, a study in the *American Journal of Obstetrics and Gynecology* revealed that replacing 5% of calories with carbohydrate or vegetable protein in lieu of animal protein is associated with a 40–50% improvement in ovulatory function.[8]

Dietary behaviors resulting in obesity and malnutrition are linked with oxidative stress and chronic, low-grade inflammation. It has been shown, repeatedly, that animal foods are associated with systemic inflammation.[9] The primary sources of AGEs implicated in the pathophysiology of PCOS are cigarette smoke and food. Reducing these dietary glycotoxins reduces the inflammatory response.[10] Foods with the highest AGEs are of animal origin and foods cooked in high temperature, dry cooking methods as compared with low heat, higher humidity cooking. Stewing, steaming, and boiling result in lower AGE production than broiling, searing, and frying. AGE tissue levels are a strong predictor of overall mortality and are consistently lower in vegetarians.[4] Reducing AGE intake improves insulin sensitivity, reduces oxidative stress biomarkers, and reduces testosterone in women with PCOS.[11]

Women with PCOS have increased serum levels of antimullerian hormone (AMH) that are two to three times higher than in women with normal ovaries. In the ovary, AMH has an inhibitory effect on follicle recruitment and on the responsiveness of growing follicles to FSH.[12] It has been shown that one hour of exercise three times per week decreases body mass index (BMI) and total and android fat mass, improves insulin sensitivity, and lowers AMH levels. This suggests that mechanisms associated with ovarian dysfunction can be improved by exercise in PCOS, possibly improving menstrual function.[13]

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56.3 MENOPAUSE BACKGROUND

The age at which menopause occurs typically ranges from ages 48 and 55 years, with a median age of 51.4 years, and the perimenopausal transition lasts for about four years.[14] Menopause is reached when the depletion of follicles reaches approximately 1000, from 2 million at birth with a peak of 5 million during the mid-reproductive years.[15] During perimenopause, declining estrogen levels can lead to cycles with a short luteal phase or an anovulatory cycle, with unopposed estrogen leading to irregular bleeding. These cycles are common in women over the age of 40 and the bleeding can be profuse.[15]

The initial years of menopause are often accompanied by vasomotor symptoms, such as hot flashes and night sweats, somatic symptoms such as fatigue, body aches, and vaginal dryness, and psychological symptoms such as irritability, anxiety, depression, decreased libido, and difficulty sleeping.[16] Survey data indicate that 60% of women experience hot flashes, 48% experience night sweats, and 41% reported trouble sleeping. Vasomotor symptoms commonly develop one to two years before the cessation of menses. Ethnicity also plays a role with African American women having the highest frequency of hot flashes followed by Hispanic American and Euro American women, respectively, while Chinese and Japanese American women reported lower rates of vasomotor symptoms.[17]

Although menopause is a universal phenomenon among women, the timing of the onset, the duration of the menopausal transition, and the timing of the final menstrual period are not. Later age at natural menopause has been associated with greater life expectancy, reduced all-cause mortality, reduced risk of cardiovascular disease and associated mortality, and reduced risk of osteoporosis and fracture, but an increased risk of breast, endometrial, and ovarian cancers. Early menopause has also been associated with earlier cognitive decline.[15] The association of reduced bone loss with later onset of menopause is related to longer exposure to estrogen, however, this is also why there is an association with increased risks of breast, endometrial, and ovarian cancers. Despite this, there does appear to be a benefit from menstrual blood loss and a reduced risk of cancer, in general.[18]

Multiple environmental and lifestyle factors impact the age of onset of menopause. Onset varies by race and ethnicity but largely in the context of demographic and lifestyle factors. Factors that result in later natural menopause include living in developed countries and urban areas and greater parity, especially for women, with higher socioeconomic status. Factors that result in earlier onset of menopause include lower socioeconomic status, living at higher altitudes, smoking, and malnourishment. Family and twin studies suggest that heritability may impact the age of onset anywhere from 30% to 85%.[15]

56.4 MENOPAUSE MANAGEMENT

Lifestyle measures can often be used to treat menopausal symptoms. Despite this, the focus on symptom relief has largely been reliant on exogenous hormone replacement therapy (HRT). It has been well characterized since 1940 that estrogenic substances could induce carcinoma of the breast[19] with an approximate 30% greater chance of breast cancer with long-term estrogen therapy. However, there is some evidence that a diagnosis of breast cancer while taking hormone replacement therapy is associated with a better prognosis. Despite decades of accumulated observational evidence, the balance of risks and benefits of hormone use in healthy postmenopausal women remained uncertain until 2002, when the first randomized, controlled trial—the Women's Health Initiative (WHI)—was conducted. The trial halted early because the stopping boundary for invasive breast cancer (26% increased risk) was exceeded. A 29% increased risk of coronary heart disease, a 41% increased risk of stroke, and a two-fold increased risk of pulmonary embolism compared with the placebo group were also documented. While there were fewer cases of endometrial cancer, hip fracture, and colorectal cancer in the treatment group, the risk-benefit profile was not deemed consistent with the requirements for a viable intervention for primary prevention of chronic disease.[20]

Compounded bioidentical hormones, despite some claims, do carry the same risks as other synthetic or commercially produced hormone therapies. *The Medical Letter*, a non-profit, advertisement-free peer-reviewed publication stated in 2010 that, "There is no acceptable evidence that 'bioidentical' hormones are safe or effective. Patients should be discouraged from taking them".[21]

Diet-related treatments are often employed to help reduce the vasomotor symptoms of menopause including phytoestrogens like soy. There are two primary types of estrogen receptors (ERs), alpha and beta. Endogenous and synthetic estrogens act non-selectively as agonists for both types of receptors while anti-estrogen drugs like fulvestrant act as antagonists at the level of all ERs. Mixed agonist–antagonists include synthetic selective estrogen receptor modifiers (SERMs), like tamoxifen, as well as phytoestrogens that act selectively, primarily on beta-receptors.

Alpha-receptors are found mainly in the endometrium, breast cancer cells, ovarian stromal cells, and the hypothalamus, while the beta-receptor is expressed primarily in the ovarian granulosa cells, kidney, brain, bone, heart, lungs, intestinal mucosa, and endothelial cells. Because estrogens tend to act indiscriminately, they impact all these tissues simultaneously. As a result, exogenous estrogens work well to prevent both bone loss and treat vasomotor symptoms associated with menopause, however, when estrogen binds to the alpha-receptors in the breast, mammary cells proliferate, with resulting cell division and DNA replication that can lead to mutations and breast cancer development. ERs are over-expressed in around 70% of all breast cancer cases.

Conversely, phytoestrogens are plant derivatives that bear a structural similarity to 17-beta-estradiol and act in a similar manner. Phytoestrogens tend to act like SERMs and have a higher affinity for beta-receptors, which are dose-dependent. Phytoestrogens have both agonistic and

antagonistic effects, although they are strong beta-receptor agonists and weak alpha-receptor agonists. The similarities between phytoestrogens and 17-beta-estradiol allow for the displacement of estrogen. Activation of the beta-receptors in the breast inhibits mammary cell growth and the stimulatory effects of activated alpha-receptors, helping to prevent tumor growth.[22] Genistein, the phytoestrogen in soy, has been found to bind the active site of the beta-ER with an affinity of 7–30-fold greater than its affinity for the alpha-ER.[23]

Overall, clinical studies utilizing soy have revealed either a positive or neutral impact on vaginal health indices that reflect vaginal moisture, elasticity, mucosal maturation, and pH, and a positive or neutral impact on hot flashes.[24] Additionally, studies evaluating vasomotor symptoms commonly observe a significant placebo effect, with up to 30% reduction in hot flashes in the placebo group.[25] Two recent meta-analyses reported that isoflavone supplementation was associated with a 34% reduction in hot flashes and that consumption of at least 15 mg of genistein reduces hot flashes by up to 50%. This total reduction includes that provided by "the placebo effect". Additionally, a prospective population-based cohort study of 1100 Japanese women found that hot flashes were significantly inversely associated with the consumption of soy products and isoflavone intake.[26] Despite the mixed outcomes on menopausal symptoms, soy has other health benefits, including favorable effects on the vascular endothelium and protection from left ventricular hypertrophy,[27] reduced risk of endometrial[28] and ovarian cancers,[29] and nephroprotection.[27] Thus, their consumption should be encouraged.

CLINICAL APPLICATIONS

Lifestyle recommendations for the treatment of menopausal symptoms:

- Smoking cessation
- Moderate physical activity and weight loss for those overweight and obese
- One alcoholic beverage per day; those who do not consume alcohol should not be encouraged to start
- Consume 15 mg of the soy phytoestrogen, genistein, daily which is approximately equivalent to
  - 3 oz of tofu
  - ½ cup tofu yogurt
  - 1 cup soy milk
  - 1 oz dry, roasted soy beans
  - 2 oz tempeh
  - ½ cup boiled soy beans
  - ¼ miso
  - 1 oz aqueous-washed soy protein concentrate (85)

In addition, vaginal estrogen may be used for symptoms of urogenital atrophy in those with no prior diagnosis of breast cancer, DVT or PE, stroke, or coronary heart disease.

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57 Female Breast and Gynecologic Cancer

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KEY POINTS

- Plant-predominant dietary patterns and physical activity are key aspects of female cancer care.
- Obesity plays a role in postmenopausal breast, endometrial, and ovarian cancer risk.
- Lifestyle interventions can be leveraged to mitigate cancer-related fatigue, pain, emotional distress, depression, anxiety, cognitive impairment, and sleep disturbances.

57.1 INTRODUCTION

In the United States, cancer remains the leading cause of death among women aged 40 to 79 years. Breast cancer is the second leading cause of death in women, with an estimated 43,250 deaths in 2022. Ovarian and endometrial cancers are the fifth and sixth leading causes of cancer death, with an estimated 12,810 deaths and 12,550 deaths in 2022, respectively.[1] Since the mid-2000s, female breast cancer incidence has been slowly *increasing* by 0.5% per year, attributable at least in part to lifestyle factors such as excess body weight and continued declines in fertility rates.[2] These lifestyle factors likely also contributed to the recent rise in endometrial cancer.[3]

57.2 ROLE OF LIFESTYLE MEDICINE IN FEMALE BREAST AND GYNECOLOGIC CANCER

Currently, 41% of men and 39% of women will develop cancer during their lifetime.[4] According to the American Cancer Society, at least 42% of newly diagnosed cancers (excluding non-melanoma skin cancer) in the United States could be prevented with positive changes in diet and lifestyle; 19% of newly diagnosed cancers may be due to smoking and 18% to a combination of excess body weight, excessive alcohol consumption, poor nutrition, and lack of physical activity. In addition, these lifestyle factors also play a key role in the health and disease outcomes of cancer survivors. Organizations such as the American Society of Clinical Oncology and the American Cancer Society have established guidelines for breast cancer survivorship.[5] What follows is a concise summary of the role of lifestyle medicine in primary and tertiary prevention of female breast and gynecologic cancers and symptom management.

57.3 PRIMARY BREAST CANCER PREVENTION

57.3.1 Nutrition

57.3.1.1 Plant-Predominant Dietary Pattern

Adherence to plant-predominant cancer prevention dietary guidelines is associated with a 19–60% decrease in breast cancer (BC) risk.[6,7] The Mediterranean diet has shown consistent empiric evidence to have protective effects against BC.[8]

57.3.1.2 Fiber

Meta-analysis revealed total fiber and soluble fiber are inversely associated with BC risk (RR = 0.92 and 0.90, respectively), with high total fiber effective in *both* premenopausal and postmenopausal women.[9] Meta-analysis has also suggested a dose-dependent response, where each 10 gram/day increase in fiber correlated with a 7% BC risk reduction.[10] This is likely due to fiber intake (irrespective of weight loss) being independently associated with reduced serum estradiol.[11]

57.3.1.3 Soy

Increased soy intake has been associated with decreased primary BC risk.[12–15] However, a 2021 meta-analysis of 18 randomized controlled trials (RCTs) did not reveal clear protective benefits (sample size was listed as a limitation)[16] The dose may account for the inconsistent findings, as a meta-analysis of prospective studies (ten years of follow-up) has suggested that increasing soy intake may be protective, with every increase of 10 mg/day correlating with a 3% decrease in BC risk[17]

57.3.1.4 Carotenoids

Pooled meta-analysis from 2012 and post-hoc analyses demonstrated that carotenoids may have varied effects on BC risk. A total of five carotenoids were independently analyzed (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene).[18,19] All carotenoids demonstrated protection against ER(–) (estrogen receptor negative) phenotypes, while α-carotene and β-cryptoxanthin protected against all breast cancers. All carotenoids except

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β-cryptoxanthin protected against ER(–)/PR(+) (progresterone receptor positive) or ER(–)/PR(–) BC.[18] However, β-carotene specifically was found to increase the risk of ER(+) and ER(+)/PR(+) phenotypes specifically.[18] This is in direct contrast to an earlier meta-analysis that demonstrated that β-carotene decreased the risk of BC[20]

57.3.1.5 ALCOHOL

The 2020 American Cancer Society (ACS) guidelines for cancer prevention advise complete avoidance of alcohol, given an increased risk for BC, even with consumption of less than one drink per day[21] The prospective observational Nurses' Health Study (n = 105,986 women) revealed that increased alcohol consumption was associated with a higher risk for BC. The association was statistically significant even at low levels of alcohol intake, equivalent to three to six drinks per week (relative risk, 1.15), with every 10 grams per day of alcohol intake increasing BC risk by 10%.[22]

57.3.2 PHYSICAL ACTIVITY

Meta-analysis demonstrates that earlier onset of regular physical activity conveys a near 30% decrease in primary BC risk.[23] Exercise may exert immunomodulatory and/or anti-inflammatory effects.[24–26] Meta-analysis further demonstrates that exercise interventions (aerobic, resistance, combined, or tai chi/yoga) might be particularly effective when combined.[27]

Baseline body fat composition may alter the measured effectiveness of exercise regimens for primary BC prevention if at least part of the effect is from the loss of fat itself. Postmenopausal women experiencing significant fat loss (>2 kg) have both a significant increase in sex-hormone binding globulin (SHBG) and a significant decrease in DHEA-S. This may decrease long-term BC risk via decreased peripheral conversion of testosterone to active estrogenic compounds,[28] however, this is not supported in all studies.[29]

57.3.3 OBESITY

Obesity is a known BC risk factor, likely due to the associated increase in estrogen and estrogenic compounds.[23,30–32] It is estimated that 25% of BC incidence is influenced by a sedentary lifestyle or obesity, and obesity confers a dose-dependent (albeit non-linear) risk of BC in postmenopausal women.[33–35]

57.3.4 SLEEP

Meta-analyses of observational studies have demonstrated that high levels of artificial light at night (LAN) (but not ambient levels) have a significant correlation with increased BC risk, however, multiple studies have otherwise demonstrated either no association or a non-clinically relevant but statistically significant increase in risk with LAN exposure.[36–38]

57.3.5 PSYCHOLOGICAL STRESS

Although not consistently demonstrated, psychological stress, particularly *stressful* or *major* life events, has been implicated in increasing BC incidence.[39–46] Appropriate support and counseling for patients experiencing significant psychological stress are warranted, irrespective of the association with BC risk.

57.4 TERTIARY BREAST CANCER PREVENTION

57.4.1 Nutrition

While there is a need for more research, all major guidelines recommend a plant-predominant diet for BC survivors.[6,47,48] Nutritional educational programs for cancer survivors have demonstrated both feasibility and success in increasing self-efficacy in preparing plant-based meals, reducing barriers to eating fruits and vegetables, and significantly reducing meat intake.[49]

57.4.1.1 Dietary Supplements

There is no consensus in terms of supplement use and prognostic outcomes in BC survivors.[50] In one trial of BC patients undergoing chemotherapy (n = 1134), adjuvant and neoadjuvant use *of* any antioxidants (carotenoids, coenzyme Q10, or vitamins A, C, or E) had an *increased* risk of BC recurrence and death (adjHR = 1.41 and 1.4, respectively), although neither of these was significant at the p = 0.05 level.[50] Additionally, adjuvant/neoadjuvant B12 supplementation was significantly associated with poorer disease-free or overall survival, although no clear association with BC recurrence was found.[50] Further study is needed.

57.4.1.2 Soy

Multiple large-scale meta-analyses (n = 330,826) of prospective studies revealed that a 10 mg/day increase in soy and soy isoflavones was associated with a 9–11% decrease in BC mortality; furthermore, every 5 g/day increase in soy protein consumption reduced risk of BC death by 12%.[12, 51]

The association between soy isoflavone consumption and BC *recurrence* is less clear, with large-scale meta-analyses of RCTs, uncontrolled, and long-term observational studies generally finding soy isoflavones protective against BC recurrence, specifically at a dose of >10 mg/day.[52–54]

57.4.1.3 Carotenoids

Dietary intervention trials in BC survivors have demonstrated that increased plasma carotenoid concentration significantly reduces the risk of BC recurrence, highlighting the importance of fruit and vegetable intake.[55]

57.4.1.4 Alcohol

The American Society of Clinical Oncology and ACS recommends BC survivors be counseled to limit alcohol consumption.[21,56] In 1897 BC survivors, those who drank more than three to four alcoholic beverages per week had

a significantly higher risk of BC recurrence (HR = 1.35) and BC-specific mortality (HR = 1.51) when compared with those who reported minimal alcohol intake.[57]

57.4.2 Physical Activity

Physical activity is well-established in BC survivors as an effective method for improving quality of life (QOL), physical functioning, sleep quality, and bone mineral density, as well as preventing bone loss and reducing fatigue.[58–63] However, a large-scale meta-analysis (n = 5761) revealed no clear association between physical activity levels and BC recurrence.[64]

57.4.3 Obesity

Multiple studies purport that obesity or overweight status may be associated with a higher recurrence risk and increased all-cause mortality in BC survivors.[65–68] However, a 2020 meta-analysis (n = 2028) of RCTs of overweight and obese BC survivors undergoing weight loss intervention found that there was low-quality evidence for weight loss benefitting BC recurrence.[65] Regardless, practitioners should strive to address obesity among BC survivors due to its association with poorer QOL and increased subsequent comorbidities.[65]

57.5 SYMPTOM MANAGEMENT IN BREAST CANCER SURVIVORS

57.5.1 Physical Activity Recommendations

Physical activity benefits cancer survivors in many areas (QOL, psychosocial symptoms, pain, fatigue, lymphedema), and is an important supportive intervention to prescribe.[69–72] Meta-analysis of RCTs revealed that BC survivors benefit most from moderate to vigorous exercise (of any modality) for ~150 minutes per week.[73] Yoga (especially when combined with other meditative interventions) has been shown to reduce fatigue, depression, and anxiety and also improve sleep.[74–77]

57.5.2 Lymphedema

Exercise (particularly combined resistance and aerobic training) is well-established as an effective method to mitigate upper-extremity lymphedema secondary to surgical and/or radiotherapy interventions.[78–86]

57.5.3 Pain and Neuropathy

Upper-extremity pain, particularly chronic pain, should be targeted with a multidisciplinary approach that includes physiotherapy as well as psychological, pharmacological, and educational interventions.[87] RCTs have revealed that yoga and high-intensity interval training (HIIT) reduce overall pain sensitivity and improve fatigue.[88,89]

A multicenter RCT involving BC patients undergoing chemotherapy found that progressive moderate-intensity resistance training in a six-week home program format was associated with a significant decrease in chemotherapy-induced peripheral neuropathy.[90]

Acupuncture has been demonstrated through large-scale meta-analyses to significantly heighten pain threshold, and improve hot flashes, neuropathy, overall pain sensitivity, physical fatigue, depression, and sleep quality.[91–94]

57.5.4 Cancer-Related Fatigue

Exercise (both aerobic and resistance training) and yoga are incredibly well-established as effective in reducing cancer-related fatigue (CRF).[59,82,95–102] Notably, exercise seems to improve both physical and cognitive aspects of CRF, with benefits consistent for many years post-treatment.[103,104] Consuming a plant-based diet has also been implicated in the improvement of CRF.[105]

57.5.5 Depression and Anxiety

Depression and anxiety are prevalent in nearly one-third to one-half of BC survivors, respectively[106–109] In a meta-analysis of over 41 RCTs, non-pharmacological therapeutics (NPTs) including exercise, psychotherapy, yoga, and mind-body interventions were significantly related to a decrease in depression symptoms.[110] Meditation and mindfulness-based stress reduction (MBSR), particularly in a *group* setting, seems superior to traditional supportive-expressive group therapy in terms of longevity of improvement in psychological distress and function in cancer survivors,[111–117] and should be considered for couples as well.[118–126]

Cognitive-behavioral therapy (CBT) is very effective for psychological symptoms, including stress, depression, anxiety, sleep quality, and even hyperarousal.[127–131]

57.5.6 Cognitive Impairment

Cancer-related cognitive impairment (CRCI) is commonly experienced among BC survivors during or after chemotherapy[132] CRCI may be modified with physical activity (exercise, yoga, and Tai Chi), stress mitigation, and sleep improvement.[133–138] CRCI is exacerbated in survivors with comorbid anxiety or depression[139] Mindfulness-based interventions may improve cognition in cancer survivors, and when combined with exercise may be more beneficial than exercise alone.[140–142]

57.6 PRIMARY GYNECOLOGICAL CANCER PREVENTION

57.6.1 Nutrition

57.6.1.1 Plant-Predominant Dietary Pattern

Associations between higher-quality diets and gynecological cancer risk are inconsistent.[7,143] A 2020 meta-analysis found that high pre-diagnosis vegetable intake was associated with decreased ovarian cancer incidence (HR = 0.78), while a high pre-diagnosis fruit intake was also associated

with decreased all-cause mortality (0.82).[144] Other large-scale (n = 142,189, n = 149,177; n = 567,742) meta-analyses suggested an inverse relationship between fiber intake and ovarian cancer risk, with a linear and dose-dependent 6–12% decrease in risk for every 10 g/day increase in fiber intake.[145–148] Intake of dietary isoflavones is also associated with a 16–18% decrease in the risk of developing endometrial and ovarian cancer[149–152] A large-scale (n = 1,404,297; n = 721,429) meta-analysis found that increased total antioxidant intake and capacity were associated with a 22–27% lower risk of endometrial cancer.[153,154]

57.6.1.2 Fats and Coffee

Intake of total fats, saturated fats, cholesterol, and retinols are suggested to significantly increase ovarian cancer risk through large-scale meta-analyses[155] This is supported by a meta-analysis that found a 7% increase in ovarian cancer risk for every additional 100 g/d of whole milk versus a 5% decrease per 100 g/d of low-fat milk.[156]

A 2018 meta-analysis (n = 14,409) studying coffee intake with endometrial cancer risk demonstrated a 25% lower risk among women who drank the most versus the least coffee per day, with effect sizes being higher in women with a BMI >30[157,158]

57.6.1.3 Vitamin D and Calcium

It is suggested that lower circulating vitamin D may increase ovarian cancer incidence, while increased vitamin D has been correlated to lower mortality,[159] however, the association is not consistent.[156,160] Vitamin D has been shown to have beneficial effects of increasing total antioxidant capacity and reducing inflammatory markers in women with precarcinogenic endometrial hyperplasia.[161]

Calcium intake in multiple meta-analyses has demonstrated an inverse relationship with ovarian cancer risk, particularly epithelial ovarian cancer.[160,162]

57.6.1.4 Alcohol

Current literature has limited evidence for an association between alcohol intake and primary gynecological cancer risk.[143,163,164]

57.6.2 Obesity and Physical Activity

The International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF) analysis revealed a positive association between adiposity and both endometrial and ovarian cancer,[165,166] with 57% of endometrial cancer cases attributed to obesity.[167–171] Furthermore, a large-scale meta-analysis (including 150,537 bariatric surgery patients versus 1,461,938 controls) demonstrated that bariatric surgery in obese women reduced the risk of ovarian and endometrial cancer by 53% and 67%, respectively.[172]

Total lifetime physical activity is inversely associated with (RR = 0.77) endometrial cancer, notably augmented in postmenopausal women.[23,173,174] More than two hours of moderate exercise per week or less than three hours of sitting per day are associated with a decreased risk of ovarian cancer.[175]

57.7 TERTIARY GYNECOLOGICAL CANCER PREVENTION

57.7.1 Obesity

Meta-analysis of obesity in endometrial cancer survivors demonstrated an increase in all-cause mortality (HR = 1.34) and cancer recurrence (HR = 1.28) if BMI was greater than 30 at the time of diagnosis.[176] Small RCTs have demonstrated the ketogenic diet to be effective for weight loss in ovarian and endometrial cancer survivors, with no adverse effects or significant alteration to blood lipid and ketones after only 12 weeks, however, longer-term follow-up is needed to assess association with recurrence risk and potential development of comorbidities.[177–179]

57.8 SYMPTOM MANAGEMENT IN GYNECOLOGIC CANCER PATIENTS

57.8.1 Pain and Cancer-Related Fatigue

More than one-half of all gynecological cancer survivors report suffering from CRF.[180] Home-based physical activity interventions effectively reduce CRF in ovarian cancer patients for long-term periods (up to nine months) and are further augmented by concurrent behavioral counseling.[181] Small-pilot studies also demonstrate that short-term fasting may significantly improve fatigue and QOL in gynecologic patients undergoing chemotherapy.[182]

57.8.2 Emotional Distress, Depression, and Anxiety

Exercise is associated with decreased self-reported depression and decreased serum brain-derived neurotrophic factor (BDNF) (a depression-related biomarker), as well as improved quality of life, pain, and distress in endometrial or ovarian cancer survivors.[183–186]

CBT and positive psychology interventions, particularly in a nurse-led format significantly improve CRF, depression, cognitive functioning, subjective well-being, mood, and sexual functioning in gynecological cancer survivors.[187–190]

57.8.3 Sleep Disturbance

CBT in addition to regular physical activity and a healthy diet can help improve sleep and quality of life in endometrial cancer patients.[191] MBSR has also been shown to significantly improve sleep time and quality among cervical cancer patients, however, the effect waned over time.[192]

57.9 CONCLUSIONS

Healthcare practitioners caring for women can share the primary cancer prevention information in this chapter with

their patients, thereby decreasing their risk of a breast cancer or gynecologic cancer diagnosis. For healthcare practitioners treating breast or gynecologic cancer survivors, educating patients about the potential for lifestyle medicine to decrease recurrence risk and manage symptoms can improve their quality of life while also helping them lead longer and healthier lives.

CLINICAL APPLICATIONS

- Plant-predominant dietary pattern has a role in both primary and tertiary prevention of breast cancer. The role in gynecologic cancer is less defined.
- Physical activity has a clear role in primary breast cancer prevention.
- Obesity increases the risk of postmenopausal breast, endometrial, and ovarian cancers; early intervention is encouraged.
- Cancer-related fatigue, pain, emotional distress, depression, anxiety, cognitive impairment, and sleep disturbances may be mitigated with a variety of exercise and mindfulness-based practices.

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58 Cardiovascular Disease, Diabetes, Obesity, and Lifestyle Medicine Considerations in Women

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KEY POINTS

- Cardiovascular disease (CVD) is the number one cause of mortality for women in the United States.
- A lifestyle medicine approach should be utilized for all women to address prevention, management, and reversal/remission of CVD and related risk conditions such as diabetes and obesity.
- Women have sex- and gender-specific differences that uniquely affect CVD, diabetes, and obesity risk, presentation, diagnosis, and treatment.
- Metabolic risk factors, such as waist circumference, and lipid levels have different threshold values for women compared with men while others, such as hypertension, may have distinct implications for CVD.
- Unique considerations can differentially impact a woman's ability to perform healthy lifestyle behaviors and lifestyle factors can have different impacts on CVD, diabetes, and obesity risk.

58.1 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death for women in the United States, accounting for more than 300,000 deaths in 2019.[1] Annually, CVD mortality is greater for women, a consistent trend over two decades.[2] Conditions such as hypertension (HTN), ischemic heart disease (IHD), myocardial infarction, and stroke are included within the umbrella of CVD. Stroke, itself, is the third most common cause of death for women, affecting more women than men every year.[3]

Data show that metabolic changes, for example, abdominal obesity and blood pressure elevation, have distinct effects on women versus men.[4] Women living with metabolic syndrome, defined by the presence of risk factors including high blood pressure, lipid abnormalities, glucose intolerance, and visceral adiposity are at elevated risk for CVD compared with men.[4,5]

Even with advances in awareness about the CVD burden in women, only a little more than half of women in the United States recognize the risk, and progress to further reduce CVD has plateaued, especially in women younger than 55 years old.[1,5]

Relative to men, research shows that women may not be given counseling about lifestyle interventions or preventive care at the same rate, even with similar risk factors.[4] Health professionals may also not be aware of unique considerations that differentially impact a woman's ability to perform healthy lifestyle behaviors or the different impacts of lifestyle factors on CVD, diabetes, or obesity risk.

This chapter will discuss sex and gender differences that contribute to 1) distinct prevalence and impacts of traditional CVD risk factors (e.g., metabolic syndrome, HTN, dyslipidemia), 2) special considerations about lifestyle risk factors for women, and 3) the impact of risk factors unique to women (e.g., preeclampsia, gestational diabetes) on the development of diabetes, overweight/obesity, and ultimately, CVD. Health professionals must understand these differences in order to specifically tailor risk stratification, management, and lifestyle medicine counseling to improve chronic disease care for women.

58.2 CARDIOVASCULAR DISEASE, DIABETES, AND OVERWEIGHT/OBESITY IN WOMEN

Due to differences in reproductive stages, genetics, epigenetics, social determinants, and environmental exposures over their lifetimes, risk factors for acquiring diabetes, overweight/obesity, and CVD can vary in women compared with men.[5] Over time, these chronic conditions impact a woman's health across the lifespan, potentially causing secondary complications and impacting future generations.[5]

Sex differences are related to biological differences in the expression of particular genes and hormones. These can result in variations in the prevalence of traditional and sex-specific risk factors, different cardiovascular impacts, and distinct pathophysiology and presentation of CVD. Gender differences generally are the result of varied cultural, environmental, or psychosocial factors that may impact behaviors related to cardiovascular health.

An understanding of particular considerations across a woman's life allows health professionals to optimally

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prescribe lifestyle medicine interventions that can prevent, manage, and sometimes lead to the remission or reversal of CVD, diabetes mellitus (DM), and overweight/obesity in women.

58.2.1 Cardiovascular Disease Pathophysiology in Women

CVD may be more difficult to diagnose in women because the underlying pathophysiology and presentation of acute coronary syndrome (ACS) may be different. Research from studies, including the Women's Ischemia Syndrome Evaluation (WISE), has found that IHD in women may be linked with abnormal coronary reactivity, distal plaque microembolization, and microvascular dysfunction, distinct from obstructive coronary artery disease (CAD) more common in men.[5,6] Differences in the burden of obstructive disease, which is more traditionally seen as synonymous with IHD, may play a role in lower rates of lifestyle counseling for prevention, barriers to effective treatment and management, and worse CVD outcomes and mortality rates for women compared with men.[5,6]

Below is a discussion of traditional, lifestyle, and sex-specific risk factors for CVD with an emphasis on the differences in prevalence, distinct impact on risks, and differing threshold values for diagnosis (where applicable) for women. A detailed discussion is also presented for diabetes and overweight/obesity.

58.3 TRADITIONAL RISK FACTORS

58.3.1 Metabolic Syndrome

The presence of metabolic syndrome can double the risk for CVD.[4,5] This is of particular concern because of gender disparities in the management and outcome of care.[7] The National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) defines the diagnosis of metabolic syndrome in women as the presence of three or more of the following findings:[8]

1. Waist circumference of more than 35 inches (88 cm).
2. Triglyceride level greater than or equal to 150 mg/dL.
3. HDL cholesterol less than 50 mg/dL.
4. Blood pressure of 130/85 mmHg or higher.
5. Blood glucose greater than or equal to 110 mg/dL after fasting for at least eight hours; revised ATP III criteria include plasma glucose greater than or equal to 100mg/dl.[9]

Though the age-adjusted prevalence of the metabolic syndrome is similar for both men and women, Mexican American and African American women have higher rates of metabolic syndrome (57% more African American women compared with African American men and 26% more Mexican American women compared with Mexican American men).[4,5,10]

The prevalence of some components of the metabolic syndrome and the effect on CVD risk is also distinct in women. Elevations in central obesity, triglycerides, and blood pressure may be responsible for much of the increased prevalence among women.[4,5,11] Examples of different impacts on women from components of the metabolic syndrome include:[4,5]

- Waist circumference: greater waist circumference increases the risk of metabolic syndrome to a higher degree compared with men.[4]
- Dyslipidemia: causes a higher risk of CAD compared with men; and higher triglyceride levels (particularly when combined with low HDL levels) have a greater impact on CAD risk in women.[4]
- Hypertension: higher risk of congestive heart failure (CHF) with HTN in women.[4]
- Hyperglycemia: elevated glucose levels after glucose load more common than elevated fasting blood glucose in women.[4]

58.3.2 Hypertension

Hypertension is a major cause of MI, stroke, and kidney failure. Women commonly develop hypertension ten years later than men because of the role of endogenous estrogen in maintaining blood pressure control through vasodilation before menopause.[6,12] However, data show that elderly women may have a higher prevalence of more poorly controlled HTN, with 23% of women over 80 with a BP <140/90 mm Hg compared with 38% of men over 80 years old.[13]

58.3.3 Dyslipidemia

Among all cardiovascular disease risk factors, lipid abnormalities pose the highest attributable risk for CVD in women.[5,6] It is important to note that dyslipidemia increases the risk for CVD in postmenopausal women, as this risk is not observed in premenopausal women with elevated cholesterol levels.[6] Notably, sex-specific guidance for primary prevention has been incorporated into the 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults and the American Heart Association (AHA)/American College of Cardiology (ACC) pooled cohort formula for CVD risk stratification includes sex in the calculation.[14]

The interpretation of a variety of biomarkers and imaging tests for CVD risk stratification in women continues to be studied. High-sensitivity CRP (hsCRP) levels are associated with CVD risk and aid with the predictive value of lipid levels[15] Research suggests that women have higher CRP levels than men (with Hispanic and African American women found to have the highest CRP levels).[16,17] According to one study, women with the largest baseline elevations of

CRP levels were found to have a five-fold increased risk for any vascular event and a seven-fold increased risk for stroke or MI over three years.[18]

Other tests including coronary artery calcium measurements and advanced lipid tests such as lipoprotein-associated phospholipase A2 (Lp-PLA2) are also being studied as potential tools for CVD risk stratification in women.[6]

58.3.4 Diabetes

Diabetes affected an estimated 34.2 million people in the United States (10.5%) of all ages, including 16.2 million (48%) women, according to the National Diabetes Statistics Report of 2020.[19]

The risk of developing type 2 diabetes (T2DM) in women is impacted by a multitude of factors including epigenetics, genetics, hormonal interplay, reproductive stage, body composition, fat metabolism, and a vast array of unique social, environmental, and lifestyle factors.[5,20]

From birth, children of mothers with gestational diabetes or T2DM carry an increased risk for CVD, T2DM, and obesity.[21,22] Female infants born to mothers with diabetes are at risk for metabolic syndrome, hyperglycemia, and increased body fat.[23] Birth weights designated as high or low are also connected to a future risk of T2DM and obesity.[24,25]

Over the lifespan, the hormonal interplay of estrogens and androgens plays an important role in energy metabolism, body composition, lipid homeostasis, and glucose levels.[26] Menopause, along with chronic hyperglycemia, may diminish the protective effects of estrogen, potentially playing a role in worsening a woman's metabolic profile as she ages.[27,28]

Diabetes in women may lead to worse CVD outcomes due to several underlying differences in pathophysiology. Studies show sex differences may factor into impairment of endothelium-dependent vasodilation, presence of hypercoagulable state, higher risk of atherosclerosis with dyslipidemia, and higher rates of co-occurring metabolic abnormalities and metabolic syndrome.[6,29–31] There is also growing evidence that women with prediabetes may also have higher rates of other metabolic abnormalities, suggesting higher CVD risk at lower glucose levels compared with men.[5,6,32,33]

Diabetes complications in women include 1) a higher risk of earlier MI and higher MI mortality, 2) lower revascularization rates, 3) a higher risk of developing congestive heart failure, 4) a higher risk of stroke, and 5) a higher risk of claudication with PAD compared with diabetic men.[5,6]

58.3.5 Obesity

Obesity is the result of excess accumulation and storage of body fat.[5,34] Over the past few decades, there has been a large increase in the percentage of overweight or obese individuals.[35] Data from 2017–2018 showed the incidence of obesity (body mass index [BMI] ≥30) was 42% among adults in the United States, with no significant differences between genders or different age groups. However, extreme obesity (BMI ≥40) was higher in women (11.5%) compared with men (6.9%).[36]

BMI is a well-established measure of overweight and obesity. Adults with a BMI ≥25 are at increased risk of developing CVD, insulin resistance and diabetes, and obstructive sleep apnea and are at higher risk for certain cancers.[34] Additionally, waist circumference, which can be used as a correlate for abdominal fat, is an independent risk factor for cardiometabolic risk, CVD events, and mortality.[34,37]

Overweight/obese women are also at an increased risk of many sex-specific cancers, including endometrial, cervical, breast, and ovarian cancer, with the risk of death from all cancers being 62% higher among women with a BMI greater than 40 versus normal weight.[5,38] Obese women also have a disproportionate increase in the risk of CAD, with data from the Framingham Heart Study showing that obesity increased the relative risk of CAD by 64% in women compared with 46% in men.[6,39]

Taken together, data show that the pathophysiology, health impacts, counseling considerations, and medical management of visceral fat accumulation and overweight/obesity in women are distinctive from men as a result of a combination of female sex-specific influences including reproductive stage and pregnancy.[5]

Obesity risk is influenced by hormonal regulation, developmental exposures, energy balance, genetic predisposition, and environmental exposure to toxic substances.[41] It is particularly important to address and manage overweight and obesity in women because exposure to maternal obesity increases the risk of obesity in the offspring.[5] Of note, epigenetic variations linked to obesity risk have been found to be sensitive to diet, exercise, and weight loss over the lifespan. [40–42]

58.4 LIFESTYLE-RELATED RISK FACTORS

58.4.1 Physical Inactivity

Clear evidence demonstrates the link between physical activity and lower risk for CVD, with greater benefits derived from greater levels of activity.[5,6] There is a moderate level of evidence that aerobic activity is beneficial for reductions in LDL cholesterol, non-HDL cholesterol, and BP.[43] Physical activity rates may be lower in women compared with men, according to survey data from the Centers for Disease Control (CDC), displaying that physical activity counseling in women can be improved.[42]

58.4.2 Diet

Data suggest that, compared with men, women consume more fruits, vegetables, and less meat.[44] However, women may also consume more sugar, with a higher glycemic index diet in general, increasing the risk of abdominal

obesity, particularly when combined with a sedentary lifestyle.[45]

58.4.3 Tobacco Use

Compared with men, data show that smoking in women is linked to a 25% increased risk of CAD.[46] Smoking, in combination with oral contraceptive use, increases the risk of stroke, MI, and venous thromboembolism.[6,47] Additionally, exposure to tobacco smoke increases the T2DM risk in both men and women.[48]

58.4.4 Exposure to Toxic Substances

Some studies demonstrate a potential link between moderate alcohol consumption and a lower risk of stroke, heart disease, and improved insulin sensitivity in non-diabetic women.[49,50] Alcohol counseling for women should explain that the reasons behind the possible benefit of moderate drinking on heart disease are not clearly known. Additionally, moderate drinking is linked to violence, injuries, and breast cancer, therefore women should not be advised to start drinking alcohol for possible health benefits.[5]

More and more data are elucidating the link between environmental toxic substance exposure with higher risk for CVD, T2DM, and obesity. Many studies have linked air pollution with a higher risk for MI and stroke.[5] Endocrine disruptors from the environment may mimic estrogen, leading to higher insulin resistance and hyperinsulinemia.[5,51] Given the advancement in available data, health professionals should consider counseling women about these environmental risks as part of a complete lifestyle medicine intervention.

58.4.5 Sleep

Because of the increased risk for sleep loss for reasons unique to women, a focus on addressing sleep disorders plays a role in CVD, DM, and obesity management. Sleep apnea raises the risk for hypertension, stroke, and MI.[79] Women with sleep apnea may present with different symptoms compared with men. In addition to snoring, the most common symptom in men, women may present with morning headaches, insomnia, or excessive daytime sleepiness as their prevailing symptoms.[52]

Insomnia alone has been linked with CVD morbidity and mortality, including CAD, HTN, and CHF.[53] Chronic sleep deprivation, defined as sleeping five hours or less, is associated with weight gain relative to people sleeping seven or more hours.[5] Weight gain may be due to sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary axis, combined with higher levels of inflammation.[53] For peri- and postmenopausal women, sleep disturbance may be linked to nocturnal vasomotor symptoms, low-estrogen state, and mood changes associated with menopause.[54]

58.5 Stress Management/Social Connectedness/Positive Psychology

Robust evidence suggests an association between higher levels of psychological stress and worse CVD outcomes in women.[55] Stress from work, finances, and home and life events doubled the risk of acute MI in the INTERHEART study.[56] Women appear to be more negatively affected by psychological stress, sleep disturbances, and occupational stress.[5] Socioeconomic factors such as lower incomes, lower levels of educational attainment, food insecurity, and low childhood socioeconomic status also impact T2DM risk in women more than men.[5,9] Additionally, racial disparities exist with higher stress scores and lower ideal cardiovascular health metrics among African American women compared with Caucasian and Asian American women.[5]

Depression is also associated with the development of CAD and poorer outcomes after CAD events.[6] Young women have higher rates of depression than men, therefore addressing mental health concerns beginning at an early age may be beneficial in improving CVD development and outcomes in women.[5,6]

According to studies, the stress response may have distinct manifestations in women that may ultimately impact cardiovascular health. Women may be more sensitive to the hypothalamic-pituitary-adrenal (HPA) axis, one of the command centers to control cortisol, catecholamine, and inflammatory cytokine levels.[5] Evidence also suggests higher levels of ghrelin and neuropeptide Y may mediate stress-driven "emotional eating" and less ability to suppress hunger leading to stress-related weight gain. [5,57,58] Additionally, women with visceral adiposity may have higher cortisol levels when challenged with acute stressors, allowing chronic stress to cause sympathetic overactivity, abdominal obesity, and insulin resistance.[59]

Stress management must be an integral part of the care of women to reduce CVD risk. The American Heart Association has widened the focus on lifestyle by including measures of well-being in their 2030 Impact Goals.[5,60] This suggests an increasing understanding that factors such as "security, prosperity, sense of connection, and purpose" are linked to ideal cardiovascular health and longevity.[5, 60]

58.6 SEX-SPECIFIC RISK FACTORS

58.6.1 Pregnancy-Related Disorders

Hypertensive disorders in pregnancy, including gestational HTN, preeclampsia, and chronic HTN, may drive future CVD risk.[5,6] According to data from one meta-analysis, women with preeclampsia had a 3.7-fold relative risk (RR) of HTN 14 years post-pregnancy, a 2.16-fold RR of IHD 12 years post-pregnancy, and 1.81-fold RR of stroke ten years post-pregnancy compared with women with normotensive pregnancies.[5,6,61] Women with earlier onset preeclampsia had worse outcomes, and preeclampsia severity was also linked with long-term CVD severity.[5,6]

Preterm delivery (PTD) is also an independent risk factor for CVD, with higher risks for women who deliver before 34 weeks of gestation.[5,6]

Diabetes impacts approximately one in every six pregnancies: 13% with known T1DM or T2DM and 86% with GDM.[5,62] Diabetes during pregnancy raises the risk for CVD and T2DM in women. GDM increases the risk of future CVD, independent of risk from developing type 2 diabetes, with a two-fold increased risk for stroke and a four-fold increased risk for MI.[5,6,63]

Women with a healthier lifestyle (no tobacco, ≥ 150 min/wk of moderate to vigorous physical activity, healthy diet, BMI <25 before pregnancy) had a 52% lower risk of GDM compared with women who did not follow these components of a healthy lifestyle.[64]

58.6.2 Lactation and Weight Gain after Pregnancy

Breastfeeding is protective and can decrease the risk of the development of metabolic syndrome.[5] For women who breastfed longer than one month, the odds ratio for metabolic syndrome decreased by 22% compared with women who did not breastfeed or who breastfed for less than one month.[65] Lactation also plays a role in weight post-pregnancy weight loss.[66] According to some studies, women who do not lose pregnancy weight between 3 and 12 months postpartum, may begin to show metabolic abnormalities even within the first year after pregnancy.[6,67]

58.6.3 Menopause

After menopause, the CVD gap between men and women narrows. Before menopause, endogenous estrogen, in particular, is thought to be cardioprotective based on studies showing the favorable effects of the hormone on vascular endothelium and lipid levels.[5,6] Postmenopausal women who are obese (BMI ≥ 30) have four times higher risk of CVD death compared with those with a BMI of 29 or less.[5,68]

Aging is linked with greater increases in total fat and abdominal obesity in women compared with men, beginning in midlife independent of baseline weight.[5,69,70] This midlife weight gain may be the result of a combination of factors including postmenopausal estrogen deprivation, sleep disturbance, "stress eating", or decreases in physical activity levels.[71–75] Although menopause itself is not a significant cause of weight gain, fat distribution may shift to more abdominal adiposity.[69] Mood changes seen in close to 25% of peri- and postmenopausal women may also be linked to weight gain as a result of disruptions to healthy behaviors.[76]

58.7 CONCLUSION

CVD is the number one cause of mortality for women in the United States. Women have sex- and gender-specific differences that uniquely affect CVD, T2DM, and overweight/obesity risk presentation, diagnosis, and treatment. In order to achieve ideal cardiovascular health, a focus on lifestyle medicine should be utilized for all women to address prevention, management, and disease reversal and remission. Understanding unique considerations in the care of women across the lifespan is key to providing intensive therapeutic lifestyle change (ITLC) in the most effective manner as part of the standard of care.

CLINICAL APPLICATIONS

- CVD is the number one cause of mortality for women in the United States and a lifestyle medicine approach should be utilized for all women to address prevention, management, remission, and reversal.
- Women have sex- and gender-specific differences that uniquely affect CVD, DM, and obesity risk, presentation, diagnosis, and treatment.
- Traditional metabolic risk factors, such as waist circumference, and lipid levels have different threshold values while others, such as hypertension, may pose different hazards for cardiovascular disease in women compared to men.
- Lifestyle and factors unique to women may have distinct implications for lifestyle medicine interventions.

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Part XI

Cardiovascular Rehabilitation and Secondary Prevention



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59 Using Digital Health Technology to Promote Cardiovascular Disease Risk Reduction in Secondary Prevention

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KEY POINTS

- A broad spectrum of hybrid and alternative secondary prevention delivery models that incorporate novel digital health technologies have been proposed for rectifying barriers to low rates of utilization of traditional cardiac rehabilitation (CR) programs, and for the provision of ongoing, evidence-based, secondary prevention interventions.
- The COVID-19 pandemic has created a digital health technology inflection point by accelerating the widespread acceptance and adoption of virtual/remotely delivered interventions, and this momentum is likely to continue in the era of COVID-19 and beyond.
- Despite the flaws and limitations of existing research, the preponderance of evidence to date is highly supportive of the great potential of digital health technologies to facilitate lifestyle modification and cardiovascular disease (CVD) risk reduction.
- Digital health interventions appear to be most effective when integrated with evidence-based behavioral change strategies and direct interaction between participants and healthcare providers.
- Additional research and healthcare policy change are needed to move the promise of new digital health technologies for CVD risk reduction toward reality.

59.1 INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally and is projected to account for over 23.6 million annual deaths by 2030.[1] Although sound clinical reasons exist for emphasizing secondary prevention in day-to-day medical practice, studies indicate that physicians often fail to provide recommended CVD risk reduction interventions and, even when provided, patients often fail to comply with the prescribed lifestyle and pharmacologic interventions.[2] Moreover, the COVID-19 and CVD pandemics have interacted to create a so-called "perfect storm" in which each pandemic is contributing to the worsening of the other.[3] Clearly, to achieve the American Heart Association's (AHA) 2030 Impact Goal of equitably increasing healthy life expectancy from 66 to at least 68 years of age across the United States and from 64 to at least 67 years of age worldwide by 2030, and to reduce premature CVD mortality, increased emphasis is needed on CVD risk reduction through evidence-based management of health behaviors and risk factors.[1]

Traditional center-based outpatient CR reduces morbidity, hospital readmissions, and mortality versus usual care.[2,4–8] Every recent secondary prevention guideline from the AHA and American College of Cardiology (ACC) provides a Class I level recommendation (i.e., there is evidence for and/or general agreement that the intervention is beneficial, useful, and effective; the intervention should be performed) for CR referral.[2,4–8] However, despite the proven benefits, the use of CR remains dismally low.[2,4–8] Multiple strategies have been proposed for rectifying barriers to participation in, and completion of, traditional center-based CR programs. These include a broad spectrum of hybrid and home-based alternative secondary prevention delivery models that incorporate novel technologies to facilitate CVD risk reduction.[2,4–11]

Modern-day cardiovascular medicine is a "high-tech" industry.[12] According to a 2017 report of the ACC Task Force on Health Policy Statements and Systems of Care,[13] key recent technological innovations of paramount importance for the future transformation of CVD care include the following: (1) digital health, with smartphone, wearable, sensor-based, and other electronic technologies; (2) big data, comprising the aggregation of large quantities of structured and unstructured health information and sophisticated analyses with artificial intelligence (including machine learning and natural language processing techniques); and (3) precision health, using approaches aimed at the identification of individual-level risks and determinants of wellness and pathogenicity. The intra- and inter-connections among emerging innovations and developments in digital health, big data, and precision health, as summarized by the ACC, are shown in Figure 59.1. In this chapter, we focus primarily on the use of digital health to promote CVD risk reduction.

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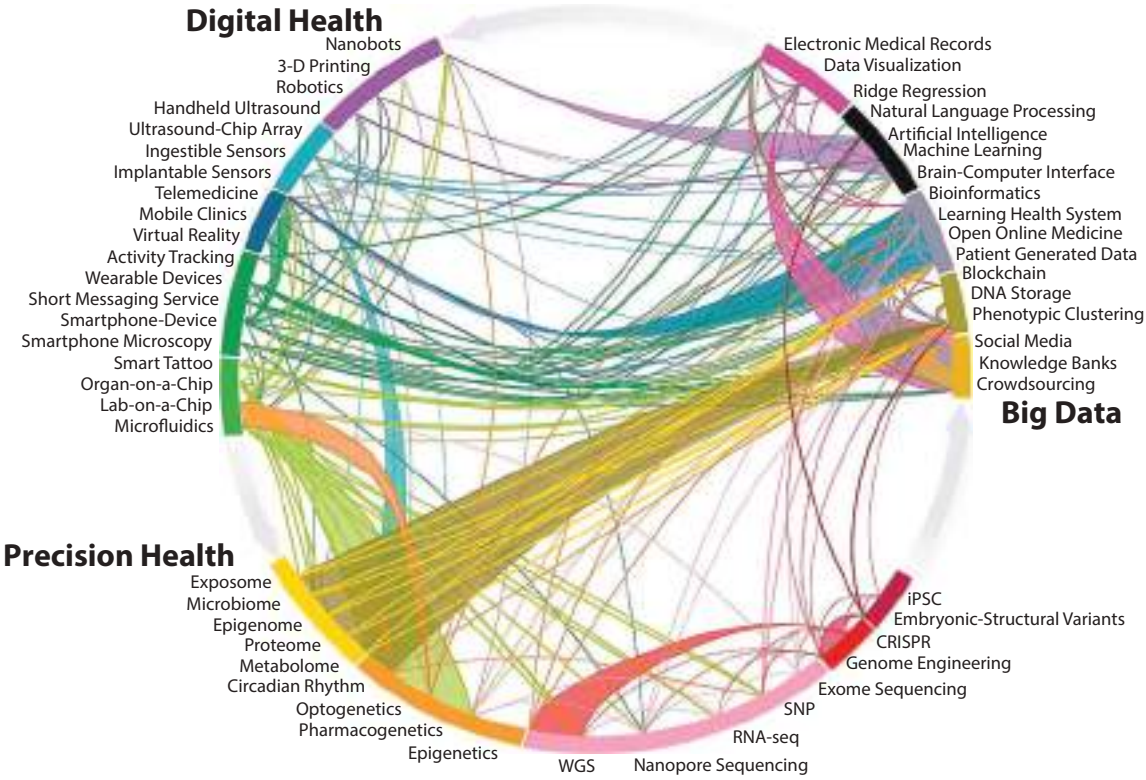


FIGURE 59.1 New innovations in cardiovascular healthcare: Infographic of emerging innovations and developments in digital health, big data, and precision health and their intra- and inter-connections. Abbreviations: 3d, 3-dimensional; CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; iPSC, induced pluripotent stem cells; RNA, ribonucleic acid; SNP, single nucleotide polymorphism; WGS, whole genome sequencing (from Bhavnani SP, Parakh K, Atreja A, et al., *J Am Coll Cardiol* 2017;70:2696-2718. With permission)

A 2015 scientific statement from the AHA on the consumer use of mobile health for CVD prevention defines eHealth (also referred to as digital health) as the use of emerging communication and information technologies, especially the Internet, to improve health and healthcare and mHealth as a subsegment of eHealth that involves the use of mobile computing and communication technologies for health services and information (see the glossary of commonly used terms in Table 59.1).[14] While digital technologies have revolutionized broad sectors of our society and economy, ranging from entertainment to dating, travel, news, and finance, the healthcare industry generally has been slower to respond.[12,13] However, given the ubiquity of mobile devices and Internet access, digital health interventions that incorporate various technologies (such as telemedicine, videoconferencing, text messaging, mobile phone apps, and data from electronic medical records, blood pressure monitors, digital scales, blood glucose monitors, heart rate monitors, activity trackers, and other wearable/monitoring devices) are now rapidly emerging as an integral component of traditional CR programs and, especially, hybrid and home-based alternative CR/secondary prevention delivery models. Moreover, COVID-19-related lockdowns and other disruptions have created a digital health technology inflection point by accelerating the widespread acceptance and adoption of virtual/remotely delivered interventions.[3] This momentum is likely to continue for the foreseeable future in the era of COVID-19 and beyond.

59.2 EFFECTIVENESS AND THE ROLE OF HOME-BASED ALTERNATIVE CR AND SECONDARY PREVENTION DELIVERY MODELS

A 2017 Cochrane systematic review of data from 23 randomized controlled trials involving 2890 participants compared the effect of home-based and supervised center-based CR in adult patients who were post-myocardial infarction or had angina, heart failure, or underwent coronary revascularization.[15] For the review, home-based CR was defined as a structured program (including exercise training) with clear objectives for the participants, including monitoring, follow-up visits, letters or telephone calls from staff, or at least self-monitoring diaries. The review found no evidence of a significant difference between home- and center-based CR, either in the short-term (3 to 12 months) or longer-term (up to 24 months), for total mortality, cardiac events, exercise capacity, multiple modifiable CVD risk factors, or health-related quality of life.

Similarly, a 2019 scientific statement from the American Association of Cardiovascular and Pulmonary

TABLE 59.1
Glossary of Commonly Used Digital Health Terms

Term	Explanation
eHealth	eHealth, or digital health, is the use of emerging communication and information technologies, especially the use of the Internet, to improve health and healthcare.
mHealth	A subsegment of eHealth, mHealth is the use of mobile computing and communication technologies (e.g., mobile phones, wearable sensors) for health services and information.
Smartphone	A handheld personal computer with a mobile operating system and an integrated mobile broadband cellular network connection for voice, SMS, and Internet data communication; most if not all smartphones also support Wi-Fi.
SMS	A text messaging service component of mobile devices. It uses standardized communications protocols to allow mobile phone devices to exchange short text messages. The terms text messaging and texting are used interchangeably to refer to both the medium and messages, and the term text message refers to the individual message sent.
MMS	The next evolutionary step from SMS. MMS allows mobile phone users to exchange pictures with sound clips on their handsets or digital cameras.
App	App is short for application, which is the same thing as a software program. Although an app may refer to a program for any hardware platform, it is most often used to describe programs for mobile devices such as smartphones and tablets.
Wireless	Being wireless means not using wires to send and receive electronic signals (i.e., sending and receiving electronic signals by using radio waves).
Wi-Fi	A wireless networking technology that allows computers and other devices to communicate over a wireless signal.
Bluetooth	This wireless technology enables communication between Bluetooth-compatible devices. It is used for short-range connections between desktop and laptop computers, a mouse, digital cameras, scanners, cellular phones, earphones, headsets, and printers.
Operating system	An operating system, or OS, is software that communicates with the hardware and allows other programs to run. Common mobile OSs include Android, iOS, and Windows Phone.
iOS	A mobile OS developed by Apple. It was originally called the iPhone OS but was renamed to iOS in June 2009. The iOS currently runs on the iPhone, iPod Touch, and iPad.
Android OS	A Linux-based open-source platform for mobile cellular handsets developed by Google and the Open Handset Alliance. Android 1.0 was released in September 2008.
Bandwidth	In computer networks, bandwidth is used as a synonym for data transfer rate, the amount of data that can be transmitted from one point to another in a given time period (usually a second). Network bandwidth is usually expressed in bits per second (bps); modern networks typically have speeds measured in the millions of bits per second (megabits per second or Mbps) or billions of bits per second (gigabits per second or Gbps).

MMS indicates multimedia messaging service; OS, operating system; and SMS, short messaging service. (From Burke LE et al., *Circulation* 2015;32:1157–213. Adapted with permission.)

Rehabilitation (AACVPR), AHA, and ACC reported on the findings of a systematic review of 23 published studies of home-based compared with center-based CR.[16] Interestingly, from a safety and wearable technology perspective, only three of the 23 studies utilized heart rate monitors and only two others used electrocardiographic telemetry monitoring for home-based CR. Consistent with the findings of the abovementioned Cochrane systematic review, the AHA scientific statement concluded that home- and center-based CR programs can achieve similar improvements in three- to 12-month clinical outcomes, and that home-based CR may be a reasonable option for selected clinically stable low- to moderate-risk patients who are eligible for CR but cannot attend a traditional center-based program. The scientific statement further recommended that prioritization be given to the testing and implementation of evidence-based hybrid approaches to CR that combine the positive and complementary aspects of both center- and home-based CR to personalize and optimize services for each patient, and to promote long-term adherence and favorable behavioral change. Regarding the latter (i.e., hybrid approaches), the Million Hearts Cardiac Rehabilitation Think Tank: Accelerating New Care Models has subsequently proposed a new model for describing CR delivery that: (1) includes a variety of modes of CR service delivery, namely, in-person (i.e., synchronous CR where patients and clinicians are in the same location at the same time and with in-person/direct patient observation during an exercise session), virtual (i.e., synchronous CR delivered with real-time audiovisual communication technology to facilitate patient and clinician interaction during an exercise session), and remote (i.e., CR delivered with asynchronous activities without real-time communication between patients and clinicians at the time of an exercise session); and (2) provides the option for an individual program to offer ≥1 mode of delivery and an individual patient to participate through ≥1 mode of delivery.[8]

Wongvibulsin et al. conducted a systematic literature review of 31 studies published from January 1990 to October 2018 that deployed digital health interventions for CR.[17] For this review, the authors defined digital as the technology employed to deliver virtual/remote care beyond

the use of the telephone (e.g., the delivery of care using the Internet, wearable devices, and mobile apps). The reviewed interventions primarily targeted physical activity counseling (100% of studies), baseline assessment (97% of studies), and exercise training (87% of studies). Approximately one-third of the studies addressed the CR core components of nutrition counseling, psychological management, and weight management, and less than a third of the studies addressed other CR core components, such as smoking cessation and lipid, diabetes, and blood pressure management. The most commonly used modalities were smartphones or mobile devices (65% of studies), web-based portals (58% of studies), and email/text messaging (35% of studies). The authors concluded that digital CR was feasible and as effective as traditional CR in improving outcomes, whether as an adjunct or an alternative to traditional CR.

In 2022, Nkonde-Price et al. reported on a retrospective cohort study of 2556 demographically diverse patients, including those who were medically complex, from a large integrated healthcare system who participated in a center-based (n = 1315) or technology-enabled home-based (n = 1241) CR program.[18] After adjusting for demographic and clinical characteristics, patients who received home-based CR had a lower odds of all-cause hospitalization at 12 months of follow-up (OR, 0.79; 95% CI, 0.64–0.97) compared with patients who received center-based CR. The authors concluded that their study strengthens the evidence supporting home-based CR, including in previously understudied patient populations.

In a multi-center study involving 12,984 patients who completed a traditional center-based CR program, very few patients had all CVD risk factors at levels currently recommended for ideal cardiovascular health at program completion.[19] These data emphasize the need for ongoing surveillance and intensive intervention aimed at residual CVD risk reduction in most patients who complete traditional center-based CR programs. In addition to their use as an alternative to center-based programs, home-based programs that incorporate novel digital health technologies can be leveraged to provide ongoing secondary prevention intervention after completion of center-based CR.

59.3 EFFECTIVENESS OF DIGITAL HEALTH TECHNOLOGIES FOR LIFESTYLE INTERVENTION AND CVD SECONDARY PREVENTION

The global smartphone penetration rate is estimated to have reached over 78% in 2020 and, according to a Deloitte survey, in the United States, the smartphone market penetration rose from 82% in 2017 to 85% in 2018.[20] The survey further indicated that the growth in smartphone penetration was strongest among older age groups (particularly those aged 45–54 and ≥55 years). From the perspective of addressing existing disparities in the provision of CR and CVD secondary prevention services, it is especially important to note that according to 2021 statistics from the Pew Research Center, 76% of individuals with an annual household income below $30,000 owned a smartphone.[21] Moreover, smartphone ownership was similar among Whites (85%), Blacks (83%), and Hispanics (85%). Thus, unlike the initial digital divide that placed Internet access and computer use beyond the reach of many disadvantaged populations, smartphones have been widely adopted across demographic groups, including ethnic minorities and older, lower socioeconomic status, and/or other currently underserved populations who may be most in need of secondary prevention interventions.[14]

The 2015 AHA scientific statement on consumer use of mobile health reviewed the scientific literature on mHealth tools related to CVD prevention.[14] Key findings pertaining to the use of mHealth to improve weight management, physical activity participation, smoking cessation, self-management of diabetes, hypertension care, and management of dyslipidemia were evaluated together with gaps in knowledge, and suggestions were made for future research. Several common themes and concerns were noted, including: (1) study design concerns such as the use of pre-post designs without concurrent control groups or randomized comparison groups, reliance on self-reported data, failure to use intention-to-treat analyses, evaluation in motivated participants and selected settings, and short duration of the studies; (2) evaluation of a single digital health technology compared with usual care rather than head-to-head studies comparing various digital health technologies with each other; (3) unanswered questions about product safety; (4) inability to demonstrate which components in an intervention are pivotal to success or whether the impact of a specific digital health product varies depending on the mode of use or delivery; and (5) absence of meaningful data on how best to incorporate the digital health technologies into a broader collaborative model of healthcare. Even with the abovementioned flaws, limitations, and unanswered questions, the authors concluded that their review of the evidence clearly demonstrates the great potential that mobile technologies can have to aid in lifestyle modification and that the current absence of sufficient evidence should not be interpreted as evidence of an absence of effectiveness. The authors encouraged healthcare professionals to rise to the challenge of producing the needed evidence on the effectiveness of digital health technologies and how best to adopt them in daily clinical practice.[14]

In a 2016 publication, Afshin et al. systematically reviewed the scientific evidence on the effectiveness of novel information and communication technologies to reduce non-communicable disease risk.[22] The authors searched PubMed for studies evaluating the effect of the Internet, mobile phones, personal sensors, or stand-alone computer software on diet, physical activity, adiposity, tobacco, or alcohol use among generally healthy adults. From 8654 abstracts, 224 relevant reports were identified. The authors concluded that Internet and mobile interventions improve important lifestyle behaviors for up to one year and that

their review supports the need for long-term interventions to evaluate sustainability. Interestingly, the authors also observed that: (1) using evidence-based behavioral change strategies could increase the effectiveness of Internet and mobile phone interventions (for example, in studies of diet/adiposity, interventions were more effective if adopting multiple modes of communication, using tailored messages, and integrating goal setting and self-monitoring; and in studies of physical activity, developing the Internet intervention content based on psychological theories of behavioral change increased both effectiveness and participant retention); and (2) interaction with healthcare providers could increase the success rate of the interventions.

In a 2017 publication, Khan et al. reviewed studies addressing digital health technologies to promote lifestyle change and medication adherence, including text messaging, smartphone apps, and wearable devices.[23] They concluded that: (1) the current literature indicates that digital health technologies will likely play a prominent role in future CVD management, risk reduction, and delivery of healthcare in both resource-rich and resource-limited settings; (2) additional clinical research and healthcare policy change are needed to move the promise of new digital health technologies toward reality; and (3) with many new digital health interventions bypassing clearance from the Food and Drug Administration, academic medical centers and professional medical organizations should provide broader guidance to consumers/patients. The authors also expressed concern that, because the development of digital health technologies is often driven by non-clinicians, unique challenges exist related to integration into daily clinical workflows. Moreover, because clinicians are increasingly burdened by the time-consuming use of electronic medical records and data overload, there may be limited capacity for them to take on additional responsibilities by processing and reacting to digital health-related data.

Through a comprehensive search of databases from 2002 to 2016, Park et al. conducted a quantitative systematic review of mobile phone interventions for the secondary prevention of CVD.[24] A large majority of studies (22 of 28, or 79%) demonstrated that text messaging, mobile apps, and telemonitoring via mobile phones were effective in improving outcomes. Key factors associated with successful interventions included personalized messages with tailored advice, greater engagement (e.g., two-way text messaging and higher frequency of messages), and the use of multiple digital health modalities. Overall, text messaging appeared more effective than smartphone-based interventions. Based on their observations and experiences, the authors speculated that future mHealth interventions will likely use a combination of different technologies (e.g., basic cellular phones, smartphones, computers, and tablets) and that with the widespread proliferation of smartphones, mHealth apps will likely expand on their connectivity with social media to maximize consumer engagement. However, in doing so, concerns of privacy and security issues will need to be adequately addressed.

A 2019 AHA scientific statement on harnessing mobile health technology for secondary CVD prevention in older adults, reported on the findings from a systematic review of 26 studies that used mHealth for secondary CVD prevention focusing on lifestyle behavior change and medication adherence in cohorts with a mean age ≥60 years.[25] Improvements in multiple health behaviors and medication adherence were observed, particularly when there was a text message component involved. In studies with app-only interventions, the majority of patients reported ease of use (>60%), patients found the app helpful, and self-reported use of the app was high. However, many of the apps tested were intended for very specific purposes. Although mobile technologies are becoming more mainstream and starting to blend more seamlessly with standard healthcare, the scientific statement concluded that there are still distinct barriers that limit implementation, including affordability, usability, privacy, and security issues. The scientific statement further emphasized that: (1) future studies on the type of mHealth that is the most effective are essential; and (2) as our population ages, identifying and implementing widely accepted, cost-effective, and time-efficient mHealth interventions to improve cardiovascular health should be a top priority.

59.4 HEALTHCARE TRANSFORMATION IN THE ERA OF DIGITAL HEALTH

Newly developed and rapidly evolving technological innovations have the potential to play a pivotal role in the shift from volume- to value-based healthcare. However, as emphasized in the 2017 report of the ACC Task Force on Health Policy Statements and Systems of Care[13] technological transformation often occurs too rapidly for existing healthcare practice to keep pace, thus creating a mismatch between the rate of development of novel technologies and preparedness of the healthcare system for effective integration and utilization of novel technologies. Thus, despite billions of dollars of investment in digital health technologies, there are numerous reasons why the digital transformation of healthcare still lags the rate of transformation that has occurred in other industries.[12,13]

Simultaneous with the publication of the 2017 ACC Task Force report, Walsh and Rumsfeld[12] proposed the following concerns among key reasons for healthcare lagging other industries in the adoption of potentially transformative new technologies: (1) healthcare is not entertainment; the healthcare system is extremely complex and simply not set up to rapidly absorb innovation; (2) the stakes in healthcare are very high, often involving life-or-death decisions and, thus, rightfully requiring convincing evidence for technology solutions before widespread clinical adoption; (3) many technology companies lack the necessary clinical insights; (4) while electronic medical records were a first step in the digital transformation of healthcare, dissatisfaction and criticism abound, with many physicians considering the introduction of electronic medical records a significant

misstep; (5) digital health companies have often been fearful of entering the healthcare regulatory process, and many have chosen not to aim innovation at the clinician-patient interface, instead solely developing consumer products; and (6) for the most part, there are non-aligned incentives or payment models in place to support digital health transformation of care delivery.

When deploying digital health technologies as a component of alternative CVD secondary prevention models, the following key policy recommendations from the AHA should be considered: (1) CR and secondary prevention programs should be reengineered to include an array of service options that meet the needs of individual patients and provide more flexible programs within and beyond the traditional clinical center to enhance access, adherence, and effectiveness; (2) such alternative approaches should not replace traditional programs, but should be used to engage the many patients who currently do not participate, and to provide ongoing monitoring and treatment after completion of traditional center-based CR programs; (3) alternative approaches should meet reputable quality standards, and existing standards may need to be customized for each model accordingly; (4) any new approach should not be widely implemented until it has been shown to be effective as evidenced by results of clinical studies published in peer-reviewed journals; and (5) third-party payers should cover the costs of evidence-based alternative models of delivery, such as hybrid programs and technology-enabled home-based models, that have been shown to be effective in peer-reviewed published clinical trials.[4,16] Regarding the latter, as a result of the COVID-19 pandemic, the Centers for Medicare and Medicaid Services (CMS) in the United States provided waivers to expand CR reimbursement to include virtual, synchronous (but not remote, asynchronous) service delivery. While the future of reimbursement for virtual CR is unknown at this time (September 2022), there is great enthusiasm to make the CMS waivers permanent.[8] It should also be noted that, in certain instances, there is currently the ability to leverage other newly reimbursable options for the provision of virtual/remote CVD secondary prevention services (e.g., chronic care management, principal care management, and remote patient monitoring) in the United States.

59.5 CASE STUDY OF AN EVIDENCE-BASED, DIGITAL HEALTH TECHNOLOGY-ENABLED, CVD RISK REDUCTION PROGRAM

We have spent over 25 years developing, testing, and implementing an evidence-based lifestyle management and CVD risk reduction telehealth coaching intervention that utilizes a variety of digital health technologies and has been shown to be effective in individuals with or at heightened risk for CVD.[26] The primary objectives of the digital technology-enabled telehealth coaching program are to help participants: (1) make and adhere to meaningful, evidence-based lifestyle changes (especially, regular exercise/physical activity, healthy nutrition, weight management, stress management, and tobacco cessation); (2) learn about CVD, CVD risk factors, and comorbidities, and acquire appropriate self-management skills (including use of relevant wearables/monitoring devices for remote patient monitoring, understanding untoward symptoms/signs, knowing when to contact their physicians/providers, and avoiding re-hospitalization); (3) address gaps in preventive care (e.g., complying with recommended preventive screenings/tests/vaccinations); and (4) comply with prescribed medications and other aspects of their regular medical care. To accomplish these objectives and help ensure the attainment of clinically meaningful/reproducible outcomes, telehealth coaching is delivered using a formal, structured, systematic approach together with rigorous continuous quality improvement protocols. The core components of the program and the key steps involved in their delivery are summarized in Figure 59.2.

There is no one single innovation that makes the telehealth coaching intervention novel; rather, it is due to the synergistic manner in which multiple novel approaches and digital health technologies have been incorporated into a single program to facilitate the provision of comprehensive CVD risk reduction services and the achievement of reproducible outcomes. A few of the many innovative aspects of the telehealth coaching intervention include the use of:

(1) A home-based program that was originally based on the protocols/procedures deployed in the Stanford Coronary Risk Intervention Project,[27] subsequently enhanced over more than 25 years and addresses not only prescribed physical activity/exercise training but also the other important core components of comprehensive CR/secondary prevention as part of a single integrated intervention. These other core components include modification of multiple CVD risk factors via education and behaviorally oriented health coaching, stress/mental health interventions, symptom management, and compliance with prescribed evidence-based CVD risk reduction medications, recommended preventive tests/vaccinations, and other aspects of regular medical care. The program is in daily use throughout the United States and Canada in a variety of real-world settings, including in English, Spanish, and French.

(2) Multiple novel digital health technologies, including telemedicine, videoconferencing, text messaging, online smartphone apps, game-based learning, and integration of data from electronic medical records, laboratories, blood pressure monitors, digital scales, blood glucose monitors, heart rate monitors, activity trackers, and other wearable devices/sensors. While the telehealth

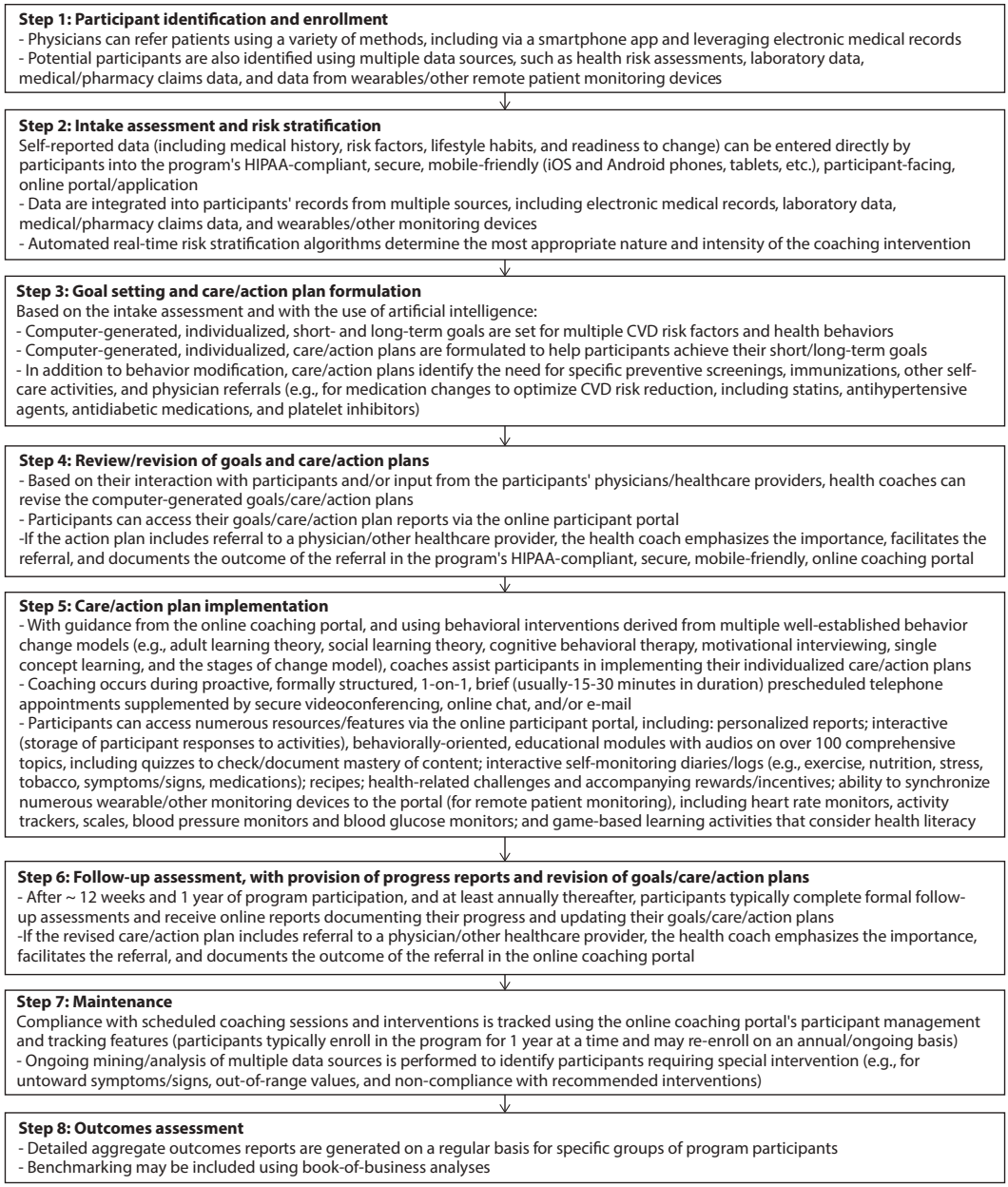


FIGURE 59.2 Summary of core components and key steps involved in an evidence-based, technology-enabled, lifestyle management and cardiovascular disease risk reduction program. Abbreviations: CVD, cardiovascular disease; HIPAA, Health Insurance Portability and Accountability Act of 1996

coaching program incorporates multiple digital technologies, individuals who are unable to use such technologies are still able to participate and achieve meaningful clinical benefits, making the intervention suitable for use with a broad spectrum of underserved populations. In fact, the minimum needed for participation is telephone access. All core participant educational materials are available in hard copy format, interactive online format (including health coaches having access to online activities completed by participants), and audio formats (for verbal learners and individuals who, for example, are illiterate or visually impaired). No special resources (e.g., exercise equipment or fitness center membership) are required but participants can elect to use and synchronize a variety of wearable/monitoring devices to the program's online portal.

(3) A sophisticated online coaching portal that provides professional health coaches access to the resources, data, and automated guidance they need to provide evidence-based, behaviorally oriented, coaching aimed at helping participants acquire the skills, motivation, and support needed

TABLE 59.2
Case Study of an Evidence-Based, Digital Health Technology-Enabled, CVD Risk Reduction Program: Key Published Randomized Clinical Trials

Reference, Objectives; Study Design/Duration	Results, Conclusions, and Implications
Gordon et al.[35] This randomized clinical trial compared the clinical effectiveness of two, less-costly and potentially more accessible, approaches to CVD risk reduction with that of a contemporary phase 2 center-based CR program. Low- or moderate-risk coronary artery disease patients (n = 155) were randomly assigned to 12 weeks of participation in a contemporary phase 2 CR program (n = 52), a physician-supervised, nurse-case-managed CVD risk reduction program (n = 54), or a comprehensive health coaching program administered by exercise physiologists guided by a computerized participant management system based on reputable national clinical guidelines (n = 49); 142 patients (91.6%) completed testing at baseline and after 12 weeks of intervention.	For patients with abnormal baseline values, statistically significant ($p \leq 0.05$) improvements were observed with all three interventions for multiple CVD risk factors. With the exception of maximal oxygen uptake, no statistically significant risk factor differences were observed among the three programs. For patients with a baseline maximal oxygen uptake <7 METs, maximal oxygen uptake increased to a greater degree in patients in the contemporary phase 2 CR program and the health coaching program versus the physician-supervised, nurse-case-managed program. These data demonstrate that an evidence-based, technology-enabled health coaching program can be at least as effective as other more costly and potentially less accessible interventions (including traditional center-based CR) in low- and moderate-risk coronary artery disease patients. The data have important potential implications for cost-containment and for increasing accessibility to clinically effective comprehensive CVD risk reduction services.
Maron et al.[36] This randomized clinical trial evaluated how the intensity of intervention after the provision of a health risk assessment affects CVD risk; 133 employees with CVD risk factors were randomly assigned for one year to a health risk assessment plus comprehensive health coaching group (higher-intensity intervention; HC group) or a health risk assessment plus information about worksite health promotion programs group (lower-intensity intervention; HRA group). The HC group participated in a one-year technology-enabled, health coaching program, whereas the HRA group received one feedback session about their CVD risk factors and information about free worksite health promotion programs. The primary outcome measure was the change in Framingham ten-year coronary heart disease risk scores.	In the HC group, the mean Framingham ten-year coronary heart disease risk score decreased by 22.6% (relative risk reduction); in the HRA group, the mean score rose by 4.3% ($p = 0.017$ for the difference between groups). The data demonstrate that a health risk assessment followed by participation in an evidence-based, technology-enabled, health coaching program can be more effective than a health risk assessment followed by one feedback session and the provision of information about free worksite health promotion programs. The data also serve to highlight that not just any kind of lifestyle management program done in any way at all will produce high levels of clinical benefit. It is evident from this study that lifestyle management programs must be appropriately designed and executed effectively to significantly impact multiple clinical variables and facilitate CVD risk reduction.
Derdeyn et al.[30]; Turan et al.[31]; Turan et al.[32]; and Turan et al.[33] This study, conducted at 50 medical centers in the United States, randomly assigned 451 patients with recent transient ischemic attack or stroke related to 70–99% stenosis of a major intracranial artery to aggressive medical management (including anti-platelet therapy, intensive management of vascular risk factors, and participation in an evidence-based, technology-enabled, telehealth coaching program) or aggressive medical management plus intracranial stenting with the Wingspan stent. The primary endpoint was any of the following: stroke or death within 30 days after enrollment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrollment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up. Patients were followed for a median of 32.4 months.	In the medical management-only group, 15% of patients had a primary endpoint event, while 23% of patients in the stenting group had a primary endpoint event. The primary endpoint rate in the medical management-only group (14.1% at two years) was much lower than was projected based on the results of the WASID trial (24.7% at two years), an observation that was attributed to differences in medical treatment in these trials, including use of telehealth coaching in SAMMPRIS but not WASID. Throughout the duration of the study, there were continued improvements in CVD risk factor control. Multivariate analyses demonstrated that of the various CVD risk factors, physical inactivity was by far the most important predictor of poor outcomes—greater physical activity decreased the likelihood of a recurrent stroke, myocardial infarction, or vascular death by 40% (odds ratio 0.6, confidence interval 0.4–0.8). The investigators attributed increases in physical activity to compliance with the telehealth coaching program, which also contributed to the high percentage of patients achieving other risk factor targets. The study highlights the potential benefits of physical activity for the prevention of recurrent stroke and the role that evidence-based, digital technology-enabled, telehealth coaching can play in helping patients achieve CVD risk factor goals. The study also helps allay concerns regarding the long-term sustainability of CVD risk factor control.

CR, cardiac rehabilitation; CVD, cardiovascular disease; SAMMPRIS, Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis; WASID, Warfarin Aspirin Symptomatic Intracranial Disease (adapted, in part, from Gordon NF et al., *Am J Lifestyle Med* 2017;11:153–166).

to implement and adhere to their individualized care/action plans.

(4) Multiple features to facilitate provider engagement and interaction with participants to improve adherence to evidence-based secondary prevention interventions. For example, using artificial intelligence, evidence-based, individualized goals and care/action plan reports and progress reports are automatically generated for program participants. Healthcare providers are able to access these reports, recommend changes, and, in certain instances, provide electronic input to their patients' health coaches. Where indicated on the basis of reputable clinical guidelines, including optimizing CVD risk reduction medication management, coaches facilitate the referral of participants to their healthcare providers.

(5) Big data mining to provide business intelligence to enhance participant engagement and optimize the nature and intensity of CVD risk reduction interventions. Data sources include health risk assessments, electronic medical records, laboratory data, medical/pharmacy claims data, and data from wearables/other monitoring devices.

The program's effectiveness has been evaluated as part of numerous formal research initiatives. The telehealth coaching program was successfully deployed as part of the aggressive medical management component of the National Institutes of Health (NIH)-funded Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) multi-center clinical trial,[28–33] and is currently being used as part of the aggressive medical management components of the multi-center NIH-funded Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2)[34] and Comparison of Anti-coagulation and Anti-Platelet Therapies for Intracranial Vascular Atherostenosis (CAPTIVA) clinical trials. The telehealth coaching program is also being used by participants in the Canadian Diabetes Prevention Program (CDPP) clinical trial (funded, in part, by the Public Health Agency of Canada) and the Telehealth-Enhanced Assessment and Management after Stroke-Blood Pressure (TEAMS-BP) multi-center clinical trial (funded by the Patient Centered Outcomes Research Institute). Results of several of the key published randomized clinical trials are summarized in Table 59.2.[28–33,35,36]

CLINICAL IMPLICATIONS

1. Newly developed and rapidly evolving technological innovations, including digital health, have the potential to play a pivotal role in the shift from volume- to value-based healthcare.
2. Hybrid and home-based digital health technology-enabled lifestyle management and CVD risk reduction programs are a viable alternative to traditional center-based CR programs.
3. Such alternative approaches should not be used to replace center-based CR but rather to engage the many patients who currently do not participate and provide ongoing, evidence-based, CVD secondary prevention interventions post-CR.
4. Healthcare professionals should rise to the challenge of producing the needed evidence on the long-term effectiveness of digital technologies and determine how best to adopt them in daily practice to help optimize patient health.

DISCLOSURES

Neil Gordon, Richard Salmon, and Prabakar Ponnusamy are members and/or employees of a population health management company (INTERVENT International, LLC).

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60 Psychosocial Risk Factors as Modulators of Cardiovascular Outcomes in Secondary Prevention

Joel W. Hughes, PhD and David Ede, PhD

KEY POINTS

- Many patients with heart disease experience psychosocial comorbidities, such as depression, anxiety, social isolation, and anger/hostility.
- These moderate risk in secondary prevention, and, for example, patients with depression have a greater risk of a poor outcome.
- Treatments for psychosocial comorbidities have generally not been shown to reduce the associated risk.
- Outpatient cardiac rehabilitation improves psychosocial comorbidities, improves quality of life, reduces risk factors, and reduces risk of mortality.

60.1 SECONDARY PREVENTION AND PSYCHOSOCIAL FACTORS

Cardiovascular disease (CVD) causes nearly one out of every three deaths in the United States, and every year, over 1.1 million Americans have a first or recurrent coronary event.[1,2] Advances in cardiology have resulted in many more patients surviving their first encounter with heart disease, leading to an increase in the population of patients requiring secondary prevention, as well as a growing number of patients living with heart failure (HF).

Secondary prevention is attempting to reduce the risk of acute cardiac syndrome (ACS) and cardiac mortality in people with established CVD. The cornerstone of secondary prevention is risk reduction in multiple areas including smoking, BP control, lipid management, physical activity, weight management, type 2 diabetes management, antiplatelet and anticoagulant agents, renin-angiotensin-aldosterone system blockers (e.g., ACE inhibitors), beta-blockers, influenza vaccination, depression screening, and cardiac rehabilitation.[3] In 2011, the most recent American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention listed cardiac rehabilitation as a class 1-A recommendation.[3] Furthermore, screening patients who are potentially at risk for depression is now recommended. These are changes from the earlier 2006 guidelines.[4] The role of psychosocial factors, like depression, in moderating risk in secondary prevention is increasingly recognized, and the importance of cardiac rehabilitation as part of secondary prevention is now well established.

Some see cardiac rehabilitation as synonymous with secondary prevention for heart disease, but it is only one of 12 areas for intervention.[3] True, cardiac rehabilitation is a comprehensive approach to secondary prevention that addresses or monitors many of the other 11 areas, and it is particularly effective when delivered in a manner that includes all the core components. Psychosocial management is a core component of outpatient Phase II cardiac rehabilitation programs in the United States (here we write from the perspective of the United States of America with respect to definitions, statutes, official statements, and business models; we recognize that the implementation and models of CR differ by country and that an international perspective on psychosocial management is important, but beyond the scope of this review)[5] and has been identified as one of the components contributing to the effectiveness of cardiac rehabilitation.[6]

60.2 PSYCHOSOCIAL FACTORS IN HEART DISEASE

Psychosocial factors have long been recognized as moderators of outcomes in secondary prevention, meaning that patients with known heart disease who have certain psychosocial characteristics may have better or worse outcomes. For example, the Type-A behavior pattern was first recognized in the 1950s,[7] prompting decades of research into coronary-prone personality types and the role of anger and hostility in primary and secondary prevention. Currently, the most prominent example of a moderating role of psychosocial factors is that patients with comorbid heart disease and depression have worse outcomes than those without depression.[8–13] In the early 2000s, excellent reviews of the broader topic of psychosocial factors in heart disease were published. For example, Smith et al.[8] described how psychosocial influences could influence the pathophysiology of coronary heart disease and identified a number of psychosocial risk factors. Those relevant to secondary prevention included hostility, depression, anxiety, social isolation, interpersonal conflict, and occupational stress.

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Psychological interventions attempting to mitigate these risks were conducted, such as the landmark Enhancing Recovery in Coronary Heart Disease (ENRICHD)[14] and Sertraline and Depression Heart Attack Randomized Trial (SADHART)[15] trials for post-MI patients with depression (or social isolation in the case of ENRICHD). The mixed results of these trials were widely discussed, and this only underscored the need for physicians to be aware of the role of psychosocial factors in secondary prevention.[13] The call to screen for and intervene with psychosocial risk factors increased. What some called the field of "behavioral cardiology"[12, 13] emerged to examine the application of behavioral, pharmacological, and rehabilitative interventions on cardiac outcomes.

In this chapter, we focus on the more recent literature and important developments. In secondary prevention, psychosocial factors such as depression[12, 16] and anger/hostility[17] are associated with poorer prognosis. Furthermore, the contribution of behavioral and psychosocial factors to risk is commensurate with that conferred by more traditional risk factors (e.g., cholesterol). Depression is the only psychosocial risk factor included in the AHA/ACC position statement,[3] and no clinical consensus has emerged for how cardiology practitioners should approach behavioral and psychosocial factors in the clinical management of coronary heart disease. However, some have recommended a "stepped care" approach in which physicians are the front-line clinicians, followed by behavioral health interventions (e.g., cardiac rehabilitation) and behavioral health specialists (e.g., psychologists) in the second and third tiers, respectively.[12]

Fortunately, cardiac rehabilitation or structured exercise programs reduce anger/hostility, anxiety, depression, and stress.[9] In our view, cardiac rehabilitation is a particularly appropriate context for addressing psychosocial factors in secondary prevention. Heart disease and psychosocial factors are profoundly affected by lifestyle, and cardiac rehabilitation is a lifestyle intervention that can address both synergistically. In our view, some targets for intervention are more amenable to addressing during physician visits than others (e.g., blood pressure control, lipid management, antiplatelet agents/anticoagulants, renin-angiotensin-aldosterone system blockers, beta-blockers, influenza vaccination), and some are more effectively targeted by the increased intervention frequency and intensity of comprehensive cardiac rehabilitation (e.g., smoking, physical activity, weight management, type 2 diabetes mellitus management, depression). Furthermore, few alternatives to cardiac rehabilitation exist besides treatment-as-usual.

60.3 WHAT ARE THE PSYCHOSOCIAL FACTORS THAT MODERATE OUTCOMES IN SECONDARY PREVENTION?

60.3.1 Anger/Hostility

Anger and hostility remain important psychosocial factors for prognosis in primary and secondary prevention of cardiovascular disease.[8,12,13] In one meta-analysis, the association between anger/hostility and outcomes was stronger for men than for women.[17] However, psychosocial interventions for hostility have been rare, and it has been suggested that the widespread adoption of pharmacological interventions acting on the putative biological mechanism (i.e., beta-blockers) has resulted in a less prominent role for hostility in secondary prevention in recent decades. For example, a more recent study reported that hostility predicted all-cause mortality, but not recurrence of acute coronary syndromes (e.g., emergency department visits that resulted in hospitalization).[18]

60.3.2 Anxiety

Anxiety also worsens prognosis in secondary prevention of cardiovascular disease.[9,19] For example, anxiety predicts mortality in stable heart disease, and the risk may be shared with depression or potentiate the risk associated with depression.[20]

60.3.3 Social Support

A classic study reported that patients who were socially isolated or who lacked a close confidant were at greater risk for mortality after a myocardial infarction (MI) than those with better social support.[21] A systematic review reported that loneliness and social isolation predict incident cardiac disease and stroke,[22] and it is generally recognized that adequate social support is necessary for recovery from acute coronary events. For example, heart transplant candidates are typically required to identify a support person during the eligibility evaluation before transplantation. Medicare guidelines for cardiac rehabilitation also require an evaluation of social support (i.e., "aspects of family/home situation") that affects treatment, although screening procedures were not specified. However, the treatment of loneliness is not merely structural, as shown in a broader population meta-analysis, which demonstrated that interventions targeting social cognition were more effective than those that merely increased opportunities for interaction.[23]

60.3.4 Depression

The fact that depression worsens prognosis in secondary prevention is now well established,[9] and screening for depression has been incorporated into the most recent AHA/ACC statements.[11] The relationship between depression and heart disease is complex, as depression is also a risk factor for the development of cardiovascular disease and cardiovascular mortality.[24,25] In primary prevention, depression has been associated with approximately a 65% increase in the risk of developing cardiovascular disease among persons initially free from heart disease.[26] In secondary prevention, depression contributes to a two- to fivefold increased risk of mortality.[10,11]

Depression is also very common in cardiac patients, with perhaps 15% to 20% of patients qualifying for a

diagnosis of major depressive disorder and an additional 15% to 20% exhibiting clinically significant symptoms of depression without meeting diagnostic criteria. Depression can be exacerbated by the stress of ACS but can also predate the cardiac event or emerge later. For example, half of the patients enrolled in SADHART were depressed prior to their ACS.[15] Therefore, depression has become an important consideration in secondary prevention for patients with cardiovascular disease, but efforts to reduce the risk of mortality by alleviating depression have not been very successful.

60.4 ADDRESSING DEPRESSION IN SECONDARY PREVENTION

60.4.1 Screening for Depression

Although screening for depression in secondary prevention is recommended[11,27,28] and has become common, there has not been an evaluation of the impact of depression screening on patient outcomes in cardiovascular care.[29] Methods for screening for depression (and anxiety) are not consistent, and recommendations in international guidelines vary.[30] Thus, one research priority is evaluating whether or not screening patients for depression improves patient care or outcomes for patients with CVD. [31]

60.5 TREATING DEPRESSION IN SECONDARY PREVENTION

A 25-year review of interventions for depression in heart disease concluded that many cases of depression remit "spontaneously" and that there is no strong evidence that either antidepressants or psychotherapy influence prognosis.[32] The conclusion of this literature is that the first-line treatments for depression in heart disease are newer antidepressants (e.g., SSRIs) or psychotherapy (e.g., cognitive behavioral therapy), that the effectiveness of these approaches is moderate at best, that these treatments do not improve cardiac prognosis much, if at all, and that patients whose depression persists continue to have elevated risk of poorer outcomes. The often-overlooked option is exercise, a key component of cardiac rehabilitation, which, as we will see, both reduces depression and improves prognosis.

60.5.1 Antidepressant Medication

Concerning antidepressants, they are often the first treatment option, and SSRIs, in particular, appear to be safe for use in patients with CVD.[33,34] However, in the SADHART trial, sertraline was only effective for patients with a history of depression.[15] In the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial, citalopram had a small to medium effect relative to placebo in reducing depression.[35] Again, most of this benefit was limited to those patients with recurrent depression.[36] In the Myocardial Infarction and Depression-Intervention (MIND-IT) trial, antidepressants improved neither depression nor prognosis.[37,38] Antidepressants have also been administered prophylactically, and escitalopram was reported to prevent depression episodes following ACS relative to placebo.[39] A recent meta-analysis reported a pooled effect size of second-generation (e.g., SSRI, SNRI) antidepressants for depression in patients eligible for CR was small ($g = 0.15$). In patients with heart failure, antidepressants are not more effective than placebos for reducing depression symptoms.[40,41]

Thus, evidence for the effectiveness of antidepressants in secondary prevention is mixed and may not match patient preference. Specifically, among the general population of patients experiencing their first episode of major depression, 41% prefer psychotherapy and 31% prefer antidepressants.[42] Furthermore, in recent years, some cardiovascular safety concerns regarding newer antidepressants have been articulated, suggesting that prescribers should carefully weigh the risks and benefits.[43–45] However, the disappointing effectiveness of antidepressants for patients with heart disease may be better understood by appreciating recent revelations on the shortcomings of antidepressants more broadly.

Fairly recently, it has become clear that much of the effect of modern antidepressants on depression is due to psychological factors like *hope*, a *sense of efficacy in doing something* about depression, and the *expectation* of getting better.[46,47] In fact, antidepressants appear to have a greater effect on depression if the patient experiences more side effects, as the side effects apparently remind the user that they are taking the medication and imply that the medication must be working.[48] It has been argued that fluoxetine would not have received approval from the Federal Drug Administration (FDA) had the studies with negative results been reported.[47] A less charitable way of saying this is that a substantial part of the effectiveness of antidepressants is a placebo effect.[46,49,50] Between the years 2002 and 2010, this erupted into a public controversy. Some associates within the field of psychiatry were not amused.[51]

Of course, there are caveats and vigorous debate,[52,53] and it must be acknowledged that antidepressants do "work", whatever the mechanism may be. For example, the response curve for both placebo and active drugs appears robust, and drug trials rarely include a study arm of patients receiving no treatment at all. The small effect of antidepressants may only be relative to the placebo, and untreated patients may not improve at all. Furthermore, in clinical practice, it is strongly recommended that patients not abruptly discontinue antidepressants without medical supervision because some patients have discontinuation symptoms and the chance of relapse into another depressive episode is high.[54] Even for antidepressants-as-placebo, the therapy infrastructure is often so poor that, for many patients, the only option may be antidepressants. However, lifestyle cognitive and behavioral habits, rather than taking medication, will be a

more enduring solution for most cases of depression and anxiety.

Why is there so little effect of antidepressants that can be attributed to the medication itself? It is not known for certain. It is suspected that the chemical imbalance theory of depression (really a metaphor) is overly simplistic.[55,56] Furthermore, treatment cannot inform etiology. For example, a headache is not caused by an aspirin deficiency. The fact that aspirin works (anti-inflammatory medications reduce prostaglandins) does not suggest an "aspirin imbalance" in a patient's brain. This is not to suggest that the serotonergic systems of the central nervous system are not involved in depression, but the chemical imbalance metaphor appears to be dramatically oversimplified. Whatever the mechanism of action for antidepressant medication, they appear more effective in patients with recurrent depression and they do not appear to influence prognosis in secondary prevention.

60.5.2 Psychotherapy

With respect to psychotherapy, cognitive behavioral therapy (CBT) used in the ENRICHD trial modestly reduced depression relative to control and did not reduce mortality rates.[14] Patients whose depression persisted continued to have a worse prognosis.[57] One alternative to CBT, interpersonal psychotherapy for depression, was evaluated by the CREATE trial but was not more effective than clinical management for depression in patients with coronary artery disease.[35] In the more recent Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS) trial, stepped care (as suggested by Rozanski[12,13]) was compared with treatment-as-usual (e.g., locally determined care by the patient's healthcare provider).[58] Those allocated to stepped care initially received problem-solving therapy via telephone followed by the option to receive antidepressants. Reductions in depression were greater for stepped care than for treatment-as-usual, potentially suggesting that patient preference (e.g., choice, agency) is important for the effectiveness of treatment. However, improvement in depression was not associated with better secondary prevention in the areas of aspirin adherence, diet, exercise, use of tobacco, or blood pressure control.[59] A Cochrane review of psychological interventions for patients with heart disease concluded that reductions in depression are small to moderate and that they are not accompanied by improved prognosis.[60] However, a subsequent Cochrane systematic review and meta-analysis reported that psychological interventions for patients with coronary heart disease led to a reduction in cardiovascular mortality. [32]

Given the disappointing effectiveness of both antidepressants and psychotherapy for addressing psychosocial factors that moderate risk in secondary prevention, alternative approaches are needed. In our view, the most promising resource for addressing depression is existing secondary prevention that includes participation in cardiac rehabilitation.

60.6 CARDIAC REHABILITATION

Outpatient (Phase II) cardiac rehabilitation is a multi-faceted secondary prevention program for patients that includes up to 36 sessions (e.g., 12 weeks) of exercise and education on lifestyle risk factor management and is reimbursed by Medicare and other insurance carriers.[61] Because cardiac rehabilitation lowers rates of reinfarction and mortality,[62] it is an evidence-based treatment recommendation for eligible patients with CVD following cardiac events such as MI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and cardiac valve surgery.[3,63] The goals of cardiac rehabilitation are to improve fitness, biomarkers such as lipids, and quality of life, and engage in and maintain secondary prevention behaviors including exercise, diet, smoking cessation, and medication management. These goals are broadly consistent with the premise of lifestyle medicine.

There is no question that cardiac rehabilitation is effective for secondary prevention. However, many eligible patients do not enroll in outpatient cardiac rehabilitation,[64–66] and, for example, only 28.6% of Medicare beneficiaries who had an event that made them eligible for cardiac rehabilitation enrolled, and only 27.6% of these completed 36 sessions.[67] Furthermore, health disparities persist in cardiac rehabilitation participation, driven by social determinants of health,[68] such that lower participation rates are observed among the elderly, sicker patients, women, minorities, and persons of lower socioeconomic status (SES).[69–71] Depression also reduces adherence to cardiac rehabilitation.[72]

Cardiac rehabilitation reliably reduces depression.[9] For example, although women starting cardiac rehabilitation have higher depression scores, they also experience a greater reduction in depression.[73] Exercise is at least as effective as antidepressant medication for depression,[74] and combined exercise and antidepressants appeared to have greater benefits on a biomarker of risk (heart rate variability) than either intervention alone.[75] Combining psychological interventions with cardiac rehabilitation reduced depression more than cardiac rehabilitation alone.[76] A small trial integrating 12 weeks of stress management training with cardiac rehabilitation reduced mortality relative to cardiac rehabilitation alone, suggesting that combining psychosocial interventions with cardiac rehabilitation may provide even better secondary prevention.[77] Finally, a program of research in the UK has reported promising results for integrating metacognitive therapy into cardiac rehabilitation. [78]

Given that cardiac rehabilitation is effective in reducing both mortality and depression, combined with the disappointing results of decades of attempts to ameliorate the poorer prognosis of cardiac patients with comorbid depression, it is our view that future efforts should focus on increasing the utilization of cardiac rehabilitation, integrating psychosocial interventions with cardiac rehabilitation or other structured exercise programs, and extending secondary prevention of CVD to include alternatives to cardiac

TABLE 60.1
Treatments for Depression in Cardiovascular Disease

Antidepressants	Antidepressants are not very effective for patients with heart disease, except for patients with a history of recurrent depression. Antidepressants do not reduce the risks associated with depression.
Psychotherapy	Cognitive behavioral therapy is somewhat effective, but does not reduce the risk associated with depression. Newer psychotherapies such as acceptance and commitment and mindfulness-based cognitive therapy have not yet been evaluated. Metacognitive therapy may be effective when integrated into cardiac rehabilitation, and possible improvements in cardiovascular prognosis have not been evaluated.
Cardiac rehabilitation	Cardiac rehabilitation, which includes exercise, is effective for depression and reduces the risk of mortality. Enhancing cardiac rehabilitation with stress management or other psychosocial interventions has promise. Extending cardiac rehabilitation with innovative delivery models or alternatives is suggested.

rehabilitation (e.g., remotely delivered secondary prevention) (see Table 60.1).

60.7 DEPRESSION IN HEART FAILURE

In the past, secondary prevention efforts primarily targeted coronary heart disease and patients experiencing ACS. The success of modern cardiology has led to an increased prevalence of patients with HF, as they survive the initial MI and live longer with heart disease. Now this population has received increased secondary prevention efforts, and stable systolic HF is an approved indication for cardiac rehabilitation. Currently, over five million Americans have HF, and nearly one million new cases are diagnosed each year.[1,2] The prevalence of HF is expected to increase 46% by 2030, and more than eight million US adults will have HF.[79]

Mortality in HF remains high, as one out of two HF patients die within five years of diagnosis.[79–81] As with other forms of heart disease, many individuals with HF experience depressive symptoms or clinical depression. At least 20–40% of patients with HF experience depression symptoms during their illness,[82] which doubles the risk of all-cause mortality.[82,83] Depression undermines disease management programs for HF[84] and is a barrier to effective patient self-management. For example, medication non-adherence increases the risk of mortality in depressed patients with HF.[85]

Some of the lessons from other heart disease conditions about psychosocial factors in secondary prevention are being repeated in patients with HF. For example, neither sertraline[86] nor escitalopram[87] is efficacious for depression in patients with HF; and although both were safe, they did not improve clinical status.[86,87] Furthermore, as with the broader population of depressed individuals,[88,89] HF patients tend to prefer behavioral treatments to antidepressants.[90]

CBT for depression and self-care in HF reduced depression symptoms at six months and showed superior remission of depression relative to the control condition (46% vs. 19%), but the trial was not powered to detect improved prognosis.[91] As with cardiac patients more broadly, exercise also reduces depression in systolic HF.[92] The HF-ACTION trial randomized 2322 patients with HF to exercise or education and usual care. Depression scores were reduced at three months and 12 months, but the clinical significance of the improvement could not be demonstrated. The effect of exercise training on depression was a 40% reduction in symptoms, and those who remained depressed continued to have an elevated risk of mortality.[93] Intriguingly, depressed patients who completed exercise training had almost a 60% reduction in mortality.[93]

60.8 FUTURE DIRECTIONS

The public health burden of CVD is likely to increase as the population ages and advances in cardiology result in more patients being appropriate for secondary prevention. Psychosocial factors are known to moderate cardiovascular outcomes, but efforts to ameliorate this risk have been challenging. Here we argued that addressing psychosocial factors in the context of cardiac rehabilitation is a promising approach, making increasing utilization of cardiac rehabilitation a critical focus.[94] There are several other directions for future research that merit comment, specifically integrating psychosocial interventions with cardiac rehabilitation or other structured exercise programs, and extending secondary prevention of CVD to include innovative delivery models and even alternatives to cardiac rehabilitation.

60.8.1 Integrating Psychosocial Interventions with Cardiac Rehabilitation

Another promising future direction is integrating psychosocial interventions with cardiac rehabilitation. Integration would result in the broader dissemination of treatments for psychosocial factors in secondary prevention and will require the development of behavioral interventions that are easier to implement. The front-line treatments at this point are antidepressant medications, which are not particularly effective, and psychotherapy, which is time- and labor-intensive. The mental health infrastructure is poor in many communities, and it would be valuable to have interventions that can be provided to more patients.

The evolution of psychotherapy to include more acceptance of distress and more mind–body interventions such as meditation may facilitate the integration of interventions

with cardiac rehabilitation. The so-called "third wave" of psychotherapy departs from cognitive behavioral therapy[95–97] by de-emphasizing the focus on dysfunctional or depressogenic cognition, instead, asking patients to accept and tolerate some distress. The major therapies in this tradition are acceptance and commitment therapy[98] and those which incorporate mindfulness meditation.[99] A meta-analysis and systematic review of mindfulness-based interventions for patients with vascular diseases included nine clinical trials (three in heart disease) and reported effects for psychological but not medical outcomes.[100] If newer therapies continue to grow in popularity and availability, it will be important to evaluate their suitability for secondary prevention. There is great enthusiasm for incorporating some of the techniques (e.g., meditation) into cardiac rehabilitation, but the research is currently lacking. Another promising new approach developed in the UK involves integrating metacognitive therapy into cardiac rehabilitation, which can be delivered in a group or self-help format.[78]

60.8.2 Innovative Delivery Models and Alternatives to Cardiac Rehabilitation

Currently, there is an emphasis on increasing the utilization of cardiac rehabilitation and developing innovative models of delivery, which has great merit. The onset of the COVID-19 pandemic temporarily shuttered cardiac rehabilitation sites, and many rapidly transitioned to remote delivery. There is great hope that new delivery models will increase enrollment in cardiac rehabilitation. Although some barriers to participation can be overcome using telehealth or other means, some patients have chosen not to participate due to competing life demands, personal priorities, or other volitional forms of non-participation.

It is our view that secondary prevention of CVD could be extended beyond cardiac rehabilitation by offering self-management programs that are alternatives (e.g., remotely delivered secondary prevention). That is, for patients who do not enroll in cardiac rehabilitation, the *de facto* provider of secondary prevention is the patient's medical provider (e.g., cardiologist, primary care physician). The success of cardiac rehabilitation and the fact physician prescribed and monitored exercise defines cardiac rehabilitation by statute (i.e., 42 CFR §§ 410.47)[61] may have resulted in many conflating secondary prevention with cardiac rehabilitation. This is not accurate, as cardiac rehabilitation is one of 12 targets for intervention. Thus, it should be possible to develop approaches that fall between physician visits and center-based outpatient cardiac rehabilitation with respect to intensity, frequency, and patient burden. This would be consistent with the spirit of the guidelines for secondary prevention.[3] This suggestion does not disparage the importance of exercise training, as patients having a good experience with a more comprehensive secondary prevention program might be subsequently willing to enroll in cardiac rehabilitation. Furthermore, physical activity (i.e., moderate-intensity aerobic activity) is a recommendation independent of that for cardiac rehabilitation. Our suggestion is to increase the intensity of secondary prevention using structured programs that are more accessible than outpatient cardiac rehabilitation to achieve more widespread dissemination of secondary prevention broadly construed. Ultimately, this could provide opportunities to address psychosocial factors that modulate cardiovascular outcomes in secondary prevention.

60.9 CONCLUSION

Many patients with heart disease experience psychosocial comorbidities, such as depression, anxiety, social isolation, and anger/hostility that moderate risk in secondary prevention. Depression is the most prominent risk factor, and decades of research have concluded that first-line treatments (antidepressants and/or psychotherapy) are only moderately effective and generally do not reduce the associated risk associated with depression. Comprehensive cardiac rehabilitation, which includes psychosocial management, is the most promising approach for addressing psychosocial risk factors and is aligned with the spirit and aims of lifestyle medicine.

CLINICAL APPLICATIONS

Psychosocial considerations in secondary prevention:

- Social support/social isolation confer greater risk of mortality: isolated patients or those with low social support.
- Anger/hostility: patients high in anger or hostility have poorer outcomes and interventions are rare. Beta-blockers may directly target the physiological mechanism responsible.
- Anxiety: high anxiety increases risk of mortality independently of depression, and comorbid anxiety and depression may have a greater effect than either alone.
- Depression: depression is common in heart disease and confers a two- to five-fold increased risk of mortality. Patients should be screened for depression.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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61 Lipid Management in Secondary Prevention

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KEY POINTS

- The benefit of lipoprotein (LDL)-cholesterol (C) reduction appears to have no lower boundary.
- Our treatment goal in managing patients with atherosclerotic cardiovascular disease (ASCVD) is to lower the LDL-C as much as possible without producing side effects.
- Most patients cannot achieve sufficiently low levels with dietary intervention alone.
- High-intensity statin treatment is the cornerstone of secondary prevention and LDL–C management in patients with ASCVD.
- Non-statin lipid-lowering drugs should be considered in patients intolerant of statins or in whom the LDL-C levels are not at goal on maximally tolerated statin therapy.

61.1 INTRODUCTION

The initiation and progression of atherosclerotic cardiovascular disease (ASCVD) is driven by low-density lipoprotein (LDL)-cholesterol (C) and reducing LDL-C reduces the incidence of both primary and secondary cardiovascular events. The benefit of LDL–C reduction appears to have no lower boundary. GLAGOV (the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial randomized 968 statin-treated patients with angiographic coronary artery disease to the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, evolocumab, or to placebo. LDL–C at 78 weeks was 93 and 37 mg/dL in the placebo and evolocumab subjects, respectively[1] The percent atheroma volume measured by intracoronary ultrasound increased by 0.05% with placebo but decreased by 0.95% with evolocumab ($p<0.001$). Analysis of the regression curve demonstrated increasing reductions in atheroma volume with decreasing LDL-C down to LDL-C levels of 20 mg/dL.[1] Similarly, FOURIER or the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with elevated risk demonstrated that evolocumab added to a statin reduced cardiovascular events at 48 weeks when compared with placebo. LDL-C levels decreased from 92 mg/dL to 30 mg/dL with evolocumab treatment.[2] Both GLAVOV and FOURIER suggest that greater LDL-C reduction produces greater reductions in cardiovascular events and both trials support the hypothesis that lower LDL-C is better in patients with established ASCVD. This chapter will describe our rationale and approach for treating LDL-C in ASCVD patients.

61.2 TREATMENT GOALS

Our treatment goal in managing patients with ASCVD is to lower the LDL-C as much as possible without producing side effects. This goal varies from present guidelines for LDL–C reduction in ASCVD patients, and there is also variation among the available guidelines. The American College of Cardiology/American Heart Association 2018 guidelines recommend high-intensity statin treatment for all patients with ASCVD and moderate-intensity statin treatment for those not suitable for high-intensity treatment. High-intensity statin treatment limits the medication choices to rosuvastatin ≥20 mg or atorvastatin ≥40 mg daily. If on maximal statin therapy LDL-C >70 mg/dL, then the addition of ezetimibe or PCSK9i is considered reasonable. [3] In contrast, the American Association of Clinical Endocrinologists (ACCE) 2017 guidelines recommend an LDL of <70 mg/dL for very high-risk patients and <55 mg/dL for those considered at extreme risk.[4] These ACCE guidelines suggest that writing groups are also appreciating the benefit of even lower LDL-C levels.

61.3 DIETARY THERAPY

Such LDL values can rarely be obtained by dietary therapy alone. Strict vegans and vegetarians can achieve low LDL-C levels, but most patients cannot achieve sufficiently low levels with dietary intervention alone. We strongly recommend that patients follow low-saturated fat diets, exercise, and practice calorie control, but do not depend on these interventions to achieve their LDL-C goals. Many clinicians cite the Lifestyle Heart Trial as evidence that diet alone can reduce atherosclerotic cardiovascular disease.[5] This trial design precludes an accurate estimation of the risk reduction based on diet alone. Therefore, we recommend a combination of pharmacologic and dietary interventions to optimize LDL-C reduction.

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61.4 STATIN TREATMENT

High-intensity statin treatment is the cornerstone of secondary prevention and LDL–C management in patients with ASCVD. Statins reduce secondary events by both LDL-C reduction and decreasing inflammation.[6] Patients with acute coronary syndromes (ACS) or recent interventions should be started on high dose statins such as atorvastatin 80 or rosuvastatin 40 mg daily. Such treatment should be continued as long as possible, but we consider decreasing the dose to atorvastatin 40 or rosuvastatin 20 after two years of higher dose therapy. We specify two years because approximately two years of aggressive therapy is the duration frequently observed in trials demonstrating atherosclerotic regression.[7] Also, aggressive lipid treatment produces maximum atherosclerotic plaque reduction within two years of treatment (Figures 61.1 and 61.2).[8] We routinely add ezetimibe to high-intensity statin treatment since the IMPROVE-IT (or Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated a 2% absolute reduction in cardiovascular events in patients with ACS treated with the combination of statin and ezetimibe vs. statin alone (p=0.016). [9]

61.5 MANAGING STATIN-ASSOCIATED MUSCLE COMPLAINTS

Approximately 10% of patients treated with moderate to high dose statins report muscle complaints that they attribute to the statin.[10] Our double-blind, placebo-controlled study demonstrated that 9.4% of subjects treated for six months with atorvastatin 80 mg daily developed muscle complaints compared with only 4.6% of placebo-treated subjects.[11] This suggests that approximately 5% of patients have true statin-associated muscle symptoms (SAMS). These patients do not generally demonstrate objective evidence of muscle injury such as elevated CK levels or documented muscle weakness. Whether or not SAMS are real, and we believe they are,[12] it is a moot point for clinicians because clinicians cannot ignore a patient's complaints and expect to maintain a good patient relationship.

We have described our approach to managing SAMS.[13,14] We determine whether the patient can tolerate the symptoms and measure CK to make sure that it is not elevated to >10 times the upper limits of normal. We reassure the patient that SAMS are almost always reversible and not progressive. We stress the importance of statin treatment in secondary prevention and the lifesaving role of statin therapy. Nevertheless, we stop the statin until the patient has no symptoms if the patient remains concerned or intolerably symptomatic. Reversal of the symptoms within several weeks of statin discontinuation supports the diagnosis of SAMS.[15] We next try the same or another statin at a comparable or lower dose. If rechallenge with a statin also produces symptoms, we try ezetimibe alone. Ezetimibe produces approximately a 20% average reduction in LDL-C levels. We then retry the statin at very low doses such as rosuvastatin 2.5 or 5 mg, atorvastatin 5 or 10 mg, or pitavastatin 1 mg—Monday and Friday. These agents are not approved for intermittent dosing, but the

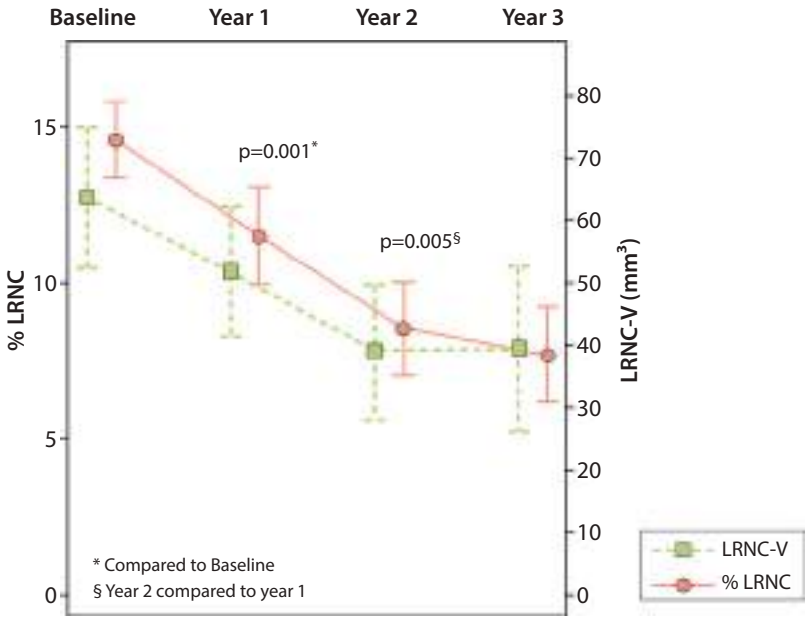


FIGURE 61.1 Carotid plaque lipid depletion and time course during three-year lipid therapy. After three years of intensive lipid therapy, lipid-rich necrotic core volume (LRNC-V) (squares) significantly decreased from 60.4 mm^3 to 37.4 mm^3. Percent LRNC (%LRNC) (circles) also significantly decreased from 14.2% to 7.4%. The plaque lipid depletion time course over three years showed that %LRNC for pooled slices containing lipid at any time point significantly decreased by 3.2% in the first year, significantly decreased by 3.0% in the second year, and decreased by 0.9% in the third year (the change from year two to three was not statistically significant). Bars around the estimates are standard error bars (taken with permission from Zhao et al. *JACC Cardiovasc Imaging* 2011).

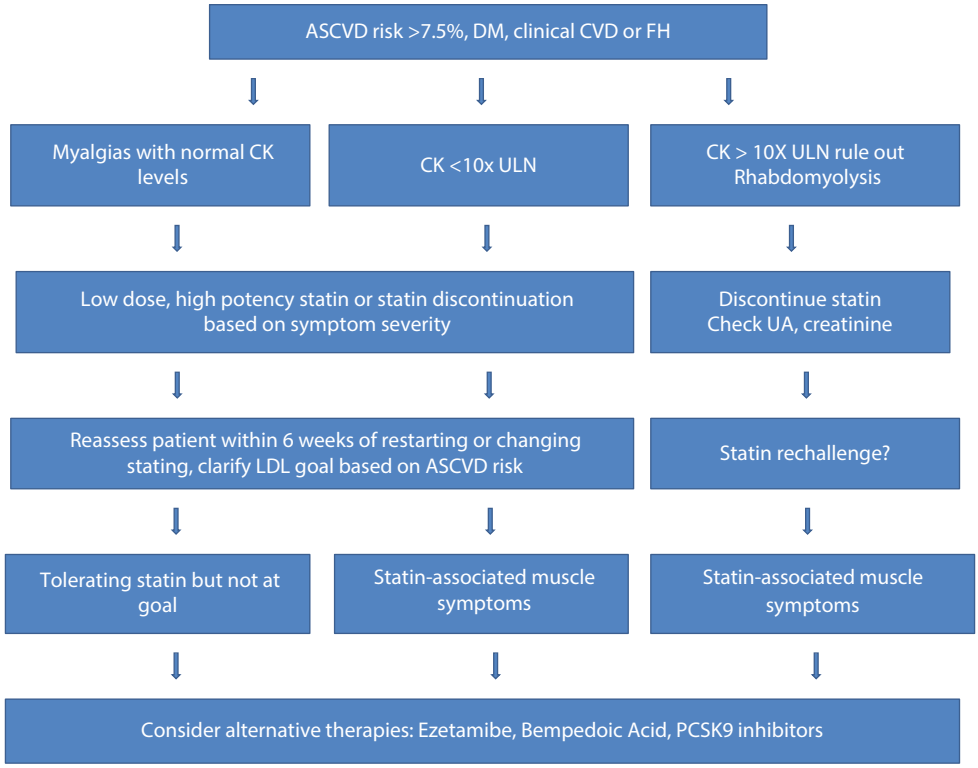


FIGURE 61.2 Clinical applications flow chart—our approach to lipid management in statin-intolerant patients.

long half-lives of these statins produce a ≈20% reduction in LDL-C with such intermittent dosing.[16] Clinicians often forget that the largest percent reduction in LDL-C per mg of statin occurs with the lowest doses. The combination of ezetimibe and low-dose statin is often able to normalize LDL-C levels in many patients. Co-Q10 supplementation is often recommended for patients with SAMS for several plausible reasons,[17] but our studies[18] and a systematic review[19] did not demonstrate that Co-Q10 supplementation is effective in SAMS. Nevertheless, we occasionally use it in selected patients. We discuss the absence of effect in controlled studies but also emphasize that some patients have had remarkable responses to Co-Q10 supplementation. We will occasionally try Co-Q10 supplementation even though its effectiveness may be only a placebo effect.

In patients who are truly intolerant to statin therapy, we use other agents such as PCSK9Is, ezetimibe, and bempedoic acid.

61.6 PCSK9 INHIBITORS

PCSK9 inhibitors are our go-to drugs in patients intolerant of statins or in whom other lipid-lowering agents cannot reduce their LDL-C levels to a sufficiently low level. PCSK9 inhibitors are approved for use in patients with familial hypercholesterolemia and in patients with documented ASCVD who do not achieve sufficient LDL-C reductions by dietary and statin therapy. FDA approval of PCSK-9 inhibitors was provided before IMPROVE-IT documented that ezetimibe, when added to a statin, reduces ASCVD events more than statins alone.[9] Present best practice, therefore, would require that ezetimibe be included in the treatment before progressing to the more expensive PCSK9 inhibitors. What level of LDL-C warrants PCSK9 therapy is the clinician's decision but as mentioned earlier, we aim for an LDL-C of at least <70 mg/dL in patients with established ASCVD.

PCSK9 inhibitors will likely be more widely used to achieve low LDL-C levels in patients with ASCVD. We do not use them prematurely, however, because they are expensive. We restrict the use to those individuals who cannot achieve a sufficiently low LDL-C level using statins, ezetimibe, niacin, fibric acid derivatives, or bile acid sequestrant resins. We do not necessarily try all these agents in patients with ASCVD before proceeding to a PCSK-9 inhibitor, but do consider these other drugs as part of our therapeutic regimen. We do proceed directly to PCSK-9 inhibition in patients with such high LDL levels that it is unlikely that other agents will be effective.

The combination of statin, ezetimibe, and PCSK9 inhibitor therapy has the potential to markedly reduce recurrent rates of ASCVD events in patients with documented disease by reducing LDL-C so low that recurrent events become extremely unlikely. Such aggressive therapy has the potential to enhance further the already excellent survival of ASCVD patients.

Patients within one year of their most recent myocardial infarction (MI) have a higher risk of ASCVD and thus may have a greater absolute ASCVD risk reduction. In FOURIER,

patients with a recent MI had an absolute risk reduction of 3.2% compared with patients who have had a more distant MI history.[20] More recently, the EVOPACS trial evaluated the effectiveness of administering evolocumab in-hospital in the acute phase of acute coronary syndrome on LDL-C lowering. In this investigator-sponsored study conducted in Switzerland, 308 patients with an ST elevation myocardial infarction of less than 24 hours or a non-ST segment elevation of less than 72 hours were randomized to receive evolocumab 420 mg every four weeks and atorvastatin 40 mg daily versus placebo every four weeks and atorvastatin 40 mg daily. The investigators demonstrated a 41% additional LDL reduction in the evolocumab group from baseline to week eight. This afforded the opportunity to achieve an LDL of <70 mg/dL (the AHA threshold) in 95% of those patients, compared with only 37% of the patients randomized to placebo and atorvastatin.[21] These data suggest that in patients with established ASCVD and recent myocardial infarction, adding a PCSK9I to a statin may help prevent another event. However, this should be interpreted cautiously since the EVOPACS trial was not designed to assess a correlation between LDL-C reduction and ASCVD events.

The PACMAN-AMI trial showed that the use of alirocumab 150 mg biweekly within 24 hours after PCI for acute myocardial infarction leads to a greater reduction in plaque burden and plaque regression at 52 weeks in the nonculprit vessel.[22]

61.7 EZETIMIBE

Ezetimibe works by inhibiting the absorption of cholesterol from the gut leading to a reduction in the amount of cholesterol that comes to the liver via the portal circulation, thus decreasing hepatocyte cholesterol content and an increase in LDL-C receptor production by the liver. Ezetimibe produces about a 20% reduction in LDL-C when used alone and a larger reduction, about 24%, when used in conjunction with a statin. IMPROVE-IT randomized patients with acute coronary syndromes to simvastatin 40 with or without ezetimibe.[9] The combination of statin plus ezetimibe produced a 2% absolute reduction in ASCVD events.

61.8 BEMPEDOIC ACID

Bempedoic acid works by inhibiting ATP-citrate lyase (ACLY), an enzyme upstream from HMG-CoA reductase. Bempedoic acid is administered as a pro-drug that must be activated by being converted into its active form, bempedoyl-CoA. [23] This enzyme is not abundant in skeletal muscle; therefore, un-acetylated bempedoic acid does not affect the skeletal muscle as it cannot be activated. The LDL-C reduction is robust (17–18% reduction), but it is not as potent as the statin lowering effect. The combination of bempedoic acid and ezetimibe can reduce LDL-C by 38%.[24] Bempedoic acid can increase uric acid levels and can also increase creatinine by interfering with renal tubular excretion. The glomerular filtration rate itself is not altered. Bempedoic acid has not yet demonstrated a reduction in ASCVD events, however, outcomes studies are ongoing.

61.9 INCLISIRAN

Inclisiran is a small interfering RNA (siRNA) directed to PSCK9 mRNA, interfering with the degradation of the LDL receptor, resulting in higher LDLR expression. It is administered as a subcutaneous injection at zero and three months and then every six months thereafter. ORION-9 randomized patients with LDL >100 mg/dL at screening to either inclisiran vs. placebo and found a reduction of 39.7% in the inclisiran group compared with an increase in LDL-C of 8.2% in the placebo group.[25] ORION-10 randomized patients with ASCVD and LDL >70 mg/dL to either inclisiran vs. placebo and found a reduction of 51.3% in LDL compared with a 1% increase in the placebo group.[26] ORION-11 randomized patients with ASCVD or ASCVD-risk equivalent and LDL >70 mg/dL to inclisiran vs. placebo and found a 45.8% reduction in LDL levels compared with a 4% increase in LDL in the placebo group.[26] Ongoing outcome trials are also underway. We recently started using inclisiran in patients who have demonstrated a suboptimal response or an allergy to PCSK9Is. It is FDA-approved along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or ASCVD who require additional lowering of LDL-C.

61.10 EVINACUMAB

Evinacumab is an antihyperlipidemic angiopoietin-like protein 3 (ANGPTL3) inhibitor. It is a recombinant human monoclonal antibody that binds to and inhibits ANGPTL3; allowing lipoprotein lipase (LPL) and endothelial lipase (EL) to enhance the clearance of VLDL remnants via remnant receptors in the liver. This leads to the reduction in LDL-C, HDL-C, and triglycerides in an LDLR-independent manner. It is FDA approved for use as an adjunct to other LDL-lowering therapies for patients with homozygous familial hypercholesterolemia. ELIPSE-HoFH showed a substantial 47% reduction in LDL levels in patients with HoFH randomized to evinacumab, regardless of the degree of LDLR function compared with placebo.[25]

61.11 PELACARSEN

Lipoprotein (a) is a genetically determined, independent risk factor for cardiovascular disease. PCSK9i has been found to provide risk reduction in recurrent ASCVD events with each 5 mg/dL reduction in Lp(a) predicted event rate reduced by 2.5%. Pelacarsen is a hepatocyte-directed antisense oligonucleotide targeting the LPA gene. Pelacarsen has been demonstrated to lower Lp(a) by 35–80%, lower oxidized phospholipids by 30–90%, reduce apo(a) and apoB, and lower LDL by 20% in patients already on lipid-lowering therapy in its phase 2 trial.[27] Phase 3 RCT (HORIZON) is ongoing to evaluate the effect of pelacarsen

on major adverse cardiovascular events in patients with a history of ASCVD and Lp(a) >70 or >90 mg/dL.

CLINICAL IMPLICATIONS

1. ASCVD is primarily driven by LDL-C. Reducing LDL-C reduces the incidence of both primary and secondary cardiovascular events.
2. The benefit of LDL–C reduction appears to have no lower boundary. Some of the different professional society prevention guidelines follow a trend targeting lower LDL-C levels for secondary ASCVD prevention. This opens the window for an aggressive lipid-lowering therapy in high-risk individuals to decrease LDL-C as low as possible.
3. It is also important to understand the cost of newer drugs, such as PCSK9 inhibitors, to maintain cost-effective care. These emerging lipid-lowering agents will continue to reduce recurrent ASCVD events.

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62 Counseling Coronary Heart Disease Patients about Their Body Weight: Implications Regarding the Obesity Paradox

Nadia Isabel Abelhad, MD, Peter G Pantlin, MD, Sergey Kachur, MD, and Carl J. Lavie, MD, Richard V Milani, MD

KEY POINTS

- The obesity epidemic continues to grow and counseling on appropriate lifestyle changes is more important than ever. In an age of misinformation, topics such as the "obesity paradox" and "metabolically healthy obese" can be interpreted to show that excess body weight may not be harmful.
- The obesity paradox is present in those with chronic disease, advanced age, and low cardiorespiratory fitness. Those with higher fitness have not been shown to benefit from excess mass. In younger individuals, obesity accelerates the onset of chronic disease and may shorten overall lifespan.
- The concept of the metabolically healthy obese is confounded by increased levels of fitness found in obese individuals without metabolic syndrome. When adjusted for fitness, studies show that excess weight in this group confers some (albeit smaller) cardiovascular risk and mortality.
- Recent data highlights abdominal obesity defined by waist circumference as an independent marker of poor cardiovascular outcomes.
- Improved imaging modalities can better quantify visceral adiposity.
- Clinical trials of medical weight loss have not demonstrated a reduction in coronary artery disease rates.
- Previously, lifestyle recommendations were recommended, however, current prospective studies signal a reduction in coronary artery disease rates when combined with bariatric surgery.

62.1 INTRODUCTION

The obesity epidemic and its associated chronic diseases are increasing due to the availability of high-calorie foods and a sedentary environment at home and work. Counseling on lifestyle interventions is a clinician's primary tool in combating obesity because the mechanisms of harm are multifactorial, making medical monotherapies largely ineffective.[1] Although the concept of decreasing caloric intake while increasing expenditure is a simple one, the changes needed to modify harmful behaviors are counter-intuitive, as overeating and a sedentary lifestyle are linked to neurochemical reward systems. Complicating matters further are recent discoveries of the obesity paradox (OP) and the "metabolically healthy obese" (MHO) phenotype, which can be interpreted by the layperson to mean that obesity and its associated sedentary behaviors are beneficial. Thus, any discussion or counseling session initiated to prevent or treat obesity needs to be comprehensive in its scope—addressing data on risks, benefits, and modifying associated lifestyle behaviors. Here, we will define obesity, discuss the data behind MHO and the OP, and touch on newer imaging modalities to quantify excess visceral adipose tissue. We will review the outcomes of non-invasive lifestyle changes and bariatric surgery as they relate to coronary artery disease. This chapter will serve as a summary of the key points in a discussion on this topic with a patient.

62.2 EPIDEMIOLOGY

The World Health Organization defines overweight as a body mass index (BMI) greater than or equal to 25 kg/m^2 and obesity as a BMI greater than or equal to 30 kg/m^2.[2] Worldwide obesity has more than doubled between 1980 and 2014 to a level of 600 million (13%). The trend is projected to worsen due to the epidemic of childhood obesity; 41 million obese children under age five as of 2016, projected by the WHO to increase to 70 million by 2025. This is a growing health problem because of obesity's associations with cardiovascular (CV) disease (CVD) and stroke, accounting for a combined 15 million global deaths in 2015 (Figure 62.1).[3]

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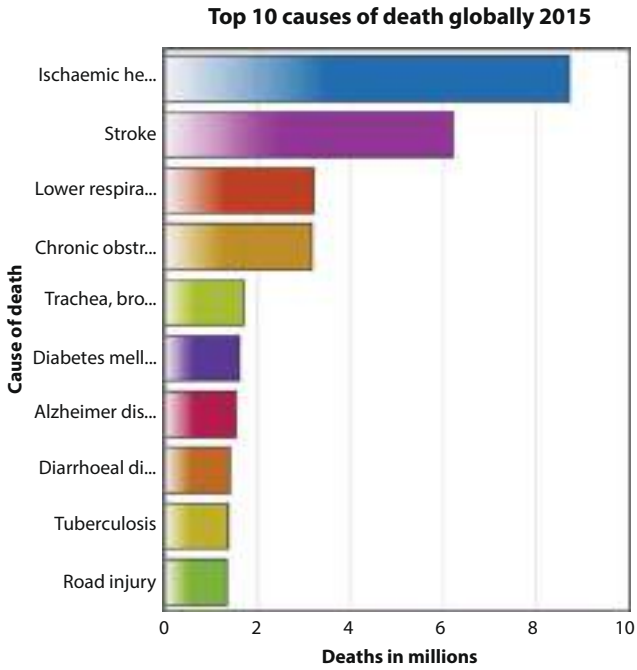


FIGURE 62.1 Leading causes of death.

62.3 MEASURING OBESITY

The BMI metric has its origins in the Quetelet index. It was derived from the heights and weights of French and Scottish armies as a means to normalize anthropometric measurement. It is an imperfect measure of adiposity because of confounding factors, such as excessive muscular development and fluid retention, among others.[4] Traditionally, body weight (and by relation BMI) is divided into body fat (BF) and lean mass (LM). Out of a cohort of 95 patients, BMI had a good correlation with both BF% ($p = 0.66$, $p < 0.001$) and LM ($p = 0.41$, $p < 0.0001$) and failed to discriminate between both ($p = 0.72$). A BMI $\geq$ 30 kg/m^2 had a good specificity (95%; 95% CI, 83–100) but a poor sensitivity (43%; 95% CI, 32–54) while a BMI $\geq$ 25 kg/m^2 had a good sensitivity (91%; 95% CI, 84–97) but a poor specificity (65%; 95% CI, 42–88) at detecting adiposity defined by excess BF.[5]

Recent data highlights abdominal obesity as an independent marker of poor CVD outcomes.[6–8] Thus, high waist circumference (WC) even in individuals with normal weight may unmask higher CVD risk.[9] As such, several organizations and expert panels have recommended that WC measures be assessed along with BMI in clinical evaluations.[1]

The development of imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have served as more precise tools to quantify visceral and ectopic adipose tissue deposition.[3] With these methods, volumetric measurements can be made of subcutaneous vs intra-abdominal adipose tissue including stores found in liver, pancreas, heart, and skeletal muscle.[2] As much, a wide variation of adiposity distribution has been observed for a given BMI.[2] Importantly, in the overweight and obese subgroups, low levels of visceral abdominal tissue represent a more favorable CVD risk profile,[10] possibly representing MHO patients. When compared with patients with excess visceral abdominal tissue, the highest CVD risk was observed, regardless of BMI.[2] With the improved imaging of ectopic fat, the question remains as to whether isolated excess adipose liver deposition is associated with higher CVD risk. Previous randomization studies have not shown associations despite its known role in the pathogenesis of dysmetabolic state.[11] Other adipose measurements such as WC-to-height and WC-to-hip ratio may be a better predictor of CVD and have been shown to predict CVD mortality independently of BMI.[12]

62.4 DOES MHO EXIST?

The mechanisms of pathology (Figure 62.2) in the obese suggest that most, if not all, of the increased risk associated with obesity could be attributable to associated metabolic derangements characterized by impaired glucose tolerance, dyslipidemia, and hypertension (HTN)—collectively diagnosed as metabolic syndrome (MetS).[13] The presence of MetS is often used to differentiate obesity into those with metabolically healthy obesity (MHO) and metabolically around this issue, as the results of older studies on the effect of MHO on coronary heart disease (CHD) and heart failure (HF) were conflicting.

In a regional health registry of 2074 individuals, metabolically abnormal obese (MAO), but not MHO, had increased CVD mortality over a 15-year follow-up.[14] Similarly, in a review based on the Norwegian Nord-Trøndelag population of 61,299 men and women over a 30-year time span, Mørkedal et al. found that increased CVD risk was present in MAO (HR = 2.0, 95% CI 1.7–2.3), but not MHO (HR = 1.1; 95% CI 0.9–1.4).[15] However, in the same study, MHO was associated with significantly more HF events.[16] In The Health Improvement Network (THIN), 3.5 million individuals were followed for 20 years; obesity was associated with significantly higher risks of HF, CHD, and stroke.[17] Also, a large meta-analysis by Fan et al. (n = 299,059; 12,125 incident cases of CVD, 2130 deaths associated with CVD, and 7071 cases of all-cause mortality) found that in patients followed for >15 years, there was an additional risk of CVD events in the MHO group, and these patients had an increased risk of mortality.[18] This latter finding was supported by another meta-analysis of eight studies conducted by Kramer et al. (n = 61,386; 3988 events) where in subjects followed for ≥10 years, MHO individuals had a 24% increased risk of major CVD events compared with the metabolically healthy lean subjects, but the risk of CVD events increased 2.65–3.14-fold in MAO individuals when compared with the MHO.[19] Although the above trials failed to adjust for confounders of mortality (age and sex), and did not include effects of cardiorespiratory fitness (CRF), they support other data stratified by CRF and LM.[20]

Of note, more recent studies have demonstrated an association between central adiposity and CHD and CVD

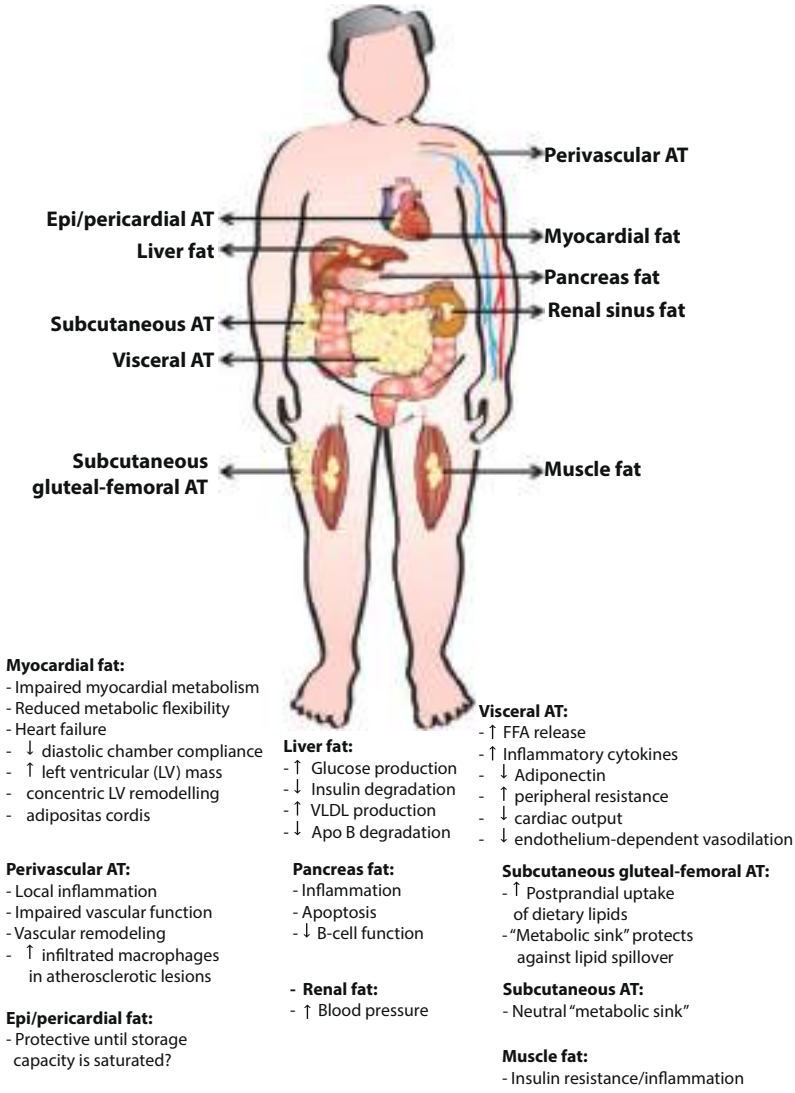


FIGURE 62.2 Mechanisms of cardiovascular risk related to adiposity in the obese.

mortality including subgroups with normal weight and BMI.[21,22] Furthermore, the degree and duration of obesity, measured by total lifetime exposure to excessive visceral adiposity, measured by WC years, has been shown to be a much stronger predictor of CHD events beyond BMI alone.[23]

Although the fitness hypothesis does explain some of the findings of the "fat-but-fit" phenomenon, variable metabolic effects from both fat distribution (visceral versus subcutaneous) and fat composition (white versus brown) lend credence to a benign adipose phenotype. Both subcutaneous distribution of fat and increasing proportions of brown fat have been associated with better metabolic profiles and lend support for a benign adiposity phenotype.[24] As of now, there are no known mechanisms for stimulating subcutaneous adiposity, exercise does preferentially reduce visceral fat and has been shown to increase fat "browning", thus modifying the metabolically harmful effects of white adipose tissue.[25,26]

Based on current data, CRF and adiposity in the case of the MHO phenotype are closely interrelated, with significant evidence for amelioration of the risks of CVD related to excess BMI with higher levels of CRF found in the MHO population. When discussing the MHO phenotype, it is thus important to note that the interpretation of MHO as a "preserved state of health associated with excess BMI" is a fallacy, and to use available data to focus on the health benefits related to higher CRF[27–29] and reduced visceral adiposity.[2]

62.5 THE OBESITY PARADOX

There is a growing body of evidence of survival benefits associated with obesity (as measured by BMI) in populations with chronic disease—a phenomenon termed the OP. Despite a shorter life expectancy in many large cross-sectional trials, those who are obese and overweight have been found to have decreased mortality risks in chronic disease populations when compared with normal-weight

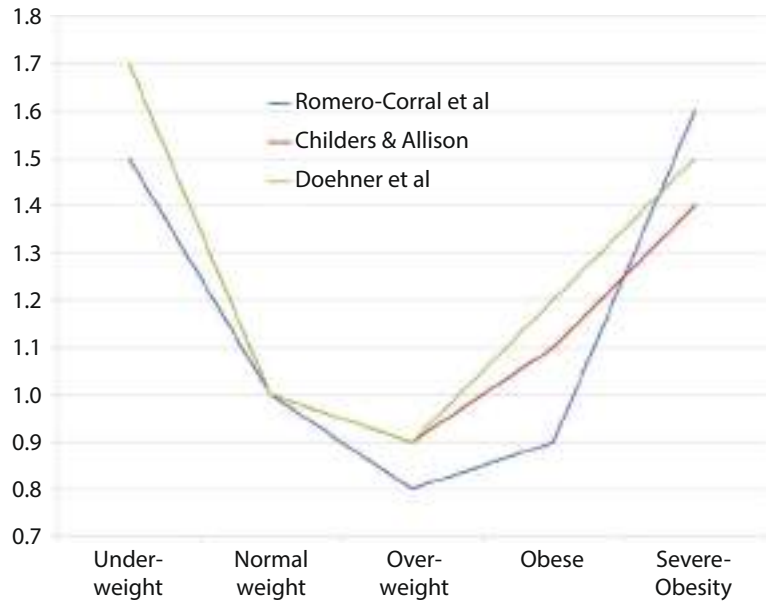


FIGURE 62.3 Mortality modification based on BMI in populations with CHD.

TABLE 62.1
Postulated Mechanisms of the Obesity Paradox

BMI is a poor measure of adiposity	
	Protective effects of lean mass confound deleterious effects of BF
	Higher BMI is associated with higher fitness due to increased muscle mass
Lean mortality	
	Catabolism of chronic disease benefits disproportionately from metabolic reserves of BF
Selection bias	
	Obese individuals enter the health system at a younger age and receive treatment earlier in the disease process
Anti-inflammatory	
	Adipose tissue secretes soluble TNF-R which provides an anti-inflammatory effect

individuals.[30–33] In the majority of these studies, the nadir of mortality occurs in the overweight group, with a U and/or reverse-J-shaped distribution of increasing mortality as BMI values diverge in the positive and negative directions (Figure 62.3).[34–36]

There are several proposed causes for the existence of the OP (Table 62.1). One view is that obesity changes neuro-endocrine profiles in a manner that may be protective.[37] Adipose tissue produces soluble tumor necrosis factor-α receptors which may be protective as a method of sequestration of free TNF-α in obese patients.[38] When it comes to hypertensive mechanisms, overweight and obese patients appear to have lower levels of circulating atrial natriuretic peptides, have attenuated sympathetic nervous system and renin-angiotensin responses, and their higher circulating volume and levels of sympathetic activation may allow tolerance of higher doses of cardio-protective medications (leading to a better prognosis in HF patients).[39] Another postulated mechanism is that higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides (super-antigens that trigger innate immunity cascades), serving as a protective mechanism against inflammation-mediated damage.[40] The most commonly cited argument for the existence of the OP is the one of metabolic reserve; that in the catabolic state characterized by chronic disease, additional body mass serves as a metabolic reserve that delays the catabolism of vital metabolites such as proteins. Conversely, the "lean paradox", a term used to describe individuals with low body fat and BMI, may identify more pertinent predictors of poor reserve and CVD outcomes.[41]

In order to better understand the effects of weight on mortality when discussing the OP, it is prudent to focus on weight trajectory rather than a static reading of BMI. In doing so, chronically ill individuals can be divided into two distinct groups: those with increasing BMI and those with decreasing BMI. On the positive end of the spectrum, the effects of increasing weight are divided between beneficial aspects of increased LM and deleterious effects from excess BF. As mentioned earlier, increases in LM are often accompanied by higher CRF and improvements in metabolic reserves, without the deleterious effects of excess BF.[42,43] In a study of nearly 10,000 patients with known or suspected CHD, only those in the bottom 20th percentile for age and gender levels of CRF demonstrated an OP, which was present by BMI, %BF, and even with WC.[44] In those with lower CRF, such as the morbidly obese, increasing BF (usually visceral adiposity) is closely linked with increases in the markers of MetS and associated CVD risks and mortality.[45,46] The OP was significantly observed in a large cohort of 6500 CHD patients from Norway followed for 13 years.[47] The OP was only present in those who did not meet the

international PA guidelines, and in this group, higher BMI was protective against mortality. However, in those who met the PA guidelines, survival was much better and BMI did not impact survival.[12] In a Norwegian follow-up study over 16 years, 3300 CHD patients were assessed for changes in BMI and PA. This study showed that changes in PA were much more predictive of survival than changes in BMI.[48] In no group was weight loss associated with improved survival. In fact, in those with "normal" BMI, weight gain was associated with improved survival and weight loss with reduced survival. Maintaining or increasing PA was associated with better survival in CHD.[13]

On the other end of the BMI spectrum, individuals who are losing mass do so in terms of either adiposity alone or adiposity with concomitant losses in LM. Evaluating the effects of weight loss on mortality has been challenging as many studies have shown higher mortality with observational weight loss, especially in the elderly population.[49,50] Yet, others have demonstrated that intentional weight loss leads to lower all-cause and CVD mortality risks.[51,52] This variability in results implies confounding factors, which have been explored in a series of studies. These categorize weight loss by categories that help discriminate between individuals who are losing BF as the result of increasing CRF, and those with unintentional weight loss characteristic of end-stage disease. The Tecumseh Health and Framingham did this based on weight loss versus fat loss and found that weight loss increased risk of death by 29–39%, while fat loss reduced risk of death by 15–17%.[53] An alternative approach has been to define intentional versus unintentional weight loss. In a nine-year follow-up of subjects enrolled in the National Health Survey, intentional weight loss lowered the mortality rate by 24% (HR 0.76; 0.60–0.97), while unintentional weight loss had a 31% higher mortality rate (HR 1.31; 1.01–1.70).[54] Wannamethee and colleagues further delineated intentional weight loss into medically prescribed weight loss and elective weight loss, finding that those losing weight intentionally had a significantly higher risk for mortality when medically prescribed than when adopted as an elective lifestyle change (RR, 0.59; 95% CI, 0.34–1.00; p = 0.05) vs (RR, 1.37; 95% CI, 0.96–1.94).[51] When measured in the setting of cardiac rehabilitation (CR), weight loss was associated with a significantly lower rate of CVD regardless of baseline BMI (HR = 0.62; p = 0.018).[55] Hamer and O'Donovan studied weight loss in the elderly in the framework of sarcopenia as measured by grip strength, thus comparing those in the lowest handgrip tertile with those in the highest. The lowest risks of mortality were in populations with stable weight and/or grip strength, whereas those losing either weight or grip strength had a significantly higher risk than the former (HR: 2.21; 95% CI: 1.32, 3.71), and the highest risks were found in elderly individuals with both weight loss and reduced strength (HR: 3.77; 95% CI: 2.54, 5.60).[56]

In regard to CHD, interventional trials of medical weight loss have not demonstrated a clear reduction in rates.[12] In contrast, reduced CHD risk has been demonstrated in prospective studies comparing obese patients undergoing bariatric surgery with non-surgical management. Statistically significant decreased rates of CVD events were seen in the surgical arm with an average reduction of 10–40 kg versus 5–10 kg (medical arm).[57,58] It has been postulated that modest short-term weight loss may not be sufficient to overcome the long-term negative effects of obesity as it pertains to the vasculature.

Farnaz and colleagues used a meta-analysis to evaluate the relationship of diabetes mellitus and obesity by BMI to HF-free survival. Men and women with no risk factors lived on average an additional three years to 15 years longer free of HF than those with risk factors, and in subgroup analyses, the authors found that obese individuals had shorter overall survival but lived significantly longer with HF than those without obesity.[59] Recent data has also suggested that higher BMI is more strongly associated with the risk of heart failure with preserved ejection fraction,[60] independent of other CVD risk factors. In subgroups with severe obesity, weight loss after bariatric surgery increases NT-proBNP levels concomitantly with improved left ventricular diastolic dysfunction. [61]

In summary, the OP is most apparent in the unfit elderly population, a group that is characterized by increasing sarcopenia as a manifestation of declining function and metabolic reserves.[62] As chronic disease develops, increased BMI is beneficial for survival in populations where BF offsets losses in LM and CRF.[63] Thus, BF is a double-edged blade, accelerating the process of developing chronic diseases, but allowing more time as CRF is eroded by the catabolic strain of chronic disease. Data supports that increases in LM are beneficial regardless of age and disease status and that the ultimate modulator of morbidity and mortality effects (i.e., biological age) appears to be bariatric surgery[12,13] and CRF.[64] When counseling the younger individual, there is increasing evidence for the long-term risks associated with excess body weight.[11] As such, younger patients should be counseled on the benefits of aggressive weight loss, especially in conjunction with physical activity (PA).[11] Since the data on weight loss is more circumspect in the elderly population, focusing counseling sessions on increasing PA would avoid the uncertainties associated with the effects of weight loss entirely.

62.6 PHYSIOLOGIC EFFECTS OF EXERCISE

As discussed above, CRF modulates the adverse effects of adiposity and MetS. CRF is maintained through PA, which in today's largely sedentary societies commonly stems from voluntary (rather than occupational) exercise training (ET). The benefits of ET are derived from modulating inflammation, decreasing adrenergic tone, and facilitating metabolic homeostasis across multiple organ systems.

ET modifies the deleterious effects of increased sympathetic tone by increasing sympatho-vagal signaling and associated parasympathetic activation. This manifests as increasing heart rate variability and decreasing blood

pressure (BP), which confer a better CVD prognosis.[65] Furthermore, ET-associated antioxidant production reduces systemic inflammatory markers in physically active people with CHD and reduces HTN by reducing oxidation-mediated nitric oxide scavenging.[66–68] Both BP and heart rate also benefit from decreased resting sympathetic activation by decreasing angiotensinogen II-mediated increases in systemic vasoconstriction and through noradrenaline suppression by plasma adrenomodullin, renalase, and atrio-natriuretic-peptides.[69,70]

Mitochondria provide energy and antioxidant capacity in most human tissues. Age-related impairment of function and decreasing numbers of these organelles results in damage to existing proteins and DNA and reduces the ability of myocytes to counter stress, such as myocardial infarction. Increased metabolic demands during exercise, and upregulation of signaling molecules such as insulin-like-growth-factor-1 increase mitochondrial division and modify energy pathways within the organelles to improve metabolic efficiency.[71,72]

Higher levels of PA have been shown to reduce the development of HF and improve prognosis in HF, regardless of BMI.[73] For those with advanced HF, Class III obesity is a relative contraindication for heart transplantation and in some institutions, ventricular assist devices (VAD). In those respective individuals who do on to get a VAD, adverse drive-line associated events are commonly observed.[74] Furthermore, advanced HF is typically a contraindication for bariatric surgery, leading to a "Catch-22". Of note, a recent retrospective study showed reduced HF hospitalizations in HF patients who underwent bariatric surgery.[75] Limitations in this study were the lack of representation of the most at-risk populations including the elderly and those with advanced HF.[17] For elderly obese subgroups at risk for HF, more studies are needed to identify methods for maintaining weight and improving functional outcomes as opposed to weight loss alone.

In summary, ET reduces resting systolic BP and heart rate, increases physical work capacity via decreased myocardial oxygen demand (i.e. rate-pressure product) at fixed submaximal workloads, and is associated with modest reductions in total cholesterol and low-density lipoprotein cholesterol. In HF, ET improves prognosis and confers risk reduction and bariatric surgery has been shown to reduce HF hospitalizations. Together, these effects translate into lower rates of CVD.[76,77]

62.7 MODIFYING LIFESTYLE

Although obesity may be associated with survival benefits in those with chronic disease, the combination of altered hemodynamics, endocrinopathy, and inflammatory effects of free fatty acid metabolism combine to significantly shorten life expectancy in the healthy population.[59] As discussed previously, both intentional weight loss and maintenance of CRF have been shown to reduce CVD risk factors associated with obesity, and as a result, PA/ET is highly recommended for health maintenance and CVD prevention.[54,77–79]

Dietary control is one of the cornerstones of modern weight-loss approaches. All diets, regardless of macronutrient composition, can produce clinically meaningful weight loss (>5%) if they induce a deficit of ≥500 kcal/d.[80] However, these have to be accompanied by appropriate macronutrient supplementation to prevent pro-arrhythmic adverse effects.[81]

Health maintenance through ET has been another cornerstone of managing body weight. Although the benefits of weight loss are scrutinized closely because of the OP and MHO, maintenance of CRF through PA/ET has unequivocally shown health benefits. In addition to improvements in mortality, PA/ET is associated with dose-response reductions in HF and CHD, with additional benefits to functional metrics like grip strength, balance, and cognition.[82–84]

In counseling patients on ET, the mode and duration of therapy should be discussed in order to maximize benefits and tailor recommendations to a patient's lifestyle. Modes of ET currently fall into one of two major approaches: moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT). MICT has been the gold standard of CR ET programs and involves continuous maintenance of workload at an intensity of 50–65% of the peak, often measured as peak O_2 uptake or peak heart rate. HIIT protocols consist of shorter high-intensity intervals (75–95% of maximal effort) interrupted by periods of rest.[60] Over the last decade, HIIT has been shown to have significant metabolic advantages to MICT therapy. Specifically, HIIT protocols produce greater improvements in CRF and have comparatively beneficial effects on metabolic derangements, such as insulin resistance, and some data suggest mortality improvements are greater with HIIT regimens.[85–88]

When discussing the duration and frequency of ET, more has not been shown to be better. Although there is evidence of a linear improvement in HF risk with increasing ET, most studies suggest a plateau of benefits. For CHD the plateau is at about 5000 metabolic equivalent unit (MET) minutes per week.[82,89] Likewise, continuous exercise exceeding 9–10 METs was not shown to improve all-cause mortality in comparison with lower intensities.[90] In women, exceeding exercise frequency of two to three times per week had significantly higher associations with CVD events.[91]

In terms of duration, 50 minutes per session appears optimal for moderate-intensity endurance exercise.[92] This is even lower for HIIT, as such protocols have shown improvements in muscle metabolism, CRF (based on oxygen uptake), and insulin sensitivity in a fraction of the exercise time (as little as ten minutes) of MICT protocols.[93–95]

Current American Heart Association (AHA) guidelines for regular PA summarize this data well: ≥30 minutes of moderate-intensity aerobic PA at least five days per week for

a total of 150 minutes/≥25 minutes of vigorous aerobic PA at least three days per week for a total of 75 minutes along with moderate- to high-intensity muscle-strengthening activity at least two days per week for additional health benefits.[96] These recommendations are delineated simply in an infographic that can be found on the AHA website (www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/American-Heart-Association-Recommendations-for-Physical-Activity-Infographic_UCM_450754_SubHomePage.jsp).

Most successful lifestyle modification approaches have revolved around persistent (≥14 treatment visits), supervised high-intensity lifestyle interventions that combine dietary counseling and planning, scheduled moderate-to-vigorous PA, and behavior therapy.[80] In many cases, obese individuals can lose between 6% and 8% of initial weight after six months, which decreases the risk of MetS, HTN, and dyslipidemia.[97] Greater than 150 minutes per week of PA alone usually yields modest short-term weight loss compared with diet but still provides significant benefit to obesity-related conditions.

Although regaining weight after lifestyle intervention is common, it can be prevented by continued participation in monthly weight loss maintenance sessions and regular PA/ET.[86]

62.8 CONCLUSIONS

Obesity causes alterations in homeostasis through numerous mechanisms affecting most organ systems. Thus, the most effective therapies are preventive—taking the form of lifestyle modification. In patients with CHD and HF, these measures when combined with bariatric surgery have been shown to improve CVD outcomes. Counseling persons on the dangers of obesity along with the necessity for weight loss and PA/ET has been somewhat confounded by the concepts of MHO and OP. In evaluating the root causes, mechanisms, and patterns associated with both MHO and OP, obesity is detrimental and benefits are closely related to low CRF and increased visceral adipose tissue. In counseling individuals, it is important to review the role of CRF in modifying disease states and to emphasize that healthy weight loss (increases in PA/ET/CRF with concomitant decreases in BF and increases in LM) is the best way to improve outcomes related to chronic diseases and reducing mortality risk (Table 62.2).

TABLE 62.2
Clinical Applications

Counseling the controversies	
Effects of excess mass are deleterious from:	
Increased sympathetic tone causing hypertension	
Increased inflammation and cholesterol dysregulation predisposing to CHD	
The obesity paradox predisposes to chronic disease:	
Protective in chronic disease associated with low CRF	
Associated with shorter disease-free and cumulative lifespan	
The Metabolically Healthy Obese	
Predisposes to CVD and HF, though to a lesser degree than alone metabolic syndrome	
Exercise Recommendations	
	≥ 30 min MICT for ≥5 days per week for ~150 min
OR	≥ 25 min HIIT for ≥3 days per week for ~75 min
AND	moderate/high-intensity muscle-strengthening activity at least 2 days per week
Dietary Recommedations	
Calorie deficit ≥500 cal per day with balanced diet	
Effective strategies	
Supervised dietary and exercise program consisting of multiple weekly sessions over several months and monthly reinforcement thereafter	

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63 Vitamins and Supplements: Evidence in the Prevention and Treatment of Cardiovascular Disease

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KEY POINTS

- Unlike prescription drug products, dietary supplements are not required to be proven safe or effective prior to reaching the consumer.
- Despite a lack of quality evidence supporting benefit, it has been reported that approximately one-half of US adults take a dietary supplement.
- In instances in which randomized trials are available, data is often conflicting and left to the patient and/or clinician to interpret.
- Clinicians may assist patients with supplement selection by becoming familiar with current evidence and national organization recommendations, evaluating potential drug-drug interactions, and educating the patient to look for over-the-counter products with a "seal of approval", indicating more stringent quality testing has been performed.

63.1 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, accounting for 18.6 million deaths in 2019.[1] In an attempt to prevent or treat CVD, many patients have turned to vitamins and supplements as an easily accessible option. Despite the valuation of the 2021 global supplement market at over $150 billion,[2] the clinical benefits of available formulations remain unclear due to a paucity of controlled clinical trials and heterogeneity among study populations. Additionally, the benefits observed with dietary intake are often inappropriately assumed to extend to supplementation in tablet or capsule form. In this chapter, we summarize existing evidence regarding the use of common vitamins and supplements for primary and secondary prevention of CVD to assist the clinician with assessing the appropriateness of supplementation.

63.2 MULTIVITAMINS

Multivitamins (MVIs) are the most commonly utilized dietary supplement in the United States, with approximately 40% of adults aged 60 years or older reporting use during 2017–2018.[3] The combinations of vitamins, minerals, and/or herbs are intended to promote adequate nutritional intake while preventing or correcting nutritional deficiencies secondary to poor adherence to dietary guidelines. Several potential benefits to MVI use have been suggested, including a reduction in cancer rates, mortality, and risk of cardiovascular disease. Despite annual MVI sales in the billions,[2] the evidence regarding cardiovascular benefit is contradictory.[4–15] The US Preventive Services Task Force (USPSTF) recently published a recommendation statement[16] regarding MVI use in which they conclude evidence is insufficient to determine the benefits and harms of MVI supplementation for the prevention of cardiovascular disease. Available randomized controlled trials[5,6,13,14] have demonstrated no difference in CVD outcomes compared with placebo, despite one trial reporting a trend toward reduction in fatal myocardial infarction (MI) with MVI use.[13] Notably, the largest of these trials[14] only followed patients for a median of 3.6 years, which was likely too short to see an effect. Several observational studies have suggested an inverse association between MVI use and coronary artery disease (CAD) incidence and/or CAD-associated mortality,[4,7,11,15] whereas others have found no association.[8–10,12] Randomized controlled trials evaluating extended MVI use in subjects representative of the general population are needed before MVIs may be routinely recommended for primary prevention of cardiovascular disease.

63.3 INDIVIDUAL VITAMINS

Vitamins that have been postulated to play a role in the primary and secondary prevention of cardiovascular disease include folic acid, niacin, and vitamins C, D, and E.

63.3.1 Folic Acid

Folic acid (vitamin B9) is Food and Drug Administration (FDA) approved for the treatment of megaloblastic anemia and supplementation has been shown to be dramatically beneficial for preventing neural tube defects when administered to pregnant women.[17,18] Folate is a cofactor in the only methyl-donating pathway in humans, facilitating homocysteine remethylation to methionine and synthesis of DNA,

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phospholipids, proteins, and neurotransmitters.[19] Inborn errors of metabolism and/or dietary vitamin deficiencies may result in excess serum levels of homocysteine. Extreme homocysteine elevations (>100 μmol/L) are associated with premature vascular disease and may be caused by homozygous genetic defects in one of three enzymes: cystathionine beta-synthase, methionine synthase, or methylenetetrahydrofolate reductase.[19,20] Whether the heterozygous condition of these abnormalities or moderate homocysteine elevation is associated with the development of premature vascular disease has been studied extensively with conflicting results.[21,22] Meta-analyses have suggested a 25% lower plasma homocysteine level decreases the risk of ischemic heart disease by 11% and stroke by 19% among individuals in prospective trials (following adjustment for known cardiovascular risk factors)[23] and that a folic acid dose of 0.8 mg daily is sufficient to maximally reduce homocysteine levels.[24] Unfortunately, early secondary prevention trials failed to define any benefit of homocysteine-lowering by vitamin supplementation, although it has been suggested they lacked sufficient statistical power to detect an association between B-vitamin treatment and decreased cardiovascular endpoints.[25] Results may have also been confounded by the 1996 FDA-mandated supplementation of grain products in the United States, which resulted in a 7% reduction in homocysteine in middle-aged and older adults, rendering additional folic acid supplementation less effective.[26]

In addition to lowering homocysteine levels, folic acid may exert a direct effect on endothelial function. In a double-blind crossover study of post-MI patients, folic acid 10 mg daily improved flow-mediated arterial dilatation (FMD) as measured by forearm brachial reactivity. Interestingly, improvement in FMD persisted after crossover with placebo but did not correlate with baseline homocysteine levels or reductions in homocysteine.[27] A subsequent meta-analysis of 611 participants in eight studies confirmed these findings.[28]

Despite average homocysteine reductions of 25% with folic acid supplementation,[29] a CVD or mortality benefit has not been consistently demonstrated when utilized for primary or secondary prevention. The largest meta-analysis to date[30] included 30 randomized trials incorporating 82,334 participants and identified a 10% lower risk of stroke and 4% lower risk of CVD with folic acid supplementation of 0.5 to 15 mg daily (with one study of end-stage renal disease patients receiving 40 mg/day). Among patients without pre-existing CVD (ten trials), folic acid supplementation reduced the risk of CVD by 10% in patients with renal disease and 20% in patients without cardiovascular or renal disease, suggesting a primary prevention effect. Findings in earlier meta-analyses of chronic kidney disease patients, however, were conflicting, with two observing no stroke, CVD, or mortality benefit with supplementation,[31,32] while another suggested a 10% CVD risk reduction.[33] Meta-analyses in patients with pre-existing CVD suggest decreased stroke risk with supplementation,[34,35], with greater benefits observed in populations with no or partially fortified grain, those achieving homocysteine reductions of ≥25%, and in individuals receiving <2 mg folic acid per day. No benefit has been observed in terms of cardiovascular events or mortality.[29,35] Importantly, no signal of harm has been noted with folic acid, with the exception of a potential increase in late diameter loss and increased restenosis in patients with bare metal coronary stents.[36]

In summary, the evidence for the cardiovascular benefits of folic acid supplementation remains inconclusive, but use has been suggested for both primary and secondary prevention. The absence of large randomized controlled trials makes recommendations for folic acid supplementation speculative, though risk of harm seems low.

63.3.2 Niacin

The finding that reduced high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL) cholesterol levels increase CVD risk dates back to the Framingham study.[37] Niacin (nicotinic acid, vitamin B3) has been found to raise HDL cholesterol while decreasing LDL and triglycerides. In addition, it lowers lipoprotein(a) levels by approximately 23%.[38] The Coronary Drug Project (1966–1975) assessed the effect of five drugs, including niacin, on the prevention of cardiovascular events in men with previous MI.[39] Although no survival benefit was noted with niacin 3 g/day vs. placebo, the incidence of non-fatal MI was reduced. Interestingly, mortality was 11% lower in the niacin group at a 15-year follow-up, despite discontinuation at study end.[40] In 2001, niacin plus simvastatin was shown to decrease angiographic CAD progression and hard endpoints.[41] Other early niacin trials also described angiographic benefits and decreased clinical endpoints without concomitant statin therapy. Given its beneficial effects on lipid profile and early encouraging studies, high-dose niacin has historically been widely used for patients with vascular disease and primary prevention in high-risk patients with adverse lipid profiles.

More recent studies, however, have cast doubt on niacin's ability to decrease cardiovascular morbidity and mortality. The AIM-HIGH study[42] examined the effects of niacin in patients already on simvastatin therapy with or without ezetimibe. Despite favorable lipid profile changes, niacin had no effect on the composite endpoint of death from coronary heart disease, non-fatal MI, ischemic stroke, hospitalization for unstable coronary syndrome, or coronary or cerebral revascularization. Of note, the mean treatment time was only three years, which perhaps was not long enough to show benefit. The HPS2-THRIVE study,[43] which compared niacin plus laropiprant (to reduce flushing) with placebo in over 25,000 patients with vascular disease, further brought the use of niacin into question. Patients receiving lipid-lowering therapy more potent than in AIM-HIGH (simvastatin 40 mg with ezetimibe 10 mg) were excluded. Again, no effect on cardiovascular outcomes was observed, but treatment was associated with an increased risk of adverse effects. Recent meta-analyses have also failed to

demonstrate a benefit to niacin for primary or secondary prevention with regard to all-cause or cardiovascular mortality, stroke, or fatal/non-fatal MI, with the exception of a potential decrease in non-fatal MI in patients not receiving statin therapy.[44,45]

Are we done with niacin? A recent review points out several issues with the newer studies.[46] One reason cited for niacin failure is that all patients were treated with background statin therapy in the two most recent trials. In addition, patients in the AIM-HIGH and HPS2-THRIVE trials had relatively good baseline lipid levels and may not represent the dysmetabolic population that is generally considered for niacin use. On the other hand, both trials used simvastatin instead of atorvastatin or rosuvastatin, which are the "high-intensity" statins recommended by current guidelines.[47] The use of more potent agents may further diminish any additional niacin benefit.

Niacin clearly has beneficial effects on LDL, HDL, triglycerides, and lipoprotein(a). It may be that the proper target population, with severe atherogenic dyslipidemia (low HDL with high triglycerides and small dense LDL), may benefit from niacin therapy. These trials have yet to be done, and at least for now, niacin therapy may be relegated to patients who have excessively high (> 500 mg/dL) levels of triglycerides or who are unable to tolerate statins (or more preferred alternatives) and considered for those with severe dysmetabolic atherogenic lipid profiles.

63.3.3 Vitamin C

Vitamin C (ascorbic acid) is an essential water-soluble vitamin that must be obtained from dietary sources. Mechanisms by which vitamin C has been proposed to reduce cardiovascular risk include: reducing atherosclerotic lesion formation by inhibiting low-density lipoprotein oxidation; acting as an antioxidant in the plasma; and enhancing endothelial nitric oxide synthase activity to increase circulating nitric oxide levels.[48–50] It has been suggested vitamin C intake of approximately 100 mg/day is sufficient to confer cardiovascular protection for non-smoking individuals.[51] The use of vitamin C and other antioxidants for the prevention of CVD remains controversial, as results of clinical trials have been conflicting.

Observational studies have demonstrated inverse relationships between vitamin C concentrations or intake and blood pressure[52,53] and some evidence suggests vitamin C supplementation may reduce the risk of cardiovascular-related death in patients with low dietary intake.[54–58] However, supplementation has not been shown to reduce cardiovascular events or mortality in randomized controlled trials[59–61] and large population-based studies evaluating the effect of vitamin C intake on mortality have yielded conflicting results.[54,62–70] Recent meta-analyses have concluded vitamin C supplementation, alone or in combination with other antioxidants, does not significantly affect mortality in healthy subjects or those with pre-existing disease states[71] or reduce CVD risk in healthy participants or in those at increased risk of CVD[72] suggesting lack of benefit for primary prevention. Of note, the findings of the second meta-analysis were based solely on one trial of male physicians, which limits generalizability. Although there is limited data regarding vitamin C supplementation in patients with pre-existing CVD, the majority of evidence suggests it does not prevent CVD progression or events.[69,73,74] Therefore, although vitamin C supplementation is unlikely to cause harm, it is not anticipated to be beneficial for patients with sufficient dietary intake.

63.3.4 Vitamin D

Vitamin D (25-hydroxy vitamin D) is primarily involved in calcium metabolism and bone homeostasis, but has been implicated in more wide-ranging effects, including the renin-angiotensin-aldosterone axis, and therefore hypertension and cardiovascular health. In addition, it has a role in diabetes mellitus, hyperparathyroidism, inflammatory response, and depression. Although vitamin D deficiency is prevalent worldwide, it remains unclear whether it is causative or simply associated with these conditions, and whether supplementation can reduce risk.

Several studies have linked deficiency to cardiovascular disease, including NHANES[75] which found an association between cardiometabolic disease and low vitamin D levels regardless of ethnic background, and the Framingham Offspring Study[76] in which low vitamin D levels were associated with a 53–80% increased risk of CVD development. A recent meta-analysis of prospective trials confirmed serum vitamin D concentrations were inversely associated with total CVD events and CVD-associated mortality.[77]

Basic animal and human research have suggested salutary effects of vitamin D supplementation, such as inhibition of the renin-angiotensin-aldosterone system and improved endothelial function in patients with low vitamin D levels.[78] However, beneficial effects of vitamin D supplementation on cardiovascular endpoints have not been demonstrated in the prevention of hypertension,[79] patients with heart failure[80] or individuals with vitamin D deficiency.[81] A meta-analysis of 21 randomized controlled trials including 83,291 patients found no benefit to vitamin D supplementation on the incidence of major adverse cardiovascular events, myocardial infarction, stroke, or cardiovascular or all-cause mortality.[82] The long-awaited VITAL trial,[83] a 25,871 patient 2×2 study of vitamin D 2000 IU per day and marine fatty acids, may have closed the door on the idea of vitamin D supplementation as a potentially beneficial intervention. After a median follow-up of 5.3 years, vitamin D supplementation failed to demonstrate benefit compared with placebo in terms of major cardiovascular events (with or without coronary revascularization), myocardial infarction, or death from cardiovascular causes.

Unlike efficacy of vitamin D supplementation, safety is well established. Increased cancer risk at very high vitamin D levels has been suggested, although studies have

been inconsistent. The Institute of Medicine[84] has defined a serum 25-hydroxyvitamin D level of over 50 ng/ml (125 nmol/L) as "potentially harmful" and it is felt supplementation of 2000 IU daily is well within safe limits. While generally agreed upon that vitamin D deficiency of <20–30 ng/ml (<50–75 nmol/L) should be treated for the prevention of bone disease, treatment for cardiovascular health, especially in patients without risk factors of deficiency, should not be recommended at this time.

63.3.5 Vitamin E

Vitamin E is a fat-soluble antioxidant that exists in several different forms (alpha-, beta-, gamma-, and delta-tocopherol and -tocotrienol). Although gamma-tocopherol is the most abundant formulation found in the human diet, many vitamin E supplements contain synthetic alpha-tocopherol, which is the most biologically active and the only formulation considered necessary to meet human dietary requirements.[85,86] It has been suggested vitamin E may slow or prevent the development of atherosclerosis via inhibition of LDL oxidation,[87] though it is unclear whether individual formulations may confer varying degrees of clinical efficacy.[88]

Despite the proposed mechanism by which vitamin E may be beneficial, the majority of available evidence suggests it is not effective for primary prevention of CVD in healthy or high-risk patients.[89–98] One exception is an analysis from the Women's Health Study (WHS), which found 600 IU of vitamin E (RRR-alpha-tocopherol) taken every other day for up to ten years reduced the risk of cardiovascular death by 24% in healthy women age ≥45 years.[92] However, there was no difference observed in the risk of other cardiovascular events, such as myocardial infarction or stroke, and a separate analysis of the WHS demonstrated the same vitamin E dose does not prevent the development of heart failure in this population.[99]

Existing clinical trial data also suggests vitamin E is not beneficial for secondary prevention of cardiovascular disease or events, including myocardial infarction, stroke, or death.[93,100,101] Supplementation has failed to demonstrate reduced progression of atherosclerosis in patients with pre-existing coronary artery disease or an ability to improve quality of life or functional indices of heart failure.[100–103] Additionally, a meta-analysis[71] conducted in 2012 found vitamin E supplementation, alone or in combination with other antioxidants, significantly increased mortality in healthy subjects and those with pre-existing disease states, though more recent meta-analyses have not reached this conclusion.[95,104] Based on the available evidence, the American Heart Association (AHA) and USPSTF currently recommend against utilizing antioxidants, such as vitamin E, for the primary or secondary prevention of cardiovascular disease.[16,105] Given the lack of proven benefit and potential increase in mortality with use, routine vitamin E supplementation should be advised against at this time.

63.4 DIETARY SUPPLEMENTS

The Dietary Supplement Health and Education Act of 1994[106] defines dietary supplements as products containing a dietary ingredient intended for ingestion to supplement the diet. In addition to vitamins, dietary ingredients may include amino acids, herbs, minerals, or other substances meant to add nutritional value. Supplements commonly touted as beneficial for cardiovascular health include coenzyme Q10, fish oil, red yeast rice, and selenium.

63.4.1 Coenzyme Q10

Coenzyme Q10 (CoQ10), or ubiquinone, is an endogenously produced fat-soluble antioxidant found in the mitochondria of the heart in high concentrations. It plays a role in the Kreb's cycle, serving as a cofactor in oxidative phosphorylation to enhance adenosine triphosphate (ATP) production, and has been demonstrated to have membrane stabilizing properties.[107] CoQ10 levels decrease with age and deficiency is associated with muscle weakness, fatigue, and soreness.[108] Additionally, it has been demonstrated that serum and myocardial CoQ10 levels are inversely associated with the degree of heart failure.[109–111]

There is low-quality evidence regarding the utilization of CoQ10 in healthy subjects for the primary prevention of cardiovascular disease. A Cochrane Review from 2013 identified only six small (n = 20–52) trials of CoQ10 100–200 mg taken daily for approximately three months, none of which reported cardiovascular events or mortality.[112] Meta-analyses evaluating the effect of CoQ10 supplementation on blood pressure have yielded conflicting results, with one reporting CoQ10 has the potential to lower systolic blood pressure by up to 17 mmHg and diastolic blood pressure by up to 10 mmHg and others reporting lesser or no benefit.[113–115] At this time, CoQ10 cannot be recommended for the primary prevention of CVD or hypertension treatment.

Although CoQ10 has been studied for secondary prevention of several cardiovascular disease states, the most evidence is available for use in the setting of acute MI and heart failure. When administered within the first 48–72 hours following myocardial infarction, CoQ10 120 mg/day has been found to reduce the incidence of angina, arrhythmias, and poor left ventricular ejection fraction (LVEF) compared with placebo after four weeks of treatment.[116] CoQ10 has also been demonstrated to reduce cardiovascular death, non-fatal MI, and total cardiac events at one year compared with placebo.[117] Reported fatigue was 6.8% in the CoQ10 group, as opposed to 40.8% in the placebo group, which may be due to CoQ10's role in ATP production. Large randomized controlled trials with a longer duration of follow up are required to confirm these results before CoQ10 may be routinely recommended following acute MI.

When added to conventional therapy, CoQ10 has been demonstrated to improve NYHA classification and symptoms of heart failure, decrease hospitalization rates, and improve quality of life in patients with NYHA Class II–IV

heart failure.[118–126] It has also been demonstrated to improve LVEF, cardiac output, and systolic wall thickening when 100–300 mg is taken daily for up to seven months, although data is conflicting.[127–131] It remains unclear whether CoQ10 may reduce heart failure-associated mortality.[132,133] While it may be considered as adjunctive therapy for heart failure, CoQ10 should not replace guideline-recommended therapies.

63.4.2 Fish Oil

Fish oil is a dietary source of omega-3 fatty acids. The two most commonly studied omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are polyunsaturated long-chain fatty acids. The role of pharmaceutical-grade EPA/DHA for the treatment of hypertriglyceridemia (triglycerides >500 mg/dL) is well-established, with doses of 2–4 g/day associated with serum triglyceride reductions of 20–60%.[134] Despite several proposed mechanisms for benefit,[135] including triglyceride and blood pressure reduction, decreased inflammation, improved vascular function, and reduced platelet aggregation, the effect of supplementation on cardiovascular outcomes remains unclear.

The AHA currently recommends one to two 3.5-ounce servings of non-fried seafood per week based on evidence suggesting consumption of fish oil from dietary sources is associated with reductions in congestive heart failure, coronary heart disease (CHD), ischemic stroke, and sudden cardiac death, especially if replacing intake of less healthy foods.[136] This concept is echoed by the 2020–2025 Dietary Guidelines for Americans,[137] which recommend adults with and without CVD consume 8–10 ounces of seafood per week (based on age and target caloric intake), to provide an average of 250 mg or more per day of long-chain omega-3 fatty acids. Despite the benefits observed with dietary intake, however, fish oil supplementation of 1–4 g/day has not been shown to be beneficial for primary prevention of CVD in randomized controlled trials of patients without prior events, including those deemed to be at high cardiovascular risk.[138–141] Recent meta-analyses have also failed to identify a clear benefit of fish oil supplementation in individuals without pre-existing CVD.[142,143] Therefore, fish oil supplementation should not be routinely recommended for primary prevention.

An AHA scientific advisory regarding fish oil supplementation and the prevention of cardiovascular disease was recently published, which included analyses of secondary prevention of CHD and sudden cardiac death in patients with prevalent CHD.[144] The review included five randomized controlled trials (24,499 patients) utilizing an average omega-3 dose of approximately 1 g/day for a mean duration of two years (range 1–6.2 years). Two of the trials demonstrated a mortality benefit with omega-3 supplementation when administered following a recent myocardial infarction, whereas the other three trials did not observe a CVD benefit. A meta-analysis[145] of 20 RCTs of patients with prevalent CHD, at high risk for CVD, or with an implantable defibrillator (n = 68,680) was also included in the review and demonstrated a reduction in CHD death with supplementation. Based on this data, the AHA statement[144] concludes that omega-3 supplementation is reasonable for the secondary prevention of CHD death, but likely will not reduce the incidence of non-fatal myocardial infarction. Notably, the most convincing evidence supporting this recommendation was from trials conducted prior to 2002 and more recent meta-analyses have demonstrated little to no benefit of omega-3 supplementation for secondary prevention of CVD.[142,143,146]

In addition to considering omega-3 supplementation for secondary prevention, the AHA also concludes it is reasonable in patients with heart failure with reduced ejection fraction (HFrEF),[144] based on the results of the GISSI-HF trial.[147] This randomized controlled trial of ~7000 NYHA class II–IV heart failure patients demonstrated a 9% reduction in all-cause mortality and an 8% reduction in cardiovascular-related death or hospitalization with omega-3 1 g daily vs. placebo when taken for a median duration of 3.9 years. Of note, the majority of patients had an ejection fraction <40%, which limits generalizability to the entire heart failure population. A subsequent meta-analysis evaluating omega-3 supplementation in heart failure patients failed to identify reductions in first heart failure hospitalization or cardiovascular mortality with use but did observe a reduction in recurrent heart failure hospitalizations compared with placebo.[148]

63.4.3 Red Yeast Rice

Red yeast rice (RYR) has been incorporated into alternative medicine practices for centuries. Red yeast is the product of rice fermentation with the fungus *Monascus purpureus*, which results in the production of monacolins. Monacolins are known to inhibit HMG-CoA reductase, an enzyme involved in cholesterol synthesis. One of the monacolins produced, monacolin K (lovastatin), is available as a prescription medication. As a result, the FDA announced in 1998 that the products were subject to regulation, which prompted RYR product reformulations in the United States to remove monacolin K, though variable amounts may remain.[149–151]

Red yeast rice has been reported to reduce total cholesterol, LDL cholesterol, and triglycerides in a manner similar to statin therapy.[152] Favorable all-cause and cardiovascular mortality reductions have been reported when used for primary prevention and red yeast extract 1.2 g/day has been shown to significantly reduce coronary events, non-fatal MI, and all-cause and cardiovascular mortality in patients with a history of myocardial infarction compared with placebo when taken for an average of 4.5 years.[153–155] Of note, products utilized in these trials contained monacolin K and results cannot be extrapolated to products currently available in the United States. Therefore, RYR cannot be routinely recommended at this time.

63.4.4 Selenium

Selenium is a trace mineral that is a key component of several selenoproteins, including glutathione peroxidase and selenoprotein P.[156] It has been shown to increase enzymatic antioxidant activity and decrease lipid peroxidation at a dose of 100 µg/day,[41,157–159] and may play a role in neutralizing peroxide intermediates, resulting in the decreased production of inflammatory prostaglandins and leukotrienes.[160] Based on these known mechanisms, it has been hypothesized selenium may be beneficial for the treatment and prevention of CVD. However, the majority of clinical research suggests selenium is not beneficial for the primary prevention of CVD at doses of 100–800 µg/day.[161–163]

There is no data supporting selenium alone for the secondary prevention of CVD except in individuals with a severe deficiency at baseline, as has been observed in patients with Keshan disease, a cardiomyopathy found in areas of China with selenium-deficient soil.[164,165] In patients with pre-existing CVD, a combination of beta-carotene 25 mg, vitamin C 1000 mg, vitamin E 800 IU, and selenium 100 µg daily did not reduce the frequency of clinical cardiovascular events compared with placebo and actually reduced cardioprotective HDL-2.[41] Additionally, a prospective randomized controlled trial of 443 elderly patients (age 70–88 years) reported taking 200 µg of organic selenium yeast in combination with CoQ10 200 mg daily for an average of 5.2 years reduced cardiovascular mortality by 53% compared with placebo.[166] A multivariate analysis confirmed statistical significance following adjustment for several risk factors and a significant reduction in NT-proBNP was observed in the treatment group at 24 and 48 months. Although extensive prior cardiac history was not reported for the participants, 74% of the study population had a past medical history of hypertension, 23% had ischemic heart disease, and 48% were reported to have NYHA Class II or III heart failure. Interestingly, a mortality benefit continued to be observed in the treatment group at 10- and 12-year follow-ups, despite stopping therapy following the initial four-year intervention period.[167,168] Unfortunately, it is not able to be discerned whether the benefits observed were due to the selenium, CoQ10, or the combination. Therefore, selenium

TABLE 63.1
Main Adverse Effects and Considerations for Vitamins and Supplements Commonly Touted as Beneficial for Cardiovascular Disease Prevention or Treatment[171]

Vitamin/ Supplement	Main Adverse Effects and Considerations
Coenzyme Q10	The most common adverse effects are gastrointestinal, including nausea, diarrhea, heartburn, and appetite suppression. Hepatic insufficiency or biliary obstruction may cause accumulation. Insulin requirements in diabetic patients may be reduced.
Fish oil (omega-3)	Avoid use in patients with known fish or shellfish hypersensitivity. Gastrointestinal symptoms are common (burping, indigestion, altered taste). May increase LDL levels. May prolong bleeding time, resulting in increased bleed risk. Liver function test elevations have been reported; monitor if used in patients with hepatic impairment. There is a potential association between fish oil use and an increased risk of prostate and other cancers, although evidence remains inconclusive.[172–175]
Folic acid (vitamin B9)	Doses >0.1 mg may obscure pernicious anemia, which may allow the progression of irreversible nerve damage. Possible risk of late diameter loss and increased restenosis in patients with bare metal coronary stents.[36]
Niacin (vitamin B3)	Skin flushing/pruritis is common; increasing the dose slowly, administering with food, using slow-release formulations, and/or taking aspirin 30 minutes prior to a dose may help. May increase fasting blood glucose (generally <5%). Increases uric acid levels; use with caution if history of gout. Risk of myopathy increases when combined with statin therapy. Other adverse effects include atrial fibrillation, abdominal discomfort, loose stools, and hepatotoxicity (rare, but severe).
Red yeast rice	Contents of available products are highly variable. US formulations may or may not contain monacolin K (lovastatin)[149–151] Monacolin K-containing products may cause statin-like adverse effects, including myopathy, rhabdomyolysis, and hepatic toxicity. Some red yeast rice products contain citrinin, a contaminant that has been associated with the development of renal failure.
Selenium	Gastrointestinal adverse effects (abdominal cramps, diarrhea, nausea, vomiting) have been reported.
Vitamin C	May cause acidification of urine, leading to precipitation of cysteine, urate, or oxalate stones. Doses >2000 mg/day may cause serum glucose elevations and interfere with glucose monitoring. Individuals with glucose-6-phosphate dehydrogenase deficiency may experience hemolysis following administration.
Vitamin D	Avoid use in the setting of hypercalcemia. Toxicity may occur with excessive doses. Symptoms may last two or more months after discontinuation and include nausea, vomiting, loss of appetite, constipation, fatigue, dehydration, irritability, confusion, weakness, and/or weight loss.
Vitamin E	Some data suggest vitamin E may increase bleed risk. Other adverse effects associated with long-term use include headache, dizziness, weakness, and fatigue.

TABLE 63.2

Drug-Drug Interactions of Common Vitamins and Supplements Taken for Cardiovascular Disease Prevention or Treatment[171]

Vitamin/ Supplement	Interacting Drug(s)	Anticipated Effect(s)	Proposed Mechanism
Coenzyme Q10	Warfarin	Reduced anticoagulant effectiveness	Coenzyme Q10 has a similar chemical structure to vitamin K2
Fish oil (omega-3)	Anticoagulant and antiplatelet agents	Increased risk of bleeding	Decreased platelet aggregation due to decreased thromboxane A2 levels
Folic acid (vitamin B9)	Barbiturates/primidone	Decreased folic acid serum levels and decreased barbiturate/primidone effectiveness	Decreased folate absorption and increased barbiturate/primidone metabolism
	Fosphenytoin/phenytoin	Decreased folic acid serum levels and decreased phenytoin effectiveness	Decreased folate absorption and increased phenytoin metabolism
	Pafolacianine	Decreased detection of malignant lesions	Reduced binding of pafolacianine to folate receptors overexpressed on ovarian cancer cells
	Pyrimethamine	Loss of pyrimethamine efficacy	Pharmacodynamic antagonism of antiparasitic effects
	Tea (green or black)	Decreased folic acid exposure	Decreased folate absorption
Niacin (vitamin B3)	Bile acid sequestrants	Decreased niacin exposure	Decreased niacin absorption
	HMG-CoA reductase inhibitors ("statins")	Increased risk of myopathy or rhabdomyolysis	Unknown
	Insulin	Decreased blood glucose lowering effect	Unknown
	Warfarin	Increased risk of bleeding	Additive anticoagulation effect and decreased CYP450-mediated warfarin metabolism
Red yeast rice	Cyclosporine	Increased risk of elevated creatine phosphokinase; rhabdomyolysis	Inhibition of CYP3A4-mediated lovastatin metabolism
Selenium	Baloxavir marboxil	Decreased baloxavir concentrations	Chelation
	Eltrombopag	Decreased eltrombopag concentrations	Chelation
Vitamin C	Aluminum antacids	Aluminum toxicity (personality changes, seizures, coma)	Increased aluminum absorption
	Amphetamine	Decreased amphetamine levels and efficacy	Lower GI and urinary pH; increased renal excretion of amphetamine
	Amygdalin	Increased amygdalin metabolism, leading to increased cyanide levels	Increased amygdalin hydrolysis and hydrogen cyanide formation; reduced cysteine levels (detoxifies cyanide)
	Cyanocobalamin (Vitamin B12)	Reduced cyanocobalamin concentrations	Unknown
	Deferoxamine	Impairment of cardiac function	Increased iron availability for chelation
	Erythromycin	Decreased erythromycin efficacy	Unknown
	Indinavir	Decreased indinavir plasma concentrations	Increased CYP3A4-mediated indinavir metabolism
Vitamin D	Aluminum antacids	Aluminum toxicity (personality changes, seizures, coma)	Increased aluminum absorption
	Bile acid sequestrants	Decreased vitamin D exposure	Reduced vitamin D absorption
	Carbamazepine	Decreased vitamin D exposure	Increased vitamin D elimination
	Cimetidine	Decreased vitamin D exposure	Increased vitamin D elimination
	Fosphenytoin/phenytoin	Decreased vitamin D exposure	Increased vitamin D elimination
	Mineral oil	Decreased vitamin D exposure	Reduced vitamin D absorption
	Orlistat	Decreased vitamin D exposure	Reduced vitamin D absorption
	Phenobarbital	Decreased vitamin D exposure	Increased vitamin D elimination
	Thiazide diuretics	Decreased vitamin D exposure	Increased vitamin D elimination
Vitamin E	Bile acid sequestrants	Decreased vitamin E exposure	Reduced vitamin E absorption
	Orlistat	Decreased vitamin E exposure	Reduced vitamin E absorption
	Warfarin	Increased bleed risk	Unknown

cannot be routinely recommended at this time, except in individuals with (or at risk for) severe deficiency.

63.5 OVER-THE-COUNTER DIETARY SUPPLEMENT SELECTION

Unlike prescription drug products, dietary supplements do not undergo an FDA-approval process requiring proof of safety and efficacy prior to reaching the consumer. In fact, once a supplement is on the market, the FDA has to prove the supplement is *unsafe* in order to restrict its use or remove it altogether. Although the FDA issued a guidance on Current Good Manufacturing Practices in 2007[169] requiring dietary supplement manufacturers to establish quality standards for manufacturing, packaging, storing, and testing of ingredients, the FDA does not perform quality control testing or define what is considered "appropriate". Unfortunately for consumers, the lack of FDA regulation allows for varying degrees of quality control, which are largely manufacturer dependent, and makes it difficult to determine an individual product's quality based on its label alone. Educate patients intent on taking a dietary supplement to look for products with a "seal of approval" indicating the manufacturer voluntarily subjected the product to more stringent quality testing. Available approvals include the Consumerlab.com Approved Quality Product Seal, the NSF Mark, and the United States Pharmacopeia (USP) Verified Mark.

63.6 CONCLUSION

Although recent surveys have revealed approximately half of US adults take a dietary supplement,[3,170] there is little evidence supporting their use for the primary and secondary prevention of cardiovascular disease. In the rare instances in which well-designed randomized controlled trials are available, evidence is often conflicting. Although guidance statements or scientific advisories from national organizations are published for some of the supplements, it is often the patient and/or clinician who is left to interpret the available evidence. In addition to the clinical data presented, the main considerations and adverse effects should be reviewed prior to recommending therapy (Table 63.1). Although patients often view over-the-counter (OTC) supplements as benign due to their ease of availability, the potential for drug-drug interactions still exists (Table 63.2). Consistent with the mantra to "first, do no harm", the use of supplements must not distract the patient from adhering to optimal guideline-directed medical therapy. However, discretionary use of supplements that have no (or minimal) adverse effects may be considered in select patients.

CLINICAL APPLICATIONS

- Although evidence is inconclusive, folic acid may be beneficial for the primary and secondary prevention of cardiovascular disease.
- Niacin should be reserved for patients who are intolerant of statins (and more preferred alternatives), those with triglyceride levels >500 mg/dl, and individuals with severe dysmetabolic atherogenic lipid profiles.
- Vitamin E, alone or in combination with other antioxidants, has been associated with a potential increase in mortality and should be avoided for primary and secondary prevention of cardiovascular disease.
- Coenzyme Q10 may be reasonable to consider as adjunct therapy for heart failure patients but should not replace guideline-directed therapy.
- Omega-3 supplementation may be considered for the secondary prevention of cardiovascular disease, in the setting or HFrEF, or for the treatment of hypertriglyceridemia. If utilized, prescription products are preferred over OTC options.
- Despite favorable effects on cholesterol and evidence suggesting reductions in mortality, coronary events, and non-fatal myocardial infarction, red yeast rice supplementation cannot be recommended at this time due to the reformulation of US products to remove monacolin K.
- There is currently insufficient evidence to recommend for or against multivitamins, vitamin C, or selenium for the primary or secondary prevention of cardiovascular disease. Increasing evidence suggests vitamin D supplementation may not be beneficial.

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Part XII

Lifestyle Components of Pediatric Medicine



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64 Pediatric Preventive Medicine: An Introduction

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KEY POINTS

- Lifestyle medicine in pediatric populations has expanded from the prevention of future diseases to the treatment of diseases acquired during childhood and adolescence.
- Prevention and treatment efforts require behavior change on the part of the caregiver and child, which can be supported by healthcare practitioners.
- Behavior change strategies with the greatest empirical support stem from functional contextual approaches, such as operant psychology.
- A better understanding of behavioral principles will inform more effective strategies to promote lifestyle change.

Pediatricians have traditionally had a strong emphasis on prevention. Early in the history of pediatrics, these preventive efforts concentrated on infectious diseases, both by improved public health measures and immunizations. More recently, pediatricians have focused their attention on the prevention of chronic diseases. With the work of David Barker and others, it has become clear that the risk for the development of chronic disease starts in utero and is determined by exposures to the fetus and, subsequently, the child, as well as exposures through adolescence and into young adult life.[1,2] Many of these environmental exposures are often a result of lifestyle factors. This presents a tremendous opportunity, but also a tremendous challenge to change the trajectory of risk, by changing lifestyle behaviors.[3]

Although a traditional focus for the prevention of chronic disease has been on risk factors, with primary prevention being the approach to treating risk factors once they develop, the work of Dr. Stamler and others has shifted the focus to health factors or ideal health. Stamler and others have shown that if individuals can reach age 50 in ideal cardiovascular health, their subsequent risk of atherosclerotic cardiovascular disease is quite low.[4] Of interest is the fact that individuals with ideal cardiovascular health, defined as normal body mass index, normal blood pressure, normal cholesterol, no type 2 diabetes, and no cigarette smoking also have a quite low risk of cancer and other illnesses and have a greatly expanded life expectancy.[5,6] Beyond this, the quality of life and freedom from morbidity are also higher than for those who have lost ideal cardiovascular health.[7] In addition, the cost of healthcare is reduced in individuals with favorable cardiovascular health.[8–10] This approach to the prevention of the development of risk factors in the first place has been referred to as primordial prevention.[11]

An important consideration is the extent to which ideal cardiovascular health is determined by genetics versus environmental influences, such as diet, physical activity, and sleep.[12] Studies have shown that ideal cardiovascular health is only about 12–18% heritable.[11,13] This means that approximately 80–85% of ideal cardiovascular health is related to maintaining a healthy lifestyle through a healthful diet, regular physical activity, and quality sleep. These data create an imperative for those healthcare providers focused on children and adolescents. Most individuals are born with ideal cardiovascular health, as well as a healthy heart, vascular system, and other organ systems. However, this ideal health status is lost by many individuals during childhood and adolescence. Disturbingly, an increasing proportion of the pediatric population is exhibiting sufficiently poor lifestyle behaviors that diseases previously only seen in adulthood are presenting in childhood,[14,15] requiring efforts not just to prevent but also to treat. This is in part why so few individuals are able to reach the age of 50 in ideal health. Most estimates indicate that fewer than 5% of individuals at 50 years have maintained ideal cardiovascular health[14] Micha et al. have shown that dietary factors are associated with a substantial proportion of deaths from heart disease, stroke, and type 2 diabetes.[16] This means that it is the pediatrician's job and the job of other child health professionals to deliver as many individuals as possible into young adulthood with ideal health status. This goal can only be accomplished by promoting a healthy lifestyle for fetuses, infants, school-age children, and adolescents.

This section focuses on lifestyle medicine related to the pediatric population, including issues related to diet, physical activity, sleep, obesity, cardiovascular health, and bone health. This chapter focuses on the behavioral principles that can be utilized to promote optimum health behaviors and change health behaviors when necessary to improve lifestyle and health.

64.1 LIFESTYLE BEHAVIORS

Lifestyle behaviors, including diet, physical activity, sedentary behavior, and sleep, are often central to the prevention

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or progression of multiple non-communicable diseases, including obesity, heart disease, cancer, obstructive sleep apnea, and diabetes. While the specific contributions of a single healthy behavior can have a positive impact on health (e.g., regular consumption of vegetables), optimal health outcomes will most likely result from maximizing the number of healthy lifestyle behaviors. Although there may be some overlap, the development of healthy lifestyle behaviors may be different than modifying an existing maladaptive lifestyle behavior. Moreover, a particular behavioral strategy used to maintain a healthy lifestyle behavior may differ from the method used to establish it in the beginning. The evidence to date for lifestyle interventions suggests targeting multiple behaviors over one behavior in isolation.[17–19] For adults, comprehensive lifestyle modification programs targeting obesity produced a 7–10% reduction in weight and meaningful changes in CVD risk factors.[17,19] Similarly, the strongest evidence to date for improving childhood obesity includes comprehensive and intensive behavioral interventions (>25 hours of contact) that target multiple lifestyle behaviors, engage both children and their caregivers, and result in typical BMI z-score reductions of 0.20 or more.[20]

The development or modification of healthy lifestyle behaviors has been studied across the spectrum of disease progression from pre-pregnancy to adulthood. Fostering healthy lifestyle behaviors early in life is a goal that has been well supported by the evidence showing increasing difficulty in reversing obesity once established in childhood that generally tracks into adulthood.[21–23] Systematic reviews on the prevention of childhood obesity have identified non-significant or small effect sizes for interventions, of which most study settings were school-based.[24] Notably, the most effective prevention programs included a home-based component with the school environment that suggests the effect of modifying lifestyle behaviors is maximized when multiple settings and agents of change are targeted.[24,25]

Conceptualizing relevant health behaviors within testable models remains a core task in the pursuit of preventing and treating diseases that are impacted by lifestyle behaviors. In the following section, we review models and principles of behavior related to lifestyle behaviors.

64.2 MODELS OF BEHAVIOR

Human behavior is complex, with a multitude of factors contributing to any given instance of behavior. While multiple theoretical models have been developed to understand behaviors, the evidence supporting each model varies in terms of behavioral changes, maintenance of changes, and health outcomes.[26,27]

64.2.1 Social-Ecological Model

Bronfenbrenner's social-ecological model has been extensively tested and adapted for understanding lifestyle behaviors.[28] The theory is founded on the principle that behaviors cannot be understood without considering their context. An individual, including the individual's biological environment, lies at the center of the model in which levels from the immediate external environment (family members and the home environment) are surrounded by more distal levels of influence such as peers and school environments. Finally, outer levels of influence are depicted, including neighborhoods, communities, regions, and policies that may influence behaviors.[29] Given that obesity and related comorbidities is a multifactorial disease in which preventive and treatment approaches are based on multiple components, the social-ecological model provides a well-matched, comprehensive view of the exposures and targets for such interventions to be tested.

However, a significant limitation of the social-ecological model is that, while useful for placing the development and progression of disease in the contexts that influence an individual's health, it does not directly identify interventions on how to modify these contexts to prevent or ameliorate disease and therefore lacks a practical quality.[30] Presumably, the ultimate goal of medicine is not just to understand health and disease but to act in order to improve the human condition. With lifestyle medicine, this is accomplished primarily through changing the behaviors of those in the contexts most proximal to health-related events (e.g., child *and* caregiver behaviors).[31] It seems a framework that incorporates the pragmatic goals of medicine and the explanatory benefits of examining behavior in context would be ideally suited to providing a foundation for the advancement of lifestyle medicine. Indeed, such an approach does exist[32] and has been central to many of the most successful strategies for behavior change, health-related and otherwise.

64.2.2 Functional Contextualism

Functional contextualism[33,34] is the philosophical framework that underlies operant psychology (learning theory) and the related field of behavioral economics, as well as psychotherapeutic practices, including acceptance and commitment therapy (ACT). It is founded on a pragmatic approach to knowledge and action, with a focus on predicting and influencing behavior by examining it relative to the context in which it occurs. Within this framework, behavior is conceptualized as an interaction between an individual and their environment—both internal (biological, psychological) and external (physical, social). In accordance with its pragmatic goal, principles of behavior are defined functionally, in terms of the effects of environmental events on behavior. This results in principles that are derived from effective action and are therefore readily applied to behavior change.

This framework is distinct from other models of behavior that have been applied to lifestyle medicine (e.g., theory of reasoned action/theory of planned behavior, stages of change), which often utilize correlational designs and cross-sectional data rather than experimental methods,[35,36] due to its emphasis on function. However, functional contextualism remains compatible with models that share a

context-based approach to examining behavior, such as the social-ecological model.

Although functional contextualism per se has not been widely discussed in relation to lifestyle medicine, the impact of approaches aligned with this philosophy is well documented. For example, patient adherence to recommendations is essential for effective intervention, as the behaviors needing to change typically occur outside of contexts where the provider directly interacts with the patient. In 2003, the World Health Organization (WHO) published a report on adherence to long-term therapies that, among other things, outlined patient-level interventions for improving adherence.[37] The report stated that "the most effective adherence-enhancing interventions directed at patients aim to enhance self-regulation or self-management capabilities" and that "such approaches are grounded in basic principles of learning" (p. 143). As such, we will review some of the fundamental principles developed within the functional contextual framework and highlight their relevance to behavior change in lifestyle medicine to inform readers' perspectives when reading subsequent chapters of this section and when practicing lifestyle medicine.

64.3 PRINCIPLES OF BEHAVIOR

The principles of operant psychology described below were empirically derived and validated through hundreds of experiments that methodically manipulated environmental events and observed consistent changes in behavior. This inductive approach has produced a robust, tightly interwoven conceptual system that is defined by its ability to predict and influence behavior.

The most fundamental and powerful concept of operant psychology for understanding and changing behavior is *reinforcement*. Reinforcement is the process by which a behavior is strengthened due to the consequence (environmental change) that follows it. Strengthening can occur as increased probability, duration, or magnitude of a behavior or as decreased latency for the behavior to occur in response to a stimulus. A critical feature of this definition is that it defines a functional relation—if a consequence does not strengthen the behavior, reinforcement, by definition, has not occurred. For example, if a child with diabetes was experiencing hypoglycemia (and its accompanying aversive physiological effects) ate some sugar (behavior), and then began to feel better soon after (consequence), eating sugar would likely be reinforced by the alleviation of the unpleasant symptoms; however, it would only meet the definition of reinforcement if the child's future behavior related to sugar intake (the behavior that produced the consequence) was strengthened, such as the child eating sugar more quickly when beginning to feel hypoglycemic or eating sugar more often to avoid symptoms of hypoglycemia.

A functional definition of reinforcement maintains the pragmatic goal of behavior change when applying this principle. Additionally, a number of structural distinctions have proven valuable when describing reinforcement and applying it to change behavior. First, the reinforcement process defining the environmental change that reinforces behavior can be considered in terms of the addition or subtraction of stimuli. When reinforcement occurs due to a stimulus being added to or increased in the environment following behavior, it is referred to as *positive reinforcement*. For example, if a parent was not paying attention to their child at a meal, the child began spitting out vegetables and then the parent started paying attention to the child, this would be positive reinforcement if the child became more likely to spit out vegetables during that or future meals. When reinforcement occurs due to a stimulus being decreased, removed, or avoided following behavior, it is referred to as *negative reinforcement*. The previous example of alleviation of hypoglycemia would be considered negative reinforcement.

Furthermore, categorizing consequences into two general classes based on the source of the event has also proved valuable in application. Social reinforcement involves events mediated by another person, such as the attention of the parent in the previous example about spitting out food (social positive reinforcement) or a patient who has been non-adherent to their lifestyle regimen canceling their doctor's appointment to avoid being admonished by their provider (social negative reinforcement). Automatic reinforcement occurs when the behavior itself produces the reinforcing event, such as when eating sugar automatically produces alleviation of hypoglycemia (automatic negative reinforcement) or eating palatable food produces pleasant stimulation (automatic positive reinforcement). A single instance of behavior can produce multiple environmental changes simultaneously, such that more than one form of reinforcement can occur concurrently. For example, spitting out food may produce both social positive reinforcement via gaining parental attention and automatic negative reinforcement via removing the disliked taste. Still, these distinctions are useful because they can help inform how one should alter the environment to produce behavior change.

Generally, when preferred events are presented following behavior it is likely to produce positive reinforcement and when unpleasant or aversive events are removed following behavior it is likely to result in negative reinforcement. However, assuming what an individual prefers or finds unpleasant is where therapeutic attempts to use reinforcement often fail. Strategies for identifying reinforcement for maladaptive behaviors (known as functional analysis or functional behavior assessment; see Beavers et al., 2013[38] and subsequently modifying reinforcement to increase adaptive skills (known as function-based treatment) have been developed elsewhere,[39] but have yet to be applied to lifestyle medicine, though examples of application exist.[40,41] Collaborations between current lifestyle medicine practitioners and applied behavior analysts (practitioners trained in operant psychology) may provide avenues by which such work and new clinical strategies could be accomplished.

For simplicity, the examples thus far have described reinforcement in terms of a single instance of a reinforcing

consequence following a behavior. Although a single behavior-consequence experience can reinforce behavior, repeated and ongoing association over time is typically needed to maintain behavior change long term. When a behavior continues to occur and the reinforcing consequence no longer follows, this will eventually lead to the *extinction* of the behavior, such that the behavior no longer occurs. Preventing a reinforcing consequence from following behavior (implementing the principle of extinction) is one of the most fundamental means of changing behavior; however, this can be challenging in application, as the availability of the consequence may not be readily altered (particularly with automatic reinforcement) and the individual may initially engage in increased or varied behavior in an attempt to obtain the consequence (known as an extinction burst). When the consequence intermittently follows behavior, this can lead to highly persistent behavior that is more difficult to change.

Another important concept is *punishment*. Punishment is the process by which a behavior decreases in strength due to the consequence that follows it. Like reinforcement, punishment takes positive and negative forms. In positive punishment, a stimulus is added or increased in the environment following behavior such that the behavior is weakened. In negative punishment, a stimulus is decreased or removed following behavior such that the behavior is weakened. Although we do not advocate for the use of punishment in lifestyle medicine, understanding that this process may already be impacting the health-related behaviors of patients is important. For example, teasing by peers (or concerns about this) may punish attempts to engage in group sports or other physical activities at school. Additionally, many medical procedures and lifestyle behaviors can automatically produce aversive stimulation for patients—whether it be medication side effects, blood draws, or the discomfort of physical exertion during exercise—which may punish the behaviors that produce these consequences, thereby contributing to non-adherence.

In addition to altering the strength of behavior, functional consequences (those that reinforce or punish behavior) can also affect the relation between other environmental stimuli and behavior.

As an individual engages in a behavior over time, they may learn that some stimuli are predictive that reinforcement is more likely and therefore become more likely to engage in that behavior when such stimuli are present. *Stimulus control* describes the increased probability of a behavior in the presence of a specific stimulus or set of stimuli (discriminative stimuli) due to a history of greater reinforcement following the behavior in the presence of those stimuli relative to their absence. For example, a child initially throws a tantrum when presented with non-preferred food at mealtime by either parent. Over time, Parent A occasionally gives in and lets the child choose another food to eat at a meal whereas Parent B never lets the child choose a more preferred food after a tantrum. Stimulus control for the child's tantrums is likely to develop so that they will be more likely to tantrum when Parent A presents a non-preferred food than when Parent B does because tantrums in the presence of Parent A are more likely to be reinforced with a more preferred food to consume.

Stimulus control can be a powerful way to influence behavior. Under strong stimulus control, the behavior may not occur unless the discriminative stimulus is present, such that the occurrence of behavior can be changed by altering when or how often the discriminative stimuli are presented. For example, when watching television, viewers are frequently presented with advertisements for energy-dense foods, which signal that these items are available at the sponsoring restaurant. The more frequently these advertisements are seen the more likely that the individual is to consume such items or similarly energy-dense foods.[42]

Essentially, any stimulus or event can participate in stimulus control if it is differentially associated with the probability of reinforcement for a behavior. In particular, reinforcing events themselves can often serve as discriminative stimuli, as their presence tends to be associated with an increased likelihood of additional reinforcement. For example, the presence of highly palatable food (stimulus) is often discriminative for the ability to eat it (behavior) and thereby experience the pleasant taste (consequence). Rules, instructions, and other verbal statements can also function as discriminative stimuli and can often quickly establish stimulus control if the individual has well-developed language skills and the behavior (or component skills for the behavior) is in the individual's repertoire. However, the ability of such stimuli to function as discriminative stimuli is highly dependent on a person's history of reinforcement following similar events. Simply telling a parent or child to do something obviously does not guarantee that they will, but they will be more likely to follow new recommendations if they have experienced reinforcement for following other recommendations. Additionally, stimulus control can be highly specific, as any change in the context may disrupt this process. For example, learning how to take a blood glucose test in the provider's office may not generalize to home. In fact, generalization (learning from a training environment being expanded to a natural environment across individuals, settings, or behaviors) ideally should be programmed into an intervention and not simply be expected to occur.[43]

Other environmental events that precede behavior can also influence their occurrence. *Motivating operations* (MOs) are events or conditions that alter the efficacy of a given consequence for strengthening (or weakening) behavior, as well as influence the likelihood that behavior will occur.[44] Deprivation from a preferred stimulus will typically increase the value of that stimulus and make behaviors to obtain it more likely. When a lifestyle change involves restricting preferred foods, the deprivation from these items is likely to act as an MO that increases their value in that barring other MOs that work to reduce their value (e.g., access to foods that adequately substitute) or punishing consequences for eating these foods (e.g., allergic reaction),

a person may be more likely to consume these foods if given the opportunity. MOs can also reduce the value of otherwise reinforcing events, as when being tired decreases the value of physical activity with peers for a child.

The principles described thus far participate interactively in a fundamental unit of analysis within operant psychology known as the four-term contingency. The four-term contingency is comprised of the context prior to the behavior (discriminative stimuli, motivating operations), the behavior of interest, and the environmental change following the behavior (consequences). From these concepts, a wealth of other behavioral processes, phenomena, and procedures have been identified that further refine the ability to predict and influence behavior, many of which have great relevance to lifestyle behavior. However, it is beyond the scope of this chapter to detail each of these and we encourage the interested reader to consult with professionals trained in these behavioral concepts.

64.4 APPLYING BEHAVIORAL PRINCIPLES TO LIFESTYLE MEDICINE IN CHILDREN

The treatment literature has shown that modifying lifestyle behaviors is supported by delivering intensive, comprehensive programs that include education but also behavioral skills training. Some of the most effective strategies for changing lifestyle behaviors include self-monitoring, goal setting, stimulus control, behavioral rehearsal, corrective feedback, behavioral contracting, commitment enhancement, creating social support, reinforcement, and relapse prevention, all of which are derived from or concordant with operant behavioral principles[37,45] For example, when done well, goal setting establishes a discriminative stimulus by indicating that reinforcement will be available if certain behaviors occur (e.g., meeting the goal of walking for 15 minutes on at least five days this week will result in earning an "app" download).

Unfortunately, these strategies can be time-consuming to implement. However, despite a desire for brief, low-intensity interventions, the overwhelming evidence suggests that lifestyle changes require more versus less intensity and that specialization of treatment content may enhance the maintenance of treatment effects over time.[20,45] For example, the Look AHEAD and Diabetes Prevention Programs tested intensive lifestyle treatments and showed moderate overall reductions in initial weight in adults but found treatment response differences were generally explained by the adoption of key treatment components such as dietary self-monitoring and reaching physical activity goals.[46] Additionally, research on obesity has found that education-only and low-dose interventions (less than 26 hours of contact time) have generally not produced significant changes in behavior or reductions in overweight or obesity in children.[47] Pediatric obesity treatments with the most available evidence have been family-based behavioral treatments and have shown clinically significant short- and long-term (ten years) reductions in weight for primarily school-aged children.[48] This approach incorporates many of the behavioral principles previously described in the intervention design.

64.4.1 Family-Based Behavioral Treatment

Family-based behavioral weight loss treatment (FBT) for pediatric obesity has been extensively evaluated in research settings.[49–55] The primary components include participant utilization of the Stoplight Eating Plan in which a daily energy intake goal is set and adapted for child age and baseline weight.[56,57] Specifically, the Stoplight Eating plan targets increasing nutrient-dense foods ("green" foods) while lowering the intake of calorie-dense foods and those high in fat and sugar content ("red" foods). Moderate intake of "yellow" foods (i.e., nutritional values between the red and green foods) is monitored. Children are given individualized goals to reduce caloric intake to achieve about a 0.5-pound weight loss each week until BMI weight status has been significantly improved (greater than 5% body weight loss).[56]

Recommendations are made to increase physical activity and reduce sedentary time based on defined minimum and maximum time duration goals (e.g., <15 hours per week engaged in screen time)[56] Activity goals are also set to increase physical activity to reach the recommended 60 minutes of daily moderate or vigorous physical activity and at least three days a week of vigorous activity.[58] Sedentary behavior goals are set to reduce daily sedentary time to no more than 60 minutes. Parents complete dietary intake and physical activity monitoring for themselves and their child during the intervention.

Additional primary components include implementing behavior modification strategies, including self-monitoring (e.g., dietary intake), stimulus control (e.g., modifying the home food environment for greater availability of nutrient-dense foods and a reduction in high-calorie foods), and goal setting with motivating rewards for positive reinforcement (e.g., provide a preferred social activity for reaching dietary intake goals). Parents receive skills training to learn how to set specific goals and give effective directions to young children. Goal setting can often be a challenging task for parents when it becomes important to avoid setting unclear or unobtainable goals. Effective goal setting begins by first understanding the behavior in specific, positive terms (e.g., to eat more vegetables at mealtimes versus eating less healthfully) and under what conditions the behavior is expected to occur (e.g., during mealtimes with family members). Next, the initial performance of the desired skill needs to be defined to set an attainable goal. Discrete, intermediate steps may be necessary to define if a child is far from producing the desired behavior. For instance, before a child regularly takes a bite of vegetables, it may first be necessary to begin with a goal of positively interacting with it, such as touching, smelling, or tasting (without actual consumption). Each of these interactions can be followed with positive consequences and mastered before transitioning to the next step of the desired behavioral goal. As this example

demonstrates, the process of goal setting often becomes a collection of smaller goals and a process that facilitates goal achievement more effectively than setting unrealistic goals from the beginning. Additionally, parents learn to implement differential reinforcement of alternative behaviors (i.e., combined use of praising positive behaviors and ignoring mild negative behaviors) and effective discipline for the management of more intensive negative behaviors (e.g., time out for behaviorally disruptive tantrums). Contingency management procedures are also taught to reward positive dietary and activity behavior changes and weight loss success each week. Rewards include verbal (i.e., immediate, descriptive praise) and tangible consequences (e.g., stickers). Inappropriate rewards include the use of food, which can place value on specific foods that can become difficult to manage, particularly when a child has unlimited access to the "reward" food. Child caregivers are encouraged to also participate in setting healthy eating and activity goals to model desired child behaviors.[49]

The effectiveness of FBT has been tested during multiple randomized controlled trials with significant reductions in child BMI associated with clinically significant reductions in child health problems related to weight.[49–52,59–62] The durability of these effects has also been demonstrated based on the five- and ten-year maintenance of treatment effects.[51] Criticisms of FBT access remain, however, given that FBT studies have generally focused on school-aged children, have not included low-socioeconomic status or minority families, have rarely been tested in clinical settings for effectiveness, and have not usually included children with greater severity in obesity.[49–51] More recent investigations have helped to address these FBT limitations, however, by using technology to help deliver FBT to lower-socioeconomic status (SES) families via primary care partnerships[63,64]

64.4.2 Motivational Interviewing

Additional approaches to behavior change not rooted in functional contextualism have been developed and evaluated for weight management, including motivational interviewing (MI). Briefly, the model for MI is based on patient-centered counseling designed to determine a patient's readiness to change, identify, and resolve any ambivalence for changing relevant health behaviors, and elicit self-motivational statements or change talk.[65] The efficacy of MI as a stand-alone approach to change lifestyle behaviors and reduce overweight and obesity among children and adolescents has been limited—although the American Academy of Pediatrics recommends it as a behavior change strategy[66, 67] In contrast to these studies showing limited outcomes, Resnicow et al. showed that a ten-session MI intervention delivered over a two-year period was most effective for reducing BMI percentile when compared with a less intensive MI intervention (four sessions) and usual care.[68] Additional evidence continues to accumulate in support of the use of MI as a treatment for lifestyle interventions, including those aimed at treating obesity.[69]

Given the strong foundation of empirical support for behavioral skills training (BST) within FBT, one alternative consideration may be using MI as a complementary approach to the standard prescribed approach. For instance, in a randomized clinical trial, 72 families all received traditional behavioral skills training for the first five weeks, followed by randomization for 15 sessions that compared the continued use of skills in traditional FBT to a self-directed treatment condition utilizing principles of MI. The results showed no group differences in child BMI z-score change from baseline to post-treatment and follow-up two years later[70] While MI may not be sufficient to change child and adolescent lifestyle behaviors and high weight status, this counseling method may be an alternative approach when combined with BST and implemented with moderate to high intensity (>25 contact hours).[20]

64.4.3 Skill versus Motivation Deficits

A challenge specific to pediatric lifestyle medicine is identifying whose behavior needs to change to accomplish the goals of prevention/intervention. In younger children, parents are primarily responsible for carrying out lifestyle recommendations, but as children age and eventually transition to adulthood they are expected to be increasingly responsible for these behaviors. Lifestyle interventions for obesity have been conducted with preschool, school-age, and adolescent youth with varying levels of child involvement. Results of parent-only and family-based interventions have been equivalent, with stronger effects observed with children relative to adolescents.[71]

The issue of whose behavior needs to change brings with it a consideration of the current abilities of the person of interest. Part of child development includes learning new skills, such as the ability to tell time and plan ahead, which may be needed to engage in lifestyle behaviors. When a disease is already presenting in youth, children may also need to learn new skills specific to the conditions they are helping to manage (e.g., self-monitoring). When these skills are deficient or absent from the child's repertoire, important lifestyle behaviors may not occur. Although easily overlooked, the same is true for parents or caregivers. Skill deficits in parenting skills (e.g., setting/enforcing expectations, using reinforcement for desired behaviors) or other relevant life skills (e.g., identifying/preparing nutritious food) will likely lead to failures in promoting healthful behaviors. As evidenced by the poor outcomes of education-only interventions,[72] correcting such skill deficits will often require more than simply telling the parent or child what to do differently. The use of BST within FBT has proven effective in addressing such skill deficits in lifestyle behaviors related to obesity.

However, the ability to engage in behavior is necessary but not sufficient for behavior change to occur. The lack of engagement in healthy lifestyle behaviors may be due

to motivational deficits. Motivational deficits occur when the outcomes for a behavior are not sufficiently valuable to reinforce that behavior. This can be when the costs (e.g., effort, resources needed) to engage in a behavior are too high relative to the value of the outcomes, when potentially reinforcing events are too delayed in time, or when other behaviors produce relatively more valuable outcomes and therefore displace the desired behavior. For example, although a teen may find sleep valuable, the outcomes for going to bed on time are delayed as staying up to engage with peers on social media at that time is both more valuable and immediately available, resulting in a motivation deficit for going to bed. Additionally, for parents, the behaviors of their children can serve as powerful outcomes for reinforcing behavior.[73] Parents may experience motivation deficits when attempting to enforce healthy lifestyle behavior for their child results in unpleasant outcomes (e.g., child tantrums when told to go to bed) or when engaging in unhealthy lifestyle behavior produces preferred outcomes (e.g., child accepts energy-dense foods and is therefore not going to starve). MI is aimed at increasing motivation for engaging in healthy and/or stopping unhealthy behaviors. This method, however, relies on verbal processes that may not be sufficiently robust to overcome the delays or costs of engaging in healthy lifestyle behaviors or compete with the long history of reinforcing outcomes parents or children have experienced for engaging in unhealthy lifestyle behaviors.

Although skill and motivation deficits have significant potential to influence the occurrence of lifestyle behaviors, research in this area remains significantly limited. The ability to quickly identify the events contributing to an individual's existing patterns of behavior has the potential to substantially improve the efficacy of behavior change programs. More extensive application of concepts and principles from operant behavior to pediatric lifestyle medicine is therefore warranted for research.

64.5 PREDICTORS OF DISEASE AND RESPONSE TO TREATMENT

Multiple difficult-to-change or non-modifiable characteristics have been linked with diseases that are affected by lifestyle behaviors. For instance, childhood obesity has been shown to have associations with race/ethnicity, genetics, and SES factors.[74] Disparities between race and ethnicity have not been fully explained by behavior differences and remain an understudied area of lifestyle research, particularly across developmental time periods.[75]

While this knowledge can be useful for clarifying contributing factors to disease prevalence, development, and response to treatment, it does not provide a direct target on which to intervene to change lifestyle behaviors. Approaches stemming from functional contextualism tend to focus on modifiable factors related to lifestyle behaviors to predict and influence disease, and therefore may more readily inform prevention and treatment strategies. Behavioral economics is one such approach that has received increased attention in recent years.

64.5.1 Behavioral Economics

In everyday life, the outcomes of one's behavior can be delayed and probabilistic, and a variety of behaviors are often concurrently available to produce alternative outcomes and the costs, in terms of the time, effort, or resources needed to obtain any of these outcomes, can vary widely. These variables have long been known to influence the value of outcomes and microeconomics has developed concepts and methods for describing their effects on the consumption of commodities. Behavioral economics integrates microeconomic concepts with the basic principles of operant psychology, allowing quantitative assessment of the interaction between environmental constraints and the value of commodities that may serve to reinforce the behavior of individuals. This approach expands the ability to describe the context in which behavior occurs, thereby establishing additional means to predict and influence behavior. Over the last several decades, the application of this approach to health-related behaviors and conditions has shown value in examining the possible contributions of these contextual factors to the development of disease, predicting response to treatment, and, in some cases, directly informing intervention.

A behavioral process that has been well-described by behavioral economic assessment is *delay discounting*. Delay discounting is the process by which a commodity loses subjective value due to the delay of its receipt. For example, $10 now is generally more valuable than $10 next week, which is more valuable than $10 next year. The rate at which delayed outcomes lose value is well-described by a hyperbolic equation[76] and, more importantly, it has shown robust associations with numerous lifestyle behaviors and health conditions, with higher rates of discounting (future outcomes lose value more quickly) associated with poorer health habits.[77] It is believed that this process influences decision-making involved in all choice behavior, with particular importance for lifestyle behaviors due to the often delayed nature of health consequences.[78] Additionally, although delay discounting changes across development,[79] it has shown trait-like qualities in its relative consistency over time for an individual.[80] In children, delay discounting has largely been examined with respect to current adiposity or predicting future weight gain. A meta-analysis of these data found a medium effect size ($d = 0.61$) for the relation between delay discounting and childhood obesity.[81] Furthermore, delay discounting has shown to be a significant predictor of drug use, such as smoking[80,82] which can negatively impact cardiovascular function and other health-related outcomes.

Despite the trait-like nature of delay discounting, recent research has demonstrated that this process can be modified, at least temporarily, through intervention.[83] Daniel et al. (2015) implemented a procedure known to improve

delay discounting and found that it resulted in reduced energy intake in children with overweight and obesity, suggesting the potential utility of targeting this behavioral process to facilitate improved lifestyle behavior.[83] However, this work is still preliminary, and more research is needed before treatment recommendations can be made[84,85]

As shown by delay discounting, understanding how people value commodities may improve efforts to predict disease risk and response to treatment, and potentially inform lifestyle intervention. Other behavioral economic assessments have also examined the value of commodities relevant to lifestyle medicine. A common method is to make a commodity (e.g., food) available at a range of costs, such as monetary price or amount of effort (completing a specified task) and examining how consumption of the commodity changes as its cost increases. When the value of a commodity is examined in isolation, it is referred to as a demand curve analysis (after the microeconomic concept of supply and demand).[86] If another commodity with a fixed cost is concurrently available, it is referred to as an assessment of relative reinforcing value.[87] Similar to delay discounting, these assessments with children and teens have been primarily examined with respect to lifestyle behaviors related to obesity and drug use. Results suggest an association between the value of food and food intake,[88] current weight,[89,90] and prospective weight gain in children.[91,92] Although the value of food, drugs, and other commodities can be modified in numerous ways, information from behavioral economic assessments of commodity value has not been directly integrated into treatments to date.

Recently, researchers have posited that the two approaches for examining value—delay discounting and demand—are related and, when examined in conjunction, provide better prediction of disease,[93,94] as well as response to treatment.[95] Preliminary research suggests that delay discounting moderates the effects of reinforcer value,[96] such that when the value of a commodity (e.g., food) is high and future outcomes lose value quickly, behavioral disorders and maladaptive lifestyle behaviors are likely to occur. Although the majority of evidence for this effect has been obtained with adults, initial results suggest that the way children value commodities is related to lifestyle behavior and disease.[95] This approach has great potential to inform more personalized intervention for patients by identifying critical behavioral processes involved in the development and persistence of lifestyle behaviors.

64.6 SUMMARY

The development or modification of lifestyle behaviors for health and wellness during childhood provides an opportunity to sustain positive health for a lifetime. The importance of promoting healthy lifestyle behaviors early in life has become clear; though the mechanisms necessary to develop such behaviors most effectively are not fully understood, in part, because the causal nature of diseases largely impacted by lifestyle behaviors is multifactorial and often dynamic over the course of development.

Despite such challenges, interventions reviewed in this chapter and those particularly based on functional contextualism have shown significant promise in modifying lifestyle behaviors (diet, physical activity, sleep) from infancy to adolescence and young adulthood. The challenge of changing lifestyle behaviors during preventive or treatment-based healthcare is the often delayed positive health outcomes and sometimes immediate negative consequences that can undermine adherence to such interventions over time. The identification of more immediately available reinforcement to improve adherence may help address this longstanding challenge of modifying lifestyle behaviors. The principles of learning elucidated here may provide the support necessary to healthcare professionals in pediatric medicine who often struggle to change their patients' lifestyle behaviors. While considerable challenges remain in translating behavioral science into lifestyle medicine, the promise for improved pediatric health sustained into adulthood is encouraging.

CLINICAL APPLICATIONS

- Education alone is not likely to be sufficient to change behavior. When possible, have patients and families demonstrate new skills and set goals around practicing them.
- Reinforcement is fundamental to behavior change. Effective reinforcement immediately and consistently follows the target behavior over extended periods of time. Work with families to identify ways to reinforce desired behaviors of children and caregivers.
- Self-monitoring lifestyle behaviors, including context, behaviors, and consequences provides key information for goal setting and contingency management to promote behavior change.
- Referral to behavioral practitioners can facilitate the delivery of intensive family-based lifestyle interventions. Consider opportunities for establishing collaborative relationships with behavioral practitioners.

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65 Cardiovascular Risk and Physical Activity in Children

Peter T. Katzmarzyk, PhD

KEY POINTS

- Physical activity levels decrease throughout childhood and adolescence, and boys have consistently higher levels of moderate-to-vigorous intensity physical activity than girls.
- Higher levels of physical activity are associated with lower levels of cardiovascular disease risk factors during childhood and adolescence.
- Childhood physical activity may be related to subclinical measures of cardiovascular disease in childhood and into adulthood.
- Children should be encouraged to meet current physical activity guidelines that call for at least 60 minutes of moderate-to-vigorous physical activity on a daily basis.

65.1 INTRODUCTION

Among adults, a physically active lifestyle is associated with a large number of health outcomes, including a lower risk of cardiovascular disease (CVD) and premature mortality.[1] Physical activity in childhood is also associated with several health benefits, including psycho-social, cardiometabolic, musculoskeletal, and cognitive outcomes.[2,3] While the health benefits of physical activity have been widely publicized, recent data indicate that 81% of adolescents globally are not sufficiently active.[4]

CVD remains a leading cause of morbidity and death in the United States and globally.[5] While children do not typically experience clinical events associated with "adult" CVD such as coronary heart disease and stroke, some children develop elevated levels of CVD risk factors and biomarkers such as blood glucose, blood lipids, and blood pressure. Some children may also begin to show subclinical signs of atherosclerotic disease. This chapter explores the association between physical activity and CVD risk in children.

65.2 DEFINITIONS AND KEY CONCEPTS

Physical activity refers to any bodily movement produced by skeletal muscles that results in energy expenditure.[6] In childhood, physical activity occurs in a variety of contexts, including the home environment, educational settings (early childhood education centers, schools, etc.), and outdoor settings, and may take the form of unstructured play activities, active transportation, structured exercise, or organized sports participation. *Aerobic activities* include forms of activity that typically use large muscle groups and are intense enough and performed long enough to maintain or improve an individual's cardiorespiratory fitness.[1] Aerobic activities include such things as walking, running, basketball, soccer, or dancing. *Muscle-strengthening activities* maintain or improve muscular strength, endurance, or power, and include behaviors such as carrying heavy items, shoveling snow, and climbing stairs, as well as the use of weight machines or free weights.[1] *Bone-strengthening activities* are those that create impact and muscle-loading forces on bone which modifies structure (shape) or mass (mineral content).[1] Bone-strengthening activities include jumping, hopping, skipping, and dancing.

Physical activity behavior is usually quantified in terms of frequency, duration, and intensity. *Frequency* refers to the number of sessions or bouts of physical activity and is usually expressed in times per week, or a similar metric. *Duration* is simply the length of time for each bout of physical activity. *Intensity* refers to the rate of energy expenditure while performing a given physical activity and is commonly reported in METs (metabolic equivalents of task), which is expressed in multiples of resting energy expenditure.[1] Physical activities are generally categorized as light (1.6 to less than 3.0 METs), moderate (3.0 to less than 6.0 METs), or vigorous (6.0 METs or greater).

The current US physical activity guidelines recommend that school-aged children and youth should accumulate 60 minutes or more of moderate-to-vigorous intensity physical activity (MVPA) each day. In addition to aerobic activity, this physical activity should include muscle-strengthening activities on at least three days each week and bone-strengthening activities on at least three days each week.[7]

Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture.[8] Sedentary behavior occurs at the opposite end of the energy expenditure spectrum as moderate-to-vigorous physical activity, and the postural component of the definition (i.e., sitting, reclining, or lying) identifies it as a potential behavioral target for interventions that are separate from physical activity *per se*.[9]

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Physical fitness is a concept that is related to physical activity. While physical activity is a behavior, physical fitness is defined as an attained set of characteristics that relates to the ability to perform physical activity and is determined by a variety of factors, including an individual's level of habitual physical activity, heredity, and diet.[10]

Mean levels of physical activity differ across age groups, and individuals may increase or decrease their physical activity at different times and rates over the life course. A related concept is *tracking*, which refers to the maintenance of a relative rank or position over time.[11,12] Tracking is often estimated using inter-age correlations (Pearson or Spearman rank-order) between observation values measured at two or more time points in the life course.

Figure 65.1 presents a model showing the association between childhood physical activity and CVD risk. There are several pathways through which childhood physical activity can potentially impact CVD risk through the life course. For example, higher physical activity in childhood can be associated with lower levels of CVD risk factors during childhood and with improved markers of subclinical CVD in childhood and adolescence. In turn, this may reduce the risk of CVD events in adulthood. Higher levels of physical activity in childhood may be related to higher levels of physical activity being maintained into adulthood, which in turn has benefits related to reduced CVD. Finally, there may be a direct pathway whereby physical activity accumulated during childhood may have a long-term, direct effect on the risk of CVD in adulthood.

65.3 PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR DURING CHILDHOOD AND ADOLESCENCE

Levels of physical activity and sedentary behavior tend to change over the life course. In general, declines in physical activity are observed throughout childhood and adolescence.[13] Figure 65.2 presents estimates of daily MVPA obtained using waist-worn accelerometers in a nationally representative sample of US children and adolescents. It is clear that physical activity levels decrease throughout childhood and adolescence, and that boys have consistently higher levels of MVPA than girls.[14] While these results were derived from cross-sectional data, an analysis of accelerometer data from 1800 participants in the longitudinal European Youth Heart Study confirmed the overall patterns, where MVPA decreased by approximately 30 minutes per day, and sedentary increased by about 2.45 hours per day between childhood and adolescence.[15] These device-based results confirm those from studies that have relied on questionnaire data to estimate levels of physical activity. For example, recent data from the 2019 Youth Risk Factor Surveillance System (YRBSS) show that the prevalence of high-school students who are active at least 60 minutes each day of the week was 27.2%, 22.9%, 22.3, and 20% in the 9th, 10th, 11th and 12th grades, and the prevalence was higher in boys (30.9%) than in girls (15.4%).[16]

Population-level race and ethnic differences in childhood physical activity are difficult to determine.[17] Based on self-reported data, the 2019 YRBSS indicates that the prevalence of high-school students who are active at least 60 minutes each day of the week was 25.6% in White students, 20.9% in Black students, and 15.3% in Asian students.[16] However, when relying on accelerometer data from NHANES 2003–2006, Black youth have the highest levels of MVPA (60 min/day), followed by Mexican American (58 min/day), and White youth (52 min/day).[18] The reasons for the differences in trends based on self-reported versus accelerometer data are not well understood, but could potentially be explained by cultural differences in reporting, and the different contexts in which physical activity is performed in different race/ethnic groups.

As described earlier, sedentary behavior refers to activities of low energy expenditure performed while in a sitting, reclining, or lying posture. In practice, this definition is difficult to operationalize in population-based surveillance studies given that it has both energy expenditure and postural components. When accelerometer data are available, the sedentary time has been defined using cut-points that denote low levels of movement, for example, <100 counts per minute.[19] Alternatively, sedentary behavior is often assessed using questions related to screen time or specific sedentary behaviors such as TV viewing or computer use.[20] Based on data from the NHANES 2003–2006, the amount of time

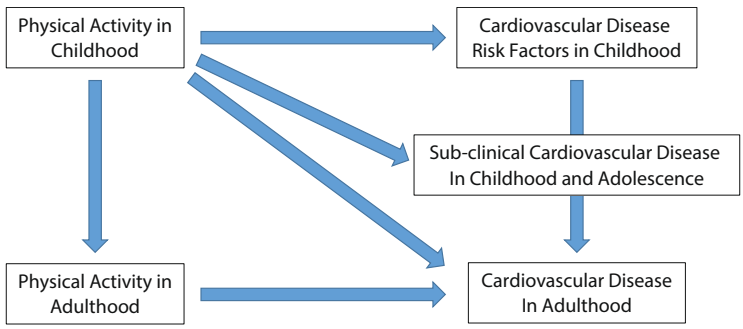


FIGURE 65.1 Association between childhood physical activity, adulthood physical activity, and cardiovascular disease (adapted from Hallal et al., 2006).[63]

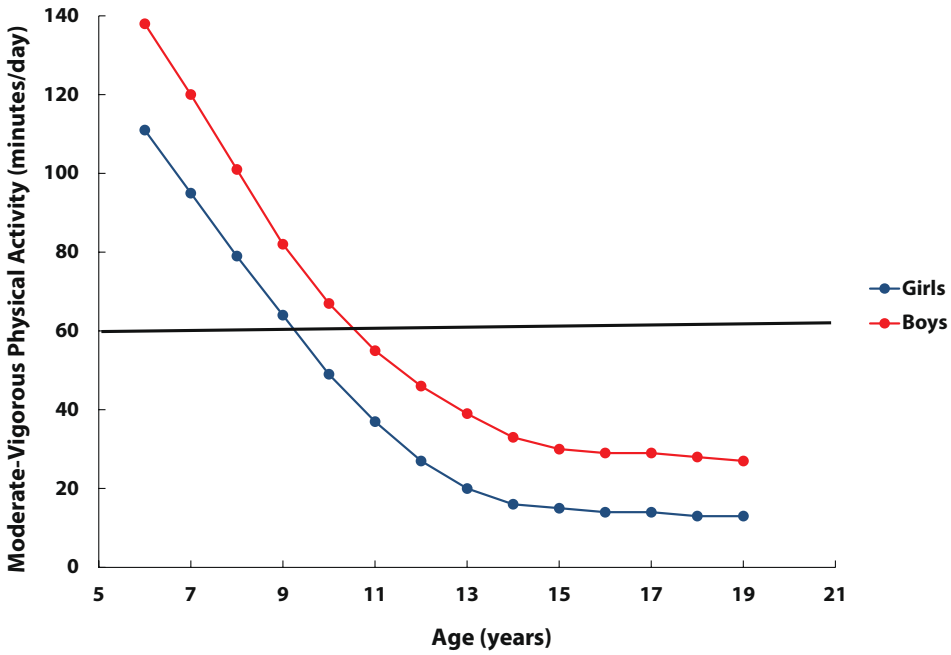


FIGURE 65.2 Levels of moderate-to-vigorous physical activity during childhood and adolescence. The markers represent age- and sex-specific 50th percentile values for accelerometer data in the US National Health and Nutrition Examination Survey, 2003–2006.[14] The solid line represents the physical activity recommendation of 60 minutes per day.

spent sedentary (<100 counts/min) increased from six hours to 7.5 hours to eight hours per day in children 6–11, 12–15, and 16–19 years of age.[19] Furthermore, 19.8% of high school students spend three or more hours per day watching television, while 46% spend three or more hours per day playing video or computer games or using a computer.[16]

65.4 PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR, AND CARDIOVASCULAR RISK DURING CHILDHOOD

The 2018 US Physical Activity Guidelines Advisory Committee conducted a comprehensive review of the association between childhood physical activity and health outcomes. They concluded that there was a moderate level of scientific evidence that physical activity is positively associated with cardiometabolic health in children and adolescents in general, but that the evidence was strong for plasma triglycerides and insulin.[1] On the other hand, there was only limited evidence that sedentary behavior is related to cardiometabolic risk factors; the evidence was somewhat stronger for television viewing or screen time than for total sedentary time.[1] In this section we will explore the association between physical activity, sedentary behavior, and CVD risk factors from evidence derived from observational and intervention studies.

65.4.1 Evidence from Observational Studies

Observational studies are those where the investigator does not intervene or provide an intervention for the participants.[21] Observational studies can be cross-sectional (i.e., conducted at a single point in time) or longitudinal (i.e., follow a cohort of participants over time). Longitudinal cohort designs are important to establish temporal associations between predictors and outcomes, which can inform the cause-and-effect nature of the association.

Many observational studies have examined the association between physical activity and CVD risk factors in children. For example, Andersen and colleagues conducted a cross-sectional study of 1732 randomly selected nine- and 15-year-old children who participated in the European Youth Heart Study.[22] The odds ratios for having a high composite risk factor score (>1 SD; comprised of systolic blood pressure, triglycerides, total cholesterol/HDL ratio, insulin resistance, sum skinfolds, and aerobic fitness) decreased across successively higher quintiles of physical activity (Figure 65.3).

A cross-sectional analysis of the association between physical activity and a composite CVD risk factor score was also conducted among 3019 children aged two to nine years who participated in the eight-country IDEFICS (Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants) study.[23] The odds of having a high composite risk factor score (>1 SD) were higher among those with low levels of physical activity, and the association was particularly pronounced among the older (>6 years of age) children.[23]

Ekelund and colleagues conducted a cross-sectional analysis of the combined associations of MVPA, sedentary time, and cardiometabolic risk factors in a pooled analysis of data from 14 studies comprising 20,871 children (aged 4–18

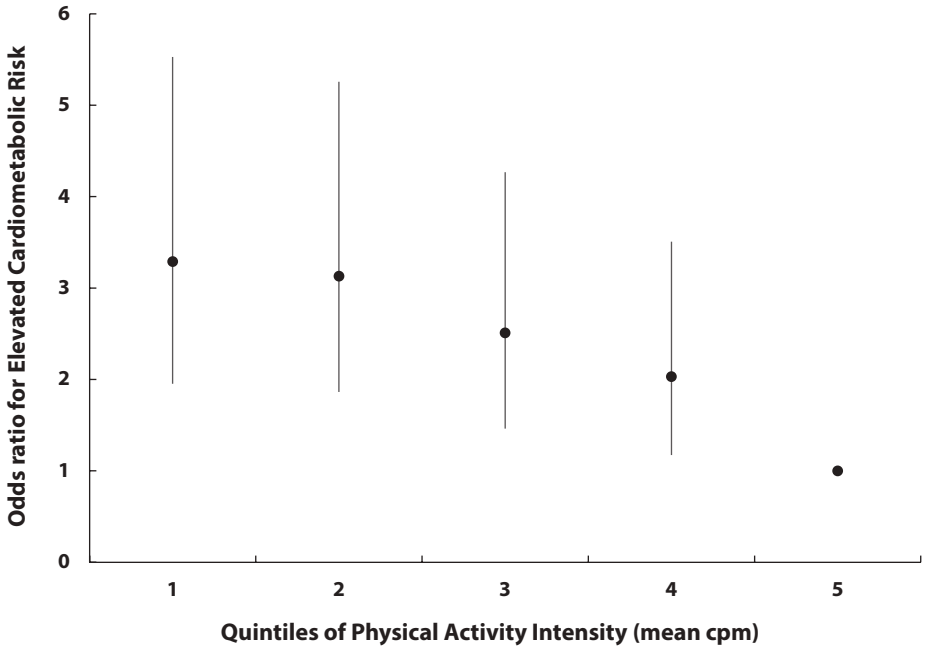


FIGURE 65.3 Odds ratios for elevated cardiometabolic risk by quintiles of physical activity intensity among 1732 nine- and 15-year-old children participating in the European Youth Heart Study.[22] Error bars represent 95% confidence intervals; cpm, counts per minute.

years) from the International Children's Accelerometry Database.[24] Higher levels of MVPA were associated with lower levels of waist circumference, systolic blood pressure, fasting insulin, and fasting triglycerides, and higher levels of HDL-cholesterol, and these associations were independent of sedentary time. On the other hand, sedentary time was not associated with any outcome independent of MVPA.[24]

In addition to studies that show associations between cardiometabolic risk factors and overall levels of physical activity in children, some studies have begun to show associations with "patterns" of activity using different statistical methods.[25,26] For example, latent class analysis of accelerometer data from youth participating in NHANES showed that those in the class with the highest average counts/minute had significantly lower systolic blood pressure, glucose, and insulin compared with youth in the class with the lowest average counts/minute.[25] Compositional data analysis has also been applied to understand the associations between different intensities of physical activity and cardiometabolic risk factors in youth participating in NHANES.[27] The results demonstrated that the composition of sedentary time, light-intensity physical activity, moderate-intensity physical activity, and vigorous-intensity physical activity was significantly associated with BMI z-score, waist circumference, systolic and diastolic blood pressures, HDL-cholesterol, and plasma glucose.[27]

As described above, the total volume of physical activity, especially MVPA, is negatively associated with CVD risk in childhood and adolescence. There is increasing interest in the role of physical activity performed at different intensities (light, moderate, vigorous) in explaining CVD risk. A growing body of literature suggests that vigorous-intensity physical activity may be an important determinant of cardiometabolic risk in children.[28] Hay and colleagues examined associations between physical activity intensities and cardiometabolic risk factors in 9–17-year-old children.[29] No significant differences in cardiometabolic risk factors were seen across tertiles of moderate- or light-intensity physical activity, but BMI z-score, waist circumference, and systolic blood pressure decreased and cardiorespiratory fitness increased across tertiles of vigorous-intensity PA.[29] Moore and colleagues examined associations between vigorous-intensity physical activity and cardiometabolic risk factors using data from the International Children's Accelerometry Database.[30] Their results indicated that substituting light-intensity physical activity with vigorous-intensity activity (adjusting for sedentary time and moderate-intensity physical activity) was inversely associated with waist circumference and insulin levels, while associations with other biomarkers were inconsistent.[30]

A recent systematic review summarized the evidence for associations between device-measured (i.e., pedometers/accelerometers) MVPA, sedentary behavior, and cardiometabolic risk factors in youth from prospective cohort studies.[31] Based on a meta-analysis of three prospective cohort studies, the authors concluded that there was a significant association between MVPA and clustered cardiometabolic risk; however, the associations between MVPA and individual risk factors were inconsistent.[31] No association was observed between sedentary behavior and cardiometabolic outcomes.

Atherosclerosis is a progressive condition that begins in early childhood. An autopsy study of children and young

adults who died of various causes showed that the prevalence of fatty streaks in the coronary arteries increased from about 50% in 2–15-year-olds to 85% in 21–39-year-olds.[32] Furthermore, the prevalence of raised fibrous-plaque lesions in the coronary arteries increased from 8% in 2–15-year-olds to 69% in 26–39-year-olds.[32] These findings are supported by data from autopsied American soldiers in the Korean War, where 77% of the soldiers had evidence of coronary atherosclerosis (mean age of 22 years).[33]

As described previously, physical activity is inversely associated with CVD risk factors in children and youth. There is also some evidence that physical activity is associated with better subclinical measures of CVD in children and youth. For example, sports participation was associated with thinner carotid intima-media thickness (cIMT) among five-year-old children.[34] Physical activity was also inversely associated with arterial stiffness in a sample of ten-year-old children.[35] In a sample of 6–8-year-old children, accelerometer-determined moderate-intensity activity, vigorous-intensity activity, and cumulative time spent in physical activity above 3, 4, 5, 6, and 7 METs were inversely associated with arterial stiffness.[36] The association between changes in physical activity and changes in arterial health (Stiffness Index) was examined in a sample of 90 six- to nine-year-old children who were followed for two years.[37] The results indicated that two-year changes in moderate-intensity, vigorous-intensity, and MVPA were inversely associated with two-year changes in the Stiffness Index.[37] On the other hand, a prospective analysis of physical activity and markers of subclinical CVD among children eight to ten years of age from the European Youth Heart Study followed for six years revealed that vigorous physical activity was associated with a cardiometabolic risk score, but not with carotid arterial stiffness.[38] Taken together, there is some emerging evidence that physical activity may be related to subclinical CVD in children and youth; however, further studies using prospective research designs are required to confirm the strength of the associations.

In summary, there is convincing evidence that physical activity is inversely associated with CVD risk factors in children and youth. There is less evidence for the detrimental effects of sedentary behavior in general, but screen time appears to be more strongly related to risk factors. In general, there is emerging evidence that physical inactivity is associated with measures of subclinical CVD in children, but more work is required to clarify those associations.

65.4.2 Evidence from Intervention Studies

Intervention studies are those in which participants receive an experimental manipulation of some sort and are typically assigned to either an intervention or a control group. While some clinical trials do not randomize the participants to study groups, the strongest design is the randomized controlled trial (RCT) in which participants are randomly allocated to the study groups. The use of randomization is an important strategy to mitigate against the results being the result of some form of bias.[39]

Trials on the effects of exercise on CVD risk factors have a long history in the field of pediatric exercise science. Table 65.1 presents a summary of meta-analyses that have described the effects of exercise interventions on CVD risk factors in children and youth.[40–46] These reviews formed part of the evidence base for the *Physical Activity Guidelines for Americans, Second Edition*.[1] This evidence led the Committee to conclude that there was "moderate" evidence that physical activity is positively associated with cardiometabolic health in children and adolescents in general, and the evidence was "strong" for plasma triglycerides and insulin. There are a number of factors that are considered when defining the levels of evidence, including applicability, generalizability, risk of bias, quantity and consistency of results, and magnitude and precision of effect.[1] In general, the assignment of "strong" evidence indicates that many studies have been published and the results are highly consistent in direction and approximate size of effect, while a grade of "moderate" indicates that a moderate number of studies have been published with some inconsistency in direction or size of effect.

In general, children have healthier levels of CVD risk factors than adults. Therefore, it is often harder to detect the effects of therapeutic interventions such as physical activity in pediatric populations. It is often easier to detect the effects of interventions among "high-risk" children and youth (i.e., with obesity, high blood pressure); however, much of the evidence base comes from trials that enrolled children with one risk factor (for example, obesity), while examining the effects of the intervention on several risk factors, which will typically dilute the effects that are observed. Future studies should be designed to study specific risk reductions in pediatric populations with elevations in specific CVD risk factors of interest.

65.5 PHYSICAL ACTIVITY IN CHILDHOOD AND CARDIOVASCULAR DISEASE RISK IN ADULTHOOD

The study of associations between childhood physical activity and CVD risk in adulthood requires long-term, prospective studies. Luckily, several such studies exist. The Cardiovascular Risk in Young Finns Study is a large population-based longitudinal study conducted in Finland, beginning with children aged 3–18 years of age in 1980.[47] This study has made several important contributions to our understanding of the epidemiology of physical activity and CVD risk over the life course. The Amsterdam Growth and Health Longitudinal Study was initiated in 1977 with approximately 600 boys and girls with a mean age of 13.1 years.[48] The initial purpose of the study was to describe the natural development of growth, health, and lifestyle of adolescents.[48] The participants have now been followed into adulthood, and many important observations have been made regarding the adolescent antecedents of adult disease.

TABLE 65.1

Summary of Meta-analyses Studying the Effects of Physical Activity on Cardiovascular Disease Risk Factors in Children and Youth from Clinical Trials

Authors	CVD Risk Factors	Number of Effects*	Results
Janssen and LeBlanc[40]	*Aerobic exercise*:	3	NS; NR
	Total cholesterol	5	ES = 0.26 (95% CI: 0.03, 0.49)
	HDL-cholesterol	4	NS; NR
	LDL-cholesterol Triglycerides	4	ES = −3.03 (95% CI: −3.22, −2.84)
	Systolic blood pressure	5	ES = −1.39 (95% CI: −2.53, −0.24)
	Diastolic blood pressure	5	ES = −0.39 (95% CI: −1.72, 0.93)
	Fasting insulin	4	ES = −0.60 (95% CI: −1.71, 0.50)
	Non-aerobic exercise:	4	ES = −0.61 (95% CI: −2.27, 1.05)
	Systolic blood pressure	4	ES = −0.51 (95% CI: −2.18, 1.06)
	Diastolic blood pressure	4	ES = −0.31 (95% CI: −0.82, 0.19)
	Insulin		
Clark[41]	Total cholesterol	NR	ES = −0.19 (95% CI: −0.60, 0.22)
	HDL-cholesterol	NR	ES = −0.16 (95% CI: −0.54, 0.22)
	LDL-cholesterol	NR	ES = −0.18 (95% CI: −0.58, 0.21)
	Triglycerides	NR	ES = −1.04 (95% CI: −1.45, −0.64)
	Insulin	NR	ES = −1.97 (95% CI: −2.47, −1.47)
Escalante et al.[42]**	*Aerobic exercise*:	2	NS/NR
	Total cholesterol	5	NS/NR
	HDL-cholesterol	4	ES = −0.49 (95% CI: −0.76, −0.21)
	LDL-cholesterol	4	ES = −0.55 (95% CI: −0.83, −0.27)
	Triglycerides	2	NS/NR
	Combined exercise:	3	ES = 0.50 (95% CI: 0.11, 0.88)
	Total cholesterol	2	NS/NR
	HDL-cholesterol	3	NS/NR
	LDL-cholesterol Triglycerides		
Garcia-Hermoso et al.[43]**	Systolic blood pressure	9	ES = −0.40 (95% CI: −0.66, −0.24)
	Diastolic blood pressure	7	ES = −0.28 (95% CI: −0.55, 0.00)
Fedewa et al.[44]	Fasting insulin	32	ES = −0.48 (95% CI: −0.22, −0.74)
	Insulin resistance	15	ES = −0.31 (95% CI: −0.06, −0.56)
Kelley and Kelley[45]	Total cholesterol	12	−0.6 (95% CI: −4.4, 3.3) mg/dl
	HDL-cholesterol	12	−1.4 (95% CI: −4.8, 1.9) mg/dl
	LDL-cholesterol Triglycerides	9	1.2 (95% CI: −4.3, 6.7) mg/dl
		11	−11.0 (95% CI: −22.8, 0.8) mg/dl
Kelley and Kelley[46]	Non-HDL-cholesterol	13	−0.7 (95% CI: −5.4, 5.0) mg/dl

ES, effect size; CI, confidence interval.

*The number of effects reported varied from the number of studies.

**Eligibility criteria included children with obesity only.

The European Youth Heart Study is an international longitudinal study that addresses the biological, environmental, demographic, and lifestyle correlates of CVD risk factors in children and adolescents. The European Youth Heart Study was initiated as a cross-sectional study of nine- and 15-year-old adolescents in 1997 in several countries;[49] in the intervening years, there have been different follow-up assessments conducted, depending on the participating countries that have contributed data on associations between adolescent characteristics and future health outcomes.

A recent analysis of 31-year follow-up data from the Cardiovascular Risk in Young Finns Study cohort revealed that compared with those who were physically inactive between childhood and adulthood, individuals who were persistently physically active had a significantly lower risk of adult clustered cardiometabolic risk (metabolic syndrome), obesity, high waist circumference, high triglycerides high insulin, high glucose, and low high-density lipoprotein cholesterol (Figure 65.4).[50] Furthermore, physical activity in adolescents (9–15 years of age) and young adults (18–24 years of age) at baseline (1986) was negatively associated with carotid artery elasticity measured 21 years later.[51] Another recent analysis of 27-year follow-up data revealed that childhood physical activity was negatively related to adulthood systemic vascular resistance and cardiac index, and the association remained significant after adjustment for several covariates and corresponding adult data.[52] Taken together, data from the Cardiovascular Risk in Young Finns Study provide convincing evidence of the

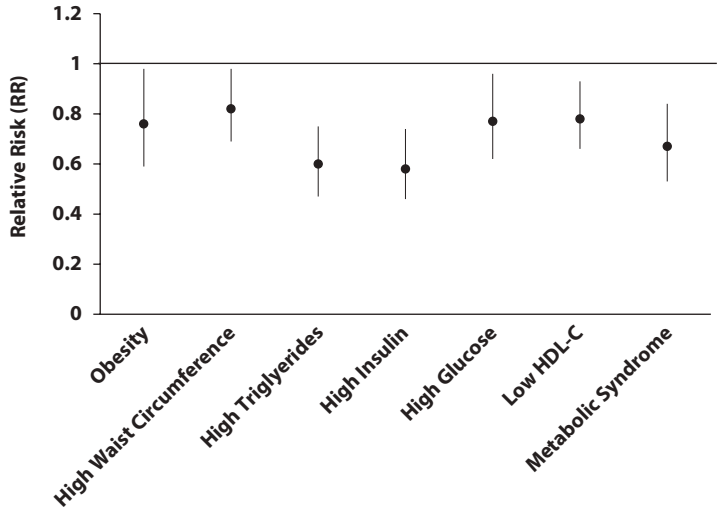


FIGURE 65.4 Relative risks of several cardiovascular disease risk factors and metabolic syndrome in adulthood comparing individuals who were persistently active from childhood to adulthood to individuals who were persistently inactive. Error bars represent 95% confidence intervals. Results are from the Cardiovascular Risk in Young Finns Study.[50]

importance of childhood physical activity in the prevention of CVD risk in adulthood.

Data from the Amsterdam Growth and Health Longitudinal Study corroborate the findings from the Cardiovascular Risk in Young Finns Study.[53] A sample of 373 participants were followed from 13 to 36 years of age, and the results demonstrated that vigorous physical activity throughout the follow-up period was associated with lower arterial stiffness.[53] An analysis of Danish adolescents approximately 15 years of age participating in the European Youth Heart Study followed for up to 12 years revealed that mean exposure to MVPA during the follow-up period was independently associated with lower levels of carotid artery stiffness in adulthood.[38] Furthermore, participants with the largest decline in MVPA between adolescence and adulthood had significantly less compliant arteries compared with the remaining sample.[38]

In summary, the available evidence from a limited number of prospective cohort studies demonstrates a significant association between levels of physical activity in childhood and adulthood CVD risk, assessed by cardiometabolic risk factors and subclinical measures such as vascular resistance and carotid artery stiffness.

65.6 TRACKING OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR FROM CHILDHOOD TO ADULTHOOD

Given that both physical inactivity and sedentary behavior are related to CVD incidence and mortality in adults,[54,55] one pathway whereby childhood physical activity and sedentary behavior may impact this risk is through the tracking, or stability, of these behaviors over time. In order to assess tracking, data from at least two points are required, which necessitates a longitudinal study design where the same individuals are followed over time.

In general, the tracking of physical activity is highest over short periods of time and decreases the further apart the two measurements are obtained.[11] Based on the available evidence, tracking appears to be lower in early childhood than in adolescence or adulthood, and lower in transitional periods of the lifespan, such as the transition between childhood and adolescence or from adolescence to young adulthood.[12]

A recent study was conducted using a large, unique dataset from the Netherlands Twin Registry (n = 43,889).[56] The results demonstrated moderate-to-high tracking over two years (median r = 0.57), whereas stability decreased over time, with a median of 0.38 for 22-year tracking. The long-term tracking from childhood into adulthood was modest, but shorter-term tracking across the lifespan was moderately to highly stable.[56]

The moderate tracking for physical activity observed in many studies suggests that behavioral patterns established in childhood may carry over into adulthood to a limited extent; however, the explained variance remains low, which suggests that there are opportunities for intervention and the potential to change an individual's physical activity trajectory.

65.7 TRACKING OF CARDIOVASCULAR DISEASE RISK FACTORS FROM CHILDHOOD TO ADULTHOOD

The stability of CVD risk factors between childhood and adulthood is an important consideration in the primordial prevention of CVD. In general, there is generally good stability of CVD risk factor clustering between childhood and adulthood, with inter-age correlations of risk factor cluster scores ranging from ~0.4 to 0.7.[57] For example, there was moderate stability in the Quebec Family Study between childhood and adulthood (12 years of follow-up)

for indicators of metabolic syndrome, as well as a composite metabolic syndrome score (r = 0.51 and 0.46 in males and females, respectively).[58] Results from long-term follow-up of participants (16 years) in the Bogalusa Heart Study showed that cardiometabolic risk factors coexist in terms not only of their levels in childhood and adulthood but also of long-term rates of change.[59]

Obesity is an important risk factor for the development of future CVD. Measures of adiposity, including BMI, show relatively strong tracking between childhood and adulthood. Indeed, the odds of having obesity in young adulthood based on having obesity as a child range from 1.3 at one to two years of age to 17.5 at ages 15–17 years.[60] A recent systematic review revealed that childhood obesity is significantly and positively associated with adult blood pressure and triglycerides and negatively associated with HDL-cholesterol.[61] Further, having obesity in addition to multiple CVD risk factors during adolescence is associated with an almost 15-fold increased risk of developing CVD before the age of 50 years.[62]

The results from tracking studies suggest that the maintenance of healthy risk factor levels during childhood will predispose individuals to have better risk factor profiles as adults. However, changes in dietary and physical activity patterns between childhood and adulthood may counteract these effects to some extent.

65.8 CONCLUSIONS

This chapter has explored the topic of CVD risk and physical activity in children. As described in the model presented in Figure 65.1, there are several pathways through which physical activity can influence CVD risk during childhood as well as into adulthood. There is good scientific evidence that physical activity is related to CVD risk factors during childhood and that physical activity may be related to subclinical measures of CVD in childhood and adulthood. The evidence for sedentary behavior is weaker, however, many studies have documented associations between higher levels of screen time and poorer CVD risk factors in children. Further longitudinal studies are needed to clarify these relationships. In general, children and youth should be encouraged to avoid extended periods of sedentary behavior and strive to meet the physical activity guidelines, which call for at least 60 minutes of MVPA daily.

CLINICAL APPLICATIONS

Age Range	Physical Activity Guidelines
3–5 years	• Preschool-aged children (ages three through five years) should be physically active throughout the day to enhance growth and development. • Adult caregivers of preschool-aged children should encourage active play that includes a variety of activity types.
6–18 years	• It is important to provide young people with opportunities and encouragement to participate in physical activities that are appropriate for their age, are enjoyable, and offer variety. • Children and adolescents ages six through 17 years should do 60 minutes (one hour) or more of moderate-to-vigorous physical activity daily: • Aerobic: Most of the 60 minutes or more per day should be either moderate- or vigorous-intensity aerobic physical activity and should include vigorous-intensity physical activity on at least three days a week. • Muscle-strengthening: As part of their 60 minutes or more of daily physical activity, children and adolescents should include muscle-strengthening physical activity on at least three days a week. • Bone-strengthening: As part of their 60 minutes or more of daily physical activity, children and adolescents should include bone-strengthening physical activity on at least three days a week.

From US Department of Health and Human Services (2018). *Physical Activity Guidelines for Americans, Second Edition*.[7]

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66 Cardiovascular Risk and Diet in Children

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66.1 INTRODUCTION

Compelling evidence shows that the atherosclerotic process begins in early childhood and progresses slowly into adulthood.[1–5] Later in life, this often leads to coronary heart disease, the leading cause of death in the United States.[6] Several risk factors are important for the development of cardiovascular disease (CVD), including family history of CVD, obesity, elevated blood pressure, dyslipidemia, diabetes, and cigarette smoking. Diets high in saturated and trans fats, excessive energy intake, and physical inactivity are lifestyle-related behaviors that can increase the risk of CVD.[7, 8]

Childhood obesity remains a major public health crisis, both nationally and internationally, placing many youths at greater risk for serious health problems. What have previously been considered adult metabolic disorders related to obesity, such as hypertension, dyslipidemias, type 2 diabetes, metabolic syndrome, and non-alcoholic fatty liver disease, are now increasingly prevalent among children.[9–11] This continues to make prevention and treatment of childhood overweight and obesity an important public health focus.

Based on data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014, approximately one in five youths had high total cholesterol, low high-density lipoprotein cholesterol (HDL-C), or high non-HDL- C.[12] Youth with obesity had a greater prevalence of high total cholesterol, low HDL-C, and high non-HDL-C than their normal weight counterparts. Additionally, more than one in ten children and adolescents had borderline high or high blood pressure.[13]

While genetics can play a role in the development of disorders of lipid metabolism and blood pressure regulation in children, these CVD risk factors are largely influenced by lifestyle-related factors, primarily overnutrition, poor diet quality, and inadequate physical activity. In this chapter, we discuss the consequences of suboptimal diet quality regarding CVD risk factors and approaches to achieving optimum nutrition in children and adolescents.

66.2 OBESITY

Childhood and adolescent overweight and obesity in the United States remain major health problems. It is estimated that approximately 19.3% (or 14.4 million) of US children between the ages of 2 and 19 years meet the criteria for obesity, with 6.1% having severe obesity, and another 16.1% meeting the criteria for overweight.[7] Non-Hispanic black and Hispanic children have higher prevalence rates (24.2% and 25.6%, respectively) than non-Hispanic white (16.1%) and non-Hispanic Asian children (8.7%)[7]. Lower-income children and adolescents are more prone to obesity than their higher-income counterparts, but the relationship is not consistent across race and ethnicity groups.[14] There is an increased risk of obesity for children if one or both of their parents have obesity.[15] Additionally, children with obesity are more likely to carry obesity into adulthood.[16]

Overweight and obesity in childhood are strongly associated with increased cardiovascular mortality in adulthood.[17–19] Pediatric obesity is associated with an increased risk of a broad range of health problems including hypertension,[20, 21] elevated serum lipid levels,[22] low HDL-C,[12] elevated hepatic enzyme levels or fatty liver disease,[23] type 2 diabetes,[24] respiratory problems including sleep apnea and asthma,[25, 26] and joint and musculoskeletal problems.[25,27]

Weight status in children is defined using body mass index (BMI), an anthropometric measurement of weight in relation to height, calculated by taking body weight in kilograms (kg), divided by the square of the height in meters. Percentile distributions relative to age and sex in the 2000 Centers for Disease Control and Prevention (CDC) growth charts are used as reference points.[28] BMI has been accepted as a useful tool to screen for possible weight-related health issues and to assess body fat, as increasing BMI levels correlate with excess body fat.[29] Children ages 2–20 years with a BMI-for-age greater than the 85th percentile but less than the 95th percentile for age and sex meet the criteria for overweight. BMI-for-age at or above the 95th percentile for age meets the criteria for obesity, and BMI-for-age greater than or equal to the 120th percentile of the 95th percentile meets the criteria for severe obesity. For children under the age of two years, the World Health Organization (WHO) sex-specific weight-for-recumbent-length charts are used.[30] Weight-for-lengths at or above the 98th percentile meet the criteria for overweight in this age group.

Fat accumulates in excess when total energy intake exceeds total energy expenditure. This creates an energy imbalance caused by a complex interplay of various

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genetic, hormonal, behavioral, and environmental factors. Excessive caloric intake from food and beverage choices, and/or a low-energy expenditure from a sedentary lifestyle, can result in overweight or obesity. While some genetic conditions and hormonal disorders may increase a person's susceptibility to weight gain, environmental factors such as lack of physical activity and an overabundant food supply are required to develop overweight or obesity. Lack of adequate sleep and excessive use of electronic device screens can also contribute to excessive weight gain in children and adolescents.[31,32] For more details on the etiology and pathophysiology of pediatric obesity, see Chapter 68.

Weight loss in children with overweight or obesity is associated with significant changes in cardiometabolic outcomes including HDL-C, triglycerides (TG), and systolic blood pressure. A 1 kg weight loss can help reduce serum TG by 5 mg/dL and increase HDL-C by approximately 1.5 mg/dL. Decreasing BMI by one unit in adolescents is expected to reduce systolic blood pressure by 6 mm/Hg.[33] Adopting a healthy lifestyle to manage weight and lower CVD risk includes incorporating a healthful dietary pattern, engaging in regular physical activity, limiting recreational screen time, getting adequate quantity and quality of sleep, and managing stress.[34] Therefore, behavior changes in these key areas should be considered as targets for intervention. Treating obesity in children and adolescents should include parental involvement, as parents serve as role models and authority figures and can impact behaviors around eating habits and activity levels.[15]

Dietary factors that can contribute to excessive energy intake relative to energy expenditure include regular intakes of sugar-sweetened beverages (SSB), greater intakes of fast food, increased intakes of dietary fats and added sugars, and eating larger portions of food. These factors are positively associated with childhood overweight.[35] Additionally, some observational research indicates that low intakes of dairy and calcium-rich foods may increase obesity risk.[35] Breakfast skipping has been indicated as a dietary behavior that is associated with obesity, whereas eating breakfast daily is associated with weight loss and weight maintenance, in addition to improving nutrient intake.[36] Increased intake of fruits and vegetables may be associated with a decreased risk of obesity in children.[35] Family meals, especially those with positive family-and-parent-level interpersonal dynamics (i.e., warmth, group enjoyment, parental positive reinforcement) and with positive parent-level food-related dynamics (i.e., positive food communication, parental food positive reinforcement) are associated with a reduced risk of childhood overweight and obesity.[37]

Lack of physical activity and a sedentary lifestyle play key roles in the development of pediatric obesity (see Chapter 65). Shorter sleep duration and poor sleep quality can increase the risk of obesity[31] (see Chapter 67).

Excessive use of electronic device screens including high amounts of television viewing, playing video games, and recreational use of computers and cell phones can contribute to excessive weight gain in children and adolescents.[32] Screen time exceeding two hours per day increases childhood obesity risk.[35] Additionally, foods high in total calories, sugars, salt, and fat, and low in nutrients are highly advertised, marketed through media, and targeted to children and adolescents.[38] This can influence food choices and increase overall caloric intake.

Emerging research suggests that formula-fed infants may be at higher risk for increased weight trajectories and increased odds for overweight/obesity later in life when compared with breastfed infants.[39] Low access to healthful foods may have unfavorable impacts on food choices and eating behaviors among children and adolescents, although it is unclear if household food insecurity is related to pediatric overweight or obesity.[35]

Furthermore, recent literature suggests that children and adolescents with high stress levels may be more susceptible to increased body weight because of biological changes, increased food consumption as a coping mechanism, and engaging in less physical activity.[40] However, the associations between economic status, food security, stress, and obesity remain areas for further research.

Regarding family climate, parental dietary dis-inhibition and restraint, negative aspects of family functioning (such as lack of parental support or over-possessiveness), and parental concern about weight status are associated with a higher risk of childhood overweight or obesity. Conversely, positive aspects of family functioning (such as family cohesion, expressiveness, democratic style, parental support, and cognitive stimulation at home) are associated with a lower risk of childhood overweight or obesity[35].

The Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity have established recommendations for practitioners working with pediatric patients and their families in all areas of obesity care.[15] Interventions are categorized into different stages according to the severity of obesity, and the appropriate stage of treatment is based on age, BMI-for-age percentile, and the presence of other health risks. The Academy of Nutrition and Dietetics Evidence-Based Pediatric Weight Management Nutrition Practice Guidelines, 2015, provide complimentary guidelines.[35] These stages of obesity treatment are outlined below.

66.2.1 Stage 1: Prevention Plus

A family-centered approach focusing on healthful eating and activity behaviors is aimed at improving BMI status. The involvement of the child's parent or caregiver is recommended, and especially important for children ages 6–12 years, along with involving the whole family in lifestyle changes. Targeted behaviors for Stage 1 obesity treatment include minimizing consumption of sugar-sweetened beverages and juice, encouraging diets with adequate fruit and vegetable consumption, limiting television and other screen time to $\leq$2 hours per day, eating a healthy breakfast daily, limiting eating out at restaurants, encouraging family meals

in which parents and children eat together, consumption of diets rich in calcium, consumption of diets high in fiber, limiting consumption of energy-dense foods, eating a diet with appropriate portion sizes and balanced macronutrients (energy from fat, carbohydrates and protein in proportions for age as recommended by USDA 2020 Dietary Guidelines for Americans), encouraging exclusive breastfeeding for six months of age with maintenance of breastfeeding after introduction of solid food to 12 months of age and beyond (consistent with American Academy of Pediatrics recommendations)[41, 42] and promoting moderate-to-vigorous physical activity for at least 60 minutes each day.

66.2.2 Stage 2: Structured Weight Management

This stage includes targeting the behaviors mentioned in Stage 1 but with more specific eating and activity goals, and the support of a registered dietitian nutritionist (RDN). Balanced hypo-caloric diets with a mild energy deficit are prescribed to achieve a healthier weight or promote weight stabilization. Nutrition prescriptions are used to help guide the clinician and are not always disclosed to the parent or the patient but can be translated into an eating plan. A planned meal and snack schedule and one hour of supervised and planned daily physical activity are included. Self-monitoring is implemented by the family, with staff support using motivational interviewing techniques to help set healthful lifestyle goals and identify barriers to behavior change.[43]

66.2.3 Stage 3: Comprehensive Multidisciplinary Intervention

The intensity of behavior changes and frequency of visits are increased in this intervention. This stage includes an interdisciplinary team of specialists with experience in pediatric overweight or obesity. During this phase, medical nutrition therapy should be provided for a minimum of three months or until baseline weight management goals are reached. More successful weight loss and weight maintenance may be achieved by increasing the frequency of contact between the patient and practitioner.

66.2.4 Stage 4: Tertiary Care Intervention

This stage may be appropriate for children and adolescents with severe obesity who have attempted the Stage 3 intervention. Interventions are more aggressive in this stage and can include the use of medications, very low-energy diets, and bariatric surgeries with standard clinical protocols.

Nutrition plays a vital role in the healthy growth and development of children. A healthful diet and regular physical activity are important to prevent and treat obesity in children and can help to lower the risk of CVD. Eating patterns established in childhood often track into adulthood, so it is important to set healthful habits early in life.

66.3 DYSLIPIDEMIA

Early identification and treatment of dyslipidemia in youth is considered the cornerstone of primary prevention for CVD.[44] Reducing atherogenic lipoproteins to recommended target levels (see Chapter 69) with a healthy diet and lifestyle including daily physical activity, tobacco smoking cessation, and maintaining a healthy body weight is the primary intervention for youth to lower lifetime risk of CVD.[45] Current pediatric dietary recommendations for treating identified dyslipidemia include a two-step approach called the Cardiovascular Health Integrated Lifestyle Diet or CHILD-1 and CHILD-2.[46] Nutritional components of the CHILD-1 and CHILD-2 diets for low-density lipoprotein (LDL)-C and non-HDL-C reduction are summarized in Table 66.1. CHILD-1 is appropriate for all children over the age of two years and is, for the most part, consistent with the 2020–2025 Dietary Guidelines for Americans.[36] The CHILD-1 is considered the first-line approach to managing elevated LDL-C and non-HDL-C levels. For children with persistently high elevated LDL-C and non-HDL-C, e.g., after three to six months of compliance with CHILD-1, the CHILD-2 diet is recommended. For both CHILD-1 and CHILD-2, weight management is recommended for children with a BMI ≥85th percentile. According to CHILD guidelines, weight-reduction approaches should focus on decreasing the child's weight-for-height (BMI) percentile while maintaining linear growth.[46]

TABLE 66.1
Comparing the Nutritional Intervention Approaches in the Cardiovascular Health Integrated Lifestyle Diet-1 and -2 for Lipid lowering in Children >2 Years of Age

Nutrient target for LDL-lowering	CHILD-1	CHILD-2
Total dietary fat	25–30% of calories	25–30% of calories
Saturated fat	< 10% of daily calories	<7 % of daily calories
Trans fat	Avoided	Avoided
Monounsaturated fat	Up to 10–15% of calories	Up to 10–15% of calories
Polyunsaturated fat	Up to 10% of calories	Up to 10% of calories
Cholesterol	300 mg or less	200 mg or less
Dietary fiber	Child's age + 5 g up to 14 g/1000 calories	Child's age + 5 g up to 14 g/1000 calories
Simple Carbohydrates	Reduction of sugar-sweetened beverages	Reduction of sugar-sweetened beverages

Approaches to achieving the total and saturated fat limits of CHILD-1 and -2 include early transition (between one and two years) to a low-fat diet.[47] This advice is supported by dietary safety data from the Special Turku Risk Intervention Program (STRIP) study that showed that dietary counseling to reduce saturated fat and cholesterol to Dietary Guidelines for Americans levels from six months of age to age 20 years could be done safely under medical supervision.[48] In the STRIP study, indicators of diet safety included optimal growth and pubertal development, nutrient adequacy, and favorable cardiovascular health metrics (lowering of LDL-C and blood pressure) in infants, children, and adolescents.

To achieve the reduced fat goals of CHILD-1, which include a minimum of 30% of energy for children aged two to three years and a minimum of 25% of energy for older children, emphasis should be placed on dietary patterns high in fruits, vegetables, and whole grains.[49] Unprocessed forms of these foods are low in fat and high in fiber and will help to add bulk to the diet. Consumption of high fiber foods has been shown to be an effective means of displacing calorie-dense, nutrient-poor foods.[47] Transition to reduced fat, unflavored milk, and lean protein sources are also recommended by age two years with special consideration given to gender and age-specific calorie and nutrient requirements for growth and development.[46]

In a systematic review of randomized controlled trials aimed at reducing dietary saturated fat to modify CVD risk factors in children, the greatest lowering of LDL-C was achieved by replacing saturated fats with polyunsaturated fats (PUFA) or a mixture of PUFA and monounsaturated fats.[50] Top sources of saturated fat in diets of children 2–18 years of age include whole milk dairy products, sweet bakery products, mixed grain-based dishes, and processed meats and poultry.[51] Counseling families to switch from whole milk to low-fat varieties or fortified plant-based milks and from red meat to skinless white meat poultry may be a useful means of lowering saturated fat without lowering energy intake.[52] Also, switching out high-fat desserts and snacks for low-fat fruits, vegetables, nuts, and seeds and substituting solid cooking fats like butter with liquid cooking oils or spreads may be effective strategies to add PUFA while lowering saturated fat in the diets of children.

The Dietary Approaches to Stop Hypertension (DASH) diet is comparable to the CHILD-1 food plan.[49] A Mediterranean-type diet, if appropriately planned, may also conform to CHILD-1.[53] These dietary patterns emphasize whole, unprocessed fruits, vegetables and whole grains, unsaturated forms of fats, and lean animal and plant sources of protein. These food patterns have been recognized as effective in modifying cardiovascular risk factors including lowering blood pressure, improving blood lipids, and promoting weight loss.[45] Greater improvement in vascular function was reported in adolescents with obesity and hypercholesterolemia on a 12-week Mediterranean-type diet intervention compared with a control group.[54] Meal plans for different calorie levels have been published for these food patterns[36] and can be modified for progressive saturated fat lowering and calorie and nutrient adequacy for children.[49] The expected LDL-C reduction for children with hypercholesterolemia on CHILD-2 (LDL) is on average 12%.[47]

Plant sterols given in the form of prepared muffins, margarines, or chews in combination with a low-fat diet contributed to average LDL-C reductions of 5 to 9%[55] in children with familial hypercholesterolemia. Concern has been raised about the potential for the malabsorption of fat-soluble vitamins in children consuming plant sterols chronically.[56] For this reason, it is recommended that food preparations with plant sterols should be reserved for children with moderate to severe elevations in cholesterol with appropriate monitoring for fat-soluble vitamin status.[46] Soluble fiber given as psyllium in a dose of up to 10 g/day with a low-fat diet provided an additional 5 to 10% reduction in LDL-C in children with familial hypercholesterolemia.[56]

A dietary pattern called CHILD-2 (TG) is recommended for children with dyslipidemia characterized by high triglyceride (TG) and/or low HDL-C.[47] This diet emphasizes a dietary pattern low in saturated fats, trans fats, and refined carbohydrates. CHILD-2 (TG) emphasizes substituting saturated fats and trans fats with unsaturated fats, decreasing intake from sugar-sweetened beverages and desserts, and substituting refined carbohydrates from highly processed breads, rice, and pasta with whole grain sources of these same foods. CHILD-2 (TG) guidelines to minimize added sugars are consistent with a scientific statement from the AHA for children to consume $\leq$25 g (100 calories or six teaspoons) per day to lower cardiovascular risk factors.[57] Processed foods high in sugar are generally high in calories, which may contribute to weight gain and elevate serum TG and lower HDL-C. Modest weight loss for children with a BMI $\geq$85th percentile should favorably modify serum TG and increase HDL-C.[36]

An increase in long-chain omega-3 fatty acids from fish or fish oil products may decrease serum TG[58] Prescription fish oil capsules as a source of long-chain omega-3 fatty acids have been shown to reduce TG levels and have been used safely in children.[59] However, they lack approval for use in children and should be used in consultation with a lipid specialist. For children with very high TG, such as those with hyper-chylomicronemia, a CHILD-2 (TG) diet and fat restriction as low as 15% of daily calories may be helpful in lowering TG and avoiding pancreatitis. Medium chain triglyceride oils (MCT) may also be considered as a source of calories in these cases as they are beneficial for disorders that have defects in bile secretion or chylomicron aggregation or clearance processes.[60]

66.4 HYPERTENSION

Non-pharmacologic approaches for the treatment of elevated blood pressure/hypertension are recommended as the first-line approach in children and adolescents with elevated blood pressure (see Chapter 70).[61] Obesity and

overweight are some of the strongest predictors of elevated blood pressure in children.[62] Lifestyle interventions that achieve weight loss have consistently been found to favorably impact pediatric blood pressure and other cardiometabolic risk factors.[63] A recent review of treatment outcomes of over 6000 children of two to 19 years enrolled in a US consortium of multicomponent pediatric weight management programs that include diet, exercise, and behavior modification showed that a modest decrease in BMI after 12 months was associated with significant improvement in diastolic blood pressure, TG, HDL-C, and fasting blood glucose in children with obesity.[64] Reinehr et al.[65] prospectively analyzed results from a one-year weight loss intervention in children with overweight and obesity between the ages of 5 and 17 years. Participants who were able to reduce their BMI by >0.25 standard deviation score (SDS) in one year (equivalent to a BMI reduction of 0.5 kg/m^2 in a seven-year-old child and 1.0 kg/m^2 in a 13-year-old) achieved an average reduction in systolic blood pressure of −3.2 mm Hg and diastolic blood pressure of −2.2 mm Hg. In this same study, a BMI-SDS reduction of >0.5 more than doubled the response in lowering both systolic and diastolic blood pressure. Given the benefits of weight loss on cardiovascular risk factors in youth, weight reduction is recommended as a primary intervention for blood pressure lowering in children with hypertension, overweight, and obesity.[61] Importantly, findings in young adults suggest that it is not necessary to achieve one's ideal body weight to gain significant blood pressure benefits.[66] Slow, gradual weight loss may be recommended for some children depending on the severity of obesity and the presence of co-morbidities.[67]

An evidence-based, best practices model regarding pediatric weight management[45] recommends calorie intake to match growth demands and physical activity needs with a focus on plant-based foods as a low-calorie source of nutrients; intake of excess fat and sugar-sweetened beverages are discouraged. A DASH dietary pattern can be so planned to accommodate the needs of the growing child.[49] The diet is prescriptive in food group serving recommendations based on daily calorie targets, and per 2000 calories, includes eight to ten servings of fruits and vegetables, two to three servings of low-fat or non-fat dairy, six to eight servings of mostly whole grain foods, two or fewer servings of lean protein foods, two to three servings of fats and oils, and five weekly servings of nuts, with limited sweets.[45] The pattern emphasizes a complement of nutrients including potassium, calcium, and magnesium that have been shown in single-nutrient studies to favorable impact blood pressure and is advocated in current blood pressure treatment guidelines as a recommended eating style to lower blood pressure in children.[61] In a recent randomized control trial, the effectiveness of a six-month diet intervention emphasizing the DASH dietary pattern was examined on blood pressure and vascular health among youth 11–18 years of age.[68] Adolescents (n=159) received face-to-face counseling with an RDN at baseline and check ins at three months, six months, and one year focused on knowledge and skills necessary to comply with a DASH dietary pattern. Fifteen behaviorally focused telephone calls were provided, teaching adolescents about healthful food selection, preparation, meal planning, handling high-risk eating situations, and setting progressive DASH-compliant dietary goals weekly. The DASH diet intervention group experienced a greater reduction in systolic blood pressure (−2.7 mm Hg) and improvement in flow-mediated dilation (+2.5%) compared with the routine care group at the six-month assessment. While blood pressure benefits at six months were not fully sustained at 18 months, flow-mediated dilation showed greater improvement (+3.1%) in the DASH group compared with routine care, suggesting long-term benefits of DASH-style eating on vascular health in adolescents with elevated blood pressure.

Reducing salt intake may also aid in blood pressure lowering in youth. Dietary salt, and its main constituent sodium, is one of the most studied food components related to blood pressure as it plays a central role in regulating fluid balance in the body. In children as in adults, excessive sodium intake leads to the expansion of blood volume and can potentially lead to the development of arterial hypertension.[69] A pooled analysis of nine randomized controlled trials of reduced salt diets compared with usual intake showed a significant blood pressure lowering in children.[70] In this analysis, a median net reduction of salt intake of 42% over four weeks correlated with a decrease in systolic and diastolic blood pressure of 1.17 mm Hg and 1.29 mm Hg, respectively. The 2017 AAP Clinical Practice Guidelines recommends lowering salt intake to 2300 mg/day, especially in children with hypertension and those with overweight or obesity, as these at-risk subgroups frequently exhibit increased blood pressure response to changes in dietary sodium.[61]

The median sodium intake of children and adolescents in the United States exceeds current guidelines with current estimates of 2840 mg/day in children four to 17 years.[70] Therefore, reducing dietary sodium to the recommended levels may be challenging. Focusing on key sources of sodium in the diets of children and working collaboratively with the family to limit those foods is an important first step. In the United States, an average of 83% of total sodium consumption comes from pre-prepared foods purchased from grocery stores and restaurants.[71] Pizza, breads and rolls, and processed meats and poultry are the greatest sources of sodium in the diets of children.[72] Therefore, teaching children and their parents how to read nutrition facts panels on product labels for sodium content and choosing products that have lower sodium would be a useful strategy for lowering sodium in children's diets. Using fresh rather than packaged meats and avoiding instant foods such as pasta, rice, and cereals, which usually contain salt, will help to reduce daily sodium intake. Foods cooked from scratch are naturally lower in sodium than most instant and boxed meals and take-out foods. To aid families in sodium reduction, their food literacy should be assessed, and they should be counseled accordingly on food-shopping skills, their ability to read food labels, and

their capacity to cook and flavor foods using low sodium methods.

66.5 STRATEGIES TO PROMOTE EATING BEHAVIOR CHANGE

A behavioral approach to dietary modification provided by an RDN is the most consistently effective approach to evoke dietary change.[45] In the pediatric population, the child and his/her family should be engaged in the counseling efforts with an RDN. To be most effective, the RDN should gather a comprehensive assessment of the child's current nutritional and weight status, current dietary intake, and eating patterns along with the family's readiness to change. This information can be a valuable resource in estimating success in implementing and sustaining lifestyle changes. Particular attention should be given to potential barriers to dietary behavior change that are rooted in social determinants of health.[73] Assessing information on food access and availability including food insecurity, availability of grocery stores in the neighborhood, transportation to grocery stores, and financial barriers should be considered to better align meal planning and dietary considerations within the specific contexts of the child and family's needs.

Modifying eating behaviors can be challenging, particularly if the food environment of a child is not conducive to making healthy food selections. Children eat like their parents in large part due to a shared food environment, shared meals, and the influence of parent modeling, particularly in young children.[74] Therefore, teaching parents how to plan, shop, and prepare heart-healthy meals for their family and engage their children in the process will help to create a home food environment that is likely to have a favorable impact on their children's health. Enhancing food planning, selection, and preparation knowledge and skills has been shown to increase fruit and vegetable intake[75] and was negatively associated with unhealthy food choices, including soft drink consumption.[76]

66.6 CONCLUSION

Diet plays a very important role in first preventing the emergence of cardiovascular risk factors, and second, in treating risk factors, such as obesity, dyslipidemia, and hypertension, when they develop in young individuals. Identifying risk-factor development in children and adolescents is important for the implementation of appropriate treatment and interventions. Unfortunately, children and adolescents do not usually live in an environment that makes healthy food choices an easy one. This means that behavior change interventions must focus on changing the home environment to encourage healthier choices. Often the best approach is for the entire family to work together to make improved lifestyle choices. This may be broadly beneficial, as often cardiovascular risk factors will cluster in families because of shared environment and shared genetics. Identification and management of cardiovascular risk factors in children and adolescents require a team of healthcare professionals, including physicians, nurses, dietitians, and exercise physiologists. Appropriate management can be successful, which should provide a sense of optimism. On the other hand, the prevention of the development of risk factors in the first place is by far the best strategy.

CLINICAL APPLICATIONS

- Identifying CVD risk-factor development in children and adolescents is important for the implementation of appropriate diet and lifestyle interventions.
- Encouraging dietary patterns emphasizing plant sources of protein rich in soluble fiber will promote weight loss, manage lipids, and lower blood pressure.
- Placing emphasis on the creation of a healthy home food environment, including the provision of ample fruits and vegetables and family meals will encourage healthful eating behaviors.
- Assess information on food access and availability to better align meal planning and dietary considerations within the specific contexts of the child and family's needs.

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67 Sleep and Obesity Prevention in Children and Adolescents

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KEY POINTS

1. Early intervention and treatment of childhood obesity is advised; therefore, screening a child's growth is essential.
2. Education regarding healthy diet, engaging in physical activity, limiting screen time, and appropriate sleep hygiene is encouraged for both the family and the children.
3. Although the mechanism relating sleep behaviors to obesity risk remains unknown, establishing healthy sleep habits at an early age is advised.
4. Adolescents tend to have very poor health behaviors including short sleep duration, high sedentary activities, and poor diets, which together lead to early indicators of dysfunctional metabolism.

67.1 OBESITY EPIDEMIC IN CHILDREN AND ADOLESCENTS

Obesity among children and adolescents remains a problem in the United States, with a significant increase in severe obesity over the past several years.[1,2] Although the impact of the COVID-19-related school and community closures on pediatric obesity is not yet fully understood; recent evidence has started to shed light on the unique lifestyle challenges presented to families and children, including loss of healthy school meals, playground and recreation center closures, and canceled school activities that may have further exacerbated obesity risk.[3,4]

Recent data has shown a steady increase in diagnosis of severe obesity, defined as a body mass index (BMI) greater than 120% of the 95th percentile for age and sex, among preschool-aged children (two to five years).[1] The highest prevalence of obesity continues to be among racially and ethnically minoritized subgroups of children and adolescents, i.e., African American, Hispanic, and those classified as other race, compared with White and Asian American.[1] Twice as many non-Hispanic Black, preschool-age children meet the criteria for obesity, compared with non-Hispanic White children (18.2% vs. 9.2%, respectively) in the United States. Children with obesity are at a higher risk for many short- and long-term health consequences, as well as a decrease in their overall life span as adults.[5]

Economists have predicted an additional $19,000 per capita medical care costs for a child with obesity versus a child of normal weight throughout their lifetime.[6] As childhood obesity has been found to progress into adolescence and adulthood, there is a larger societal burden, including reduced income at an individual level, decreased productivity at the employer level, and reduced tax revenues at the government level,[7] all of which may further increase the estimated societal cost of childhood obesity.[8] In addition, children with obesity often have poorer psychosocial functioning related to body image disorders, lower self-esteem, higher levels of stress and anxiety, and increased risk of depression.[9–12] Additionally, children with obesity are at a greater risk of being bullied or teased at school, which leads to poorer social skills and increased difficulties with social situations.[9]

The combined impact of the psychosocial and sociocultural determinants of health problems associated with obesity, as well as the increased risk of cardiovascular disease, diabetes, and other comorbidities of obesity are present throughout the lifespan.[13,14] The early years of life may present a critical window of time during which interventions to prevent childhood obesity could have profound effects. For the last several decades, the major focus has been on increased activity and improving dietary intake; however, these programs have yet to change the trajectory as the prevalence continues to rise, indicating a need for the consideration of additional factors to prevent and treat obesity in children.[15–17]

67.2 POOR SLEEP HEALTH IN CHILDREN AND ADOLESCENTS

Chronic short sleep patterns are becoming an alarming issue in all ages. Findings from the 2016–2018 National Survey of Children's Health (NSCH) show that approximately one-third of children aged four months to 17 years of age obtained insufficient sleep for age per parent-report.[18] Youth from racially and ethnically minoritized groups and with low socioeconomic status had the highest rates of short sleep duration.[18] Young children are at particular risk, as sleep problems are one of the most common parental complaints to pediatricians,[19] and preschool-age children are more likely to be diagnosed with a sleep disorder than any other age group.[20] Poor sleep patterns in childhood tend to

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persist into adulthood and develop into chronic sleep problems.[21,22] Adolescence is another unique period of risk for poor sleep health due to a combination of physiological, environmental, and psychosocial factors that increase the propensity for delayed and short sleep.[23] Approximately 60% of middle-school-age students and 70% of high-school-age students report obtaining insufficient sleep on school nights according to data from the Youth Risk Behavior Surveys.[24] Evidence is also emerging of the impact of the COVID-19 pandemic on childhood sleep due to factors including reduced structure and variable schedules with school shutdowns and the transition to online learning.[25]

Poor sleep health, including short sleep duration, has been posited to increase risk for obesity due to changes in physical activity, dietary intake, and impact on metabolic hormones, including leptin, ghrelin, cortisol, and growth hormones.[26–33] Short sleep duration may also decrease metabolic rate (i.e., resting energy expenditure) and is linked to insulin resistance and increased risk for type 2 diabetes.[34–36] Notably, there is strong evidence that short sleep duration is associated with an increased risk of childhood obesity.[37–40]

67.3 SLEEP ASSOCIATED WITH OBESITY AND OTHER HEALTH BEHAVIORS

The association between sleep and obesity will be discussed in the next section. As the specific mechanism linking sleep and obesity is unknown, literature exploring the possible metabolic dysfunction, as well as associated changes in diet and activity behaviors, will be explored.

67.3.1 Sleep and Obesity

The impact of sleep health on obesity has been proposed as the missing link to improved health behaviors, leading to improved health outcomes including many obesity-related comorbidities (i.e., insulin resistance, type 2 diabetes).[41–55] The association between short sleep duration and obesity/adiposity has been well documented, with the majority of studies using self-report measured sleep and a cross-sectional design.[46,56–60] More specifically, short sleep duration (compared with recommended sleep duration for age) has been shown to increase risk of obesity, especially among 3–13 years of age, whereas sleep duration in line with recommended amounts has been found to be protective against obesity.[61] In the Heartfelt Study of almost 400 adolescents, the odds of obesity increased by 80% for each hour of lost sleep.[59] Similarly, in a sample of over 300, four- to ten-year-olds, children with obesity slept less than children without obesity and showed more variability in their sleep on the weekends, compared with school days.[60] In a cross-sectional study, short sleep duration (less than nine hours per night) at age seven years was associated with obesity, independent of TV watching and time spent in sedentary activities (examined by accelerometry).[57] Of the few longitudinal studies conducted, results have been inconsistent, with some finding an association with shorter sleep duration in early childhood and increased weight during later childhood and others showing no association.[62–64] Over 300 children (aged three years) were followed through age six with annual assessments of sleep, physical activity, and television viewing.[42] Longer sleep duration at age three was found to predict decreased BMI percentiles from age three to six years. In a birth cohort in New Zealand (n = 244), sleep and other health behaviors were measured from age three to seven years, and short sleep duration at ages three to five years was found to predict higher adiposity at age seven years. However, in a similar study conducted in the United States with over 800 Hispanic children aged 4–19 years, self-reported sleep duration did not predict increased weight gain one year later.[62] In a more recent study conducted in Denmark with 8–11-year-olds, sleep duration was also not found to be predictive of weight gain over time.[63] The inconsistencies in results could be attributed to methodological issues with the sleep data, as the majority of studies used self-report sleep duration data versus objective measures such as actigraphy. Together, these data suggest the link between sleep and obesity may be "beyond sleep duration" and other components of sleep need to be explored.[65] One such component is the timing of sleep and its relationship with obesity. Although less studied, research to date has found that late bedtimes are associated with adiposity and weight gain in both children and adolescent populations.[65–67] These findings have been concluded independent of sleep duration, indicating that the timing of sleep may be as important as the number of hours of sleep.

Sleep duration has been associated with metabolic regulation, in particular insulin sensitivity, within pediatric populations. In a sample of youth ages 10–19 years, self-reported sleep duration was associated with insulin sensitivity measured with a hyperglycemic clamp.[68] In adolescents with obesity, sleep duration, measured by actigraphy, was found to be inversely associated with glucose, triglycerides, HDL, and other metabolic markers in one study, even after controlling for other lifestyle factors and body composition,[69] and associated with HOMA-IR in another.[70] Similarly, another study found that adolescents who slept 7.75 hours per night had the best insulin sensitivity compared with adolescents who slept less (five hours/night) or more (ten hours/night),[71] though these findings were no longer significant after adjusting for markers of adiposity. In another study of youth ages 2–15 years, abdominal adiposity mediated the relationship between insulin sensitivity and self-reported sleep duration.[72] In a large sample of adolescents, actigraphy-measured longer sleep duration was associated with lower metabolic risk scores including HOMA-IR.[57] However, these studies are limited by the use of either only fasting glucose and insulin rather than more sensitive measurements, or subjective assessment of sleep duration.

Two studies have examined sleep and insulin sensitivity in youth utilizing both objective sleep measurement and more sensitive measures of insulin sensitivity. Shorter actigraphy-measured sleep duration was significantly associated with oral glucose tolerance tested insulin resistance in a sample of

adolescents with overweight and obesity assessed during the academic year.[54] A randomized crossover laboratory study found that adolescent boys had lower HOMA-IR following three nights of four hours in bed compared with three nights of nine hours in bed.[31] Further work is needed in this area, as much of the literature is conflicted, which may be due to various methods of data collection as well as factors included or not included in analyses (i.e., adiposity, pubertal status, and other health behaviors like diet and activity).

67.3.2 Sleep and Diet

The relationship between sleep and diet behaviors is limited in children and adolescent populations. Sleep restriction has been found to alter dietary intake in adolescents in experimental studies.[73,74] Adolescents were found to have diets composed of higher glycemic index, two times higher consumption of sweet/dessert foods, and more calories and carbohydrates after five nights of sleep restriction (6.5 hours in bed/night) compared with consumption after healthy sleep (10 hours in bed/night).[73,74] Adolescents also rated pictures of sweet/dessert foods more appealing than other foods following sleep restriction compared with after healthy sleep.[74] Adolescents performed more poorly on a food-related inhibitory control task and exhibited higher food reward following one week of sleeping five hours per night compared with one week of sleeping nine hours per night, suggesting that insufficient sleep may impact dietary choices by increasing the reward value of foods.[75]

Sleep timing has also been associated with dietary habits, independent of sleep duration. Children and adolescents with later bedtimes (i.e., after midnight for adolescents) compared with those that go to bed early (i.e., before midnight) have been shown to consume larger quantities of sugary or caffeinated beverages.[76–79] Similarly, individuals falling asleep after midnight also report consuming more sugary, salty, and fatty foods throughout the day.[76,77,80]

Adolescents are more likely to skip breakfast and eat the majority of their meals toward the end of the day, which may be related to adolescents' tendency to prefer to stay up late and sleep late.[81,82] Moreover, healthy foods may be less easily available late at night. In an experimental study of adolescents, a "morningness" preference was protective against evening caloric intake when randomized to increase sleep duration by moving bedtime earlier, while no such effect was shown for "night owls".[83] While research is limited in youth, irregular timing of meals and meal frequency has been linked to poor health consequences in adults, including cardiovascular disease, type 2 diabetes mellitus, and obesity.[84] Given that teens are at high risk for irregular eating behaviors, future research should focus on sleep and meal timing in adolescence.

67.3.3 Sleep and Physical Activity and Screen Time

The relationship between physical activity levels and sleep is limited due to a small number of studies and primarily relying on self-report measures. Some studies have found a relationship between short sleep duration and less physical activity, higher electronics use, and greater sedentary behaviors in youth,[85–88] while one study found that longer self-reported sleep duration was associated with more screen time and lower physical activity levels.[89] A study of over 1200 six- to ten-year-olds in Sweden showed that objectively measured total sleep time did not change after moderate-to-vigorous physical activity (MVPA); however, sleep efficiency did improve for each additional bout (minute) of MVPA.[90] In contrast, in a cohort of 275 eight-year-olds, for every unit of increase in PA (counts/minute) during the day, objectively measured sleep duration that night was decreased along with sleep efficiency.[91] Lastly, the link between short sleep duration and higher sedentary activity was shown in a sample of over 3000 European adolescents, with short sleep duration (defined as less than eight hours per night) associated with higher sedentary time and TV time.[92]

Two experimental studies have examined changes in sleep duration and physical activity. In a within-subject counterbalanced design, 37 8–11-year-old children were randomized to either increase or decrease their average bedtime by 1.5 hours/night for one week[93] During this time, the children wore wrist accelerometers and completed a physical activity recall questionnaire. During the week of decreased sleep, children had lower mean physical activity levels and reported watching more television the next day compared with the week of increased sleep. An experimental study with adolescents objectively measuring sleep and activity found that time spent in sedentary behaviors was increased during two weeks of habitual short sleep duration (five to seven hours per night) compared with two weeks of increasing sleep duration by 1.5 hours.[94] In this study, no difference was found for light or moderate-to-vigorous physical activity, suggesting that the extra wakefulness during insufficient sleep is comprised of sedentary time.[94]

67.3.4 Influence on Health Behavior Patterns

As health behaviors co-occur, it is important to understand how patterns of health behaviors predict obesity. For example, obese children tend to report having two or more poor eating and activity behaviors (e.g., high consumption of sugared sweetened beverages and low activity levels).[95] One possible reason for the discrepancy in findings for the studies described earlier could be the potential relationships that exist between each of the health behaviors (i.e., diet, physical activity, screen time). To date, few studies have examined the possible influence of multiple behaviors patterning together[96–99] and, to our knowledge, few have included sleep in conjunction with other health behaviors. One approach to that would be person-centered and encompass multiple behaviors using novel statistical methodologies, like pattern analysis.[100] In a secondary analysis of over 1000 young children, the bi-directionality of the relationship between sleep duration and health behavior (i.e., diet, activity, screen

time) patterns were examined using a latent class analysis approach.[41] This study found that sleep duration acted as a mediator between the relationship between health behavior patterns and obesity. As research continues to disentangle the relationship between these obesity-related health behaviors, future work should consider examining the potential pathway in which these behaviors co-occur.

67.4 PEDIATRIC OBSTRUCTIVE SLEEP APNEA AND OBESITY

Children and adolescents with obesity are at increased risk for obstructive sleep apnea (OSA): prevalence of OSA is approximately 1–5% in otherwise healthy children but increases to upwards of 30% in children with obesity.[101,102] OSA is characterized by repeated partial or total obstruction of the upper airway during the night resulting in multiple arousals from sleep. Untreated, OSA can have severe negative consequences, including cardiovascular morbidity, cognitive deficits, and mood and behavior problems.[102,103] Greater severity of OSA has been associated with fat distribution, exercise function, and insulin resistance.[47] In a study of 31 obese children ages 5–18 years, visceral fat distribution assessed with MRI/MRS was associated with OSA severity measured by polysomnography (PSG).[104] Children with OSA ages 7–12 years, compared with weight-matched children without OSA, had lower cardiac output and oxygen consumption at peak exercise capacity independent of weight status.[105] Despite similar levels of obesity, adolescent patients with moderate or severe OSA had higher fasting insulin and HOMA-IR compared with patients with mild or no OSA.[106] Similarly, in a sample of 62 children ages 5–16 years referred for snoring, severity of OSA correlated with fasting insulin, independent of BMI.[107] Gozal and colleagues[108] conducted a study of 260 children ages 4–11 years and found that children with both obesity and OSA had the lowest levels of G protein-coupled receptor 120 (GPR 120), a long-chain free fatty acid receptor that plays a role in energy homeostasis and protects against insulin resistance and systemic inflammation, potentially contributing to food intake, weight, and glucose metabolism in youth with OSA. The extant studies are limited in the use of non-standard criteria for defining OSA and variable measurement of OSA ranging from full polysomnography to parent-report of symptoms. Future research is needed to further understand the role that OSA may play regarding weight, exercise function, energy balance, and glucose metabolism.

67.5 IMPROVING SLEEP IN CHILDREN AND ADOLESCENTS

67.5.1 Assessment of Sleep Behaviors and Symptoms

A comprehensive evaluation of sleep behaviors is necessary to thoroughly assess for both medical and behavioral sleep disorders and disruption. Input from both youth and their parents can be helpful, as each may have a unique perspective about sleep difficulties. A clinical interview should inquire about typical bed and wake times, any bedtime routine or preparation, and what activities the child performs before bed while attempting sleep, and during night wakings (e.g., getting out of bed, seeking parents, reading, watching TV, using a tablet). Any medications (over-the-counter or prescription) or recreational drugs the child or teen uses to help with sleep should be queried. Lastly, it is helpful to ask about any strategies the family has tried previously to help with sleep and their perceptions of what has been helpful or not. A range of sleep assessment tools are also available to help supplement the clinical interview (Table 67.1).

67.5.2 Treatment of Sleep Disorders

Recommendations for the treatment of sleep problems and disorders vary depending on type. Many children and adolescents have poor sleep habits and practices that contribute to insufficient sleep and daytime sleepiness in the absence of a specific sleep disorder or diagnosis. For these youth, sleep hygiene recommendations may help to improve sleep and daytime functioning. Sleep hygiene is the habits and conditions that generally promote healthy sleep. Patients with sleep difficulties often engage in sleep-related habits that can inhibit adequate sleep, for example, the use of caffeine or other stimulants in an attempt to increase alertness during the day, which inadvertently reduces sleep drive and prolongs sleep onset at night.[112] While sleep hygiene is not a standalone treatment for insomnia, these strategies are necessary to lay a foundation for healthy sleep practices in children and adolescents. Sleep hygiene recommendations encourage sleep practices that promote sleep, including engaging in a bedtime routine, avoiding electronics at least one hour before bedtime to avoid bright light and stimulation, following a consistent sleep/wake schedule (e.g., not varying bed or wake times by more than two hours throughout the week), and maintaining a quiet, dark, and cool sleep environment. Simultaneously, it is necessary to reduce practices that inhibit sleep, including caffeine consumption, exercise within two hours of bedtime, daytime napping, and an uncomfortable sleeping environment.

Cognitive-behavioral therapy for insomnia (CBT-I) is considered the first-line treatment for adults,[113] and while less studied, evidence exists supporting CBT-I for adolescents.[109,114] Key components of CBT-I for adolescents include sleep hygiene (described above), stimulus control, sleep restriction, and cognitive restructuring.

- *Stimulus control* involves using the bed and bedroom only for sleeping in order to strengthen the association between the bed/room and sleep while weakening the association between the bed/room and wakefulness.[115] For adolescents, this may mean no longer doing homework, watching TV,

TABLE 67.1
Available Tools to Assess a Patient's Sleep Behavior

Sleep Assessment Tool	Description
Polysomnography (PSG)	PSG is the "gold standard" for measuring sleep and involves the measurement of multiple physiological channels (brain activity, respiration, heart rate, eye movements, and limb movements) and is usually completed in a sleep laboratory. PSG is clinically indicated if there are concerns about sleep-disordered breathing (loud snoring, pauses in breathing, gasping for air during sleep) or unusual movements during sleep. PSG is not recommended for insomnia.
Actigraphy	A watch-like device worn on the non-dominant wrist that provides estimates of sleep based on motor activity using an accelerometer. The advantages of actigraphy include the ability to monitor sleep in the home environment in real time over a prolonged duration (one to two weeks). Unfortunately, actigraphy is not readily available to many clinicians.
Sleep diary	A sleep diary completed by the child and/or parent is a simple and inexpensive way to obtain prospective information about sleep patterns and practices. Ideally completed upon awakening each morning, a sleep diary provides critical data regarding typical sleep/wake patterns, including attempted bedtime, perceived sleep onset time, frequency and duration of night wakings, and morning wake time. Information from the sleep diary can then be used to help guide the clinician's questions regarding sleep practices.
Sleep questionnaires	Dedicated sleep questionnaires can also be helpful to screen for sleep problems or gain additional information for further queries. A variety of questionnaires are available for a multitude of sleep problems. For example, the Pediatric Insomnia Severity Index (PISI) is a brief, six-item measure available in both child- and parent-reports that assesses sleep domains relevant to insomnia, including sleep onset problems, sleep maintenance difficulties, daytime sleepiness, and nocturnal sleep duration.[109,110] For symptoms of breathing difficulties during sleep, the Pediatric Sleep Questionnaire (PSQ) is a parent-report measure for youth 2–18 years and yields four subscales including snoring, excessive daytime sleepiness, inattention/hyperactive behavior, and sleep-related breathing disorders.[111]

using tablets and cell phones, eating, or reading in their bed/room.

- *Sleep restriction* sets a strict amount of time that the teen is allowed to spend in bed each night that more closely aligns with the amount of sleep they are currently obtaining with a goal of reducing the amount of time spent in bed awake. Similar to stimulus control, the goal of sleep restriction is to reduce associations between the bed/room and being awake. Sleep restriction is accomplished by delaying bedtime while maintaining wake time, resulting in partial sleep deprivation, and increasing the homeostatic drive to sleep so teens can fall asleep more quickly and have reduced night wakings. After sleep has become more efficient, bedtime can slowly be moved earlier to allow for a healthy sleep duration. Caution should be used with sleep restriction to avoid the negative effects of insufficient sleep on daytime functioning (e.g., academic performance, operating an automobile) or in certain medical conditions (e.g., bipolar disorder).
- *Cognitive restructuring* aims to modify the negative thoughts and cognitive distortions about sleep that may serve as perpetuating factors maintaining insomnia symptoms. Negative cognitions about sleep can result in increased arousal, support behaviors that interfere with sleep, and strengthen negative associations with the sleep environment.[116] The goal of cognitive restructuring is to break the cycle of negative thoughts about sleep in order to decrease arousal and improve sleep by identifying and replacing negative beliefs with more adaptive thoughts and attitudes. Relaxation strategies such as diaphragmatic breathing and imagery, done in conjunction with cognitive restructuring, can also help to reduce arousal and disruptive thoughts.

There are a number of empirically supported behavioral treatments for younger children with insomnia, aimed at helping with difficulties such as bedtime resistance and difficulty falling asleep or returning to sleep independently.[117,118] The American Academy of Sleep Medicine Practice Parameters provides guidance on recommended behavioral treatments for young children.[119] Parent education on sleep and sleep hygiene is recommended, with a focus on helping the child develop positive sleep habits. Parents are encouraged to devise a bedtime routine that includes a set of enjoyable and calming pre-bedtime activities leading up to sleep onset. After putting the child to bed at a designated bedtime, parents should then try to reduce the child's dependence on external cues (e.g., parent presence) to fall asleep. This may be done by ignoring the child until morning while monitoring for safety, doing brief check-ins at pre-determined periods (e.g., every five minutes, or at five minutes, then ten minutes), or remaining in the child's room as they fall asleep but providing minimal attention and limiting interaction. Positive reinforcement (e.g., rewards, sticker charts) may be used in conjunction with these strategies. For any sleep intervention, it is important to work together with families to find a treatment that is both evidence-based and acceptable to parents.[120]

For obstructive sleep apnea, the first-line treatment in children is typically surgical removal of tonsils and

adenoids. However, pre-operative sleep appears to be a risk factor for obesity in youth, and getting the right amount of sleep at the right time may have important implications for dietary intake, physical activity, sedentary activity, and metabolic function. More research is needed to understand the mechanisms behind the sleep and obesity relationship, particularly experimental studies, in order to demonstrate causality, along with the use of rigorous methodological procedures. Pediatric obesity is a significant public health concern, coinciding with an increase in chronic sleep restriction in today's youth. Thus, new obesity prevention and treatment targets, such as sleep, are strongly needed.

CLINICAL APPLICATIONS

Presenting Problem	Possible Diagnoses	Recommended Treatment
All ages		
Snoring, pauses in breathing, gasping for air during sleep	Obstructive sleep apnea	Polysomnography; referral to pediatric sleep clinic
Irregular sleep/wake times	Poor sleep habits in the absence of a discrete sleep disorder	Scheduled, consistent, bed/wake times
Poor sleep habits (e.g., use of electronics at bedtime and/or to fall asleep)	Poor sleep habits in the absence of a discrete sleep disorder	Sleep hygiene recommendations
Younger children		
Difficulty falling asleep independently (need for a parent's presence to fall asleep or return to sleep after night wakings)	Insomnia	Behavioral treatments for independent sleep; referral to pediatric behavioral sleep medicine specialist
Bedtime resistance	Insomnia	Bedtime routine; positive reinforcement; referral to pediatric behavioral sleep medicine specialist
Older children/adolescents		
Difficulty falling asleep	Insomnia	Cognitive-behavioral therapy for insomnia (CBT-I); referral to pediatric behavioral sleep medicine specialist
Frequent night wakings	Insomnia	CBT-I; referral to pediatric behavioral sleep medicine specialist

In addition to the sleep difficulties and disorders discussed in this chapter, many other sleep symptoms and disorders (such as parasomnias, restless leg syndrome, and circadian rhythm sleep disorders) were not able to be mentioned due to space constraints. Referral to a pediatric sleep specialist is recommended to rule out a sleep disorder. The Pediatric Sleep Council maintains a list of American Academy of Sleep Medicine-accredited sleep centers specializing in pediatrics: www.babysleep.com. The Society of Behavioral Sleep Medicine offers a list of behavioral sleep medicine providers, including pediatric specialists: behavioralsleep.org.

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68 Childhood Obesity

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KEY POINTS

- Universally screen all children in primary care at least annually for excess weight gain using age- and sex-specific BMI percentiles (≥2 years) or weight-for-length percentiles (<2 years), and for lifestyle factors that may contribute to obesity.
- Tailor obesity interventions to the severity of obesity and the family's readiness to change.
- Use motivational interviewing techniques to help families identify factors that they value and select attainable lifestyle change goals.
- When goals for lifestyle change have been identified, work with families to use developmentally appropriate cognitive behavioral strategies including self-monitoring, accountability, and positive reinforcement to engrain new healthy habits.
- When available, connect families to intensive multidisciplinary family-centered interventions (≥26 contact hours/year have the strongest evidence for enduring BMI and lifestyle changes) and consider advanced interventions like pharmacotherapy or bariatric surgery for youth with severe obesity with complications.

68.1 INTRODUCTION

Childhood obesity represents a relatively new chronic disease epidemic from medical and public health perspectives. The prevalence of childhood obesity has increased markedly since the 1980s, paralleling the increase of obesity in adults over the same period[1,2] Multisector population-level responses have been evaluated for obesity prevention over the last two decades,[3,4] but the healthcare system still struggles to implement evidence-based treatment interventions broadly or to offer interventions that effectively reach Black, Hispanic, and Native American populations that face great health disparities related to childhood obesity[5,6] In the decade prior to the COVID-19 pandemic, the rate of increase in the prevalence of childhood obesity had slowed compared with prior decades[7] However, the lifestyle sequelae of the COVID-19 pandemic resulted in rapid increases in childhood obesity prevalence and severity in the United States, affecting low-income and minority groups most dramatically.[8] Comorbid conditions such as type 2 diabetes are projected to increase significantly as generations of children carry obesity into adulthood.[9]

Because the costs in terms of quality of life, direct medical costs, and indirect societal costs of this epidemic are very high, dissemination of evidence-based interventions within the healthcare system is urgently needed, especially for the highest-risk groups. Medical providers want to help children who suffer from reduced quality of life and health consequences of excess weight gain and help families prevent these problems but have historically encountered obstacles to doing so. There has been a lag in responding to this emergent epidemic by the US healthcare delivery[10] and medical education systems.[11,12] Thus, many practicing clinicians report that they lack adequate training, have low self-efficacy in weight management counseling for children, and lack access to or awareness of appropriate resources for evidence-based treatment.[13]

The overall purpose of this chapter is to serve as a reference for medical providers who wish to incorporate the prevention and treatment of childhood obesity into their practice. Specifically, the chapter emphasizes lifestyle-change approaches that support families in changing nutrition, physical activity, sleep, and other habits to maintain or achieve healthy child growth. A range of lifestyle approaches is discussed within a staged approach to childhood obesity treatment that matches treatment intensity to the severity of obesity and the readiness of individual families. Treatment options discussed also include pharmacotherapy or surgical interventions that should be considered for children who have severe obesity and comorbid conditions.

68.2 KEY RESOURCES

When considering the prevention, assessment, and treatment of childhood obesity, there are a few key resources that are helpful to be familiar with: 1) The 2007 *Expert Committee Recommendations* focused on primary care practice.[14] An update to these American Academy of Pediatrics recommendations will be published in 2022 in the form of a *Clinical Practice Guideline for Childhood Obesity* with accompanying extensively referenced *Technical Reports*. 2) The *2013 Scientific Statement on Severe Obesity in Children and Adolescents from the American Heart Association* addressed the etiology and comorbidities of severe obesity in detail[15] 3) The 2017 *Endocrine Society's Clinical Practice Guideline for Pediatric Obesity* represents a contemporary clinical management guideline.[16] 4) The *United States Preventive Service Task Force (USPSTF) 2017 Recommendation Statement on Screening for Obesity in Children and Adolescents* sought to identify the treatment

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intensity required for effectiveness based on a comprehensive review of interventions.[17]

68.3 DEFINITIONS

The term obesity refers to excess adiposity. BMI (weight[kg]/height[m^2]) is the accepted clinical surrogate of adiposity for children aged two years and older, and weight-for-length is the appropriate measure for children under two years:[18]

≥2 years of age (reference standard to use: CDC BMI Growth Charts 2–20);[19] <2 years of age (reference standard to use: WHO Weight-for-Length Growth Charts Birth–24 months[20]); "overweight" (weight for recumbent length for age and sex ≥97.7th percentile):[16]

Overweight (BMI ≥85th percentile through the 94th percentile for age and sex)
Obesity (BMI ≥95th percentile for age and sex)
Severe obesity (BMI ≥120% of the 95th percentile or ≥35 kg/m^2)[15]

68.4 ETIOLOGIES

Childhood obesity results from the complex interactions of genetic, epigenetic,[21] lifestyle, biopsychological, and socioenvironmental factors. The major etiologies for childhood obesity are presented in Table 68.1. In addition to the etiologies listed, any pediatric condition that impairs energy balance (e.g., poorly controlled asthma or musculoskeletal conditions limiting mobility) may also contribute to excess weight gain.

68.5 COMORBID CONDITIONS

Obesity in childhood and adolescence can affect numerous organ systems. In some cases, the effects of a given degree of obesity on the body systems of a growing child can differ from the effects seen in an adult. For example, obesity may worsen respiratory conditions in children due to their smaller airway diameter, increasing the risk of collapse from external pressure. Some orthopedic problems such as Blount disease or slipped capital femoral epiphysis (SCFE) occur prior to the fusion of the growth plates. Considerations for the role of lifestyle-based weight management of important comorbid conditions are described in Table 68.2. While lifestyle-change strategies represent a foundation of childhood obesity treatment, the risk of harm to the child posed by a comorbid condition and the severity of the obesity may prompt more intensive intervention as noted in Table 68.2.[14,16,22–37]

68.6 PREVENTION OF CHILDHOOD OBESITY

68.6.1 Risk and Protective Factors

Risk factors for the development of childhood obesity are now widely accepted to arise in the preconception and prenatal stages of life.[38] Postnatally, evidence-based risk factors associated with childhood obesity include sugar-sweetened beverage intake, increased screen time, decreased sleep duration, early adiposity rebound (the point where BMI begins to increase from its nadir in early childhood), and adverse experiences including violence or abuse. Protective factors include increased physical activity and increased family, school, and/or community involvement in prevention.[16,39,40] These represent attractive targets for potential prevention efforts across multiple settings and at individual and public health levels. In a recent meta-analysis, breastfeeding of any duration decreased the odds of obesity onset by age six years, with each month of breastfeeding decreasing the odds of early child obesity by 4% and the greatest benefit (one-third reduction in odds of obesity) seen from six months of exclusive breastfeeding.[41] For its many benefits, exclusive breastfeeding has been recommended for the first six months of life, continued thereafter along with complementary foods through 12 months of age.[42]

68.6.2 Screening

Early recognition of accelerated weight gain paired with early intervention strategies may prevent the progression to overweight or obesity. We recommend universally screening all children in primary care at least annually for excess weight gain using age- and sex-specific BMI percentiles (≥2 years) or weight-for-length percentiles (<2 years)[14,17]

68.6.3 Effectiveness of Prevention Interventions

A 2011 Cochrane review of interventions for preventing childhood obesity found strong evidence to support that these interventions as a whole produce small meaningful reductions in BMI.[43] The authors identified six policies and strategies believed to be influential in successful obesity prevention programs. Four were school-based (curricula inclusive of healthy eating, physical activity, and body image topics; improved nutritional quality of school-provided food; more physical activity time; and support for teachers and staff to execute health-promoting activities), one was home-based (parent support and a home environment that fosters healthy eating, physical activity, and decreased screen time), and one transcended any one setting (environments and cultural practices that consistently support healthy eating and physical activity). A comparative effectiveness meta-analysis of obesity prevention programs by setting showed that the strongest evidence for obesity prevention came from combined diet-physical activity interventions delivered in schools with both home and community components, and from physical activity-only interventions delivered in schools with a home component.[3] These results support a collaborative approach across settings to prevent obesity.

TABLE 68.1
Etiologies of Childhood Obesity

	Key Clinical Features	Examples
Social determinants	Resource limitations are important targets for screening and intervention Mediated by toxic chronic stress	• Poverty • Food insecurity, low access to healthy foods • Lack of neighborhood safety, lack of open spaces for exercise/play • Adverse early childhood events • Interpersonal and structural racism • Barriers to accessing healthcare (e.g., distance, transportation, loss of wages)
Lifestyle	Normal linear growth Generalized distribution of excess adiposity	Individual and family-level choices influencing nutrition, physical activity, sedentary behaviors, and energy balance including: • Nutritional quality • Daily screen time • Sleep quantity
Endocrinologic	Decreased linear growth	• Hypothyroidism (untreated) • Growth hormone deficiency • Cushing syndrome
Hypothalamic dysfunction	Pituitary hormone deficiencies Increased hunger/poor satiety Decreased resting energy expenditure	• Treatment of hypothalamic/pituitary tumors (e.g., surgery/radiation for craniopharyngioma) • Direct effects of a tumor, trauma, or inflammatory disease
Medications	Weight gain temporally associated with medication initiation	• Atypical antipsychotics, systemic corticosteroids, depo-medroxyprogesterone, select mood stabilizers, antidepressants, and anticonvulsants
Genetic syndromes[16]	Severe obesity before age five, developmental delay, dysmorphic features, and/or hyperphagia	*Developmental delay + dysmorphic features* • Prader–Willi syndrome • Bardet–Biedl syndrome • Albright hereditary osteodystrophy *(+) Hyperphagia without developmental delay or dysmorphic features* • MC4R deficiency • Leptin/leptin receptor deficiency • POMC deficiency

MC4R, melanocortin 4 receptor;
POMC, proopiomelanocortin.

68.7 TREATMENT OF CHILDHOOD OBESITY

68.7.1 Overview of Treatment Goals

A holistic view of the child and family should guide the weight management treatment plan. Overarching goals include improving quality of life, family functioning, and healthy child development while achieving meaningful BMI change that will yield physical and mental health benefits. This should be accomplished in a manner that encourages shared decision-making between families and providers and incorporates their values, cultural beliefs, and socioeconomic challenges.

68.7.2 Clinical Weight Loss Goals

Weight loss goals should be guided by the child's age, degree of excess weight at baseline, presence of comorbidities, and the patient/family's readiness to change. For all children, an ideal endpoint is at least a BMI <95th percentile, based on the compelling opportunity to reverse cardiometabolic risk[44] And, in some children, a BMI less than the 85th percentile is advisable. This is in recognition of the fact that within the overweight BMI range (85th–94th percentile), the correlation between BMI and excess adiposity is not as strong (~50% specificity compared with 95% specificity for a BMI in the obesity range).[18] There are also important differences in the relationship between BMI and body adiposity that should be considered on an individual basis.[45] Thus, an endpoint less than the 85th percentile may be appropriate in children with additional risk factors (e.g., personal or family history of obesity-related comorbidities) but may be overly restrictive for a child with healthy lifestyle habits, normal screening labs, and benign family history. For children with obesity, the recommended rates of weight loss by age group are as follows: 2–5 years: weight maintenance or up to 1 lb/month; 6–11 years: 1 lb/month–2 lb/week; 12–18yo: 1–2 lb/week.[14] More rapid losses should prompt investigation for unhealthy weight loss methods. Predicting the amount of weight loss that might occur and be maintained with a given change in energy balance can guide weight management. Unfortunately, many fitness software applications do not account for the body's

TABLE 68.2
Select Conditions Comorbid with Childhood Obesity

Conditions by System	Prevalence and Diagnostic Considerations	Treatment Considerations
Pulmonary		
Obstructive sleep apnea (OSA)	Occurs in 19–61% of youth with obesity; risk increases with increasing BMI.[22] Diagnosed by polysomnogram, which is indicated for children with obesity and frequent snoring.	Tonsillectomy is the first-line treatment when there is tonsillar hypertrophy but is less effective when obesity is present.[23] Positive pressure therapy is often needed for moderate to severe OSA. Severe OSA should prompt stage 4[a] treatment of obesity.
Cardiovascular		
Hypertension	Prevalence 4–25% in youth with overweight and obesity. Hypertension is diagnosed based on auscultated BP ≥95th percentile for sex, age, and height or ≥130/80 (whichever is lower) at three different visits. See updated tables in the 2017 AAP Clinical Practice Guidelines.[25]	Elevated BP (≥90th to <95th percentile or ≥120/80, whichever is lower) should be treated with lifestyle management; stage 1 hypertension (≥95th to <95th percentile BP + 12 mmHg or ≥130/80) in children with obesity may be treated with lifestyle weight management (including DASH diet) for three months, then antihypertensive medication added if needed; Treatment of stage 2 hypertension (≥95th percentile + 12 mm Hg or ≥140/90 mm Hg) begins with combined lifestyle and medication management within stage 4[a] obesity treatment.[25]
Lipid abnormalities	Universal screening recommended by sexual maturity rating 2 (Tanner 2). Non-fasting non-HDL or fasting LDL can be used to screen for familial hyperlipidemia. Mild-moderate hypertriglyceridemia with low HDL is the most common abnormality.[26]	Treatment decisions are based on the average of two fasting samples. LDL >100 mg/dL and <160 mg/dL and triglycerides <400 mg/dL are typically treated with lifestyle modification in children. Statins are considered by lipid management experts for children above eight years with LDL >160 mg/dL or >130 mg/dL if cardiovascular risk factors are present such as diabetes. The risk for pancreatitis increases if fasting triglycerides exceed 400 mg/dL.
Orthopedic		
Blount disease (tibia vara)	This stress injury to the medial tibial growth plate creates bowing of the legs. Two peaks of incidence occur in toddlers/preschoolers with overweight and adolescents with severe obesity.[27]	This potentially disabling condition is treated with either bracing or surgery, which impair mobility for prolonged periods. Any orthopedic condition that impairs the mobility of a child with obesity should be treated urgently with lifestyle-based weight management, and stage 4[a] treatment could be considered based on severity.[28]
Endocrine	Elevated HgA1c 5.7–6.4%	Lifestyle-based weight management is the primary treatment.
Impaired glucose metabolism or prediabetes	Elevated fasting glucose = 100–125 Screening beginning at Tanner stage 2 for children with severe obesity may identify those at the highest risk of T2DM[29]	Metformin is not supported by long-term studies for weight loss or diabetes prevention.[30] The Endocrine Society recommends against using metformin in children with prediabetes.[16] Risk for insulin resistance peaks mid-puberty and often resolves by Tanner stage 5.[31]
Type 2 diabetes (T2DM)	Prevalence in adolescents has increased in recent decades but remains a rare diagnosis. The incident rate is 12.5 cases per 100,000 US youth per year, but is higher in black, Hispanic, and Native American youth.[32]	Management by a pediatric endocrinologist is recommended. Lifestyle management plus stage 4 treatment of obesity should be considered. Bariatric surgery is particularly efficacious for T2DM in adolescents.[104]
Polycystic ovary syndrome (PCOS)	PCOS is the most prevalent endocrinopathy affecting women of reproductive age (8–13%). It is associated with overweight/obesity and metabolic disease, especially type 2 diabetes. Diagnostic criteria for adolescents include irregular menstrual cycles (starting one year after menarche) + clinical or biochemical hyperandrogenism without another etiology identified. Note: ultrasound is *not* recommended until eight years post-menarche.[105]	First-line treatment includes multicomponent lifestyle modification (including sleep, mood, quality of life, and other sources of insulin resistance including high glycemic diets and low physical activity). Weight loss improves hormone abnormalities and symptoms of PCOS (hirsutism, menstrual irregularity) and mitigates metabolic risk. Pharmacotherapy for PCOS is used to treat signs of hyperandrogenism (combined oral contraceptive ± anti-androgens), insulin resistance (e.g., metformin), and obesity (anti-obesity medications).[106]
Hypothyroidism	Not recommended as part of routine screening of every child with obesity, but test in the setting of thyroid symptoms, family history, or linear growth faltering.[14]	Subclinical TSH elevations can be seen in children with obesity. Treatment decisions are guided by a pediatric endocrinologist.[34] Reassessment of thyroid function could be considered if diligent efforts fail to yield success in weight management for a child with a family history of thyroid disease.

(*Continued*)

TABLE 68.2 (CONTINUED)
Select Conditions Comorbid with Childhood Obesity

Conditions by System	Prevalence and Diagnostic Considerations	Treatment Considerations
Gastrointestinal		
Non-alcoholic fatty liver disease (NAFLD)	NAFLD is present in 29–38% of children with obesity. The screening test is alanine aminotransferase (ALT): >22 units/L in females or >26 units/L in males, which suggests NAFLD, per 2017 NASPHGAN guidelines. Diagnosis is a spectrum that may progress from fatty infiltration, to steatohepatitis, to fibrosis, and cirrhosis.[35]	In adults, 10% weight reduction resolves 90% of cases of steatohepatitis. Lifestyle-based weight management including reduced sugar intake is the primary treatment. ALT as a surrogate marker of liver inflammation is inexpensive but correlates less with histology than liver elastography, CT, or MRI. If ALT is persistently (>3 months) above twice the upper limit of normal, assess labs for autoimmune, infectious, and genetic causes of liver disease in consultation with a pediatric hepatologist.[35]
Dermatology		
Acanthosis nigricans	Most children with acanthosis have normal blood glucose. This darkened, thickened skin found at the neck, axillae, and/or groin is a sign of insulin resistance and hyperinsulinemia.[36]	Fades with successful lifestyle-based weight management. Parents should avoid scrubbing away acanthosis because melanocytes reside in the deepest layer of the epidermis.[37]
Mental Health		
Depression, anxiety, disordered eating, low self-esteem, body dissatisfaction, impaired quality of life	Youth with obesity have a ~34% higher risk of developing depression. Of those seeking treatment, up to 50% have depression or anxiety.[107] Universal screening using validated tools is recommended.[16] These psychological conditions have complex interactions with an individual's experiences of bullying, stigma, external and internalized bias, and discrimination.[78,108]	Professionally structured/delivered multicomponent lifestyle interventions have been shown to improve depression and anxiety[107] and are not associated with increased eating disorder risk.[109] Screening should guide referral to intensified interventions including psychotherapy or medication management.

[a] Stage 4 treatment of obesity is indicated when BMI is very high (>99th percentile or >140% of the 95th percentile) or for severe comorbidities. These weight management interventions, including restrictive diets, medications, and surgery, are typically offered by pediatric weight management experts at referral centers.

reduction of resting energy expenditure after weight loss. One noteworthy exception is the NIH Body Weight Planner,[46] which accounts for this metabolic adaptation (found at www.niddk.nih.gov/health-information/weight-management/body-weight-planner)[47] If available, indirect calorimetry is a useful tool to quickly and non-invasively measure resting metabolic rate, allowing calorie goals to be tailored to factors that affect metabolism including body composition, sleep quality/duration, prolonged fasting, and recent weight fluctuations.[48]

68.7.3 Interpreting Treatment Effects

Outcome measures reported in obesity studies have been poorly standardized, which can make it difficult to compare conclusions across heterogeneous interventions and populations. The most widely reported measure in the last two decades has been the change in BMI z-score. However, there are important limitations to using the BMI z-score. First, it is difficult to apply clinically. Second, the BMI z-score is an inaccurate and statistically invalid measure of adiposity for children and adolescents with severe obesity.[49] BMI for youth with severe obesity should be expressed relative to the age- and sex-specific CDC growth chart's 95th percentile, either as a percent above the 95th percentile or the distance (in kg/m^2) from the 95th percentile. For example, a 14-year-old girl with an actual BMI of 36 kg/m^2 and a 95th percentile BMI of 27 kg/m^2 is 132% above the 95th percentile or +9 kg/m^2 from the 95th percentile. Clinically, an "extended" BMI growth chart can facilitate the monitoring of weight trends for patients with severe obesity[50] The CDC has defined a new metric called the "Extended BMI z-Score" that overcomes the statistical limitations of the historical CDC BMI z-score, and for which new growth charts are currently in development.[51]

68.7.4 2007 Expert Committee's Staged Intervention Framework

The 2007 Expert Committee Guidelines proposed a structure for healthcare delivery of pediatric obesity interventions in four stages, which provide increasingly intensive interventions, beginning with structured weight management in the primary care setting and advancing to comprehensive, multidisciplinary management in a tertiary care center[14] Movement through these stages is based on the severity of the patient's obesity, comorbidities, age, the family's motivation to change, available resources, and treatment progress. The primary goal of treatment is permanent, healthy lifestyle habits, which may be achieved using the following strategies: 1) patient/family-driven identification of priority behaviors reflective of their values

and preferences, and paired with goal setting; 2) motivational interviewing; 3) implementation of self-monitoring and planned reinforcement; 4) optimization of multidisciplinary expertise to address the physical and psychosocial needs of the family; and 5) excellent communication with the primary care provider (in stages 3 and 4). A few salient models of implementing treatment that have been tested are described below.

68.7.5 Behaviorally Based Multicomponent Lifestyle Treatment

68.7.5.1 Overview

Behaviorally based lifestyle interventions are recommended as a first-line treatment for childhood obesity.[14–16] Most behaviorally based interventions target more than one behavior (e.g., nutrition, physical activity, sleep) and are variably referred to as "multimodal", "multicomponent", or "multidisciplinary" interventions.

A series of 2016–2017 Cochrane reviews for children from preschool through 17 found that multicomponent lifestyle interventions had modest, positive effects on weight status. The overall quality of evidence ranged from very low to moderate and was limited by a high risk of bias, heterogeneous assessments of diet, physical activity, and behavior, and poor ethnic diversity. Gaps for future study include strategies to achieve post-intervention maintenance of effect and stronger data on comorbidities and cost.

68.7.5.2 Family-Based Behavioral Treatment

The most extensively tested behavioral pediatric weight management is an approach developed by Epstein and colleagues called family-based behavioral treatment (FBT)[52] FBT is an intensive intervention originating from family systems theory and traditionally has simultaneously treated the parent(s) and child. Standard FBT is delivered in 16 weekly sessions that target *nutrition* (using the traffic light diet paradigm), *behavior* (e.g., self-monitoring including documentation of caloric intake/exercise/weight, goal setting, and preplanned rewards for meeting self-determined goals), and recommendations for *physical activity.*[53] FBT has demonstrated efficacy in improving weight status up to 25 years after program involvement.[54] Despite FBT's impact on weight, lack of insurance coverage and significant training, resources, and participant time have been barriers to its widespread adoption. Additionally, the efficacy of FBT has been inadequately studied in youth with severe obesity, adolescents, and those of lower socioeconomic status. One strategy to ease dissemination barriers is to deliver a similar program only to parents of young children, which can be as effective.[55,56]

68.7.5.3 Mindfulness

Mindfulness is an emerging intervention strategy in pediatric obesity that aims to enhance self-regulation of targets including child and parent stress response and lifestyle behaviors[57–59] In one RCT, adolescent girls with overweight/obesity, risk for type 2 diabetes, and depressive symptoms who received a six-week (1 hour/week) group intervention, with activities teaching breath awareness, mindful eating, mindful movement (yoga), and meditation, had greater improvements in depression and insulin resistance compared with a cognitive behavioral control[59]

68.7.6 Office-Based Interventions: Motivational Interviewing

Motivational interviewing (MI) is an effective and versatile evidence-based tool, which can be used one-on-one, or with groups, in multiple weight management prevention and treatment settings. MI is a patient-centered counseling style that encourages families to take the driver's seat in identifying and exploring potential behaviors that may be modified to improve health. As few as three visits with MI-trained PCPs plus two to three phone calls by MI-trained dietitians over 2 years significantly improved BMI in the Brief Motivational Interviewing for Body Mass Index (BMI^2) study.[60] MI paired with point-of-care electronic clinician decision support may also be an effective approach for dissemination.[61] Specific MI techniques that healthcare providers can master to help families move from a place of ambivalence include: asking open-ended questions and using reflective listening to elicit change talk from the patient/family (e.g., "I want to…because", "I can…"). The AAP's "*Change Talk: Childhood Obesity*" is a free online resource that can help providers develop MI skills[62] (found at: https://ihcw.aap.org/resources/).

Next Steps: A Practitioner's Guide of Themed Follow-up Visits to Help Patients Achieve a Healthy Weight[63] is a tool designed by the National Initiative for Children's Healthcare Quality and the AAP to help clinicians conduct pediatric weight management visits around evidence-based targets. Topics include meal patterns and snacks, portion sizes, screen time and sleep, and bullying and teasing. It also includes counseling materials for providers and self-directed activity books for families. The *Next Steps* guide and flip chart is available for purchase on the AAP's website.

68.7.7 Nutrition Interventions

68.7.7.1 Balanced Hypocaloric Reduction

The first nutrition intervention in a staged weight management treatment approach is often a balanced reduction in calories, accomplished through individualized small changes, matched to a family's readiness to change. This approach is relevant across practice settings (from primary care to referral weight management centers) and is commonly delivered through weekly to monthly multidisciplinary visits using techniques including motivational interviewing and collaborative goal setting. Common dietary targets include reducing sugar-sweetened beverages, calorie-dense/nutrient-poor snacks, and portion sizes, increasing intake of home-cooked meals, vegetables, fruits,

whole grains, and lean protein, improving meal routine (not skipping meals, avoidance of grazing), and increasing awareness of hunger and satiety cues.[14,16]

68.7.7.2 Traffic Light Diet

The Traffic Light Diet is a widely used schema that can similarly achieve balanced, moderate hypocaloric restriction. It was developed by Epstein et al. and serves as the core nutrition component of multidisciplinary FBT programs.[64] This system divides foods into green (low-calorie, no limit), yellow (intermediate calories, eat in moderation), and red (high calorie + all sugar-sweetened beverages, avoid). Families are instructed to stay under a specified daily caloric limit and to limit red foods to fewer than five per week.[54]

68.7.7.3 Ideal Macronutrient Composition

For children and adolescents with overweight and obesity, there is not one specific dietary macronutrient composition (i.e., relative proportion of protein, carbohydrates, and fat) that is clearly superior to achieve significant and sustained improvements in BMI.[65] Existing evidence supports that a low-carb, high protein diet may be most effective for moderate *short-term* weight loss compared with a low-fat diet, but long-term results are similar at two years.[65] Thus, a reduction in total energy intake, through any macronutrient combination, may improve weight-related outcomes. On a practical note, when implementing a low carb (<60 g/d), high protein diet, patient selection for adherence and tolerance and supervision by a medical provider and dietitian are key for success.

68.7.7.4 Very-Low Calorie Diets and Meal Replacement

Very-low calorie diets (VLCDs) typically provide 500–800 kcal/day in the form of a formulated high protein, low carb, low fat micronutrient-enhanced liquid/soup/bar (i.e., meal replacement), high protein, low carb whole foods, or a combination. Meal replacement products can reduce the burden and increase the accuracy of self-monitoring and may facilitate healthy eating through stimulus narrowing.[66] Among 5–18-year-olds with obesity, VLCDs result in a mean initial 10.1 kg weight loss (after 3–20 weeks of intervention) and 5.3 kg weight loss at longer-term follow-up (5–14.5 months from baseline).[67] Adherence to this diet is difficult. In practice, the initial phase of a VLCD should be delivered under close medical supervision, followed by a supervised transition to a balanced low-calorie diet. Adult studies demonstrate that VLCDs do not result in greater, long-term (at two years) weight loss than moderately calorically restricted diets (1000–1500 kcal/day), chiefly because of greater weight regain following the VLCD, and are more costly.[68] Meal replacement as part of a moderate caloric restriction (1300–1500 kcal/day) in adolescents may be a tool to achieve short-term weight loss (at ~4 months), but sustained BMI reduction (at one year) compared with an isocaloric diet from conventional foods is similar[66]

68.7.8 Physical Activity and Sedentary Behavior Interventions

68.7.8.1 Physical Activity

Evidence supports physical activity as an adjunct to nutritional and behavioral lifestyle interventions to achieve small, short-term reductions in weight outcomes with very low risk[69–71] While the independent effect of physical activity on BMI is less clear, well-supported benefits of physical activity in children and adolescents with obesity include improvements in vascular function, cardiorespiratory fitness, and cardiometabolic risk factors.[72] The 2018 Physical Activity Guidelines for Americans recommend that 6–17-year-olds engage in at least 60 minutes per day of moderate to vigorous activity through a combination of aerobic (e.g., fast walking, biking), muscle-strengthening (e.g., playing on a jungle gym, resistance exercises), and bone-strengthening (e.g., jumping rope) activities[73] Nationally recognized guidelines for physical activity for children five and younger[74] recommend that one to five-year-olds get at least 60 minutes (and up to several hours per day) of unstructured activity *plus* daily structured activity for at least 30 minutes (one to three-year-olds) and 60 minutes (three to five-year-olds); one to five-year-olds should not be sedentary for more than one hour, except during sleep. Physical activity at this age is focused on developing motor skills.

While an hour or more per day of physical activity is the goal for most children, there is data to support that as few as 10–20 minutes of high-intensity interval activity may result in meaningful physical and cognitive health benefits in youth with overweight and obesity.[75,76] Additionally, physical activity interventions for children with obesity are more likely to be successful if they 1) are individualized to match baseline fitness/exercise tolerance levels[77] and 2) address stigma (particularly weight-based teasing), which can have significant adverse effects on a child's body image, motivation, and desire to participate in any physical activity[78]

68.7.8.2 Sedentary Behavior

Reduction of sedentary behavior is an essential, independent behavioral target of obesity treatment programs. Screen time is a ubiquitous example of a sedentary behavior. Increased duration and frequency of screen time among 5–17-year-olds of any weight status have been associated with higher cardiometabolic risk scores, lower fitness, and lower self-esteem[79] The AAP's 2016 media use policy statements[80,81] recommend the following by age: <18 months: no screen media except for limited video chatting; 18–24 months: evidence-based educational shows/apps *with* parent interaction; two to five years old: ≤1 hour of high-quality programming, ideally with an adult to promote learning; 5–18 years old: no specific maximum, but parents are encouraged to place consistent limits they choose; emphasis is placed on ensuring sleep and physical activity goals are reached and creating media-free family time. For all ages,

screens should not be accessed while eating or in the hour before bedtime, and no screens should be kept in the bedroom. The free AAP Family Media Use digital planning tool can help families design an individualized plan[82] (www.healthychildren.org/English/media/Pages/default.aspx).

68.7.8.3 Sleep Interventions

Sleep is a relatively new target for pediatric obesity interventions. The National Sleep Foundation recommends the following hours of sleep per night by age: one to two-year-olds (11–14 hours), three to five-year-olds (10–13 hours), 6–13-year-olds (9–11 hours), and 14–17-year-olds (8–10 hours).[83] Observational data support that restricted sleep is associated with double the odds of developing obesity in childhood.[84] And each one hour increase in sleep per night has been associated with a 0.05 kg/m^2 reduction in yearly BMI gain.[85] A systematic review and meta-analysis of interventions targeting sleep in children and their effects on health, BMI, diet, and physical activity[86] found only one study that successfully extended sleep duration (and also reduced BMI) through motivational coaching that focused on improved routines.[87] Possible mechanisms to explain the sleep duration-obesity link include increased time awake and related increased opportunity for intake, fatigue leading to decreased physical activity, and dysregulation of hunger and satiety hormones. There is a mixed body of evidence that on the whole supports an association between sleep restriction and unhealthy dietary patterns in children.[88]

68.7.8.4 Anti-Obesity Medications

Combined with ongoing lifestyle efforts, anti-obesity medications can be used as adjunct tools for a subset of youth with obesity.[14,15] While there is no universally accepted guideline for the timing of initiation, pharmacotherapy should be considered if lifestyle intervention for ~6 months has been unsuccessful in curbing weight gain and/or improving obesity comorbidities.[16,89] It is generally accepted that medications should not be used in those <16 years who are overweight, without obesity. Medications should be prescribed and monitored by a clinician experienced in their use and potential adverse effects. A planned assessment of effectiveness and tolerability and a decision to continue should be made within 12 weeks of starting the goal dose. BMI stability (as opposed to reduction) may be a reasonable definition of medication effectiveness in youth.[89] Medication choice should be tailored to the individual and state-specific prescribing regulations should be consulted. For rare monogenic obesities, metreleptin is indicated for leptin deficiency and setmelanotide for mutations in leptin receptor, pro-opiomelanocortin, and pro-protein convertase subtilisin/kexin type 1[90] The most common medications used in US pediatric weight management programs for primary obesity are topiramate, phentermine, metformin, and orlistat.[91] Liraglutide and orlistat are FDA approved for obesity in adolescents 12–17 years old, and phentermine for ≥17 years old. From limited existing adolescent data, placebo-subtracted BMI/weight loss efficacy ranges from no significant change with topiramate[92] to a 5–6% reduction for liraglutide[93] and high-dose phentermine/topiramate[94] Results from phase three clinical trials of phentermine/topiramate and once-weekly injectable semaglutide in youth are expected in 2022. Off-label use of medications for obesity, like for all other conditions, requires sound medical judgment after weighing risks, benefits, and alternatives. The AAP reinforces that the term "off-label" does not suggest "improper, illegal, contraindicated, or investigational use".[95]

68.7.8.5 Metabolic and Bariatric Surgery

In the United States, severe obesity affects 6.1% of youth[96] and is associated with significant cardiometabolic risk including premature death.[15] Given few effective treatment options for severe obesity, metabolic and bariatric surgery (MBS) is increasingly being considered as a tool to achieve significant, sustained weight loss. From the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study (the most robust prospective trial of MBS in the United States), at three years postoperatively, mean weight loss was 28% after Roux-en-Y gastric bypass and 26% after sleeve gastrectomy, and remission across comorbidities was 95% (type 2 diabetes), 76% (prediabetes), 74% (elevated blood pressure), 66% (dyslipidemia), and 86% (abnormal kidney function)[33] Comparing five-year outcomes between Teen-LABS and adult LABS participants who underwent bypass, adolescents were 51% and 27% more likely to be in remission from hypertension and type 2 diabetes, respectively, versus adults. However, it is worth noting that weight loss response to MBS at an individual level is heterogeneous.[97] Risks of MBS include possible need for additional surgeries (e.g., leak, cholecystectomy, internal hernia) and micronutrient deficiencies.[98,99] It is recommended that females avoid pregnancy for 12–18 months postoperatively, and a contraception plan should be established prior to surgery. The American Society for Metabolic and Bariatric Surgery's 2018 pediatric guidelines and the AAP's 2019 statement and technical report on pediatric bariatric surgery[100,101] are very closely aligned. The guidelines highlight low access/adoption of MBS in youth with severe obesity despite growing evidence of efficacy and safety. They recommend that MBS candidacy should be driven primarily by medical necessity and that those with younger pubertal stage, intellectual disability, or treated mental illness or disordered eating should *not* be denied evaluation by a qualified multidisciplinary team. Indications for MBS include BMI ≥120% of the 95th percentile or ≥35 kg/m^2 with comorbidities (e.g., obstructive sleep apnea [apnea-hypopnea index >5], type 2 diabetes, hypertension, idiopathic intracranial hypertension, non-alcoholic steatohepatitis, Blount disease, slipped capital femoral epiphysis), or a BMI ≥140% of the 95th percentile or ≥40 kg/m^2 regardless of comorbidity status. A multidisciplinary team, which typically includes at a

TABLE 68.3
Clinical Applications

Application	Description
Evidence-based behavioral targets for obesity prevention and/or treatment	a) Nutrition: Decrease sugar-sweetened beverages, high calorie processed snacks, portion sizes; increase vegetables, fruits, whole grains, home-cooked meals b) Physical activity: 60 minutes (moderate to vigorous)/day c) Sedentary behavior: Decrease screen time d) Sleep: Increase duration to meet age recommendations e) Behavior: Self-monitoring and goal setting, eating behaviors (e.g., appetite/satiety awareness, loss of control eating) f) Intensity: ≥26 hours/year of multidisciplinary intervention
Motivational interviewing techniques	1. *Reflections* (encourage parent to reconsider barriers and convey empathy): "You eat fast food because you are too tired to cook when you come home from work and that is frustrating for you". 2. *Reframing*: "You are able to cook two nights a week. What allows you to succeed in that?" 3. *Open-ended questions*: "Tell me about what makes eating more vegetables hard". 4. *Affirmations*: "You feel that exercising together as a family is important, you value time with your family". 5. *Roll with resistance*: Resist the urge to solve the problem for the family. Avoid saying what they "should" do. 6. *Summaries*: "Preventing diabetes is important to you, so you plan to begin buying more whole grains".
Possible obesity-focused physical exam findings	Vitals: Elevated manual blood pressure (taken with correctly sized cuff); abnormal heart rate; hypoxia Head: Dysmorphic features Eyes: Abnormal visual field testing and papilledema (if concerned clinically for idiopathic intracranial hypertension) Nose and mouth: Nasal turbinate edema; tonsillar hypertrophy Neck: Enlarged or nodular thyroid Cardiopulmonary: Evidence of heart failure which may include murmurs, S3, S4, peripheral edema, or pulmonary rales/rhonchi/wheezing Abdominal: Hepatomegaly; right upper quadrant or epigastric pain Musculoskeletal: Abnormal gait/limp; pain with passive rotation of the hip(s) (SCFE); bowed legs (Blount disease) Skin: Acanthosis nigricans; skin tags; hidradenitis suppurativa; abscesses; cellulitis; hirsutism, alopecia, severe acne Neuro: Developmental delay Psych: Depressed or anxious mood; flat affect

SCFE, slipped capital femoral epiphysis.

minimum a surgeon, pediatric medical provider, psychologist, and dietitian, will assess the patient and family's ability to adhere to pre- and postoperative recommendations. Goal setting, self-monitoring, and positive peer interactions are targeted pre- and postoperatively to help patients reach fluid, protein, and vitamin adherence goals and minimize risks including excess loss of lean muscle mass, micronutrient deficiencies, and weight regain[102,103]

Table 68.3 highlights the key clinical applications of this chapter.

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69 Identification and Management of Children with Dyslipidemia

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KEY POINTS

- Children with dyslipidemia, especially those with elevated low-density lipoprotein cholesterol (LDL-C), are at risk for developing atherosclerotic cardiovascular disease.
- Children should be screened for dyslipidemia with either a fasting lipid profile or a non-fasting, non-high-density lipoprotein (HDL)-cholesterol.
- Heterozygous familial hypercholesterolemia is a common genetic dyslipidemia (1:250 individuals) associated with moderate to severe elevations in LDL-C and premature cardiovascular disease.
- Lifestyle-associated dyslipidemia, often the result of obesity, is associated with elevated triglycerides and low HDL-C.

69.1 BACKGROUND

Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] CVD is not merely an adult phenomenon.[2–5] In children with lipoprotein abnormalities, damage to the arterial endothelium can occur as early as the first decade of life. Over the past decade, screening guidelines to identify children with lipoprotein abnormalities have changed[6] While identifying children with genetically high cholesterol remains a priority, with the increased prevalence of overweight and obesity, identifying children with lifestyle-related abnormalities has also become necessary. In this chapter, we will review the definition of dyslipidemia in childhood, how to screen for dyslipidemia, discuss treatment recommendations regarding diet and lifestyle, and offer guidance for medication initiation. We will present two clinical cases to highlight the management of different dyslipidemias.

69.2 DYSLIPIDEMIA AND LIPID VALUES IN CHILDREN

Dyslipidemia is defined as an abnormality of lipoprotein metabolism resulting in elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and/or low levels of high-density lipoprotein cholesterol (HDL-C). Non-HDL-C, calculated as TC minus HDL-C, is a measure of all the atherogenic apolipoprotein B (apo B)-containing lipoproteins in the circulation and may also be elevated.

Both cholesterol and triglycerides are lipids (or fats) that can be acquired through production in the body or by absorption of food. Cholesterol is necessary for hormone production and is a major component of cell membranes, fat-soluble vitamins, and bile. Triglycerides supply energy to the body. Due to the hydrophobic nature of lipids, they travel in the bloodstream attached to hydrophilic lipoproteins. The polar outer layer of plasma lipoproteins contains apolipoproteins that are important for lipoprotein metabolism.[7]

69.2.1 Progression of Atherosclerosis

The arterial fatty streak is the first lesion in the progression of atherosclerosis visible to the naked eye. This can be seen in children and adolescents with dyslipidemia. While generally reversible, if abnormal lipid levels continue over time, the fatty streaks can progress to irreversible fibrous plaques. These plaques can increase in number and severity as children become adults.[8]

69.2.2 Normal versus Abnormal Lipoprotein Values

Optimal, borderline, and high lipid level classifications are found in Table 69.1.[6] For children and adolescents, the "borderline" or "high" levels correspond to the 75th and 95th percentiles, respectively, and "low" levels to the 10th percentile. Similarly, for young adults ages 20 to 24 years, the "borderline" or "high" level values of TC, LDL-C, and non–HDL-C correspond to the 75th and 95th percentiles. However, for TGs, "borderline" levels correspond to the 75th percentile and high levels to the 90th percentile. For HDL-C, "optimal" levels are greater or equal to the 50th percentile, "borderline" levels are between the 25th and 50th percentile, and "low" levels are below the 25th percentile.[6]

69.3 SCREENING FOR DYSLIPIDEMIA

69.3.1 Universal Screening

In 2011, the Cardiovascular Risk Reduction Guidelines from the National Heart, Lung, and Blood Institute

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TABLE 69.1A

Cholesterol Level Classification for Children and Adolescents (in mg/dL)[6]

Lipid Category	Optimal	Borderline-High	High	Low
TC	< 170	170-199	≥200	
LDL-C	< 110	110-129	≥130	
Non-HDL-C	<120	123-144	≥145	
TG				
0-9 yr	<75	75-99	≥100	
10-19 yr	<90	90-129	≥130	
HDL-C	>45	40-44*		<40

*Borderline low

TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, non-HDL-C=non-high density lipoprotein cholesterol, TG=triglycerides, HDL-C=high density lipoprotein cholesterol

TABLE 69.1B

Cholesterol Level Classification for Young Adults (20-24 yrs, in mg/dL)[6]

Lipid Category	Optimal	Borderline-High	High	Low
TC	< 190	190-224	≥225	
LDL-C	< 120	120-159	≥160	
Non-HDL-C	<150	150-189	≥190	
TG	<115	115-149	≥ 150	
HDL-C	>45	40-44*		<40

*Borderline low

TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, non-HDL-C=non-high density lipoprotein cholesterol, TG=triglycerides, HDL-C=high density lipoprotein cholesterol

(NHLBI) Expert Panel were released. The panel recommended that all children be screened for dyslipidemia at least once between the ages of 9 and 11 years and again between the ages of 17 and 21 years.[6] Universal screening recommendations were created to identify patients who may not have been screened for dyslipidemia using the previous guidelines.[9,10] Selective screening can miss up to 30–60% of children with dyslipidemia as parents may be unaware of their own personal or family history of dyslipidemia or too young to have developed early atherosclerosis.[9,11–15] One benefit of universal screening is reverse cascade screening, which can identify affected family members. Relatives of children with hypercholesterolemia are also frequently at increased risk of early CVD.[16,17]

69.3.2 When Should I Screen and What Laboratory Studies Should I Obtain?

The lipid screening guidelines in children and adolescents are shown in Table 69.2. It is recommended that all children

TABLE 69.2

Cholesterol Screening Recommendations by Age[6]

Age	Screening Recommendation	Labs
< 2 years	No screening	
2-8 years	No routine screening	
	Screening if: • Family history of early heart disease** • Parent with TC ≥ 240 mg/dL • High risk condition (see Table 3)	FLP x 2*
9-11 years	Universal Screening	Non-FLP
	If non-HDL-c ≥ 145 or HDL-c < 40	
	Then obtain	FLP x 2*
	If LDL-c ≥ 130 or non-HDL-c ≥145 or HDL-c < 40 or TG > 100 (age < 10yr) or > 130 (age ≥ 10yr)	FLP
	Then obtain	Repeat FLP*
12-16 years	No routine screening	
	Screening if:	
	New knowledge of CVD risk, same as 2-8 yr	FLP x 2*
17-21 years	Universal Screening	
	Ages 17-19:	Non-FLP
	If non-HDL-c ≥ 145 or HDL-c < 40	
	Then obtain	FLP x 2*
	If LDL-c ≥ 130 or non-HDL-c ≥145 or HDL-c < 40 or TG > 100 (age < 10yr) or > 130 (age ≥ 10yr)	FLP
	Then obtain	Repeat FLP*
	Ages 19-21:	Non-FLP
	If non-HDL-c ≥ 190 or HDL-c < 40	
	Then obtain	FLP x 2*
	If LDL-c ≥ 160 or non-HDL-c ≥190 or HDL-c < 40 or TG ≥ 150	FLP
	Then obtain	Repeat FLP*

CVD=cardiovascular disease; FLP=fasting lipid profile; non-FLP=non-fasting lipid profile; LDL-c=low-density lipoprotein cholesterol; HDL-c=high-density lipoprotein cholesterol; non-HDL-c=non-high-density lipoprotein cholesterol (total cholesterol – high density lipoprotein cholesterol); TC=total cholesterol; TG=triglycerides. *2nd lipid profile should be obtained 2 weeks-3 months after the first lipid profile. **Positive family history: a first or second-degree relative with documented CVD (e.g., angina pectoris, peripheral or cerebral vascular disease, myocardial infarction, coronary artery disease, or sudden death) by age < 55 years for a male and < 65 years for females

and adolescents between the ages of 9 and 11 years and 17 and 21 years be screened for dyslipidemia. The Expert Panel selected the initial screening age of approximately 10 years since lipid levels change throughout childhood, most notably during puberty, when there can be up to a 20% decrease in cholesterol levels.[6]

Universal screening can be performed using either a non-fasting lipid panel (non-FLP), where TC and HDL-C are

obtained and the non-HDL-C is calculated, or by obtaining a fasting lipid panel (FLP). The FLP includes the TC, HDL-C, TG, and a calculated LDL-C. The LDL-C is calculated indirectly using the Friedewald formula: LDL-C = TC – (HDL-C – TG/5). If there is significant hypertriglyceridemia (i.e., >400 mg/dL) this formula is not accurate. Instead, one can use the non-HDL-C value to determine if further evaluation is necessary. In 2020, Sampson and colleagues published a new and more accurate LDL-C formula for patients with hypertriglyceridemia (TG ≤800 mg/dL) and/or low LDL-C (LDL-C <70 mg/dL).[18] This may become the predominant formula used to calculate LDL-C in the future.

If there are abnormalities on the non-FLP, then a FLP should be obtained twice, and the average should be used to determine management. If the initial test is a FLP and there are abnormalities, then a repeat FLP should be performed, and the results of the two tests should be averaged. When two FLPs are averaged, the second FLP should be obtained two weeks to three months after the first, once some diet and lifestyle modifications have occurred.

For children 2 to 8 years and 12 to 16 years, selective screening based on personal and family history is recommended[6] Table 69.3 details the conditions for which selective screening should be performed. In 2019, the American Heart Association published a statement on cardiovascular risk reduction in children at high risk for early CVD. This statement proposed a risk stratification schema that accounts for individual risk conditions as well as the compounded effects of multiple conditions (Figure 69.1).[19]

Screening should occur every three to five years in those with a family history of premature CVD (age ≤55 years for males, ≤60 years for females) and annually in those with other risk conditions.[19] Treatment recommendations should be based on the average of two FLPs, with the second FLP ideally two weeks to three months after the first.

69.3.3 Evaluation for Secondary Causes of Dyslipidemia

After a child has been identified with abnormal lipids, the practitioner should perform a thorough evaluation. A complete family history is necessary and should include identifying first- and second-degree relatives with a history of dyslipidemia, premature CVD, diabetes mellitus, and hypertension. For children with severe dyslipidemia, primary genetic causes of dyslipidemia are likely. However, a thorough evaluation for secondary causes should also be performed (Table 69.4).[20] Most secondary causes can be found through a careful medical history and physical exam. Laboratory studies should be obtained to evaluate for diseases that can lead to or are associated with dyslipidemia. These include hepatic function tests for fatty or obstructive liver disease; fasting blood sugar and hemoglobin A1c level for diabetes in the obese; thyroid function tests for hypothyroidism; a urinalysis; blood urea nitrogen; and creatinine level for renal disease.

TABLE 69.3

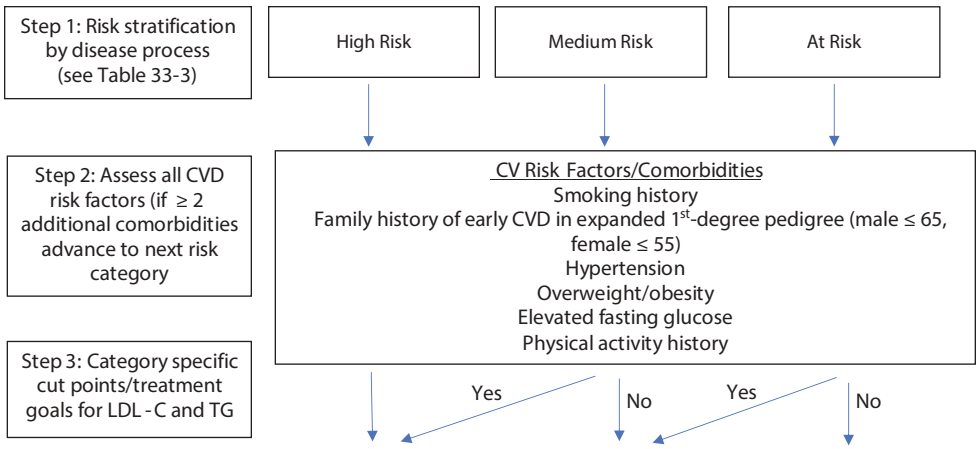
Risk Factors and Special Risk Conditions for Screening Children for Dyslipidemia, ages 2-8 and 12-16 years[18]

- High risk factor/condition
  - Homozygous familial hypercholesterolemia (HoFH)
  - End-stage renal disease
  - Diabetes (Type I and Type 2)
  - Solid organ transplant vasculopathy
  - Kawasaki disease, with persistent aneurysm
  - Childhood cancer survivor (stem cell transplant)
- Moderate risk factor/condition
  - Severe obesity (BMI ≥120% of the 95th percentile or absolute BMI ≥35 kg/m^2)
  - Heterozygous familial hypercholesterolemia (HeFH)
  - Elevated Lp(a)
  - Chronic kidney disease (pre-dialysis)
  - Aortic stenosis
  - Childhood cancer survivor (chest radiation)
- At risk
  - Obesity (BMI ≥95th percentile)
  - Insulin resistance with comorbidities (dyslipidemia, non-alcoholic fatty liver disease, polycystic ovarian syndrome)
  - White-coat hypertension
  - Hypertrophic cardiomyopathy and other cardiomyopathies
  - Pulmonary hypertension
  - Kawasaki disease with regressed aneurysm (zMax ≥5)
  - Chronic inflammatory disease (JIA, SLE, IBD, HIV)
  - Status post coronary artery translocation for anomalous coronary arteries or transposition of the great arteries
  - Childhood cancer (cardiotoxic chemotherapy only)

BMI=body mass index; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; IBD, inflammatory bowel disease; HIV, human immunodeficiency virus.
(Adapted from de Ferranti, S. D., et al. (2019). "Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association." Circulation **139**(13): e603-e634.)

69.4 CLINICAL CASE 1

A 13-year-old male, A.S., presents to the lipid clinic for evaluation of hypercholesterolemia. A FLP was checked due to his father's history of early heart disease, having undergone a coronary artery bypass graft at the age of 41 years. His paternal grandfather experienced a myocardial infarction at the age of 49 years. His 15-year-old brother has hypercholesterolemia and is on a statin. A.S. plays football and baseball at school. His daily sedentary time is two hours on the weekdays and three hours on the weekends. At home, his family eats a low-saturated fat diet. A.S. buys lunch at school, typically chicken nuggets or pizza. He snacks on pretzels, fruit, or cereal. He drinks juice or water with breakfast and dinner and chocolate milk with lunch. On physical examination, his height and weight are at the 60th and 90th percentile, respectively; his BMI is at the 91st percentile, placing him in the overweight category. His blood pressure is 116/74. The remainder of his exam is



	High risk	Moderate risk	At risk
LDL - C			
• Treatment threshold	LDL - C ≥ 130	LDL - C ≥ 160	LDL - C ≥ 160
• Treatment	Lifestyle change and statin initiation simultaneously	Lifestyle change x 3 months, if remain above goal start statin	Lifestyle change x 6 months, if remain above goal start statin
• Treatment goal	LDL -C < 100	LDL - C < 130	LDL -C < 130
TG			
• Treatment Threshold	TG > 400 or TG 150-400 and non-HDL ≥ 145		
• Treatment	Lifestyle change and pharmacotherapy initiation simultaneously	Lifestyle change x 3 months, if remain above goal start pharmacotherapy	Lifestyle change x 6 months, if remain above goal start pharmacotherapy
• Treatment goal	TG < 150 and non-HDL <145		

Adapted from de Ferranti, S. D., et al. (2019). "Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association." Circulation **139** (13): e603-e634.).

CVD, cardiovascular disease; LDL-*C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *HDL*; high-density lipoprotein

FIGURE 69.1 Risk stratification and treatment algorithm for high-risk pediatric populations (adapted from Sampson et al.,[18] in mg/dL).

benign. An average of two FLPs reveal (in mg/dL): TC 444, HDL-C 64, LDL-C 366, TG 69, and non-HDL-C 380. All other labs are within normal limits.

69.5 COMMON GENETIC CAUSES OF HYPERCHOLESTEROLEMIA IN CHILDHOOD

69.5.1 Heterozygous Familial Hypercholesterolemia

Heterozygous familial hypercholesterolemia (HeFH) is an autosomal codominant disorder that occurs in approximately one in 250 people in the general population.[21] HeFH is one of the most common genetic lipid disorders in the pediatric population. It is caused by one or more LDL receptor gene defects that lead to either a defective or a diminished number of LDL receptors. This results in decreased LDL-C clearance from the circulation by the liver and an accumulation of LDL particles in the blood. Children with HeFH may develop subclinical atherosclerosis with evidence of greater carotid intima-media thickness (CIMT) and abnormal brachial artery reactivity, indicating endothelial dysfunction.[22,23] While youth with HeFH generally do not manifest clinically apparent coronary artery disease until adulthood, if left untreated, they have a high risk of developing premature atherosclerosis.[24]

In Clinical Case 1, given the family history and severe LDL-C elevation, A.S. appears to have HeFH. In children and adolescents with HeFH, both TC and LDL-C levels will be well above the 95th percentile for age and sex, starting as young as age two years. Commonly, these children have normal TGs and normal or low HDL-C, unless the patient is overweight or obese; in which case, the child may also have high TGs and low HDL-C. When there is concern for HeFH, it is important to obtain a thorough family history. The patient usually has one parent with significantly elevated TC and LDL-C, and a history of tendon xanthomas

TABLE 69.4
Secondary Causes of Dyslipidemia: The Four "D's"

Diet	High saturated/trans fat
	Excessive carbohydrate
	Excessive alcohol intake
	Anorexia nervosa
Disease:	Cardiac
	Heart transplantation
	Congenital heart disease
	Hepatic
	Intrahepatic cholestasis
	Chronic liver disease
	Primary biliary cirrhosis
	Hepatitis (acute or chronic)
	Biliary atresia
	Alagille syndrome
	Renal
	Chronic renal failure
	Nephrotic syndrome
	Hemolytic-uremic syndrome
	Rheumatic
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Storage
	Gaucher disease
	Glycogen storage disease
	Tay-Sachs disease
	Niemann-Pick disease
	Other
	Post-cancer therapy
	Klinefelter syndrome
	Progeria
	Burns
Drugs	Oral estrogens and progestins
	Oral contraceptives
	Anabolic steroids
	Corticosteroids
	Thiazide diuretics
	Beta-blockers
	Bile-acid binding resins
	Glucocorticoids
	Protease inhibitors (most)
	Retinoic acid derivatives
	Anticonvulsants
Dysmetabolism:	Diabetes, Type I and Type II
	Obesity
	Insulin resistance
	Acute intermittent porphyria
	Hypopituitarism

(Figure 69.2) or a family history of premature CVD in first- and/or second-degree relatives. Tendon xanthomas are not generally seen in children and adolescents with HeFH as they normally develop in adulthood. However, they may be palpable on a parent, particularly if they were untreated until adulthood.



FIGURE 69.2 Tendon xanthomas. From: Durrington, P. Dyslipidaemia. *Lancet* 2003; 362:717–731. In Rippe JM (ed): *Lifestyle Medicine* 3rd ed, CRC Press (Boca Raton), 2019. Reproduced by permission of Taylor & Francis Group.

69.5.2 Familial Combined Hyperlipidemia

Another common cause of hypercholesterolemia is familial combined hyperlipidemia (FCHL). This autosomal dominant genetic disorder is the most common genetic lipid disorder in the United States, affecting approximately one in 200 people. There is phenotypic variation among family members with FCHL, with the most common lipid phenotype showing elevated LDL-C and TGs, and low HDL-C. FCHL may also be seen in those with overweight, insulin resistance, or hypertension. FCHL should be suspected when the FLP demonstrates mixed dyslipidemia consisting of elevated TC levels (200–400 mg/dL), elevated TGs (200–800 mg/dL), and low HDL-C (<40 mg/dL), along with a family history of hypercholesterolemia or premature CVD.

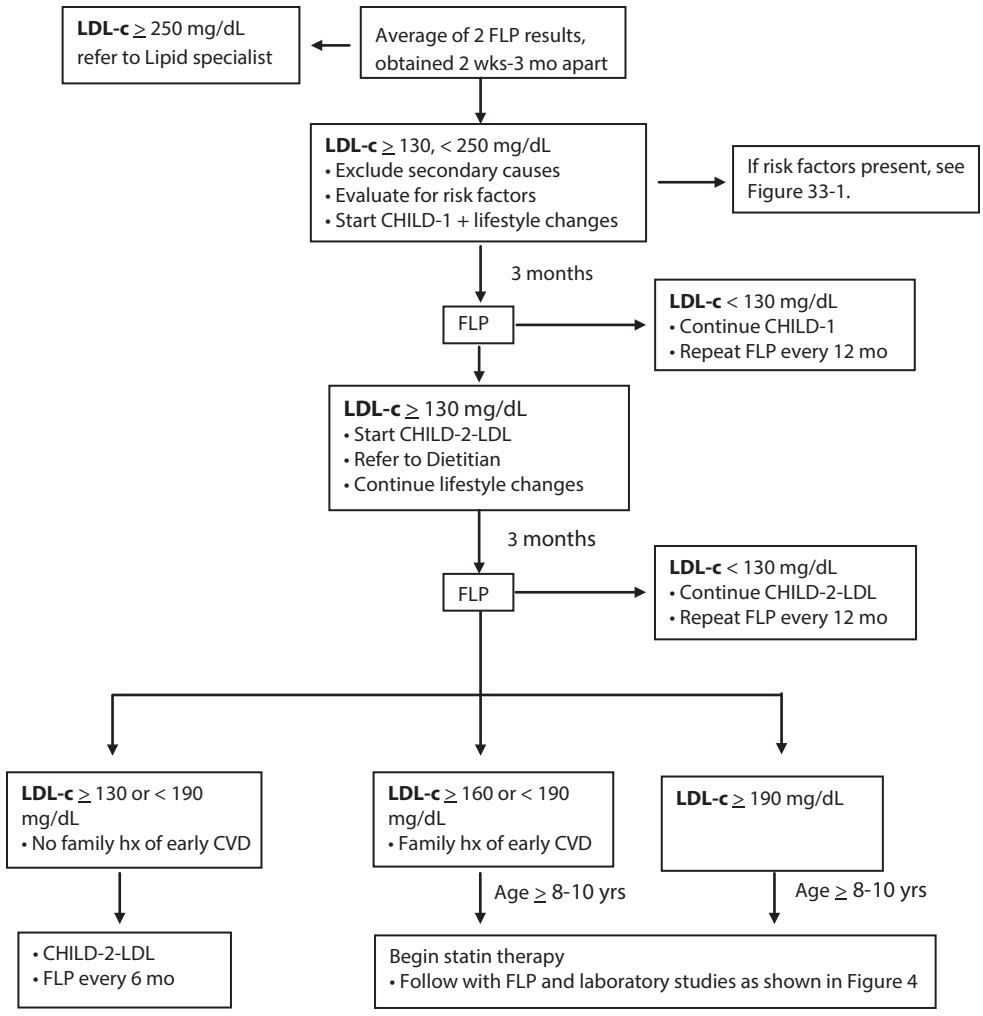
69.6 THERAPY FOR PURE HYPERCHOLESTEROLEMIA

69.6.1 Dietary and Lifestyle Intervention

The NHLBI guidelines outline a staged approach to dietary intervention for dyslipidemia in children (Figure 69.3). The first step is called the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1). After a trial of CHILD-1, a more intensive lipid-lowering dietary regimen can be undertaken, if necessary, focusing more on lowering LDL (CHILD-2-LDL) or triglycerides (CHILD-2-TG). Before implementing a CHILD-2 diet, a medical dietitian who is experienced in treating dyslipidemia should be consulted.[6]

69.6.2 Cardiovascular Health Integrated Lifestyle Diet

The CHILD-1 consists of a low saturated fat (<10% of total calories), moderate total fat (≤30% of total calories), low cholesterol (<300 mg/day), and minimal trans-fat diet.[6,25] Sugar-sweetened beverages, high sodium, high sugar, and fried foods should be limited. Other lifestyle changes should be encouraged, including weight



CVD=cardiovascular disease; FLP=fasting lipid profile; hx=history; LDL-c=Low density lipoprotein cholesterol; mo= months; wks= weeks

FIGURE 69.3 The NHLBI guidelines staged approach to dietary intervention for dyslipidemia in children.

management, decreasing sedentary time to no more than two hours daily, and increasing moderate to vigorous physical activity to at least one hour daily. After three months of CHILD-1 and lifestyle changes, a repeat FLP should be obtained. If the LDL-C remains elevated for age, then the family should meet with a dietitian and the CHILD-2-LDL implemented.[6,25] The Child-2-LDL recommends that dietary fat intake be limited to 25% to 30% of total calories, with saturated and monounsaturated fats at no more than 7% and 10% of daily calories, respectively. Trans fats should be avoided. After three months on CHILD-2-LDL, a repeat FLP should be performed (Figure 69.3).[6]

69.6.3 Adjunctive Dietary Therapies

Phytosterols (plant sterols and stanols) are naturally found in plant-based foods and used to lower LDL-C. A meta-analysis found that doses <3 g/day are effective in lowering LDL-C by 5–10% in adults and children with HeFH.[26] Viscous fibers have also been shown to reduce TC, LDL-C, and non-HDL-C. Foods that are high in viscous fibers include oats, barley, legumes, fruits, and vegetables, as well as supplements containing psyllium husk and methylcellulose.[27,28] Recommendations for children include up to 6 g/day of supplemental psyllium fiber for ages <12 years and up to 12 g/day for children ≥12 years. Adjunctive dietary therapies should be considered in children who are unable to lower their LDL-C with dietary and lifestyle management alone and those who are either too young to start a statin or whose LDL-C is nearing the statin therapy threshold.

69.6.4 Pharmacological Intervention for Elevated Low-Density Lipoprotein Cholesterol

Due to the genetic nature of HeFH and FCHL, many children and adolescents are not able to achieve their goal

LDL-C and/or non-HDL-C levels with diet and lifestyle changes alone.

69.6.4.1 When to Start Medication

Medication should be considered in children between 8 and 10 years with LDL-C over goal levels (based on risk factor stratification). The LDL-C cut points for consideration of starting a statin medication are outlined in Figure 69.3 for those with standard risk and Figure 69.1 for those with CVD risk factors (Table 69.3). Some high-risk patients may eventually need more than one lipid-lowering medication and should be referred to a lipid specialist.

69.6.4.2 Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors (Statins)

Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line medication to reduce LDL-C and non-HDL-C in the pediatric population.[29,30] Statins reduce intracellular cholesterol by inhibiting the rate-limiting enzyme in endogenous cholesterol biosynthesis, HMG-CoA reductase. This leads to the upregulation of LDL receptors in the liver, increasing hepatic clearance of LDL-C from the circulation. Statins also decrease very low-density lipoprotein (VLDL) and intermediate-density remnants, which result in modest TG lowering.

The FDA-approved statins for use in the pediatric population are listed in Table 69.5. These statins are approved for use in children ages ten years or older (≥8 years for pravastatin). The safety and efficacy of statin use throughout childhood and adolescence have been demonstrated in several clinical trials.[31–35] No difference in adverse events has been noted in the pediatric compared with the adult population[36] Studies in children have demonstrated that statins can slow the progression of atherosclerosis and may decrease the future risk of developing atherosclerosis if started at a younger age.[37,38]

69.6.4.3 How to Initiate, Titrate, and Monitor Children on Statin Medication

Figure 69.4 outlines how to initiate, titrate, and monitor children and adolescents on a statin medication. The lowest possible dose should be used when starting. The statin should be taken once a day, ideally at night, although atorvastatin and rosuvastatin can be taken in the morning due to their longer half-lives. After six to eight weeks of consistent use, an FLP, glucose level, and hepatic enzymes, should be obtained. If LDL-C levels are at target, then therapy should continue at the same dose with a repeat FLP in eight weeks, then three months, and then every six months. Hepatic enzyme levels can be measured annually if they have been normal and no dose adjustment has been made in the interim. If LDL-C target levels are not achieved, the statin should be increased by the lowest increment, and a repeat FLP should be obtained in six to eight weeks. If this increased dose does not result in goal LDL-C, ensure that the child is taking the medication as prescribed. If there is adequate adherence, then the physician should refer to a lipid specialist for consideration of a second lipid-lowering medication.[6]

It is important that patients have routine monitoring while on statin therapy (Figure 69.4). Liver and muscle toxicity are the most common concerns for patients and families. Prior to starting a statin, the physician should assess

TABLE 69.5
Medications for Reducing Elevated LDL-c in Children and Adolescents[30]

Medication Class	Medications and Starting Doses	Effect on Lipids	Potential Side Effects
HMG-CoA reductase inhibitors (statins)	Atorvastatin‡: 10 mg QHS or QD Lovastatin‡: 10 mg QHS Pravastatin*: 10 mg QHS Simvastatin‡: 5 mg QHS Rosuvastatin‡: 5 mg QHS or QD	Decrease LDL-C Increase HDL-C Decrease TG	Elevated liver enzymes, CK levels, hemoglobin a1c; muscle cramps and weakness; myopathy; rhabdomyolysis
Bile acid sequestrants	Cholestyramine†: 2 gm daily divided 2-4 times per day Colestipol granules†: 5gm QD Colesevelam HCl for Oral Suspension‡: 1 packet (3.75 gm packet) QD or 1 (1.875 gm packet) BID mixed with liquid	Decrease LDL-C Increase HDL-c Increase TG	Gastrointestinal symptoms, including: bloating, gas, abdominal cramping
Cholesterol absorption inhibitors	Ezetimibe‡: 10 mg QD	Decrease LDL-C Increase HDL-c Decrease TG	Elevated liver enzymes; gastrointestinal upset, myopathy

BID=twice daily; CK=creatine kinase; gm=grams; QHS=every night; QD=everyday; Y=years
*Approved for pre-pubescent children (age 8 years and older)
†Not FDA approved for children
‡FDA approved for children 10 years and older

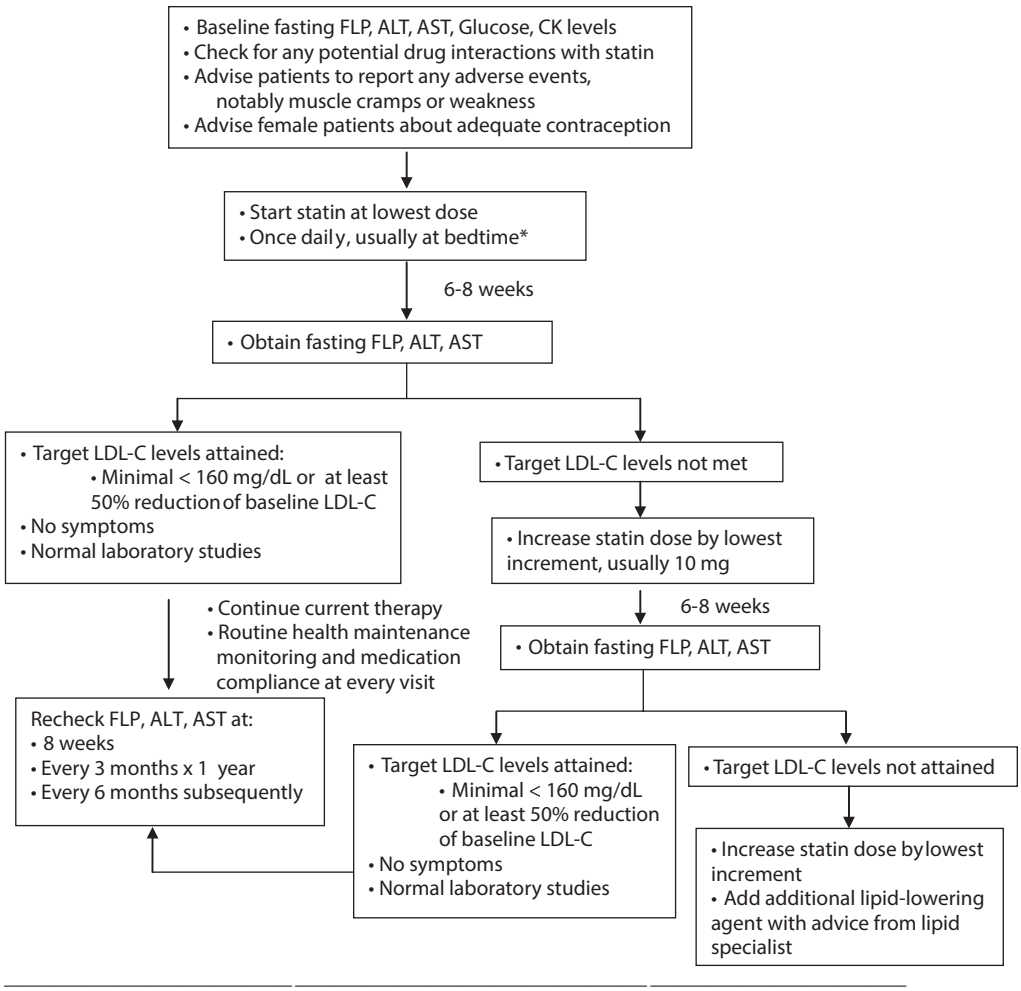


FIGURE 69.4 How to initiate, titrate, and monitor children on statin medication.

for contraindications to use.[30] Once menses have started, girls should be counseled that statins may be teratogenic; physicians should document that female patients are not pregnant and, if sexually active, are using adequate birth control. The patient's medications should be reviewed to assess for potential drug interactions. Patients should limit grapefruit juice if they are taking atorvastatin or simvastatin due to inactivation of the intestinal cytochrome P450 3A4, which increases the blood levels of these statins.[39]

After starting a statin, patients should report any side effects, notably muscle pain, cramps, or weakness. If symptoms are present, they should be evaluated in relation to recent physical activity. If the symptoms seem excessive for the physical activity performed, the medication should be stopped, and a creatinine kinase (CK) level checked. The clinical spectrum of statin-induced myotoxicity includes an asymptomatic rise in CK levels, myalgia (muscle weakness or soreness without CK elevation), myositis (myalgia with CK >10 times upper limit normal), and rhabdomyolysis (widespread destruction of muscle with CK >10 times upper limit normal and decreased renal function). In a meta-analysis of statin use in children, risk of myotoxicity was no greater for those taking a statin versus a placebo.[34] Nevertheless, if myositis is suspected, the statin should be discontinued due to the rare possibility of rhabdomyolysis, which can be life-threatening. After starting a statin, there can be minor elevations of liver transaminase levels (<3 times the upper limit normal). Therapy can continue as these fluctuations are often transient. If the transaminase levels are >3 times the upper limit of normal, the medication should be stopped, and levels should be rechecked in two weeks. Medication can resume, commonly at a lower dose, when symptoms and/or laboratory abnormalities have normalized.[30]

69.6.4.4 Therapy Goals

For those with no risk factors, once a statin is started, the initial therapy goal is LDL-C of ≤160 mg/dL or 50% of

the starting LDL-C. Once that is achieved, then a goal of ≤130 mg/dL can be considered, with an ideal goal of ≤110 mg/dL. For those with CVD risk factors, the initial therapy goal while on a statin is an LDL-C level of <100–≤130 mg/dL depending on risk level (Figure 69.1). As described previously, statin medications should be increased by single dose increments until the goal is met or another agent added.[6,30] There is a balance between achieving the desired LDL-C level and increasing the dose of medication. With increasing doses of statin, there are smaller improvements in LDL-C with the additional risk of side effects.

69.6.4.5 Cholesterol Absorption Inhibitors

Ezetimibe inhibits cholesterol absorption at the level of the intestinal villi, decreasing the absorption of dietary cholesterol, upregulating LDL-C receptors, and improving LDL-C clearance from circulation. Ezetimibe is dosed at 10 mg daily. The addition of ezetimibe can lead to an additional 20% LDL-C lowering when used with a statin, without significantly increasing adverse events in children and adults.[40–42] Ezetimibe should be considered as a second medication for those children who do not meet LDL-C goals while on a statin alone.[6]

69.6.4.6 Bile Acid Sequestrants

Prior to the use of statins, bile acid sequestrants were the medication of choice for children because they were felt to be safer as they were not absorbed.[25] However, between the poor palatability of these agents and the well-documented safety and efficacy of statin medications, bile acid sequestrants are no longer first-line therapy for children.[6]

69.6.4.7 Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newer class of medication for those with persistently elevated LDL-C despite statin and ezetimibe therapy. They are human monoclonal antibodies to PCSK9, an important regulator of LDL-C metabolism. Evolocumab is currently the only PCSK9 inhibitor approved for children (≥10 years) with familial hypercholesterolemia. It is a subcutaneous injection given every two or four weeks. In the phase III trial for evolocumab, those in the treatment arm experienced a 38% greater reduction in LDL-C compared with those randomized to placebo.[43]

69.6.5 Clinical Case 1 Follow-Up

- A.S. returned to the clinic after six months of diet and lifestyle changes. He started packing his lunch for school, going to the gym four days per week, and lost 5 lb. However, his LDL-C did not change significantly. He was started on atorvastatin 10 mg and was up-titrated first to 20 mg and then to 40 mg without any side effects. His most recent laboratory studies showed (in mg/dL): TC 221, HDL-C 73, LDL-C 138, TG 51, and non-HDL-C 148.

69.7 LIFESTYLE-RELATED DYSLIPIDEMIA

69.7.1 Clinical Case 2

A 12-year-old male, N.T., presents to the lipid clinic for evaluation of dyslipidemia. N.T. had a FLP first checked at the age of 10 years as part of universal screening. At that time, his TGs were elevated to 231 mg/dL, and he was instructed to eat healthier. Labs were not rechecked until two years later. Mom reports that N.T. started gaining excess weight around the age of five years but experienced a 60 lb weight gain over the past two years. Family history is negative for early heart disease and dyslipidemia in first- or second-degree relatives. N.T. is not involved in organized sports but does participate in gym class daily. His sedentary time is four hours daily on weekdays and eight hours on weekends. His breakfast consists of high sugar cereal with whole milk and juice. For lunch, he eats a turkey sandwich with cheese on white bread, chips, and an apple. He drinks sweetened iced tea. His after-school snack typically consists of cookies or pudding. Dinners are mainly lean meat, mashed potatoes or pasta, vegetables, and juice; for dessert, he eats ice cream. On physical examination, his height and weight are at the 57th and 97th percentile, respectively. His BMI is at the 98th percentile, placing him in the obese category. His blood pressure is 107/64. A physical exam revealed faint abdominal striae on his abdomen and acanthosis nigricans behind his neck. His FLP reveals (in mg/dL): TC 199, HDL-C 39, LDL-C 82, TG 389, and non-HDL-C 160. His thyroid studies were normal. His ALT was mildly elevated and AST was normal. His glucose and hemoglobin A1c were normal.

69.7.2 Combined Dyslipidemia of Obesity

Nearly half of all overweight and obese children have at least one abnormal lipid value.[44] In this population, the most common dyslipidemia is combined dyslipidemia of obesity (CDO). CDO is characterized by elevated TG, low HDL-C, elevated non-HDL-C, and normal or mildly elevated LDL-C levels. The LDL-C particles tend to be the small, dense subtype.[45] In Clinical Case 2, given N.T.'s BMI and lipid profile, it is highly likely that he has CDO.

Patients with CDO are also frequently found to have elevated insulin levels and central fat deposition. In the Framingham Offspring Study, CDO was found to be one predictor of early clinical cardiovascular events, such as myocardial infarction and death from CVD.[46] Those with elevated TG levels and TG/HDL-C ratios at 12 years of age and similar lipid values in adulthood were also at increased risk for experiencing premature CVD as an adult.[47]

69.8 FAMILIAL HYPERTRIGLYCERIDEMIA

Familial hypertriglyceridemia (FHTG) is an autosomal dominant lipid disorder with a prevalence of approximately one in 500. It is caused by increased VLDL production and/

or decreased VLDL catabolism. In patients with FHTG, certain lifestyle factors or medications can increase VLDL production and worsen hypertriglyceridemia, including a high-carbohydrate diet, obesity, insulin resistance, alcohol use, or estrogen therapy. Patients should be counseled regarding these precipitating factors.

In patients with FHTG, the lipid profile is notable for markedly elevated TGs (250–1000 mg/dL), normal or mildly increased TC (usually <250 mg/dL), and low HDL-C levels. LDL-C levels are generally low or normal. The ratio of TC/TG tends to be lower in FHTG than in FCHL. Eruptive xanthomas (Figure 69.5) may be seen in patients with TG levels >1000 mg/dL and should alert the practitioner to obtain a lipid profile. Patients with severe hypertriglyceridemia (>2000 mg/dL) are at risk for developing pancreatitis.[48]

69.9 THERAPY FOR HYPERTRIGLYCERIDEMIA

69.9.1 Dietary Therapy

Most children and adolescents with hypertriglyceridemia will see normalization or significant improvement in their triglycerides with diet and lifestyle changes. Similar to dietary therapy for pure hypercholesterolemia, a trial of the CHILD-1 diet should be used for patients with CDO, followed by a more intensive dietary regimen CHILD-2-TG if dyslipidemia persists.[6] In a child with CDO, the dietary history should include not just the food the child is eating, but also what and how much the child is drinking. Eliminating sweetened beverages (e.g., soda, iced tea, lemonade, sports drinks) will almost always lead to a reduction in TG levels and weight loss. Additionally, there should be an increase in complex carbohydrates and fiber and consumption of low-mercury fish at least twice weekly. Along with dietary changes, increasing exercise, decreasing sedentary time, and weight loss are very important. After three months of dietary changes, a repeat FLP should be performed. Therapy goals for those without risk factors are outlined in Figure 69.6 and for those with risk factors in Figure 69.1.

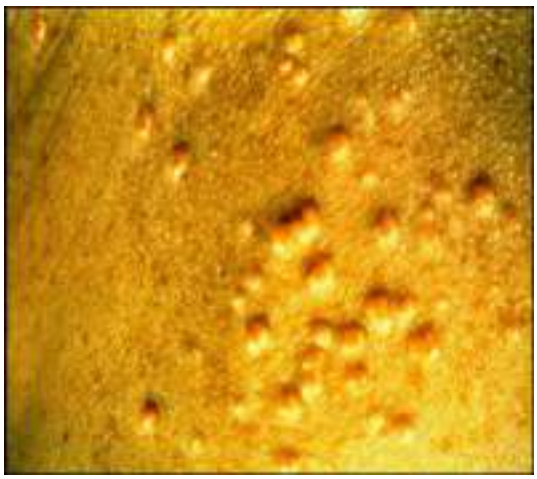


FIGURE 69.5 Eruptive xanthomas (from: Leaf DA. Chylomicronemia and the chylomicronemia syndrome: A practical approach to management. *Am J Med* 2008; 121:10–12. In Rippe JM (ed): *Lifestyle Medicine* 3rd ed, CRC Press [Boca Raton], 2019. Reproduced by permission of Taylor & Francis Group).

69.9.2 Pharmacologic Therapy

Changes to diet and lifestyle, in addition to weight loss, when necessary, are usually sufficient to reduce TG levels. If the child has been adherent to dietary changes, medication can be considered if the TG levels remain greater than target (Figure 69.6). If the average of two fasting TG levels is ≥500 mg/dL or a single fasting TG level is ≥1000 mg/dL, this is likely due to genetic hypertriglyceridemia and the patient should be referred to a lipid specialist.

69.9.3 Omega-3 Fatty Acids

Omega-3 fatty acids (or fish oil) decrease the synthesis of TGs by increasing the degradation of fatty acids. The use of omega-3 fish oil capsules at doses of 2–4 g/day can lower TGs by 30% to 45% and increase HDL-C levels by 6% to 17%. However, it may increase LDL-C levels up to 31%[49] There have been mixed results in the adult literature regarding omega-3 fatty acids and primary CVD reduction.[50] Those with elevated TGs and low HDL-C levels appear to be a subgroup in which CVD risk reduction may be seen.[51] Studies in children have been limited by small sample sizes but have not shown a significant difference in TG levels in those taking omega-3 fatty acids. There have been no significant reports of adverse effects.[49,52] There are a few FDA-approved fish oil capsule preparations as well as several over-the-counter options. Dosing for TG-lowering effect should be 2000 to 4000 mg daily of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) components.

69.9.4 Fibric Acid Derivatives

Fibric acid derivatives, or fibrates, work in a complex way to break down VLDL-C and TGs and decrease hepatic synthesis of TG. Fibrates have been shown to lower TGs and increase HDL-C levels without an increase in LDL-C levels. Although not currently FDA-approved for children, a small study in children demonstrated efficacy in lowering TG levels.[53] Prescribing fibrates in the pediatric population should only occur under the guidance of a lipid specialist.

69.9.5 Clinical Case 2 Follow-Up

Three months after the initial visit, N.T. returned to the clinic. He decreased his sugar-sweetened drinks to one serving daily, transitioned to 2% milk, and increased his fruit and vegetable intake. He also joined the soccer team and lost 9 lb, improving his BMI percentile. His lipid panel had significantly improved and showed (in mg/dL): TC 150,

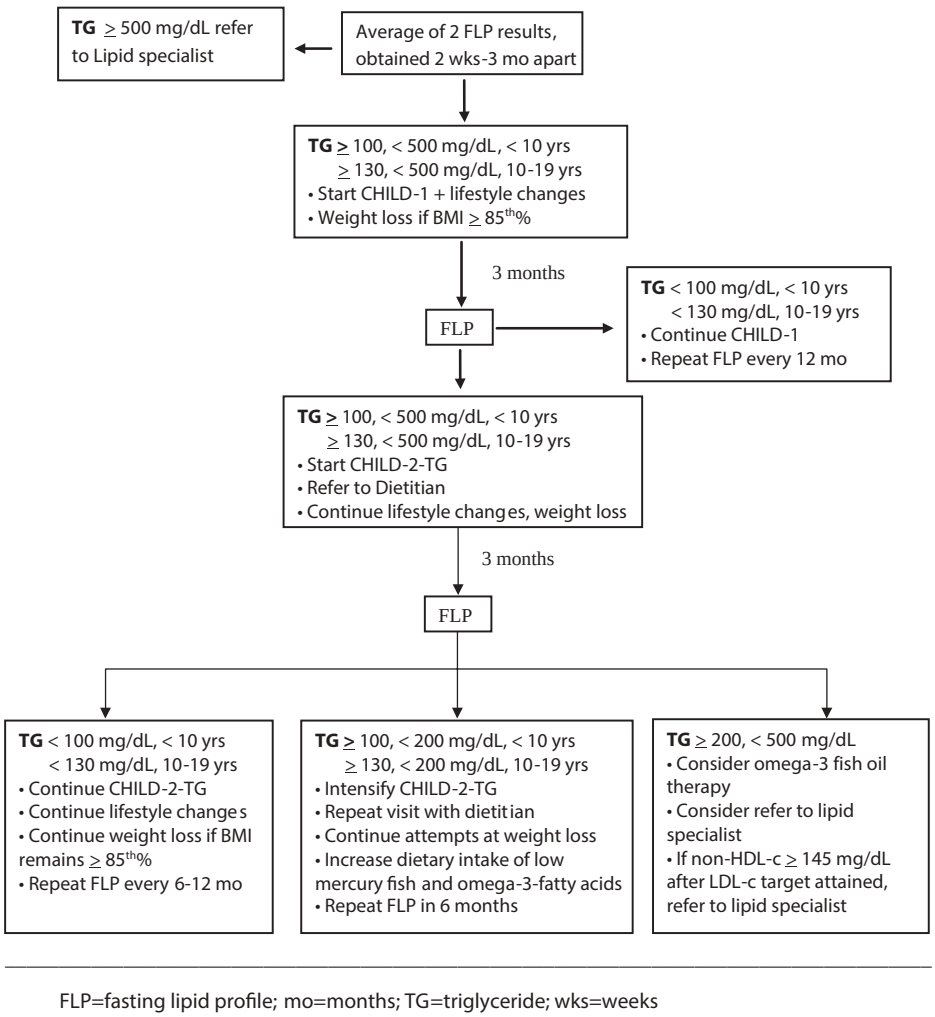


FIGURE 69.6 Therapy goals for those without risk factors.

HDL-C 42, LDL-C 80, TG 139, and non-HDL-C 108. His ALT normalized.

69.10 CONCLUSION

Children with dyslipidemia are at increased risk for premature CVD. Identifying who is at risk has taken on more urgency in the current era due to the increasing prevalence of childhood cardiovascular risk factors, including obesity, hypertension, poor diet, and sedentary behavior. For nearly all children and adolescents with dyslipidemia, the first step in therapy is diet and lifestyle changes. While this can be quite challenging, even small alterations can significantly reduce cardiovascular risk and frequently relieve the need for lipid-lowering medication. However, for children with certain forms of genetic dyslipidemia, as well as those who are unsuccessful in making adequate lifestyle changes, pharmacological therapy may be required. Statin medications are the first-line treatment in the pediatric population for lowering LDL-C levels. Other medications are rarely used and, if necessary, the patient should be referred to a lipid specialist. After a concerted effort on the part of the patient and family with diet modification and increasing physical activity, omega-3 fatty acids may be considered for significantly elevated triglycerides. It is imperative that those who care for children and adolescents identify patients at risk for early CVD and treat or refer them appropriately. Doing so can reduce the lifetime risk of CVD morbidity and mortality, improving the lives of a large number of our youth.

CLINICAL APPLICATIONS

- Increasing numbers of children and adolescents are being diagnosed with dyslipidemia. These children are at risk for developing premature cardiovascular disease.
- Universal screening should occur once from 9–11 years and again between 17 and 21 years using either a non-fasting lipid profile or a fasting lipid profile. If abnormalities are found as detailed in this chapter, then a repeat fasting lipid profile should be repeated in two weeks to three months after dietary and lifestyle changes.

- Before medication is considered, dietary changes and increasing physical activity should be considered in nearly all children and adolescents with dyslipidemia.
- Heterozygous familial hypercholesterolemia is a common genetic dyslipidemia that is characterized by LDL-C levels >95th percentile. It is important to identify as it will lead to premature cardiovascular disease if left untreated. First-line medication treatment is a statin medication at age ten, or age eight years if considered high-risk.
- Combined dyslipidemia of obesity is being seen more frequently and is characterized by elevated triglycerides, mild-moderately elevated LDL-C, and low HDL-C. Treatment is dietary changes, increasing physical activity, and weight stabilization or loss; medication may be needed if lifestyle changes are not made.

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70 Diagnosis, Management, and Treatment of Systemic Hypertension in Youth

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KEY POINTS

- Elevated blood pressure in children and adolescents is most likely to be primary hypertension and is associated with increased risk for cardiovascular disease.
- Children and adolescents should have blood pressure measured and assessed at each health maintenance visit.
- Children and adolescents with persistent blood pressure elevation should be treated first with increased physical activity and a Dietary Approaches to Stop Hypertension (DASH) type diet along with a reduction in dietary sodium.
- When lifestyle changes are not sufficient to lower blood pressure in children and adolescents with hypertension, pharmacologic agents should be considered. When pharmacologic agents are used, lifestyle interventions should be continued.

70.1 INTRODUCTION

Approximately 2–4% of all children are hypertensive.[1,2] Hypertension (HTN) in youth is an accepted risk factor for HTN in adulthood, while HTN in adulthood is a major cause of heart failure, atherosclerotic heart disease, stroke, and chronic kidney disease (CKD)-related morbidity and mortality.[3] Knowledge of how best to diagnose, manage, and treat systemic HTN in the child and adolescent is essential for the primary care and subspecialist provider.

This chapter is meant to provide a summary of recent proposed changes related to the diagnosis, management, and treatment of high blood pressure (HBP) in youth. Information provided in this text relies upon recommendations made in the 2017 American Academy of Pediatrics "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents".[4,5] A summary of the 30 key action statements (KAS) and the 27 additional recommendations made in the guideline is provided at the end of the chapter. A case and questions have also been included at the end of the chapter to reinforce the main points.

70.2 DIAGNOSIS AND PREVALENCE OF HYPERTENSION

HTN, defined by an office systolic or diastolic BP greater than the 95th percentile persistent over three or more outpatient visits, or in adolescents ≥130/90 mmHg, is estimated to occur in approximately 2–4% of all children (Table 70.1).[1] Masked hypertension (MH) is defined as normal BP in the office and abnormal BP outside of the office.[4] It is estimated that 10% of children have masked hypertension.[6] However, diagnosing MH typically requires wearing a 24-hour ambulatory blood pressure monitor (ABPM) and finding high out-of-office BPs but measuring normal in office BP.[4] Given the limited availability of ABPM devices, we may underestimate the prevalence of masked hypertension. The prevalence of white coat hypertension (WCH) is also probably underestimated for similar reasons but is currently believed to occur in as many as 13% of children.[7] The prevalence of HTN is highest among children with overweight status and obesity.[8]

The 2017 CPG included several modifications of prior guidelines. These included the replacement of the term pre-hypertension with the term elevated blood pressure (EBP). A simplified blood pressure (BP) table was included to allow for more efficient recognition of abnormal BP (e.g., flagging of high BP values; thresholds in Table 70.2). A role for oscillometric BP measurements was included in the diagnostic algorithm. Updated tables of BP values were developed, removing children with overweight status and obesity from the data set used to derive normative BP values as these children skewed the distribution upward.[9] Simplified diagnostic criteria for HBP once children were 13 years of age and above that aligned with the adult BP classification system were developed (Table 70.1). Finally, recommendations for greater inclusion of ABPM, screening, and data from clinical trials conducted to meet the Food and Drug Administration (FDA) pediatric exclusivity provision were included.

70.3 DIAGNOSIS

Before 1977, BP was not routinely assessed in children. It was not until the mid-1970s and the convening of a dedicated Task Force focused on examining hypertension in youth that the National High Blood Pressure Education Program (NHBPEP) of the National Heart Lung and Blood Institute (NHLBI) began to generate data examining BPs in youth.[4] It was through this process that normative BP ranges were determined. These studies showed that a child's BP was related to age, height, and sex.

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TABLE 70.1
Definition of Hypertension[4]

For Children One to <13 Years of Age	For Children ≥13 Years of Age
Normal BP: <90th percentile	Normal BP: <120/<80 mmHg
Elevated BP: ≥90th percentile to 95th percentile; or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥95th percentile, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥95th percentile + 12 mm Hg or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg

TABLE 70.2
Simplified Blood Pressure Table[4]

Age (years)	Blood Pressure (mm Hg)			
	Boys		Girls	
	Systolic	Diastolic	Systolic	Diastolic
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

Given the paucity of long-term outcome data, it has not been possible to link a level of childhood BP to later cardiovascular disease (CVD), though recently a study that modeled data from longitudinal epidemiologic studies spanning the life course has shown that young adult BP exposure is a significant predictor of adult-onset major cardiovascular events. Therefore, the use of normative BP ranges with cut points based on percentiles to define HTN has remained in place.

For children 1–13 years of age, the diagnosis of HTN is based on age, sex, and height-based BP percentiles. For children greater than or equal to 13 years of age, the diagnosis of HTN was made to align with BP cut-off values consistent with the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[10] The diagnosis of systemic HTN is based on repeated measurement of systolic and/or diastolic BP that, when averaged over three visits, equals or exceeds the 95th percentile (Figure 70.1).[4] In addition, the terminology was modified to reflect the recognition of BP >90th percentile or greater than 120/80 mmHg as associated with target organ damage (TOD), replacing the term pre-hypertension with "elevated BP".[4]

Given that the use of the full BP tables is cumbersome, a simplified table with a negative predictive value of 99% was created as a way for healthcare staff to more immediately determine which children require reassessment of BP, based on initial oscillometric (or manual) measurements. (Table 70.2) This table reduces the number of BP values from 476 to 52 values. Using the simplified table, healthcare providers need only be aware of a child's sex and age to determine whether the BP requires repeat measurement. The simplified BP is derived from the fifth height percentile and 90th BP value for each age and gender.

Diagnosis of HTN requires multiple measurements of BP (Figure 70.1). The initial BP may be an oscillometric measurement using a validated (www.dableducational.org) and calibrated device or an auscultatory measurement using an aneroid or mercury sphygmomanometer. Appropriate technique, including the use of an appropriately sized BP cuff size, is essential (https://www.youtube.com/watch?v=bYcCkiXJA_Q&t=9s). Once the average of two oscillometric BP readings has been determined to be elevated, then two confirmatory auscultatory measurements should be obtained. These measurements are then averaged. If the average of the auscultatory measurements is greater than the 90th percentile, then a classification of the BP is assigned: either elevated BP, Stage 1 HTN, or Stage 2 HTN.

The frequency with which the BPs are repeated is determined by the stage. Lifestyle counseling should be initiated in all cases—including among children with normal BP. If the BP is elevated, then the BP should be repeated at six months and again at 12 months. If at 12 months the BP is still categorized as elevated, then further diagnostic evaluation should be pursued. If the BP is classified as Stage 1 HTN and the person is asymptomatic (e.g., no reported headache) then it should be repeated in one to two weeks using auscultation (and not oscillometric). If the BP remains in the Stage 1 category, then it should be repeated in three months. If Stage 1 HTN persists at the time of the third visit, despite lifestyle and nutrition counseling, then ABPM (if available) should be ordered for confirmation of diagnosis and for distinguishing systemic Stage 1 HTN from WCH. Diagnostic evaluation, including echocardiography, should also take place at this time and pharmacologic treatment initiated if HBP is confirmed. Finally, if the BP is Stage 2, then upper and lower BP should be checked. Upper and lower extremity BP measurements should include the right arm and either leg and may include an additional measurement in the left leg. This measurement is obtained to assess for coarctation of the aorta (or mid-aortic syndrome). If the BP is higher in the right arm compared with the leg, especially

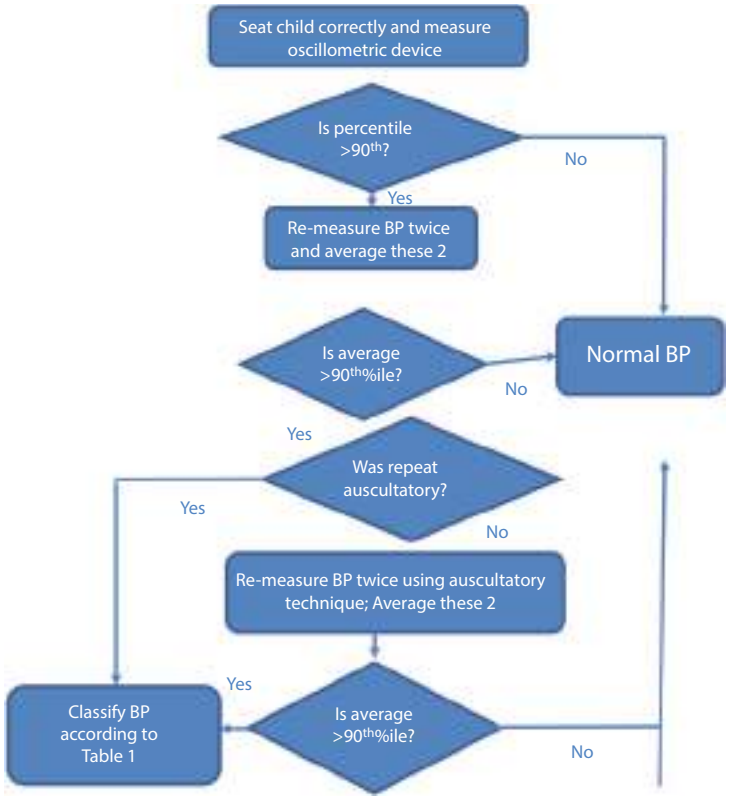


FIGURE 70.1 The 2017 modified BP measure algorithm.

if there is greater than a 20-mmHg gradient between the upper and lower extremities, then evaluation for coarctation of the aorta should be carried out. Next, the BP should be repeated within one week, and referral to subspecialty care considered. If the BP is still elevated in the Stage 2 range at the time of repeat measurement, then diagnostic evaluation for potential secondary causes should commence. The child should have echocardiography to evaluate for left ventricular hypertrophy. The child should be referred to subspecialty care within one week and treatment initiated. A BP measurement in the Stage 2 range and where the child is symptomatic or where the BP is greater than 30 mmHg above the 95th percentile (or >180/120 mmHg) is an indication for immediate evaluation and suggestive of hypertensive urgency. Symptoms of hypertensive urgency may include headache, dizziness, nausea/vomiting, or chest pain.[11]

In all cases, especially with elevated BP and Stage 1 HTN, a high index of suspicion for WCH should be maintained given that initial office measurements are typically higher and repeated measurement often results in a more accurate assessment of the true BP.[12]

Evaluation of BP should begin at three years of age for most children and most children should undergo repeated measurement at each well child visit. Children with risk factors for HBP, including premature birth, a history of congenital heart disease (aortic arch obstruction or coarctation of the aorta), and kidney disease, should undergo BP screening beginning at birth and at each patient encounter.

70.4 AMBULATORY BLOOD PRESSURE MONITORING

The 2017 CPG provides greater detail regarding when to perform ambulatory BP monitoring in children. Indications for ABPM include the following:

1. Confirmation of the diagnosis of HTN in children and adolescents with repeatedly elevated office BP readings; evaluation for WCH.
2. Evaluation for MH in children and adolescents with a history of repaired coarctation of the aorta.
3. Evaluation of BP pattern and risk for hypertensive TOD in children and adolescents with high-risk conditions, such as CKD.
4. Evaluation for possible HTN in children and adolescents with obstructive sleep apnea (OSA) syndrome.
5. Evaluation of BP in pediatric heart and kidney transplant recipients.
6. Assessment of treatment effectiveness in children and adolescents receiving antihypertensive medications.
7. Monitoring of treatment efficacy and possible MH in children and adolescents with CKD.

The use of ABPM has become more common and is now recommended by the US Preventive Services Task Force (USPSTF) to confirm a diagnosis of hypertension among

adults 18 years of age and older.[13] The USPSTF has not yet adopted recommendations for routine use of ABPM in pediatric patients. Current recommendations regarding ABPM use in pediatric patients are based on US guidelines. European guidelines also endorse the use of the ABPM device, but unlike the US guidelines, only when considering antihypertensive medication initiation or for further evaluation of the blood pressure if there has been a hypertensive response during the treadmill test.[14]

ABPM devices are typically no larger in size than a cell phone and record BPs periodically throughout the day and night (e.g., every 20–30 minutes). Limitations of ABPM measurements include a lack of normative data for children below 120 cm in height and the lack of existing outcome data linking ABPM data from childhood with cardiovascular events in adulthood.

The SHIP-AHOY study has addressed several unknowns regarding the value of ABPM including the enhanced sensitivity and specificity of ABPM use for identifying left ventricular target organ injury (e.g., left ventricular hypertrophy [LVH])[15] among persons with systemic hypertension. The presence of an office BP above the 85th percentile has excellent test characteristics for using ABPM most efficiently to diagnose HTN in an outpatient setting.[16] There is now much more population-based data on which to base normal values and definitions for hypertension using ambulatory monitoring.[17,18] Benefits of proposed ABPM use include (1) options for repeated measurement allowing for more data to determine how often and by what degree the BP is elevated both during the day and at night and (2) additional information regarding BP trends (e.g., presence or absence of nocturnal dipping). However, poor tolerability of the ABPM device has been associated with a higher prevalence of ambulatory HTN in adolescents.[16]

70.5 NEONATES AND INFANTS

Information regarding normative BP ranges in neonates and infants is limited. The International Neonatal Consortium recommends that oscillometric BP devices be used to assess BP in newborns and infants but recognizes the potential limitations of such devices in this population when measured BP is either too high or too low.[19] Risk factors for neonatal hypertension include gestational age, birth weight, and maternal factors. Common causes of neonatal hypertension include umbilical catheter associated thrombosis, renal parenchymal disease, and chronic lung disease.[19] The incidence of neonatal HTN is approximately 1%.[20] At present, it is recommended that readers refer to work published by Dionne et al. regarding normative BP values for this population.[20,21]

70.6 WHITE COAT HYPERTENSION

WCH can be found in up to 50% of children with elevated BP. [22] More common than essential hypertension in youth, the diagnosis of WCH relies on the presence of an abnormal in office BP and normal out-of-office BP. ABPM is the preferred method for diagnosing WCH as home measurements and school nurse measurements of home BP may be unreliable.

70.7 MASKED HYPERTENSION

MH occurs when patients have normal office BP but elevated BP on ABPM, and it has been found in 10% of unselected children studied by ABPM.[6] Children at greatest risk for MH may include children with CKD, a history of solid organ transplantation, a history of aortic coarctation, and other secondary forms of systemic HTN.[4] MH has also been associated with the development of TOD.[25,26]

70.8 HYPERTENSION EMERGENCY AND URGENCY

A BP that is greater than 30 mmHg above the 95th percentile (or >180/120 mmHg in an adolescent) requires immediate referral for care in an emergency setting.[4] Patients with such extreme elevations in BP should undergo immediate evaluation for secondary causes.

In such patients, treatment should also be initiated immediately. However, BP should not be reduced by more than 10% during the first eight hours and by no more than 20% during the first 24 hours. Children with extreme elevation in BP are at risk for acute target organ effects, including encephalopathy, acute kidney injury, and congestive heart failure (CHF). Treatment may be initiated with oral antihypertensive agents if the patient is able to tolerate oral therapy and if life-threatening complications have not yet developed. Intravenous agents are indicated when oral therapy is not possible because of the patient's clinical status or when a severe complication has developed (such as CHF) that warrants a more rapid and controlled BP reduction. In such situations, the BP should be reduced by no more than 25% of the planned reduction over the first eight hours, with the remainder of the planned reduction over the next 12 to 24 hours.[27,28] The ultimate short-term BP goal in such patients should generally be around the 95th percentile.

70.9 ASSOCIATED COMORBIDITIES

Excess body weight raises BP.[29] This is most clearly shown by the difference in BP tables between the Fourth Report and the 2017 AAP guideline showing slightly lower BP levels for age, height, and sex in the current tables.[4] The prevalence of hypertension is about three-fold higher in children with overweight/obesity than in normal-weight children. Gaining excess adiposity is associated with incident HTN implying that obesity prevention is the most effective form of HTN prevention. Children with obesity are more likely to sustain the presence of abnormal BP from visit to visit than normal-weight children. Measurement of BP requires attention to proper cuff size so that BP is not over-estimated.[4] Children with obesity are more likely to have MH.[30]

The mechanism of HTN associated with obesity is likely a hyperdynamic state with increased sympathetic tone, increased sodium retention, and higher cardiac index.[31]

70.10 CHRONIC KIDNEY DISEASE

Elevated BP often accompanies CKD.[32] Since HTN chronically injures the kidney, typically by reducing nephron mass, and since HTN is associated with microalbuminuria, controlling HTN is important in CKD management. ABPM is required for the most accurate monitoring. The treatment goal is to achieve BP below the 50th percentile in ambulatory BP tables. Monitoring of proteinuria is important and if present an ACE or ARB agent should be prescribed. Unlike children with essential HTN, children with CKD and other secondary causes of HTN tend to have higher diastolic BPs. Renal disease represents the most common cause of secondary HTN, accounting for 34% of cases.[33]

70.11 DIABETES MELLITUS

The presence of type 1 (T1DM) or type 2 (T2DM) diabetes in association with HTN increases cardiovascular risk.[34] T1DM and T2DM are associated with early vascular injury and microalbuminuria. The threshold for initiation of antihypertensive pharmacologic therapy is lower for those with diabetes; all children with diabetes and elevated blood pressure (>90th percentile or 120/80, whichever is lower) require treatment.[35]

70.12 SLEEP-DISORDERED BREATHING AND OBSTRUCTIVE SLEEP APNEA

Sleep-disordered breathing (SDB) refers to a spectrum of sleep-related abnormalities that include: (1) primary snoring, (2) sleep fragmentation, and (3) OSA.[35] Numerous studies have demonstrated a relationship between SDB and abnormal BP.[36–38] While elevated BP has been reported among adults and children with OSA, a recent study found that, among children with varying degrees of OSA (mild: apnea hypoxia index [AHI] <1; moderate, AHI: 1-4; severe, AHI ≥5), nighttime SBP was highest among those with severe OSA.[39] Findings suggest that nighttime BP most likely correlates with OSA severity. However, OSA is also strongly associated with elevated blood pressure during the day.[40]

70.13 ATTENTION DEFICIT HYPERACTIVITY DISORDER AND COGNITION

Stimulant medication use has been associated with elevations in BP and case reports have suggested that stimulant medication use can be associated with the elevation of blood pressure.[42] However, the presence of HTN has been associated with abnormalities in executive function and working memory among young adults.[43] Recent evidence suggests that the presence of HTN in youth is also associated with cognitive deficiencies, including attention and working memory.[44] Children with HTN may be more likely to have attention deficit hyperactivity disorder (ADHD) and learning deficits (LDs), compared with subjects without HTN.[44] Diagnosing hypertension in the setting of ADHD medication use that increases BP requires careful monitoring and clinical decision-making. ABPM and home BP monitoring are useful as BPs obtained when medication has been cleared by the system can inform diagnosis.[41]

70.14 PRIMARY HYPERTENSION AND EVALUATING FOR SECONDARY CAUSES OF ESSENTIAL HYPERTENSION

70.14.1 Essential Hypertension

The predominant cause of HTN in youth is essential or primary HTN. Genetic and environmental factors may play a key role in the diagnosis. Children with essential HTN tend to be older (i.e., six years of age or older,[46,47] have a family history of HTN[48,49] and have an overweight or obese status).[7,50]

70.14.2 Coarctation and Congenital Abnormalities of the Heart

Coarctation of the aorta is a congenital abnormality with narrowing of the aorta within the juxtaductal region of the aortic arch. Persons with coarctation of the aorta may have evidence of hypoplasia of the aortic arch or other congenital defects of the heart. Coarctation of the aorta is associated with physical examination findings of diminished pulse value in the lower extremities. Patients with coarctation of the aorta may also have an elevated arm-to-leg BP difference with a gradient of at least 20 mmHg. Repair is ideally performed during infancy. However, post-repair, individuals remain at risk for re-coarctation and systemic hypertension. The estimated prevalence of HTN post-repair ranges from 17% to 77%.[51] Routine office-based assessment of BP is often insufficient as the prevalence of MH may be higher than initially appreciated.[52]

70.14.3 Monogenic Hypertension

Monogenic forms of HTN are uncommon, although the exact incidence is unknown. Monogenic forms of HTN should be suspected in hypertensive children with a suppressed plasma renin activity (PRA) or elevated aldosterone to renin ratio (ARR), especially if there is a family history of early-onset HTN. Potential monogenic forms of HTN include familial hyperaldosteronism type I (FH-I), glucocorticoid remediable aldosteronism, Liddle syndrome, pseudohypoaldosteronism type II (Gordon syndrome), apparent mineralocorticoid excess, familial glucocorticoid resistance, mineralocorticoid receptor activating mutation, and congenital adrenal hyperplasia.[52] All manifest as HTN

with suppressed PRA and increased sodium absorption in the distal tubule. Other features may include serum potassium abnormalities, metabolic acid-base disturbances, and abnormal plasma aldosterone concentrations. Clinical presentations of the monogenic forms of HTN can be highly variable.[53]

70.14.4 Endocrine-Related Causes

Endocrinopathies are rare but important secondary causes of HTN.[53-57] Clues to the presence of an endocrinopathy are electrolyte or calcium abnormalities, growth disturbance, and physical examination features related to known syndromes (e.g., Cushingoid appearance). Signs of sympathetic nervous system excess (tachycardia, HTN, flushing) might suggest hyperthyroidism or conditions associated with excess catecholamines such as a pheochromocytoma. Hyperaldosteronism is a common cause of resistant HTN in adults[56,57] and may be associated with more treatment-resistant HTN in youth.

70.14.5 Medications and Environment

A wide array of environmental stimuli and medications can impact BP. HTN should only be diagnosed based on resting BP or ambulatory BP and in the absence of pain or stressful stimuli. In the otherwise healthy patient, stimulant medications increase BP on average 2–3 mmHg but can have exaggerated responses in some individuals. In these settings, the risk of HTN versus the benefit of treatment for ADHD must be evaluated in decision-making.

70.15 TARGET ORGAN DAMAGE AND HYPERTENSION

70.15.1 Left Ventricular Hypertrophy

Defining TOD in the pediatric population can be challenging. Alterations in ventricular geometry can occur among children with systemic hypertension. The best-studied measures of LV target organ injury are measures of LV structure (LV mass and the relationship of LV wall thickness or mass-to-LV cavity volume) and systolic function (LV ejection fraction). LV structure is usually stratified into four groups based on LV mass (normal or hypertrophied) and relative LV wall thickness (normal or increased) (Table 70.3). These four are as follows: (1) normal geometry with normal LV mass and wall thickness; (2) concentric geometry with normal LV mass and increased LV wall thickness; (3) eccentric LVH with increased LV mass and normal LV wall thickness; and (4) concentric LVH with both increased LV mass and increased relative wall thickness.[58,59] Assessments for TOD are recommended at the time of consideration for initiation of antihypertensive therapy. If increased LV mass is present, this indicates that the blood pressure elevation is also having a demonstrable adverse effect on the heart. Treatment of HTN with antihypertensive medication has been shown to reduce left ventricular mass.

TABLE 70.3
Ventricular Geometry and Hypertension

	RWT <0.42	RWT >0.42
Normal mass	Normal geometry	Concentric geometry
Increased mass	Eccentric hypertrophy	Concentric hypertrophy

70.15.2 Ophthalmologic Examination and Hypertensive Retinopathy

The prevalence of hypertensive retinopathy among children with HTN is not well known, however, it has been estimated that approximately 18% of children with severe HTN suffer from retinal changes related to their hypertension diagnosis.[60] Changes thought to occur because of severe HTN include retinal hemorrhages, exudates, and optic disc edema. Proposed risk factors for the development of hypertensive retinopathy in adults include duration of HTN, severity of elevation in SBP, and age.[61] Risk factors for hypertensive retinopathy in youth have not been well studied but are likely similar.

70.16 TREATMENT OF SYSTEMIC HYPERTENSION

70.16.1 Non-Pharmacologic Treatment

Healthy lifestyle decreases the likelihood of a child or adolescent developing systemic HTN. Adoption of a healthy lifestyle is also a critical first step in the treatment of diagnosed systemic HTN in children and adolescents. The American Heart Association defines a healthy diet target as including:

- Reduction in total sodium intake to ≤1500 mg/day
- Intake of four to five cups of fresh (or frozen) vegetables and fruits per day
- Two or more 3.5-ounce servings of fish/shellfish per week (≥200 g/wk)
- ≤36 fl ounces of sugar-sweetened beverage per week
- >4 servings/week (nuts/seeds, 1-ounce legumes, half cup)
- Two or fewer 1.75-ounce servings/week (<100 g/week) processed meats
- <7% energy secondary to saturated fat[61]

The Dietary Approaches to Stop Hypertension (DASH) approach is similar to the AHA healthy diet target but goes beyond to include the consumption of low-fat milk products.[62]

TABLE 70.4
Antihypertensive Agent Class

First and Second Line Antihypertensive Agent Classes	Agent(s)	Mechanism of Action	FDA Approved
Angiotensin-converting enzyme inhibitor	Benazepril, Enalapril, Fosinopril, Lisinopril, Quinapril, Ramipril (Captopril)	Inhibits the conversion of angiotensin I to angiotensin II	Yes (No)
Angiotensin receptor blocker	Candesartan, Irbesartan, Losartan, Olmesartan, Valsartan	Antagonizes the angiotensin II receptor	Yes
Calcium channel blockers	Amlodipine, Felodipine (Nifedipine)	Inhibits calcium influx	Yes (No)
Diuretic	Hydrochlorothiazide	Thiazide diuretic:	No

A diet rich in intake of fruits, vegetables, and legumes has been associated with lower BP in adolescents.[64] Higher sodium intake has been associated with increased arterial stiffness, a pre-clinical measure of CVD.[65] The DASH diet has also been associated with a decrease in obesity, an important step for reducing the burden of hypertension development.[66]

70.16.1.1 Exercise

Physical fitness and increased physical activity are important strategies in the prevention of the development of HTN and in HTN treatment. Increased physical activity over a three-year interval slows age-related rises in BP.[67] Meta-analyses of clinical trials assessing the impact of exercise interventions in healthy children show modest reductions in BP, particularly if interventions last longer than six months.[68,69] There are no clinical trials of exercise intervention specifically for HTN treatment.

70.16.1.2 Sleep

Adequate sleep and high-quality sleep are also critical to maintaining a normal BP in children and adolescents. Inadequate sleep duration of less than five hours per night in children and adolescents has been linked to an increased risk of HTN and is also associated with an increased prevalence of obesity.[40] OSA has been shown to be an independent risk factor for elevated SBP and diastolic blood pressure (DBP), even after adjusting for confounding factors such as increased BMI.[40]

70.16.2 Pharmacologic Treatment

Although, in most cases, treatment using a non-pharmacologic approach is preferred, children who remain hypertensive despite a trial of lifestyle modification or who have symptomatic HTN, Stage 2 HTN without a clearly modifiable cause, chronic kidney disease, or diabetes mellitus with any stage of HTN, should be considered for treatment with pharmacologic therapy. Therapy should begin with a single agent and at a low dose. Recommended classes of antihypertensive therapy for the treatment of systemic HTN include angiotensin-converting enzyme inhibitors (ACEi), calcium channel blockers (CCB), diuretic (e.g., hydrochlorothiazide), and angiotensin receptor blockers (ARBs). There exist unique reported benefits for each agent. A summary of the different classes and agents can be found in Table 70.4.

BP should be assessed on therapy every two to four weeks and the dose adjusted until the BP is initially lower than the 95th percentile and, ultimately, lower than the 90th percentile for age, sex, and height. A maximal dose should be attempted unless side effects develop. If the BP is not controlled with a single agent, then a second agent can be added. Hydrochlorothiazide (HCTZ), while not typically recommended as a first-line therapy, is frequently added to help combat the salt and water retention that typically occurs with the use of other antihypertensive medications. Even if a child is receiving pharmacologic therapy, continued attempts at lifestyle intervention are recommended.

70.17 SUMMARY

The 2017 Clinical Practice Guideline for the Management of High Blood Pressure in Children and Adolescents provides an evidence-based, updated clinical guide. Current guidelines provide (1) updated tables with new normative BP values; (2) an algorithm for diagnosing HTN that includes the use of oscillometric devices as well ambulatory BP monitoring devices; (3) the inclusion of a simplified BP table for screening and for more rapid determination of the need for reassessment of BP; (4) use of adult criteria for the diagnosis of HTN in children over 13 years of age; (5) simplified process for evaluating for secondary causes of HTN; (6) new timing of echocardiography and definitions of LVH (and LV geometry); (7) inclusion of screening for high BP using ambulatory BP monitoring; and (8) inclusion of the data from pediatric clinical trials of antihypertensive agents. Thirty recommendations (key action statements) relevant to the diagnosis, management, and treatment of systemic HTN in children were generated. Recommendation grades that reflect the level of existing

evidence used to support each recommendation are provided in the document.

70.18 CASES

70.18.1 Case 1

J.T. is 13 years old with elevated blood pressure during a recent well child visit one week ago. His BP at that time was 150/80 via oscillometric measurement. J.T. has been asymptomatic and denies headache, chest pain, chest pressure, dizziness, or lightheadedness. He is on no medications. His sister cooks the meals at home. The family has now transitioned to eating at home once concern was raised regarding his BP one week ago. However, total caloric intake remains high.

The family joined the gym and plans to go three days per week for one to two hours. Multiple family members have HTN, including J.T.'s mother, father, and older sister. There is also a family history of multiple family members with obesity, including J.T.'s parents. His maternal grandfather has peripheral vascular disease. His maternal great-grandmother died at 36 years of age from a heart attack. His paternal grandfather had a cardiomyopathy and died suddenly at 70 years of age. There are multiple distant family members with CHF.

In the office:

BP 152/86 (oscillometric) | Pulse 72 | Ht 5' 8.5" (1.74 m) | Wt 278 lb (126.1 kg) | SpO2 98% | BMI 41.65 kg/m^2

Repeat BP at that visit

BP	Pulse	Site	Cuff Size
144/74	–	Right arm	Large
Comment: resting; manual			
138/70	–	Right arm	Large
Comment: resting; manual			

In general, J.T. is in no apparent distress but is an unhealthy weight. He is normocephalic and there are no facial dysmorphic features. He has a normal respiratory effort and clear lung fields bilaterally. His precordium is normal. There is a regular rate and regular rhythm with a normal S1 and a normal S2. There are no murmurs. There is no rub. There is no click. There is no gallop. His abdomen is soft and non-tender. There is no palpable liver edge or spleen edge on his exam. Extremities are warm and well perfused. There are 2+ pulses without brachiofemoral delay. There is no edema. There is no cyanosis or clubbing.

70.18.1.1 LABS

K 3.9. Na 139. Cr 0.72 (normal). Glucose 110 mg/dL UA neg. HgbA1c 5.1%.

J.T. has an average manual BP of 141/72 mmHg. Given that he is 13 years of age, by the 2017 CPG, he has Stage 2 hypertension.

Given this finding, you measure the BP in J.T.'s arm and in his leg. The leg systolic BP is 6 mmHg higher than the arm systolic BP.

Given J.T.'s age and strong family history of hypertension, the most likely cause of his HTN is essential hypertension. Renal causes of hypertension are the most common cause of secondary hypertension but given J.T.'s age and family history, this diagnosis is less likely. While it is possible that J.T. has a monogenic form of HTN, this too is less likely.

Finally, given that the BP in his leg is higher than in his arm, diagnosis of aortic coarctation of mid-aortic syndrome is unlikely.

ABPM will be useful in assessing the BP outside the office setting.

J.T.'s ABPM confirms the diagnosis of HTN.

He undergoes a screening echocardiogram which shows left ventricular hypertrophy and concentric hypertrophy. He is started on a low dose antihypertensive agent.

70.18.1.2 Repeat Visit Four Weeks Later

J.T. remains an unhealthy weight. Competitive sports participation was discouraged until his blood pressure was more normal (e.g., no longer Stage 2 hypertension). Recreational activity was encouraged. He has been playing basketball after school. He denies symptoms of chest pain or pressure.

J.T.'s sister continues to cook the family's meals.

Additional labs were obtained. His total cholesterol is 189 mg/dl, HDL 29 mg/dl, TG 126 mg/dL, and non-HDL 160 mg/dL.

BP 134/88 | Pulse 78 | Ht 5' 8.5" (1.74 m) | Wt 274 lb 0.5 oz (124.3 kg) | SpO2 98% | BMI 41.06 kg/m^2

Repeat BP

BP	Pulse	Site	Cuff Size	Time	Date
130/70	–	Right arm	Large	09:25 AM	11/9/2017
Comment: manual; resting					
130/68	–	Right arm	Large	09:25 AM	11/9/2017
Comment: manual; resting					

J.T. is now in the Stage 1 hypertension range following lifestyle change and an antihypertensive agent with an average manual BP of 130/69 mmHg, and weight loss of ~2kg.

J.T. would like to participate in competitive sports. Based on the 2017 CPG, he can now safely participate in competitive basketball?

J.T.'s goal BP, in the absence of known kidney disease, is ≤130/80mmHg. In the presence of kidney disease, ideally,

the mean arterial pressure by ABPM would be less than the 50th percentile. However, his BP remains elevated.

Ideally, once one antihypertensive agent is started at a low dose, the best option is to increase the dose and then, if needed, add another agent after the dose of the first agent has been maximized. Lifestyle intervention is reinforced regardless. And even though his BP is improved, he should continue his antihypertensive medication.

CLINICAL APPLICATION

- Elevated blood pressure in children and adolescents is most likely to be primary hypertension and is associated with an increased risk for cardiovascular disease.
- Children and adolescents should have blood pressure measured and assessed at each health maintenance visit.
- Children and adolescents with persistent blood pressure elevation should be treated first with increased physical activity and a Dietary Approaches to Stop Hypertension (DASH)-type diet along with a reduction in dietary sodium.
- When lifestyle changes are not sufficient to lower blood pressure in children and adolescents with hypertension, pharmacologic agents should be considered. When pharmacologic agents are used, lifestyle interventions should be continued.

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Part XIII

Lifestyle Medicine and Nursing



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71 Lifestyle Nursing: Lifestyle Medicine and Nursing

Gia Merlo, MD, MBA, MEd and Carolyn Sweetapple, RN, PhD, MBA

KEY POINTS

- Synergies exist between lifestyle medicine and the training and competencies of the nursing profession.
- The current healthcare system is taking a tremendous toll on the well-being of nurses and the healthcare team.
- Innovative clinical models of care that leverage the expertise of nurses as part of the lifestyle medicine team may be part of the solution.
- Lifestyle medicine leadership can play a crucial role in advancing knowledge, adoption, and acceptance of innovative clinical models of care that include a role for lifestyle medicine nurses.

71.1 INTRODUCTION

This chapter, and the four chapters that follow, introduce the exciting potential for nursing professionals to impact the trajectory of lifestyle medicine adoption. This chapter covers how nursing is well positioned to provide and lead lifestyle medicine, the challenges facing nursing today, why it is important to address those challenges, and the benefits to society and nurses by doing so. With a new approach that is bold but familiar, incorporating lifestyle principles into nursing practice professionally and personally will lead to improved outcomes for patients and families and improved health and well-being for nurses.

Nurses play a critical role in the development, provision, and assessment of clinical interventions in various practice settings. As the largest single group of healthcare professionals, nurses are on the frontline of providing sick care as well as providing well care. Within the healthcare team setting, nurses often are the leaders to multiple team members including nursing assistants, patient care associates, and the unit secretary, among others. Nurse managers often serve as the point person on the team to collaborate with pharmacists, physical therapists, environmental service workers, respiratory therapists, and social workers. There are many nuances within the nursing practice that position nurses to drive lifestyle medicine as team leaders.

Much has changed in the education, training, and responsibilities of nurses throughout the years. The incorporation of social determinants of health into the healthcare team process highlights the disparities and inequities of our current healthcare system. To create social, physical, and economic environments that promote well-being, the importance of lifestyle medicine principles is embedded in quality and patient safety. Evolution of lifestyle principles into nursing curricula and practice will further enhance a profession proudly founded in patient education, counseling, and health promotion. Operationalizing that knowledge and practice to provide team leadership will result in a healthier society and better patient outcomes.

Unfortunately, the profession has been faced with some significant challenges. Nursing shortages caused by workforce demands, the retirement of nurses, and the stresses resulting from the COVID-19 pandemic have led to attrition and retention issues. Nurses are not just providers of healthcare, they are consumers in a high-demand, high-stress profession. The need to focus on well-being for nurses is delineated in the 2022 book edited by Gia Merlo and Kathy Berra *Lifestyle Nursing*, which is a part of the Lifestyle Medicine series edited by James Rippe. *Lifestyle Nursing* further emphasizes that healthcare providers are not immune to the stressors of society and the pressures of work. The value of self-care is well documented on an individual and macro level. A healthy nurse results in more nurse engagement, better retention, less compassion fatigue, and protection against burnout. A healthy nurse benefits a healthier society through better patient and family outcomes.

Hope is on the horizon. Lifestyle medicine principles where nurses take a leadership role in promoting the unique contributions of each team member can benefit society and nurses. This chapter will introduce you to the issues and possible solutions. The four chapters following will provide a roadmap to implementation.

71.2 THE NURSING PROFESSION

A reputation for compassion and dedication has earned the registered nurse (RN) profession recognition as the most highly trusted profession for the past 20 years.[1] Nurses complete a rigorous program of didactic and clinical study and work with patients, families, and communities using the core values of the nursing process[2] The nursing process

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follows the scientific method and includes assessment, diagnosis, planning, implementation, and evaluation.[2] It is through the critical thinking exemplified in the nursing process that registered nurses synthesize objective and subjective data to provide holistic care to patients.

Nurse practitioners (NP) are registered nurses who have completed a graduate degree at a master's or doctorate level which provides clinical and didactic instruction and training in a designated NP specialization.[3] In addition to instruction and training, a national certification exam must be passed in the specialization area from the American Academy of Nurse Practitioners (AANP), the American Nurse Credentialing Center (ANCC), the Pediatric Nursing Certification Board (PNCB), or the National Certification Corporation (NCC)[3] Finally, the NP must apply for licensure in the state within which they will practice.

According to the American Association of Nurse Practitioners (AANP), the national organization for NPs, the scope of practice for NPs includes the diagnosis, evaluation, and management of acute and chronic health issues. Included in the management of patients is education, counseling, and promotion of health and disease prevention to individuals and families. Nurse practitioners practice in alignment with an ethical code, national certification, and current practice standards using an evidence-based approach to care. While licensing requirements for NPs vary by state and by specialization, all states have a process by which NPs are recognized as advanced practice RNs with advanced training in a clinical specialization.[3]

Despite the licensure of NPs as independent licensed practitioners, currently, 25 states allow NPs full practice authority. Rules and policies of various state agencies still prohibit NPs from practicing to the full scope of their licensure. Research has shown that states with full practice authority are better positioned to improve access to care, grow their workforce, and address healthcare disparities while delivering quality health outcomes for patients.[3]

Full practice authority has not resolved all the barriers to practice independently. Historically, physicians have been cautious about the role of the NP as a licensed independent practitioner. In a brief issued by the Primary Care Coalition from Austin, Texas, reservations include lack of training time, educational requirements that vary from state to state, and less clinical rotation than primary care residents[4] Interestingly, the coalition did recognize the emphasis on NP training in health promotion, patient education, and disease prevention in NP training. In Chapter 75, advanced practice nursing approaches to lifestyle medicine will be reviewed in greater detail.

71.3 NURSING CHALLENGES

In the United States, nearly 70,000 RNs will retire annually from the workforce between 2022 and 2030.[5] The trend is due to the substantial number of baby boomer RNs hitting retirement age who joined the workforce in the 1970s, and the COVID-19 pandemic is anticipated to accelerate this retirement rate. According to a 2020 national survey of registered nurses conducted by the National Council of State Boards of Nursing (NCSBN), the median age of nurses in the workforce was 52 years. Nurses who are aged 65 years or older account for 19% of the RN workforce and comprise the largest age category.[6] In an integrative review study by Falatah, fear of disease, stress, anxiety, and workforce shortages were predictors of a higher intent to leave among nurses, particularly among nurses over 60 years of age.[7]

Recruitment of new nursing entrants is on the rise. According to the Bureau of Labor Statistics in 2022, the RN workforce is expected to grow from 3.0 million in 2020 to 3.3 million in 2030 at a rate of 7% per year[8] The Bureau also projects the outlook for advance practice nurses to grow by 45% between 2020 and 2030. Promisingly, most of the NP entrants will be certified in primary care and 70% will be delivering primary care in the years to come.[3] Unfortunately, attrition and demand are rising greater than the levels of recruitment of new nursing entrants. The Bureau of Labor Statistics also projects 175,900 openings for RNs each year through 2029 when nurse retirements factor into the number of nurses needed in the United States. According to the United States Registered Nurse Workforce Report Card and Shortage Forecast: A Revisit, the shortage of registered nurses is projected to be over 500,000 by 2030[8,9] In this state-by-state analysis, the authors forecast the RN shortage to be most intense in the southern and the western regions of the country.

Additional reasons attributed to the shortage are increasing work demands and problematic relationships with providers. Demand for services has risen due to an aging population, which will require an increased need for geriatric care, including care for individuals with chronic diseases and comorbidities. Finally, problematic relationships with providers have been cited as a reason for intent to leave the nursing profession. In a study by MacKusick and Minick, nurses reported that holistic patient care is emotionally and physically demanding, and these demands increase greatly when a lack of camaraderie exists.[10] For these reasons, the well-being of nurses and the healthcare team is suffering and ought to be addressed.

71.4 TOLL ON NURSES' WELL-BEING

In a 2005 study by Buerhaus et al., more than 75% of RNs believe the nursing shortage presents a major problem for the quality of their work life, the quality of patient care, and the amount of time nurses can spend with patients[11] Additionally, the nurses reported increased stress, lowered patient care quality, and increased intention to leave the profession. Clinicians in all disciplines are experiencing higher rates of burnout, depression, addiction, and suicide.[12]

As a predecessor to burnout, negative outcomes are first seen in the form of compassion fatigue. Compassion fatigue (CF) is defined as "the physical and mental exhaustion and emotional withdrawal experienced by those that care for sick or traumatized people over an extended period

of time"[13] Compassion fatigue occurs when nurses develop decreasing empathetic capacity from repeated exposure to others' suffering[14] Nurses report that CF starts with discomfort and feelings of detachment and distance from their patients progressing to the nurses experiencing physical symptoms such as irritability, trouble sleeping, exhaustion, and forgetfulness[15]

Maslach and Jackson define workplace burnout as a psychological response to job stressors characterized by emotional exhaustion, detachment, and a sense of ineffectiveness.[16] Burnout is a cumulative process marked by long-term exposure to increasing workload and institutional stress. In a study of registered nurses in three hospitals by Kelly et al., more than half the sample experienced moderate burnout and 28% experienced high burnout.[17] Willard-Grace et al. found that physicians and advanced practice providers were 1.5 times more likely to turnover when they had high burnout.[18]

The impact of burnout is wide-ranging. There is a bi-directional relationship between clinician well-being and patient care and safety. According to the NAM, clinician well-being supports improved patient relationships and a high-functioning team.[19] Conversely, there is a negative impact on clinicians' ability to provide quality care when clinicians are not well, including medical errors and unsafe prescribing.[19] The COVID-19 pandemic has created challenges to the well-being of clinicians across the world. One of the solutions may be the protective nature of high-quality teams.

71.5 THE VALUE OF THE TEAM APPROACH

The Institute for Healthcare Improvement (IHI), the international organization committed to improving health and healthcare worldwide, has been a proponent of a team-based care approach as a high-leverage change for over 15 years. Optimizing the care team by having members work to the highest level of their expertise, licensure, and abilities has consistently resulted in greater access, better patient outcomes, and more team member satisfaction.[20]

Lee and Cosgrove suggest a framework that engages other caregivers in multi-disciplinary teams with teamwork done by design.[21] With a shared vision and real collaboration, better care can be achieved by leveraging the skills and talents of all team members. And finally, the systems, processes, and structures, traditionally organized around physicians, should be changed to a team-based approach focused on the patients.[21] With continuing the focus on effective communication and training, team optimization will build team members who have time to do the work they find more challenging and satisfying.[20] Ultimately, an optimized team is a more resilient team.

Why are certain teams and providers more resilient to structural and systems issues? The creation of a culture that rewards and values positive nurse/physician relationships may be part of the answer. Research suggests that strong practice cultures that include teamwork, communication, and psychological safety have increased adaptive reserve to stress and burnout.[22] Magnet hospitals have consistently demonstrated that good relationships between nurses and physicians positively affect patient outcomes[23] St. Luke's Hospital in Florida found that teaching rounds enhanced nurse-physician relationships and promoted nursing education, satisfaction, and retention[24] A study of workplace resilience by Hayes, Chumney, and Buckingham found that survey participants who trusted their teammates, their team leader, and their senior leaders were three times more likely to be fully engaged and highly resilient.[25]

Psychological safety within teams is another factor in building a resilient team. Psychological safety is defined as a team culture that permits team members to take interpersonal risks at work.[26] O'Donovan and McAuliffe performed a systematic review of factors that contributed to psychological safety in healthcare teams.[27] Knowing that your voice is heard, sharing mistakes, asking for direction freely, and trusting your leaders were among the factors identified. These factors are all critical for creating a foundation of team learning and trust.

Lastly, team learning is an important predictor of team performance.[28] Team learning is the process of reflection and action to obtain and process information to detect, understand, and adapt to changes in an environment which, in turn, improves team performance.[26] Ortega's research found that teams that receive training to create a climate of learning perceive a higher degree of psychological safety. The IHI stresses that team learning takes time and positive experience to build trust within a team. With regular practice to fine-tune team skills, shared goals, and clear roles and responsibilities, teams learn to rely on and trust their team members.[20]

The team approach to well-being has resulted in greater access to care and quality outcomes.[29] Each member of the team helps the patient towards wellness through their unique contribution with a shared goal to foster lasting change.[30] There is power in a team to enhance the patient experience and outcomes when nursing takes a larger role. A discussion of the intersection of nursing and lifestyle medicine follows in the next section.

71.6 INTERSECTION OF NURSING AND LIFESTYLE MEDICINE

Nurses are untapped potential partners who believe in and adopt lifestyle medicine quickly. Nursing education and competency have advanced over the years into diverse practice settings, greater scopes of practice, and different specialties[31] Lifestyle medicine principles are being taught in nursing school but may be underappreciated. A body of literature in nursing exists that is siloed and could be leveraged to spread the impact of whole-person lifestyle care. The nursing discipline foundationally focuses on human wholeness, health, healing and well-being, the environment-health relationship, and caring[31] Nurses' knowledge, skills, and academic preparation to counsel and coach patients can

improve health outcomes to advance well-being. In Chapter 73, we will discuss nursing educators' perspectives on the integration of lifestyle medicine into nursing curricula, and, in Chapter 74, a further discussion of clinical nursing approaches to lifestyle medicine will be explored.

As such, nurses play a crucial role in the implementation of lifestyle interventions with patients. Consistent with the tenets of lifestyle medicine, nurses address social disparities, nutrition, stress management, and substance use avoidance.[31] Embedded in the philosophy and training of a nurse is a balanced approach that, when leveraged, complements the lifestyle medicine approach to health. The IHI recognizes the need to better address the needs of patients with chronic illnesses such as diabetes and congestive heart failure. Care coordination and home visits must extend into the community. Nurses through their training and experience can collaborate with patients through the continuum of care, supporting and educating patients on health promotion and wellness. Increased clinician availability and enhanced access to care, with the inclusion of the patient and family in the plan of care, can occur because of enhanced collaboration between multiple team members.[32]

Evidence-based training and mentorship from lifestyle medicine physicians can further refine these competencies. Lifestyle medicine physicians can provide evidence-based education with a focus on health promotion rather than a focus on disease. This education can be incorporated into the curricula of nursing schools, residency programs, medical schools, and NP schools.

71.7 CALL TO ACTION

Charles Darwin said, "It is the long history of humankind that those who learned to collaborate and improvise most effectively have prevailed".[33]

What can we do to survive within a broken healthcare system? We can focus on our role as individual practitioners working within teams while system and structural issues at a macro level are transformed. We can practice our art and our skills in medicine and not focus on what we as individuals cannot change. We can insulate ourselves from the factors that contribute to compassion fatigue and burnout. Here is the call to action and a list of actionable items that can be done today.

First, the team approach is critical to protect against the toll of the workforce shortage. We must leverage our scarce human resources to meet the increasing demand. Good team alignment leads to more reach, more patient contact, and more efficiency. Leveraging and promoting the unique skills of each member allows us to practice at the top of our licenses. Team alignment leads to better patient outcomes, more job satisfaction through meaningful work, and more support through challenging times.

Second, to create a high-functioning team, we need more awareness of what each discipline brings to the team. Through our next four chapters, the contributions nursing and advance practice nurses bring to the table will be discussed. Additionally, there are resources in Section 77.8 to familiarize yourself with the scope of practice and competencies of registered nurses and advance practice nurses. We will introduce you to how nursing education and competencies have changed over the years. Lastly, we will introduce how lifestyle medicine is taught in nursing schools through rigorous curricula.

Next, we are asking you to partner with nursing schools to continue the advancement of curricula and knowledge in lifestyle medicine. We are looking for leaders in the field to promote the team approach and serve as role models. We are looking for leaders to explore the opportunities and potential of a new workforce that leverages the skills and talents of all team members. We are looking for leaders to spark enthusiasm and innovation in a team approach. We are looking for leaders to transfer knowledge to the practice environment. Building trust and competency within a team requires leaders invested in education, training, and reinforcement of the principles of lifestyle medicine.

Lastly, self-care resonates with nurses. As lifestyle medicine practitioners, we must continue to advance approaches to medicine that are vision and value aligned with true health and well-being. Nursing theory is built on a foundation of person, environment, and health, promoting behavior modifications to improve well-being[34] The Nursing Code guides nurses to hold themselves accountable for their own health and safety as they would their patients.[35] Nursing education programs are focusing on the promotion of nurses' health and well-being.[36] A team that is 100% vision aligned for well-being will result in work fulfillment and leave more time to practice the art and skill of medicine.

71.8 SUMMARY/CLINICAL APPLICATIONS

Lifestyle medicine is an evidence-based approach to helping individuals and families adopt and sustain healthy behaviors in preventing, treating, and, oftentimes, reversing chronic diseases. Nurses are often the primary providers providing patient education and counseling and are well-positioned to address lifestyle interventions with patients. By operationalizing lifestyle medicine principles into nursing practice professionally and personally, better patient outcomes and improved nurse well-being can be realized.

As new team-based clinical models in healthcare continue to evolve, the role of nursing can be expanded. The evolution of lifestyle principles into nursing curricula and practice will further enhance a profession proudly founded in patient education, counseling, and health promotion. These tenets of nursing are aligned with lifestyle medicine to create efficient clinical teams that can increase the reach, increase patient contact, and advance the practice of lifestyle medicine for better patient outcomes.

This section of the book has chapters that address/explore nursing contributions to lifestyle medicine. In this overview chapter, a call to action is stated along with resources for further reading on nursing training and education. The nurses' code of ethics, self-care, and the historical changing

roles of nurses are covered in Chapter 72. The nursing educator's perspective on integrating lifestyle medicine into the nursing curriculum is covered in Chapter 73. Staff nurse clinical approaches to lifestyle medicine are addressed in Chapter 74 and advanced practice and specialized nursing approaches to lifestyle medicine are covered in Chapter 75.

71.9 RESOURCES

The following resources will direct you to more information about nursing training, competencies, scope of practice, and licensure:

Academy of Medical-Surgical Nurses: http://www.medsurgnurse.org
American Association of Colleges of Nursing (AACN): http:// www.aacnnursing.org/
American Association of Critical-Care Nurses: http://www.aacn.org
American Association of Nurse Practitioners: http://www.aanp.org
American Association of Nursing Leadership: https://www.aonl.org/
American Association of Occupational Health Nurses: http://www.aaohn.org
American College of Nurse-Midwives: http://www.acnm.org
American Holistic Nurses Association: http://www.ahna.org
American Nurses Association: http://www.nursingworld.org
American Nurses Credentialing Center: https://www.nursingworld.org/ancc/
American Psychiatric Nurses Association: http://www.apna.org
Center for Disease Control: Nurse Practitioner (NP) Resources: www.cdc.gov/dhdsp/pubs/toolkits/np-resources.htm
National Council of State Boards of Nursing: http://www.nscsbn.org/index.htm
National League of Nursing (NLN): https:///www.nln.org
Sigma Theta Tau International: http://www.nursingsociety.org

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72 Code of Ethics, Self-Care, and Historical Changing Roles of Nurses

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KEY POINTS

- From the earliest days of nursing, healing through lifestyle interventions, such as the provision of clean water, fresh air, sanitary conditions, and healthy food, has been fundamental to nurses' healing powers and health promotion.
- The pillars of lifestyle medicine are codified in the Code of Ethics for Nurses and are stated as fundamental to both patient care and nurse duties to self.
- As the largest and one of the most trusted healthcare professions, nurses are uniquely positioned to address the nation's need for accessible, high-quality, person-centered, compassionate care.
- The COVID-19 pandemic and recent landmark government reports identify nurses as well-positioned to bring solutions to social justice and health equity.
- Nurse wellness and self-care are a triple good, first, upholding the duty laid out in the Code for the moral duty of self-care, second, serving as healthy role models for their patients and the public, and third, being empowered with resilience and strength to buffer themselves from illness, injury, and burnout.

72.1 INTRODUCTION: WHAT IS NURSING?

Professional nursing is defined as "the protection, promotion, and optimization of health and abilities, prevention of illness and injury, alleviation of suffering through the diagnosis and treatment of human response, and advocacy in the care of individuals, families, communities, and populations" (p. 1).[4] By definition, the *Scope and Standards of Practice* and the Code are inseparable from nursing's essential contract and relationship with society.[5] A research study using a focus group by Paans et al.[24] examined the essential attributes that define an excellent nurse. According to the study, an excellent nurse should have nine core abilities: to be analytical and apply critical thinking skills; to communicate clearly and effectively; to cooperate within a team and lead and inspire the team; to innovate new, more efficient approaches to problems in the workplace; to be empathic under pressure and use holistic interventions; to disseminate knowledge with patients and members of the team; to use evidence-based research to improve nursing interventions; to coordinate patient care accurately and safely; to be introspective by utilizing constructive criticism to self-reflect and grow professionally.

72.1.1 Evolution of Nursing

The art of caring for the sick began in early civilization, when nurses were innovators, creating and advancing the art of healing the sick.[15] Before the 19th century, religion had a profound impact on the evolution of nursing. Nurses, both women and men, could be found on the front lines treating the injured and sick during the War of Crusades of the 11th, 12th, and 13th centuries. Before formal nursing schools were established, nursing care was passed down through the generations through knowledge sharing and hands-on experience. Nursing eventually became an established profession in the 19th century. Today, nurses comprise the largest group of the American healthcare system with more than 4.1 million registered nurses (RN), 944,000 licensed practical nurses (LPN) and licensed vocational nurses (LVN),[27] and 355,000 nurse practitioners working in diverse roles across the healthcare landscape.[1]

72.1.2 19th-Century Nursing

Nursing evolved into a profession during the 19th century, moving away from a religious order and in the direction of a professional group of individuals.[15] This same century, when it was frowned upon for women to work outside the home, gave rise to nurse pioneers who would change nursing forever.

72.1.3 Florence Nightingale

Florence Nightingale (1820–1910) heard about the plight of soldiers during the Crimean War, and for the first time, professional nursing care was rendered to injured, sick soldiers.[15] Florence Nightingale led a group of professional nurses to Crimea in 1854 to help the wounded and sick.[2] Nightingale's time in Crimea led to her ground-breaking

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Nightingale principles.[16] Nightingale's principles were documented in her book, *Notes on Nursing* in 1860, which was used in early nursing schools. The Nightingale principles focus on holistic practices, health promotion, and disease prevention including cleanliness, clean water, fresh air, light, and basic sanitation.

72.1.4 Clara Barton

Clara Barton (1821–1912) was a visionary nurse who helped change the world with her humanitarian spirit. Clara Barton's career began in education, and she opened the first public school in New Jersey (Strickler, 2018).[28] When the Civil War broke out in 1861, she shifted her attention to providing care for wounded soldiers as a self-trained nurse. She went on to found the American Red Cross, recognizing the need to care for people after disasters, not just during wartime. Clara Barton lived a life providing service to others. She was a civil rights activist and an advocate for women's rights.

72.1.5 Linda Richards

Linda Richards (1841–1930) is known as America's first trained nurse.[15] She attended the New England Hospital for Women and Children nurse training program, where nursing students trained up to 16 hours a day. During their training program, nursing students were not allowed to know the names of the medications they were administering to the patients, and exams were not a part of the curriculum. During her career, she established care facilities for the mentally ill.

72.1.6 Mary Eliza Mahoney

Mary Eliza Mahoney (1845–1926) was the first licensed professional nurse of color.[20] She graduated from the New England Hospital for Women and Children Training School for Nurses in 1879, as one of the three graduates from an original class of 40 students. At the time, the school only allowed one person of color per year into the program. As one of the original members of the Nurses Associated Alumnae of the United States and Canada, she was faced with discrimination. She was a pioneer for women of color. As a result, she co-founded the National Association of Colored Graduate Nurses, and in Boston, she was one of the first women to register to vote.

72.1.7 Lillian Wald

Lillian Wald (1867–1940) was inspired to become a nurse after witnessing the care a nurse rendered her sister during the birth of her child.[15] She attended the New York Hospital Training School with additional training at the Women's Medical College in New York City. In 1893, she started a new field of nursing, Public Health Nursing, providing care to the poor and advocating for individuals to take control of their own health. Lillian and Mary Brewster started the Visiting Nurses Service in New York City, while Lillian was additionally a tireless advocate for free school lunches, school nursing, public parks, and racial harmony.

72.1.8 Nursing Education

The Civil War prompted the need for formal nurse training.[2] During the Civil War, approximately 20,000 women and men provided nursing care to the sick and wounded. The Women's Hospital of Pennsylvania and the New England Hospital for Women and Children were two of the earliest hospital nurse training programs. In 1873, three hospital-based professional nurse diploma training programs, known as the Nightingale Schools, were started in the United States. The early nursing programs were associated with hospitals and offered little classroom education. Nursing education moved into college-based training by 1960, and while the baccalaureate-trained nurse was thought to be superior to the hospital-trained diploma nurse by higher institutions, the hospital-based programs held that their students received exceptional bedside nurse training. As the debate continued, the community college nurse training program emerged offering an associate degree program for nurses. The community colleges were able to offer a less expensive route to becoming a nurse when compared with traditional four-year college programs. The debate continued into the late 20th century when research showed the baccalaureate-trained nurse was equated to better patient outcomes. During the 20th century, racial and gender equality in nursing programs and employment transformed the healthcare landscape.

72.1.9 Modern Nursing

Nurses care for patients in a vast array of settings.[10] The nursing profession offers diverse opportunities in many different areas involving healthcare, including the following: hospitals; private homes; rehabilitation centers; research centers; pharmaceutical companies; insurance companies; schools; public health; the armed forces; clinics; and specialized care. The majority of registered nurses can be found working in hospitals. Nursing education has evolved to become multifaceted and diverse. Today, educational pathways include: licensed practical nurses or licensed vocational nurses (12–18 months of training) who work under the supervision of RNs; associate degree RNs and diploma trained RNs (two to three years of training) offered through community colleges or hospitals; bachelor of science (BSN) RNs (four years of training), which includes expanded education in leadership, research, physical and social sciences, and public health; accelerated BSN or master's (MSN/MS) degree in nursing (12–18 months of training) for individuals with a baccalaureate in a different field; MSN or MS degree in nursing (18–24 months of training)

for advanced practice RNs in various fields including nurse practitioner, clinical nurse specialist, clinical nurse leaders, educators, nurse midwives, nurse anesthetists, and administrators; doctor of philosophy in nursing (PhD), which focuses on research; and doctor of nursing practice, which focuses on clinical practice (DNP) (three to five years of training) (Wakefield et al., 2021). What do all nurses have in common? The American public has ranked nurses as number one in ethics in honesty for the last 19 out of 20 years according to the annual Gallop Poll of Professions.[26]

72.2 THE PRINCIPLES OF MEDICAL ETHICS AND NURSING'S CODE OF ETHICS

Ethical tenets are fundamental to the practice of every nurse, physician, and employee in a healthcare setting, as each provides services to patients seeking care for their health. The principles of medical ethics date back to the time of Hippocrates, and these have been further explored and applied in modern times by philosophers Beauchamp and Childress in their book, *Principles of Biomedical Ethics,* now in its eighth edition.[6] The authors synthesized what are today the four primary principles of medical ethics; 1) autonomy or the patient's right to self-determination; 2) non-maleficence or non-harm; 3) justice or fair and equal treatment; and 4) beneficence or to benefit the patient[6,30] Nurses are guided by these four principles and by their own *Code of Ethics for Nurses with Interpretive Statements* (Code). This section offers a brief history of the Code and the evolving principles, practice, ethics, mission, and role of nurses in their social contract with the public and in relation to nurses themselves.

72.2.1 The Code of Ethics Defined

The Code "establishes the ethical standard for the profession and provides a guide for nurses to use in ethical analysis and decision-making" (p. vii); it is a non-negotiable standard[3] As an evolving document, the Code serves to guide nurses as they respond to the present and changing health and nursing needs of patients and populations. It is an expression of nursing's history and social obligations, and provides immutable ethical practice guidelines for every nurse, in every role and setting.[11]

72.2.2 The Code of Ethics History

The creation of the Code began in 1896 when nurses came together to write the Articles of Incorporation for the American Nurses Association (ANA) with the key purpose of creating and maintaining a nursing code of ethics. This culminated in the publication of the first Code in 1950, with revisions in 1956, 1960, 1968, 1976, 1985, 2001, and the current 2015 edition.[12]

From its first publication in 1950 to today, this dynamic text has evolved to be comprised of two components: the nine Provisions which set forth nursing ethical obligations, and the accompanying Interpretive Statements which give detailed guidance for application in today's world. The provisions are broadly organized as: Provisions 1–3 lay out the foundational commitments and values of the nurse; Provisions 4–6 address duties to self and others and associated boundaries; and Provisions 7–9 extend nursing's breadth and depth of responsibilities beyond a single patient.[3]

72.2.3 The Code's Nine Provisions with Interpretive Statements

72.2.3.1 Provision 1

"The nurse practices with compassion and respect for the inherent dignity, worth, and unique attributes of every person" (p. 1)[3] This ethic is further defined as "respect for the inherent dignity, worth, unique attributes, and human rights of all individuals" (p. 1).[3] The right to healthcare is deemed universal, and nurses are to create trusting relationships with patients and value the worth and rights of every person regardless of gender, language, religion, or language.[3]

72.2.3.2 Provision 2

"The nurse's primary commitment is to the patient, whether an individual, family, group, community, or population" (p. 5).[3] Provision 2 elaborates a nurse's chief commitment to the patient and expands the concept of the patient beyond the individual while ensuring that members of the team provide the information necessary for patients to make informed choices.[3]

72.2.3.3 Provision 3

"The nurse promotes, advocates for, and protects the rights, health, and safety of the patient" (p. 9)[3] Privacy and confidentiality are central to the trust between nurse and patient. Provision 3 asserts patients govern access to their personal information, and nurses are vigilant on behalf of vulnerable populations. Nurses are to help promote a "culture of safety" (p. 11)[3] including acting in any situation that puts the interest of the patient at risk.[3]

72.2.3.4 Provision 4

"The nurse has authority, accountability, and responsibility for nursing practice; makes decisions; and takes action consistent with the obligation to promote health and to provide optimal care" (p. 15)[3] Each nurse is responsible and accountable for outcomes of the nursing care delivered or delegated, and with the expanding scope of nursing practice, are to continuously evaluate their own competence.[3]

72.2.3.5 Provision 5

"The nurse owes the same duties to self as to others, including the responsibility to promote health and safety, preserve wholeness of character and integrity, maintain competence, and continue personal and professional growth" (p. 19).[3]

Provision 5 confers moral worth to all human beings and to the nurse herself. "the same duties that we owe to others we owe to ourselves" (p. 19)[3] Furthermore, as "nursing care addresses the whole person as an integrated being, nurses should also apply this principle to themselves"[3]

72.2.3.6 Provision 6

"The nurse, through individual and collective effort, establishes, maintains, and improves the ethical environment of the work setting and conditions of employment that are conducive to safe, quality health care" (p. 23)[3] Nurses are responsible for helping to establish a moral environment of caring and kindness, dignity, and respect.[3]

72.2.3.7 Provision 7

"The nurse in all roles and settings, advances the profession through research and scholarly inquiry, professional standards development, and the generation of both nursing and health policy" (p. 27)[3] Each nurse is responsible for advancing nursing knowledge in the form of research, development, dissemination, evaluation, or application.[3]

72.2.3.8 Provision 8

"The nurse collaborates with other health professionals and the public to protect human rights, promote health diplomacy, and reduce health disparities" (p. 31).[3] "Health is a universal human right" (p. 31)[3] and the Code elevates health diplomacy to be on par with international treaties, while calling on nurses to partner with others to address structural disparities and basic human rights.[3]

72.2.3.9 Provision 9

"The profession of nursing, collectively through its professional organizations, must articulate nursing values, maintain the integrity of the profession, and integrate principles of social justice into nursing and health policy" (p. 35).[3] The Code envisions nursing organizations as powerful forces for advancing health and social justice worldwide.[3] The Code's final statements are far-reaching calls to action, "social justice extends beyond human health and well-being to the health and well-being of the natural world" (p. 37)[3] and "as nursing seeks to promote and restore health, prevent illness and injury, and alleviate pain and suffering, it does so within the holistic context of healing the world" (p. 37).[3]

72.2.4 The Code—Changes Over Time—Significance Today

The Code has evolved and harkens to key national and international documents on health and human rights. It reflects nursing's fundamental ethic of service to others, while articulating nursing advocacy in an increasingly intersectional world, expanding nursing's role in addressing the health of humanity while at the same time calling on nurses to give themselves the same care and concern.[12]

72.2.4.1 Human Dignity

The concept of human dignity was signed into the United Nations Declaration of Human Rights in 1948, and since the Code of 1960, the concept has evolved from patient care to human dignity for all, including the nurse.[12]

72.2.4.2 Patient Rights Include Privacy and Confidentiality

In 1948, the United Nations Universal Declaration of Human Rights declared the right to privacy as a universal human right, yet this concept has been present since Nightingale's pledge and the Code's beginnings.[12]

72.2.4.3 Culture of Safety and Expanding Nurse Responsibility

The "concept of a culture of safety" (p. 50)[3] enters the Code of 2015, which likewise offers the most expansive interpretation for the scope of practice, including nurse authority, accountability, and responsibility for practice.[12]

72.2.4.4 Health as a Human Right

In 1946, the World Health Organization (WHO), defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being".[8] From the beginnings of modern nursing to today, nursing's role has evolved from addressing the health of the patient and public to promoting health as a universal human right. The Code puts forth an expansive, compelling case for the why and how of nurses' role in addressing these issues.[12]

72.2.5 Nurses as Leaders in Healthcare Transformation and Social Justice

Four landmark reports call for nurses' pivotal role in attaining "the high quality, accessible, and compassionate care that individuals, families, and communities richly deserve", with recommendations for how to support and empower nurses in this role.[23]

- *Nursing, Health, and the Environment: Strengthening the Relationship to Improve the Public's Health*[18] concluded that, "the environment is one of the primary determinants of individual and community health" and "nurses occupy a unique position" as key contributors (p.1).
- *The Future of Nursing: Leading Change, Advancing Health* determined that nurses have distinctive insights and competencies to offer, and should have leadership responsibilities in the redesign of US healthcare.[19]
- *Assessing Progress on the Institute of Medicine Report The Future of Nursing* established there is yet more to do to support nurses' ability to meet the need for high-quality healthcare.[22]

- *The Future of Nursing 2020–2030: Charting a Path to Achieve Health Equity* calls for governments, nurse educators and their institutions, and multiple non-governmental organizations to empower nurses to help bring broad solutions to health equity issues.[23]

72.2.6 The Code, Nurse Self-Care, and Nurse Well-being

- Nursing ethics since the 1800s have asserted the nurse's duty to self, while the Code has evolved to assert, "what I owe to others as moral duties, I likewise owe to myself as a moral duty … self-respect, then, becomes one of the many duties owed oneself" (p. 78).[3] Nurse self-care serves as a triple good—healthy nurses uphold duty to self, model health practices for others, and are less likely to suffer burnout, illness, or injury.[12] The Code calls for nurses to care for themselves as for their patients, specifying nurses are to "eat a healthy diet, exercise, get sufficient rest, maintain family and personal relationships, engage in adequate leisure and recreational activities, and attend to spiritual or religious needs" (p. 19)[3] along with seeking work-life balance.

72.3 Nurse Self-Care, Self-Compassion, and Wellness

The ANA Code includes the ethical duty of nurses to incorporate self-care into their lives to protect their state of wellness.[17] As with the safety instructions on an airplane flight, in an emergency, passengers are to apply their own oxygen mask before assisting others with theirs. The same applies to nurses when it comes to care and compassion, nurses must apply care and compassion to themselves in order to give the best care and compassion to others.[9]

72.3.1 Nursing Health, Burnout, and COVID-19

In every role and setting, nurses can suffer burnout, with baseline rates in US nurses estimated from 35–45%. Nurses are regularly confronted with moral distress caused by constraints or lack of capability to help patients, including lack of time, resources, and other adversities.[23] As a result, nurses suffer health disparities. In the United States, nurses have worse physical health than the general population, particularly regarding physical activity, sleep, and diet. These are compounded by high rates of injury and hazard exposure, which are exacerbated in understaffed or under-resourced workplaces.[23]

Along with poorer physical health, mental health challenges are frequent and widespread among nurses,[23] with the nursing profession experiencing high rates of burnout.[29] Burnout is described as emotional exhaustion, reduced personal accomplishment, and depersonalization. Emotional exhaustion first depletes emotional reserves, which is followed by diminished feelings of personal accomplishment, and eventually, depersonalization results in the development of negative attitudes.

Nurses have been on the frontlines of pandemics throughout history, and the challenges of the recent global pandemic, COVID-19, have led to higher rates of nurse burnout, which can cause higher rates of nurse suicide, depression, anxiety, medical errors, and substance abuse.[31] A systemic review by Galanis et.al.[13] found 34.1% of nurses suffered from emotional exhaustion, another 15.2% from a lack of personal accomplishment, and 12.6% from depersonalization. Nurses are at a significantly elevated risk of mental health consequences, including depression, anxiety, and peritraumatic dissociation as a result of the pandemic.[23]

72.3.1.1 Burnout and Negative Impact on Health

Burnout carries a risk of significant health consequences, including shortening of telomeres—the protective caps at the end of chromosomes.[7] Premature telomere shortening due to burnout is associated with a higher risk of diseases such as heart disease, cancer, pulmonary fibrosis, and aplastic anemia. A cross-sectional study by Wei et al.[31] examined the prevalence of nurse burnout pre-COVID-19 and during COVID-19 on a biological level by measuring telomere length. The study found decreased telomere length in the nurses providing care during COVID-19 when compared with the nurses pre-COVID-19.

72.3.1.2 Presenteeism

Presenteeism, which occurs when an individual comes to work despite feeling cognitively, physically, or emotionally impaired[25] is also more common in the nursing profession and likewise contributes to burnout.[21] Causes include a sense of duty or high level of responsibility, psychological factors impeding the ability to say "no", the inability to find coverage, employment conditions, and relationships with colleagues.[25] Presenteeism can negatively impact productivity, lead to medical errors, increase cost, and burnout, which ultimately negatively impact the nurse, patients, organization, and cost. Perceptions of perfect attendance and organizational commitment need to be changed to increase the well-being of nurses and those under their care.

72.3.2 Barriers to Nurse Self-Care and Self-Compassion

A qualitative study by Egan et al.[9] examined the barriers to self-care and self-compassion among nurses. Poor eating habits and unhealthy food choices were attributed to a lack of time and energy. Additionally, nurses expressed these same factors as barriers to regular exercise. High nurse-to-patient ratios can negatively impact the well-being of the nurse and the patient. The study noted one of the

main concerns expressed by nurses was the inability to take a break. Nurses noted they would work entire shifts without eating, hydrating, or using the bathroom. Many nurses stated they continued to smoke cigarettes to ensure a guaranteed off-site break, and several others in the study expressed the need for a few minutes of solitude during the workday to decompress. Heavy workloads, paperwork, and time constraints leave little to no opportunities to decompress. Not wanting to be perceived as weak or burden other nurses with their workload, nurses hesitate to reach out for help.

Lack of awareness of policies or resources available in the workplace was also noted as a barrier to self-care. According to *The Future of Nursing* report,[23] it is clear that individual solutions are not enough and that systemic factors impacting clinician health and well-being must be addressed.[23]

72.3.3 Stakeholders

Employers play a key role in creating conditions that support the well-being of nurses, notes *The Future of Nursing* report,[22] with multiple areas for meaningful impact including measuring and elevating nurse well-being, improving the culture, system redesign, and support for individuals. Resilience is "the capacity of dynamic systems to withstand or recover from significant disturbances … face adverse situations, remain focused, and continue to be optimistic for the future" (p. 320)[22] Resilience interventions occur at three levels: the primary level offering individual nurses training and support, the secondary level of screening then providing support, and the tertiary level of interventions for nurses whose resilience level was broken, offering healing and support for the eventual return to work (p. 320)[22]

The Institute for Healthcare Improvement (IHI) notes there is growing interest in a model whereby employees would be provided with psychological personal protective equipment (PPE), similar to the concept of physical PPE. The IHI has developed a tool, *Psychological PPE: Promote Health Care Workforce Mental Health and Wellbeing*,[18] and provides steps for leaders at different levels to offer assistance and safeguards for the mental well-being of the staff to be used at the start or end of a work shift.

Nurse leaders and educators can have a significant impact on the well-being of nurses as role models, educators, influencers of organizational practices, and advocates. Nurse education is foundational for the well-being of nurses, with growing evidence for the importance of resilience training and making nursing student well-being an "institutional priority" (p. 329).[22] Importantly, in the New Essentials of the American Association of Colleges of Nursing (AACN), Domain 10 is to "demonstrate a commitment to personal health and well-being", including to "demonstrate healthy self-care behaviors that promote wellness and resiliency" (p. 53).[4]

72.3.4 Nurse Self-Care Resources

There are many varied resources and initiatives from numerous organizations highlighted in the *Future of Nursing*[22] When it comes to the well-being of nurses, the report concludes that "while health care organizations must create the workplace conditions for well-being and integrity to thrive, nurses are also responsible for identifying their own needs and investing in their well-being" (p. 317),[22] responsibility rooted in Provision 5, and the responsibility to eat healthy, sleep, exercise, and participate in leisure and spiritual pursuits (p. 317)[22] The report provides resources for nurses and these include the following.

The Healthy Nurse, Healthy Nation challenge[22] launched in 2017 includes a roadmap for individualizing self-care and well-being assessment and SMART goals. It includes support and annual surveys for nurses to monitor their progress and be role models for others. Whether yoga or tai chi, spinning or hiking, food delivery services or batch cooking at home, a monthly massage or a hot bath, a frolic with a puppy or a play date with the kids, whether hiring someone or asking a friend or family for help, or meditation or movement tracking apps—each nurse must find what works and obtain support. The ANA HNHN provides a nurse-centered launching point to get started.

Mindfulness, including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), along with cognitive-behavioral therapy (CBT), show promise in helping nurses become aware of emotional reactions and then have the ability to choose their response.[23] MINDBODYSTRONG is an evidence-based intervention taught by nurses to new nurses, while exercises in gratitude and deep breathing are also proving effective. Evidence is demonstrating that brief mindfulness sessions can yield positive results and there is an array of mobile technologies to support nurses' sessions.[23]

72.4 CONCLUSION

From the early days of modern nursing to the Code, to reports by numerous national committees and nursing organizations, nurses have been appreciated as leaders for solving the nation's health crises and social disparities, and likewise are the calls that leadership from across society must rally together to create real-world solutions for the well-being and empowerment of the nation's nurses, who have given and continue to give so much.

CLINICAL APPLICATIONS

- Acknowledge the evolution of nursing history that will empower nurses to face future challenges to the nursing profession and educate the public in regard to the significance of nursing history.

- Discuss the importance of the nursing code of ethics which specifies nurses are to care for their patients and themselves through interventions, including eating a healthy diet, physical activity, stress management, social connections, and rest, and therefore, all nurses are empowered to educate themselves and their patients on the lifestyle choices for optimal health.
- Empower nurses to reduce healthcare disparities, improve healthcare outcomes, and recognize self-care as an ethical duty through the application of the nursing code.
- Help nurses identify burnout, the negative effects of burnout, the barriers to self-care, self-care needs, and self-care resources.
- Educate stakeholders on the importance of creating and supporting healthy resources that will support nursing self-care.

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73 Nursing Educators' Perspectives on Integrating Lifestyle Medicine into the Nursing Curriculum

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KEY POINTS

- Nurses often serve as health role models for their patients.
- Nursing faculty often serve as health role models for their students.
- Academic accreditation and professional nursing organizations have identified the need for curricular content, focused on lifestyle behaviors, within nursing.
- Few schools of nursing currently integrate lifestyle medicine content within their curricula.
- Curricular ideas need to be shared so that greater integration of lifestyle medicine content occurs within nursing curricula.

73.1 OVERVIEW OF LIFESTYLE NURSING

Lifestyle nursing is a specialty within lifestyle medicine, specifically addressing needs from the lens of nurses at the baccalaureate, graduate, and doctorate levels. The first textbook on lifestyle nursing (eds. Gia Merlo and Kathy Berra) was published in August 2022 as part of the Lifestyle Medicine Series (ed. James Rippe).[1] The need to address discipline-specific competencies and educational content in lifestyle medicine is compelling. As the largest healthcare profession in the United States, over four million nurses work to maintain and improve the health of patients. The goal of health improvement for patients is always challenging and recent stressors impacting the healthcare system, exerted by the pandemic, have highlighted the need for and barriers against addressing lifestyle behaviors and health advancement within population health. A disproportionate number of individuals experienced significant health effects of Covid-19.[2] Chronic diseases and conditions exposed large numbers of people to the ill effects of the disease.[3] Routine practices of healthy lifestyle behaviors likely strengthened the health and well-being of others without those diseases.[4] Even before the pandemic, statistics were grim regarding nurses' health.[5] American Nurses Association (ANA) Health Risk Appraisal results revealed that nurses reported poor intake of fruits and vegetables and high levels of stress and the majority of nurses were in the overweight body mass index category. Although positive health practices, such as tobacco avoidance, seven hours of sleep nightly, and low intake of sugar-sweetened beverages were identified, there is still a need for overall health improvement within the nursing profession.

Integrating the six main health behaviors associated with lifestyle medicine (e.g., nutrition, physical activity, stress management, sleep, avoidance of risky substances, and social connection) into each day has been shown to strengthen health and well-being within clinical practice.[6] The need for lifestyle medicine is clear; the healthcare system needs more healthcare professionals with a strong background in lifestyle medicine science and practice. To adequately prepare nurses for supporting patient health within clinical practice, more nurses need to become familiar with key lifestyle medicine concepts. One viable solution includes the integration of this content within nursing curricula. We know that clinician health practices have an influence on their patients.[7] Increasing the number of nurses who are positive, healthy role models will improve nurses' health and positively impact their patients' health.[8] Now is the time to seriously consider how schools of nursing and academic organizations can monitor and direct nursing education and curricula, and integrate this critical content for maximal health benefit in the United States.

A variety of policies and initiatives developed by professional nursing organizations are relevant to, and supportive of, this lifestyle medicine practice suggestion. The Healthy Nurse Healthy Nation effort, from the ANA, is one excellent example that emphasizes the importance of personal well-being in nursing. The critical need for including lifestyle medicine concepts within nursing education is clear. The American Association of Colleges of Nursing Essentials document[9] identifies four future care environments that nurses must be prepared to work within: disease prevention and promotion of health and well-being; chronic disease care; regenerative or restorative care; and hospice/ palliative care. All four types of care are necessary, but advocacy for emphasizing prevention, health promotion, and well-being is critical since the health of the nation

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depends on that approach (AACN, 2021). It is easier to keep people with few health risks healthy than it is to improve the health of people with many risks, and there are significant health and cost incentives associated with such care.[6] This approach helps achieve the quintuple aim of improving patient experiences (quality and satisfaction), improving the health of populations, decreasing per capita costs of healthcare, improving care team well-being, and addressing health equity.[10] These initiatives highlight important health parameters for nurses and provide a foundation for the advocacy of lifestyle medicine content integration into nursing education and practice.

73.2 HISTORICAL PERSPECTIVE ON NURSING ROLES

From the beginning, nurses have promoted health for individuals, families, and communities in a variety of care environments such as hospitals, clinics, corporations, schools, and communities. Some of the earliest writings about nursing by Florence Nightingale highlighted the power of self-care practices and lifestyle in strengthening overall well-being.[11] Although there has been less emphasis over time on health promotion and well-being within nursing, a return to full integration of that content is recommended.

73.3 NURSING EDUCATION REVIEW

Many paths exist to become a registered nurse (RN). To achieve the RN license, students might apply to a diploma program (generally affiliated with a healthcare system), a two-year associate degree program, or a four-year undergraduate, baccalaureate degree program (see Table 73.1). The vast majority of nurses enter one of those types of programs (98.1%) versus entering a graduate-level program (1.1%).[12] While all program types provide the educational base required to sit for a state licensure exam to become an RN, significant differences exist in the specific courses taken by students.

Associate degree nursing (ADN) programs generally take two to three years to complete and include nursing-specific and liberal arts courses. On average, 70 course credits are required for graduation and to sit for a state nursing licensure exam. Liberal arts courses, typically considered prerequisites for entry into an ADN program, include psychology, communication, English, biology, anatomy and physiology, chemistry, sociology, and possibly statistics. Nursing coursework focuses on skills and clinical practice within health assessment, nursing practice, medical-surgical nursing, pediatric nursing, maternal-newborn nursing, psychiatric-mental health nursing, community health nursing, microbiology, and immunology. About 700 hours are required within the clinical practice environment as an opportunity to learn and practice key nursing skills. The American Association of Colleges of Nursing (AACN) does support associate degree nursing education despite their description of the baccalaureate degree as the base level required for professional nursing practice.[13]

Bachelor's degree programs in nursing generally provide more comprehensive education than that found in ADN programs. On average, 120 credits are included in these types of programs with an emphasis on physical assessment, nursing theory, statistics, ethics, and leadership. Liberal arts courses such as the humanities, social sciences, and basic sciences are included within the curriculum, generally during the first two years of study. Core nursing courses follow in years three and four. Clinical courses generally offer 700-800 hours of experience in a wide variety of hospital and community settings, although some programs do incorporate more hours (e.g., up to 1300 hours at some schools, such as Case Western Reserve University[14]). As the major educational entry program for nursing, the bachelor's degree prepares graduates to work in complex healthcare settings.[15] Accelerated programs for bachelor's degrees exist within some educational institutions. They offer programs lasting 12–18 months and feature a fast-paced learning environment for students who already have an undergraduate degree in another field (and have completed prerequisite coursework) or those who may already have an ADN. Both accelerated and four-year undergraduate nursing programs have fairly stringent requirements in regard to curricula and offer little room for elective courses, although four-year programs generally offer more opportunities for electives than accelerated programs.

Graduate entry programs have existed within the nursing profession for a number of decades. People who have graduated with a degree in a field other than nursing enter these programs to become an RN. Typically lasting 18 to 24 months, graduate entry programs provide graduate education for students who want to transition into nursing programs from non-nursing degrees. Graduates of these programs may achieve various degrees, including BSN (Bachelor of Science in Nursing) and MN (Master's in Nursing).

Master of Science in Nursing (MSN) programs accept nurses into their programs who are interested in becoming nurse practitioners. Colleges and universities vary in the number and type of programs offered. Master programs that prepare nurse practitioners in acute care, pediatrics, women's health and midwifery, palliative care, gerontology, family care, psychiatric-mental health, nurse anesthesia, nursing informatics, and administration are most common. Clinical nurse specialist master's programs are also offered at some institutions. RNs enrolled in these programs frequently work while taking courses and fit the clinical course requirements around their work schedules. At the end of these two-year programs, graduates are prepared to sit for board exams in their practice specialty and upon passing are able to practice within the scope defined by the state in which they will be working.

Transitional programs exist within nursing to help nurses without a bachelor's degree get an advanced master's degree. For example, RN to MSN programs provide entering students with the ability to take graduate courses to become nurse practitioners. Other such programs, such as a BSN to PhD program, enable BSN-prepared nurses to get a PhD for future academic and research work.

TABLE 73.1
Examples of Nursing Education

Nursing Education Programs	Abbreviation	Example Educational Areas	Length of Program	Number of Course Credits Required	Number of Clinical Hours Required
Associate degree nursing	ADN	Foundations of nursing, clinical nursing	2–3 years	70	700
Bachelor's degree	BSN	Liberal arts, sciences, and nursing specialization courses (e.g., care of patients, families, and communities, and professional issues in nursing),	4 years; the accelerated program is 12–18 months if the undergraduate degree has already been earned	120	700–800; some schools offer up to 1300 hours
Graduate entry	MN	Nursing practice, theory, research, ethics, leadership, and nursing specialization courses	18–24 months; degrees include BSN and MN (Bachelor of Science in Nursing and Master in Nursing)	63–72	500–1000
Master of Science in Nursing	MSN	Adult gerontology, acute care NP, primary care NP, family NP, nurse-midwifery, pediatrics NP, primary care/acute care, psychiatric-mental health NP	2 years	42–49	500–600
Doctor of Nursing Practice	DNP	Practice, practice leadership, education leadership, executive leadership	1–2 years	33–43	500–1000
Other forms of doctoral education (PhD)	PhD	Research areas in health services, adults and aging, and children, youth, and families	3–4 years	48–63	0

Increasing numbers of nurses are completing graduate degree programs in nursing.[12] Doctor of Nursing Practice (DNP) programs are one of those graduate degree programs that have seen exponential growth in the past ten years. The first clinically focused nursing doctorate program was launched at Case Western Reserve University in 1979.[16] The concept of this educational structure is similar to that found within medical and dental schools and provides an alternative for nurses interested in doctoral preparation for clinical work environments.

Doctoral education in nursing also includes PhD programs. Nurses enter these programs with aspirations of becoming researchers and academicians. While most of the students entering PhD programs already have a master's degree in nursing, some direct entry programs move BSN-prepared students through to the PhD. Nurses enrolled in these programs frequently work throughout their programs. It is common for financial support to be available through educational institutions; nurses may also work as faculty to tap into the educational support provided to employees through the educational institution.

The educational options available within the nursing profession are vast. Not only are the standard degree options described here available at many institutions across the United States, but the specific programs of study available to students may also be quite different between those colleges and universities. This educational variability, as well as many clinical, administrative, research, educational, policy, and advocacy jobs and settings available to nurses with different degrees, is part of what makes nursing an attractive profession. Nevertheless, stringent guidelines have been established by academic accreditation organizations (e.g., the Commission on Collegiate Nursing Education [CCNE] and the Accreditation Commission for Education in Nursing [ACEN]) that specify content that must be covered to offer a complete nursing education that fully prepares nurses for their professional work.

73.4 LIFESTYLE NURSING EDUCATION JUSTIFICATION

The need for schools of nursing to increase their focus on wellness and health promotion within curricula is clear.[15]

Increased focus on lifestyle medicine content is needed for future nurses given their poor health practices and the movement within healthcare systems to focus more on population health and wellness.

Nursing faculty are guided in their curricular development efforts by various accreditation institutions. The AACN is particularly relevant, as its "Essentials" document describes the core competencies required for professional nursing practice.[15] Domains and competencies for entry-level professional practice, as well as advanced-level education, focus on knowledge for nursing practice, person-centered care, population health, scholarship for nursing, quality and safety, interprofessional partnerships, systems-based practice, informatics and healthcare technologies, professionalism, and personal/professional/leadership development. The domain especially relevant to lifestyle medicine is population health.[9]

> Domain 3: Population Health Descriptor: Population health spans the healthcare delivery continuum from public health prevention to disease management of populations and describes collaborative activities with both traditional and non-traditional partnerships from affected communities, public health, industry, academia, health care, local government entities, and others for the improvement of equitable population health outcomes.

The emphasis on competency-based education, as described by AACN, is further support for the inclusion of lifestyle medicine and practices within nursing education. It is only by learning this core content and practicing healthy lifestyle behaviors that future nurses will be adequately prepared to attend to their own well-being while also addressing the health promotion and wellness needs of their patients.

Nursing schools have the opportunity to create robust curriculua that meet the quadruple aims of the Agency for Health Care Research and Quality (AHCRQ) goals of improving: population health; experience of care; per capita costs; and health status and resiliency of healthcare providers.[17] This will move the nursing profession in the direction of assuming more responsibility for lifestyle behavior change within their profession and for patients. Modeling curricular paths in nursing after published models from undergraduate and graduate medical curricula is advised.[18] Integration of lifestyle medicine content within nursing education represents one of the best opportunities to positively impact the health of patients.[19]

73.5 CURRENT WORK ENVIRONMENT CHALLENGES FOR NURSING

The rise of burnout and mental health concerns experienced by nurses is associated with the pandemic[20] but existed prior to that time too.[21] Patients are acutely ill when hospitalized which means that care needs are greater. As workload increases, work stress and attrition, as well as patient mortality, are negatively affected.[22] Nurse staffing issues also impact safety and quality of care.[23] Working as a nurse in a hospital environment has become quite challenging. Nurses' health would benefit from the integration of lifestyle medicine within nursing practice.

An increase in interdisciplinary care models, within clinical environments, further highlights the acute challenges for nurses who do not have a solid foundation in lifestyle medicine. As physicians and other healthcare professionals embrace the positive impact of lifestyle in their own lives and that of their patients, nurses will be at a disadvantage when working on care teams if they do not have an educational foundation in lifestyle medicine. Nurses need advanced knowledge of the evidence documenting the numerous positive effects of lifestyle medicine practices as well as practical and personal experience in the benefits associated with lifestyle medicine.

While the emphasis within nursing is on the promotion of health for sick and well individuals, the nursing profession, in general, does not represent or model ideal health. The Nurses' Health Study highlights the impact of unhealthy lifestyle practices on overall well-being.[24] If the Healthy People 2030 goals[25] for the nation are to be achieved, nurses must devote more time and attention to their own health in order to positively impact their patients' overall well-being. Chapter 78 focuses on self-care and provides details on what nurses can do to improve their own health and well-being.

73.6 LIFESTYLE NURSING CLINICAL APPLICATIONS

Poor adherence to lifestyle modifications has negative health ramifications for a variety of conditions including hypertension,[26] diabetes, and cardiovascular disease.[6] Health and well-being will improve for patients when core lifestyle behavior content is incorporated into nursing practice. The need for lifestyle nursing practice within clinical environments is clear and the opportunities for RNs, master's prepared practitioners, and doctoral nurses to integrate lifestyle nursing into their care plans is immense.

73.7 LIFESTYLE NURSING EDUCATION APPLICATIONS

Current curricular efforts in a few US nursing programs may serve as introductory examples for other institutions to consider for their student populations. The whole-person approach espoused by the nursing profession suggests that lifestyle medicine concepts are already an integral component of nursing philosophy. This fact means that it is easy to make the case for the inclusion of lifestyle medicine concepts within nursing. Professional nursing organizations are now advocating for the inclusion of wellness and well-being content for nursing students. The AACN Core Competencies for Professional Nursing Education explicitly state that nursing students must practice wellness and resilience activities to

enhance their own health as well as doing the same for their patients.[9] While there are few, if any, published articles that describe specific curricula in this area, informal reports are available from nursing faculty who describe undergraduate and graduate nursing courses that focus on health promotion and wellness, which include all of the same content comprised by lifestyle medicine.

A handful of schools have integrated specific lifestyle medicine content into nursing courses. These integrated courses are usually a part of a health promotion course that includes concepts of nutrition, wellness, and leadership in the curriculum. Some courses address the vital nature of social connections and health through values identification, culture, relationship building, time management, and communication strategy content.[27] The ANA's Healthy Nurse Healthy Nation[28] Health Risk Assessment and a sleep assessment are utilized within other courses. Self-reflection is often built into the process to encourage consideration of personal progress.[29]

In 2020, New York University's Rory Meyers College of Nursing added a three-credit elective course for graduate and doctoral students that offers 50 contact hours in one semester of instruction, discussions, and group activities titled "Wellness Through the Lens of Lifestyle Medicine". The vision for this course evolved in the spring of 2020 during the COVID-19 pandemic with the faculty-led weekly support wellness meetings with Meyers' doctoral students.

This course is in line with the fundamentals published in 2022 by the American Association of Colleges of Nursing which included a focus on self-care and well-being in Domain 3. The course provides core knowledge; students in this graduate-level course prepare before class by reading assigned literature and then engaging in student-led discussions on the subject and focusing on a discussion-based lecture based on the practical applications of the course material. A similar course has been offered for undergraduate nursing students at NYU since 2021.

New courses need to be developed within other schools of nursing for the full integration of lifestyle medicine content within nursing programs to be realized. More courses are required to provide a solid base of content in this topical area in order to fully impact the lifestyle behavior practices of nurses and nursing students. Adopting this curricular approach is consistent with accreditation organization mandates and is the natural next step to fully embrace our potential for whole-person health and well-being within nursing and across the United States. While a dearth of information is available regarding the incorporation of lifestyle medicine content within nursing curricula, advocacy statements for pre-professional education exist and present strong arguments for the expansion of those efforts.[30]

A curriculum content table (see Table 73.2) is shared with the hope that university curriculum committees across the country find this to be a helpful stimulus for their curriculum development efforts.

73.7.1 Additional Curricular Applications

Additional curricular options include the integration of ACLM-certified programs, as well as the inclusion of ACLM courses within curricula so that evidence-based, best practices are taught, and students graduate having familiarity with established programs that lead to positive health outcomes.[31] Examples include the Complete Health Improvement Program (CHIP), the Chanwuyi Lifestyle Medicine Program, The Life Project, and the 15-Day Whole-Food Plant-Based Jumpstart Program. Including current ACLM courses within nursing lifestyle courses might also be considered. For example, the "Physician and Health Professional Well-being Course" could be offered to graduate students with the "Family Physician's Introduction to Lifestyle Medicine" document serving as required reading.[32]

TABLE 73.2
Curricular Applications

Six Pillars	Foundational Course Content	Advanced Course Content	Course Activity Ideas
Nutrition	X	X	Seven-day dietary recall and review
Exercise	X	X	Exercise is medicine
Stress	X	X	Brief mindfulness activity practice at the beginning of each class with reflections
Substance Abuse	X	X	Case study review(s)
Sleep	X	X	Four-week sleep hygiene tracking and review
Relationships	X	X	Paper assignment to review current evidence on the importance of social connections to health
Behavioral economics	X	X	Guest lecture by business school behavioral economist
Introduction to lifestyle medicine	X		SMART goal creation; self-care plan implementation
Lifestyle medicine in practice		X	SMART goal creation; patient plan implementation

Resources developed for current clinicians would also be helpful references for nursing students. The National Academy of Medicine[33] created an evidence-based resource compendium that includes tools and strategies to enhance healthcare workers' well-being. Schools of Nursing should consider how those resources can foster a culture of well-being for students, faculty, and staff. The American Nurses Association's initiative, titled Healthy Nurse Healthy Nation, includes resources to foster nurses' mental health.[28] It would not be hard to develop new courses on well-being for undergraduate nursing students using the clinician well-being resources previously mentioned. Recently, enhanced attention has been directed to clinician well-being, but redirecting those resources to students is also vital for creating a healthier healthcare workforce.

Advocacy for offering more lifestyle medicine courses within curricula has occurred[34] and should continue so that the full potential of nurses and nursing students to actualize health and well-being within their own lives and that of their patients is realized.

73.8 SUMMARY

The American Nurses Association acknowledged the need for greater attention to healthy lifestyle practices when it created the Healthy Nurse Healthy Nation initiative.[28] The challenges integrated into that program are designed to encourage increases in daily healthy behaviors among nurses. Those efforts are critical for current nurses. The need is great in regard to preparing future nurses to be experts and role models for healthy living. Integration of lifestyle medicine curricula within undergraduate, graduate, and doctoral nursing programs shows promise. Curricular examples are available and greater consideration of this need, with the active creation of new courses within nursing programs, is required to improve nurses' health and that of their patients.

CLINICAL APPLICATIONS

- Personal nursing well-being can be enhanced by following lifestyle principles.
- In contrast with medical education, many nursing degree-granting educational programs can be targeted for lifestyle nursing education.
- While medical education has a rigid curriculum in most institutions, nursing education has flexible elective course options in many degree-granting programs.

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74 Staff Nurse Clinical Application of Lifestyle Medicine

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KEY POINTS

- There are four million registered nurses in the United States.
- Nursing is one of the most trusted professions by patients.
- This places nurses in a unique position to share the benefits of lifestyle interventions.

74.1 HISTORY OF LIFESTYLE INTERVENTIONS IN NURSING

In *Notes on Nursing*, Florence Nightingale addressed the need for pure water, uninterrupted sleep, and the mind's impact on the body[1] Modern nursing is rooted in these lifestyle interventions. An interdisciplinary organization, the American College of Lifestyle Medicine (ACLM), has an actively growing member interest group (MIG) made up of hundreds of registered nurses (RNs) and advanced practice registered nurses (APRNs). The RN/APRN MIG mission is "To support RNs and APRNs in the use of evidence-based Lifestyle Medicine principles in nursing practice and to advance the cause of Lifestyle Medicine in the nursing profession through ACLM membership, networking, education, certification, publications, and presentations".[2] Notice the focus on evidence-based therapeutic lifestyle interventions, which nurses may use in their daily practice.

The case for the role lifestyle medicine interventions can play in preventing and potentially reversing chronic diseases is laid out throughout the chapters of this book. This chapter's focus will be on lifestyle interventions available to all nurses, not just those practicing in an APRN role or working within a lifestyle medicine (LM) focused clinic. This chapter intends to offer suggestions and spark personal exploration regarding how lifestyle interventions may be incorporated into the daily practice of the reader, both personally and professionally.

74.2 CRITICAL ROLE OF NURSES IN HEALTHCARE LIFESTYLE INTERVENTIONS

There are currently four million registered nurses in the United States,[3] and nursing is the largest healthcare profession in the United States.[4] Nursing is also recognized as being one of the most trusted professions. With this trust comes the responsibility to provide the best possible care for health.[5] Regular physical activity, daily stress management, a healthy diet, and avoidance of risky substances such as tobacco and alcohol are widely accepted as contributing to optimal health and disease avoidance.[6] Nurses are uniquely positioned to provide examples of these behaviors and patient education regarding modifiable risk factors for chronic diseases. A nurse's own behaviors may influence, positively or negatively, the quality and amount of information shared with the patient. Because they are seen as role models, when nurses engage in behaviors that may be damaging to their own health, they may also be negatively impacting the health of others.[6]

74.3 SCOPE OF PRACTICE FOR THE REGISTERED NURSE

Nurses may be concerned about incorporating lifestyle medicine interventions into their practice. Often, there may be uncertainty about what falls within their scope of practice. Westmoreland et al. describe the unique services nursing offers and define the scope of nursing practice in specific situations. Three major classifications of the scope of practice exist.

- The first classification of nursing services is delegation. They enhance the health of the patient and require a physician's order. Few lifestyle medicine interventions typically fall into this classification.
- The second category of nursing services is interdependent. These services also enhance the health of the patient by assessing, monitoring, detecting, and preventing complications related to a medical diagnosis. They require the nurse to make judgments and have knowledge of signs and symptoms of potential problems and prevent complications. Many lifestyle medicine interventions may fall into this category.[7]
- Last, nursing services may be independent. The nurse may enhance health by assessing, monitoring, and treating with a focus on nursing diagnosis. The connection between the whole patient, body, mind, and spirit is being addressed. Nursing knowledge is required to help the patient and family as they navigate their response to new health

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information. While other healthcare professionals are involved in the first two classifications, nursing has the primary responsibility for this third function.[7] Multiple lifestyle interventions can be included here.

74.3.1 Stress Management

Nurses in any practice setting may benefit from practicing personal daily stress management. The Well-being Initiative[8] was developed by the American Nurses Association (ANA) and the American Nurses Foundation (ANF). This initiative offers free resources to foster nurses' mental health and well-being. These factors play a critical role in productivity, personal and professional quality of life, and overall health and wellness.

Nursing staff may also take advantage of workplace wellness programs. These programs vary in their offerings but frequently address physical activity, nutrition, and tobacco cessation, all essential aspects of daily stress management.[9] As identified earlier, the nurse is looked to by the patient as a role model.[6] Modeling these behaviors benefits both the nurse and the patient.

The inpatient hospital setting can be stressful for both nursing staff and patients. Large numbers of people coming and going, noises made by people and machines, and the busyness of frequent activities may contribute to feelings of stress. Regular daily activity routines, food intake, sleep patterns, and socialization are all disrupted for the hospitalized patient. Each patient will perceive the experience differently and respond based on their perceived stress and ability to cope with that stress.

Strategies to assist a patient in coping with these stressors may be as simple as listening to the patient share their experience and feelings or facilitating communication between the patient and family members. The nurse may also teach the patient and family members techniques for and the potential benefits of deep breathing or progressive muscle relaxation exercises to prevent and manage feelings of stress.

Similar interventions may be taught and practiced with adults, teenagers, and children in an outpatient setting. Stress may be experienced in these areas when diseases are newly diagnosed. Or a child may be fearful of healthcare visits due to previous experience with uncomfortable procedures. Patients may also be experiencing stress in their daily work, school, or personal lives.

Nurses working in occupational health or worksite wellness may offer interactive programs or educational workshops regarding ways to minimize the negative impacts of stress. Physical activity programs are an essential component of worksite wellness programs.[10] In addition to physical benefits, physical activity produces both emotional and psychological benefits[11] This is just one example of a specific lifestyle intervention positively impacting another.

74.3.2 Quality Sleep

Interestingly, human beings may deliberately deprive themselves of sleep without any apparent gain. No other species does that.[12] The first standard of nursing practice is assessment.[3] The first sleep intervention the nurse may do for the patient is raising their awareness of how much quality sleep they routinely get, how they feel upon awakening, and whether they feel fatigued throughout the day.

Another critical question is whether the patient has ever been told they snore or have sleep apnea.[13] Obstructive sleep apnea is a common disease, but few patients are diagnosed or treated.[14] Some patients may be concerned about going into a sleep lab for an overnight study. A simple assessment tool, the STOP-Bang questionnaire, available online or as a short paper questionnaire, may be offered to the patient as a self-administered initial screening for predicting the severity of obstructive sleep apnea.[14] Once the patient is aware they have an elevated score, they may more readily enter into a conversation about the possible next step of a home-based sleep study. Although the RN will not be ordering these tests, this nursing interaction may pave the way for appropriate treatment and improved quality of life and health.

Three other vital assessment areas include caffeine, alcohol, and general fluid intake. Worldwide, caffeine is the most commonly used stimulant.[12] The patient may not recognize the potential negative impact on their sleep of those late-evening glasses of iced tea or chocolate bars. Or the patient may be under the false impression that having a drink in the evening will help them fall asleep or sleep more soundly throughout the night.[12] Even more straightforward is the possibility that late-evening fluid intake may be contributing to nocturia. The nurse may take the opportunity of a patient's complaints regarding poor sleep quality to explore whether any of these habits may be contributing to their sleep disturbances.

74.3.3 Quality Food

From the beginning of professional nursing, Florence Nightingale acknowledged the possible effect of food on the patient.[1] Nutrition topics currently included on licensure exams for registered nurses include nutrition assessment and monitoring, diet therapy (including enteral and parenteral nutrition), and patient education and counseling.[15] As knowledge continues to develop regarding best nutrition practices, the nurse with an interest in lifestyle interventions must stay abreast of current research as well as what is being reported in the mainstream media. Members of the public regularly receive poor-quality information about what to eat to promote health, especially regarding obesity.[16]

Many nurses have learned about specific diets to address certain disease states, such as a low-fat diet for patients with heart disease and a low-sugar diet for someone with diabetes. This has led to much confusion for both patients and nurses regarding what to eat after receiving more than

one diagnosis. Part II, Nutritional Aspects of Lifestyle Medicine, will lay out the case for recommending a whole food plant-based diet to reverse and prevent multiple disease states.

A current diet assessment is the place to begin with a patient who has expressed interest in the possibility of making changes. It may be as simple as asking questions regarding what they typically eat and drink during the day. This can be done at the bedside. Or, for the more involved patient or the nurse with time for a more in-depth interaction, a comprehensive nutrition screening tool may be more appropriate. A review of the results with the patient and their support persons can help identify both current positive habits as well as areas of opportunity. While the patient may appear discouraged because their current diet is so "bad", the nurse can offer the encouragement that these are also additional possibilities for achieving their desired goal through lifestyle. A dietitian knowledgeable regarding a whole food plant-based diet is an invaluable resource for both the patient and the nurse.

Optimal nutrition is vital for the prevention and possible reversal of multiple diseases. Exploration in this area may include trying new foods or cooking methods or meeting with other like-minded individuals to share a meal. When armed with evidence-based nutrition practices, nurses can improve their own health as well as educate their patients, leading to improved health outcomes and increased quality and length of life.

Box 74.1 is an example of the use of lifestyle interventions by an RN in a hospital setting. While traditional cardiac rehab intervenes only after the patient receives a cardiac diagnosis, this LM nurse has worked with her team to initiate an opportunity for disease prevention education. The impact is being seen and heard not just by patients but also by their family, friends, and other hospital staff.

BOX 74.1 Nursing Narrative of Lifestyle Interventions for Patients with Coronary Artery Disease

Our "CAD (Coronary Artery Disease) Risk" program is for patients who had a heart catheterization during their current hospitalization, had any CAD greater than 0%, and had no intervention or myocardial infarction. The Inpatient Cardiac Rehab Team takes the opportunity to provide education regarding heart disease and lifestyle factors to these patients and their support people. This education includes an explanation of what the heart does and the result of their catheterization, the relationship between inflammation and coronary artery disease, information about what constitutes a heart attack and angina, and a personalized discussion of heart disease risk factors. Patients and their families and friends express great appreciation for this education and information on potential lifestyle factors. After overhearing these conversations, many hospital staff have changed their language from "clean cath", which was previously used to describe a heart catheterization without intervention even when CAD was found, to "some CAD". This change in language is beginning to shift the message to these patients from "your heart is fine" to "you have some CAD and here's what you can do to prevent its progression".

74.3.4 Physical Activity

Lack of regular physical activity is widespread throughout the United States and significantly raises mortality risk.[17] Overwhelming evidence has repeatedly shown the significant mental and physical health benefits of regular physical activity. In response, the American Medical Association (AMA) and the American College of Sports Medicine (ACSM) developed the "Exercise is Medicine" campaign.[18] Multiple sources have specifically suggested that regular physical activity may delay the development of cardiovascular disease and decrease the incidence of coronary heart disease events.[19] Although nurses are aware of many of the benefits of physical activity, they may not be comfortable making specific exercise recommendations to patients. There may be concern about the risk of harm to the patient.

As with each of the other aspects of lifestyle interventions, nurses can start the process of positively impacting the patient by beginning with an assessment. Exercise is Medicine recommends adding two questions to the patient's health history regarding how many days per week they currently engage in vigorous PA and for how many minutes at each session.[20] Part III, Physical Activity, will guide the nurse regarding recommended physical activity levels and screening recommendations. Armed with this information and the patient's answers to the above questions, the nurse then has the opportunity to discuss with the patient their current PA levels and the potential benefits of working toward the recommended targets. Change cannot happen if the patient is unaware of these guidelines and their possible health advantages.

Patients can sometimes become discouraged if they feel the PA recommendations are too strenuous or time-consuming. The most recent edition of the *Physical Activity Guidelines for Americans* states that any amount of physical activity has some health benefits.[21] These guidelines also include evidence showing that physical activity can have immediate health benefits such as anxiety reduction, lowering blood pressure, and improving sleep quality and insulin sensitivity. This knowledge can encourage the patient with an "all-or-none" mindset. Studies have shown that healthcare practitioners with higher levels of PA are more likely to recommend PA to their patients.[22] And as previously established, nurses can also act as positive or negative health behavior role models for their patients.[6] So, a nurse with a pattern of regular physical activity can

benefit not only herself but the patients she educates and for whom she cares.

74.3.5 Social Connections

Social connections are significant predictors of health, both good and bad. As such, they can be seen as either a risk or a protective factor.[23] Social connections are critical coping mechanisms during times of stress. Unfortunately, some stressful situations, such as the recent COVID-19 outbreak, require many patients to find new ways to connect.[24] Helping patients explore and find the best ways to make and maintain social connections is an area of opportunity for nursing.

Assessment is, once again, the place to start. Does the patient live alone? Do they have regular contact with friends or family members? If adult children live with them, are these positive, supportive relationships? Are they working from home? Are they members of any groups such as a bowling league, book club, or faith community? Are these groups meeting in person or solely virtually? Have there recently been any significant changes in their social connections, such as the death of a spouse or the loss of a job?

These questions do not have to be asked during a lengthy intake interview, although a minimal initial assessment regarding whether the patient lives alone and information about their support person is typically included as part of many initial nursing assessment forms. Further information regarding the patient's social connections may be gathered through conversation during a dressing change or brief office visits for lab work follow-up. Once the nurse has gathered information regarding the patient's current level of social connections, she can educate the patient about the potential benefits of having strong social connections, as outlined in other chapters of this book. Then the nurse can begin to explore possible ways to connect with others that are appropriate for this patient.

The nurse, once again, can benefit both herself and the patient by role-modeling strong social connections.[6] By developing and nurturing these connections, the nurse can personally benefit from the protective effects on the physical and mental health of social connections.[25] The patient may benefit indirectly from the health benefits experienced by the nurse and directly by being encouraged and motivated by their caregiver who can speak to the personal benefits.

74.3.6 Risky Substances

Substance use is common and takes place throughout many cultures and populations. In 2021, the United Nations reported that of the 275 million people who used substances within the past year, more than 36 million had a substance use disorder (SUD).[26] Mortality rates and mental and physical health quality can be directly correlated with substance consumption rates.[27,28] Substances used may be legal or illegal. Features of SUD include loss of control, social or work impairment, risky use, and craving for the substance.[29]

Screening for unhealthy substance use is recommended by the US Preventive Service Task Force for all adults over the age of 18, while the American Academy of Pediatrics recommends substance use screening for all primary care visits for children 12 to 17 years of age.[30,31] Most people experiencing challenges with substance use do not pursue treatment, partly because they do not feel they have a problem.[32] Once again, nurses have an opportunity to assess, raise awareness of the potential for health improvement, and educate on possible interventions.

One practice model used in the healthcare setting is SBIRT—screening, brief intervention, and referral to treatment.[33] The initial screening may be done by nurses working in the emergency department or primary care practices using tools such as the NIDA Quick Screen for Alcohol and Other Substances.[34] Patients with positive prescreens may then receive a full screening tool such as the DAST-10 for further risk stratification.[33] If the additional screening was positive for risky substance use, a ten- to 20-minute intervention session could be offered. This is followed by referral to community resources if the screening score indicates hazardous use or possible SUD.[33]

Although primary care practices and emergency departments are popular SBIRT settings, the reasons for patient visits vary significantly between them. While the reason for an emergency department visit may offer a teachable moment, SBIRT delivery in this setting can be particularly difficult due to time constraints. SBIRT studies have generally shown smaller reductions in substance use in emergency department patients when compared with similar studies carried out in primary care settings.[33]

Motivational interviewing (MI) is one patient-centered intervention with significant support in the literature and can easily be included by the nurse during any screening or brief interaction intervention. MI techniques include eliciting change talk, developing discrepancy, and rolling with resistance to change.[35] Nurses interested in expanding their clinical behavior-change toolbox will want to look in other chapters of this book for further information on these techniques. Other lifestyle intervention tools that nurses may use to assist patients with avoidance of risky substance use include mindfulness,[36] regular physical activity,[37] and a healthy diet.[38]

As a trusted resource, nurses frequently hear concerns from patients regarding substance use that may not be shared with others. The nurse has the potential to raise patient awareness of problematic substance use and make a positive impact through brief interventions. Nurses with a strong knowledge of lifestyle interventions such as mindfulness, regular physical activity, and quality food may also provide support for patients recovering from SUD.

Box 74.2 includes tips for fitting lifestyle interventions into specific brief patient encounters in an outpatient setting. Many nurses are concerned that they do not have time in their already busy schedules to implement LM interventions. This nurse shares examples of quick questions to ask and resources that are easily shared.

BOX 74.2 Tips for Fitting Lifestyle Interventions into a Brief Outpatient Interaction

- After reviewing the patient's medical history and identifying chronic conditions such as hypertension, diabetes mellitus, hyperlipidemia, or cancer, I ask: "Have you made any changes to your diet, exercise, or overall lifestyle since this diagnosis?"
- After administration of the patient health questionnaire (PHQ-9) or generalized anxiety disorder (GAD-7) screening, I ask: "What do you do when you're feeling stressed or overwhelmed? Do you have a trusted friend or supportive community?"
- After reviewing a patient's smoking status, alcohol, and other substance use, I ask: "Have you ever quit before? Is this something you might be interested in pursuing today?"
- During an assessment of a patient's vital signs, I asked: "Are you exercising on a regular basis? If so, how many minutes per day, and days per week?"[38]
- Applicable smart phrases were added to the after-visit paperwork to reiterate the lifestyle changes we had discussed. Examples include: "Please watch Game Changers (on Netflix), Forks Over Knives, or PlantPure Nation (on YouTube) for more information; Recommend removing dairy from your diet—please visit Switch4Good.org to learn more".
- I also kept a binder full of patient education handouts gathered largely from ACLM and Physicians Committee for Responsible Medicine (PCRM) from which I pulled tip sheets—regarding anything from the pillars of lifestyle medicine to condition-specific lifestyle approaches—to share and send home with willing patients.

74.4 NURSE COACHING

Health coaching is one of the latest tools used in healthcare to manage chronic diseases. Other chapters of this book describe the practice of health coaching and lifestyle change. The large number of RNs and the significant amount of time they spend with patients puts the nurse in an excellent position to provide this health coaching. Coaching can be used to decrease the impact of a chronic illness's symptoms and prevent these diseases.[40] The ACLM defines LM as "the use of evidence-based, lifestyle, therapeutic intervention … to prevent, treat, and often reverse disease".[41] Due to the additive power of these intentions paired with the nursing profession's size and the significant amount of nurse-patient interaction time, nurse coaching can be a powerful LM instrument.

While multiple coaching certifications are currently available, only one board certification is offered specifically for nurse coaches by the American Holistic Nurses Credentialing Corporation (AHNCC). These exams are accredited by the Accreditation Board for Specialty Nursing Certification (ABSNC). ABSNC accreditation allows nursing credentialing organizations to obtain and maintain accreditation by demonstrating compliance using a peer-reviewed system. The American Nurses Credentialing Corporation Magnet Recognition Program® recognizes all the AHNCC examinations.[42]

AHNCC is the national certification organization for nurse coaches. According to Margaret Erickson, CEO of the AHNCC, since nurse coaches practice as nurses first, "our examination is based within the context of the Nurse Practice Act". This exam differentiates the nurse from others practicing the role of health and wellness coaching, such as social workers, nutritionists, business professionals, and physical fitness trainers.[43]

Eligibility criteria for the nurse coach exam include specific requirements regarding licensure, practice hours, minimum education level, number of nurse coach-specific CNEs, mentored or supervised coaching experience, and the candidate's agreement at the time of application. Nurses who complete the requirements for nurse coach certification through the AHNCC earn the designation Nurse Coach Board Certified. Any nurse who meets the requirements for this certification and holds one of the holistic nurse certifications offered by the AHNCC earns the designation Health and Wellness Nurse Coach Board Certified.[44]

74.5 CONCLUSION

As the largest healthcare profession in the United States, nurses have the opportunity in a wide variety of settings to make a significant, positive impact on the lives of patients through the use of lifestyle interventions. As one of the most trusted professions, nurses are uniquely positioned to listen to patients and make lifestyle recommendations to potentially reverse or prevent disease. The examples given here encompass just a few of the many possible interventions available to the nurse to positively impact the patient.

CLINICAL APPLICATIONS

- The nursing intervention begins with an accurate assessment and listening to the patient.
- Nursing lifestyle interventions do not have to be of long duration to be powerful.
- Start with interventions that are most pertinent to the current clinical practice setting.
- The potential impact includes the nurse, the patient, the patient's family and friends, and fellow staff members.

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75 Advanced Practice and Specialized Nursing Approaches to Lifestyle Medicine

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KEY POINTS

- Advanced practice registered nursing (APRN) dates to the 1800s.
- There are four specialties under the APRN umbrella: certified nurse midwife (CNM), certified registered nurse anesthetist (CRNA), certified nurse practitioner (CNP), and clinical nurse specialist (CNS).
- APRN education aligns with the mission and values of lifestyle medicine.
- RNs and APRNs have demonstrated how they are able to address gaps in care and rise to the changing healthcare landscape.
- APRNs are well suited to be integral members of the lifestyle medicine team.

81.1 A BRIEF HISTORY OF NURSING AND ADVANCED PRACTICE REGISTERED NURSING

Documentation of nursing dates to the Roman Empire era around 300 AD.[1] Historical contributions to science made by nurses demonstrate the depth and breadth of the profession. Florence Nightingale was a nurse who provided care for wounded soldiers in the 1850s. She has been credited for advancing the nursing profession in the 19th century by focusing on decreasing wound infection and improving hygiene in practice[1] The concept of an advanced practice registered nurse (APRN) has its roots back in the mid-1800s. Catherine S. Lawrence was the first nurse to administer anesthetics during the American Civil War in 1861.[2] Today, nearly 44,000 nurse anesthetists are practicing in the United States.[3] Another advanced practice nurse role, the clinical nurse specialist (CNS), was first conceptualized in the 1800s when hospitals educated nurses in specialized psychiatric nursing care. The first official CNS program was established in 1955 at Rutgers University.[2] Today, CNSs are clinician experts defined by areas such as population (pediatrics, adults, women's health); setting (emergency room, critical care, outpatient); disease or specialty (diabetes, oncology, transplant); type of care (psychiatric, inpatient, rehabilitation); or type of problem (pain, wounds, stress).[4]

Nurse-midwifery began in the United States when Mary Breckinridge started the Frontier Nursing Service in 1925.[5] Nurse-midwifery was not nationally recognized until 1954. Up until that point, nurse midwives had a more general practice that also included other pediatric care services[6] The nurse practitioner is a more recently developed APRN role. The first nurse practitioner program was established in 1965 at the University of Colorado School of Nursing. This was in response to physician shortages as well as an opportunity for nurses to grow professionally in public health and to obtain a graduate-level education[2] APRN practice has evolved over the last century to include national associations, certifications, and licensures that ensure quality and cost-effective care is provided by this profession.

81.2 DEFINITION OF AN ADVANCED PRACTICE REGISTERED NURSE

An APRN has a graduate-level degree at the master's, post-master's, or doctorate level. There are four specialties under the APRN umbrella, including certified nurse practitioner (CNP), certified registered nurse anesthetist (CRNA), certified nurse midwife (CNM), and clinical nurse specialist (CNS). They all share the foundational education and experience of the RN, while also having their own role in healthcare. CRNAs are an example of how APRNs can fill gaps in care. Currently, more than 50 million anesthetic procedures are provided by CRNAs each year.[7] In fact, 80% of anesthesia providers in rural counties are CRNAs. A certified nurse midwife specializes in women's healthcare including, health maintenance, prenatal, labor and delivery, and post-partum care.[8] A CNS has a graduate degree and is certified in a specialty. While a CNS typically focuses on education, research, and consulting, they can also apply for authority to prescribe medication.[8] A nurse practitioner (NP) provides comprehensive care including assessment, diagnosis, evaluation, and treatment. RNs and APRNs are educated to provide whole-person care with a focus on primary, secondary, and tertiary prevention. Trained as an RN and an APRN, nurse practitioners are skilled at not only assessing for physical symptoms but also psychosocial and

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environmental data[8] Extensive experience in education can also set these providers apart in the arena of lifestyle medicine.

APRNs are regulated through licensure, accreditation, certification, and education (LACE)[9] Although there are national standards in education, accreditation, and certification for APRNs, states have their own specified levels of practice authority.[10] The APRN Consensus Model is an attempt to provide uniform regulations for roles, licensure, accreditation, certification, and education for APRNs in the United States. There has been some progress, but there remain states that have not implemented all elements.[11] For nurse practitioners, 26 states, DC, and two US territories have full practice authority.[12] Thirteen states and three US territories have reduced practice authority and 11 states have restricted practice for nurse practitioners. Full practice authority allows nurse practitioners to practice under the exclusive licensure authority of the state board of nursing. The National Academy of Medicine and the National Council of State Boards of Nursing support this model.[12] The other models either reduce or restrict NPs' ability to engage in one or more areas of practice. These models also have requirements related to collaborative agreements, supervision, delegation, or team management by another health provider.[12]

81.3 APRN EDUCATION AS IT RELATES TO LIFESTYLE MEDICINE

APRNs are trained to view and treat patients in a whole-person manner. There is an understanding of the multidimensional influences on health from family, community, social, political, and economic environments. After establishing a therapeutic relationship, APRNs are skilled at prioritizing health concerns and providing patient-centered, culturally competent care.[13] In addition to nursing-specific coursework, graduates receive liberal education related to cultures and spiritual beliefs. Combining the arts, sciences, and humanities in liberal education prepares the nurse for a unique perspective on healthcare. This includes providing ethical care and acting as an advocate, as well as promoting health equity and social justice with the understanding of structural racism, bias, and social determinants of health[13].

> The study of history, critical race theories, critical theories of nursing, critical digital studies, planetary health and climate science, politics, public policies, policy formation, fine arts, literature, languages, and the behavioral, biological, and natural sciences are key to the understanding of one's self and others, civil readiness, and engagement and forms the basis for clinical reasoning and subsequent clinical judgments.[13]

The American College of Lifestyle Medicine values statement aligns with APRN education, which focuses on using evidenced-based practice, high standards, integrity, healthy equity, and treating the whole person[14] The American Association of Colleges of Nursing has core competencies that are required within APRN education and within these competencies are ten domains.[13]

Domain one is knowledge for nursing practice. This includes translating theories and nursing science into practice. This domain also covers the synthesis of knowledge, ethical decision-making, and socially responsible leadership. APRNs are taught to practice clinical judgment based on the integration of knowledge, evidence, and decision models. Domain two is person-centered care. This begins with fostering and promoting therapeutic relationships. This involves the ability to communicate effectively with patients from a diverse background with preferred methods of learning.

Next, APRNs are trained to provide patient-centered care in the areas of assessment, diagnosis, implementing a plan of care, evaluation, promoting self-care management, and care coordination. Lifestyle medicine asks patients to modify their lifestyle and behavior change is challenging. It would be difficult for a practitioner to guide a patient through lifestyle medicine behavior modifications if they cannot formulate a person-centered plan of care. An example of this is in pediatric weight management programs. Hampton-Anderson and Craighead discuss how African American children benefit less from these traditional programs and how there is a need for programs to consider disparities in eating disorders, psychosocial factors, and cultural factors.[15]

Domain three is population health. APRNs receive education related to assessing the target population and the system's ability to address needs; analyzing population data and comparing benchmark data; using evidenced-based methods to prioritize care for the population; collaborating with stakeholders to implement culturally appropriate intervention and evaluation methods; cultivating effective partnerships to further the pursuit of population health and health equity; socioeconomic landscapes relating to care being provided; health policy; advocacy; and disasters and public health emergencies. Lifestyle medicine implemented at a population health level can address social determinants of health. Health Equity Achieved through Lifestyle Medicine (HEAL) and the ACLM Health Systems Council are two examples of population health initiatives led by ACLM.[16]

The fourth domain is scholarship. There is a breadth of evidence supporting lifestyle medicine in the prevention or management of heart disease and its impact on telomeres, cancer, erectile dysfunction, cognitive function, stroke, diabetes, pain, and weight management.[17] As lifestyle medicine continues to grow as its own discipline, APRNs can play a critical role in the evaluation, translation, implementation, and generation of lifestyle medicine-related scholarship and research. Their education also covers scholarship-related topics such as ethics, IRB guidelines, and methodologies in quality improvement, research, and evaluation.

Domains five and eight relate to quality, safety, and information technology. APRNs receive education on

utilizing data, benchmarks, and outcome metrics to lead quality improvement initiatives. Allowing APRNs to lead quality improvement initiatives can help with reimbursement as well since APRNs are included in the Merit-Based Incentive Payment System (MIPS)[18] In addition, APRNs can utilize quality improvement initiatives, research, and publications as part of their requirements for renewing state licenses and national certification.[2,19]

The sixth and seventh domains pertain to collaborating with other professions and system-based care. Implementing lifestyle medicine on a large scale will need a system-wide, team-based care approach. It would benefit the team to have APRNs who have experience and training in team-based care dynamics that promote inclusion, equity, and diversity. In addition, the ninth domain focuses on professionalism, expanding on concepts of ethics, innovation, communication, leadership skills, accountability, social justice, civility, laws, policies, and regulations.

The tenth domain is centered around the APRN and encourages "participation in activities and self-reflection that foster personal health, resilience, and well-being".[13] Having the concept of self-care within the education of RNs and APRNs will not only reduce the risk of provider burnout but will also be useful in providing optimal lifestyle medicine care. For example, studies have shown that physically active healthcare providers are more likely to counsel their patients on this healthy lifestyle habit.[20] APRN experience and training align well with lifestyle medicine. There is a wealth of opportunities for this profession to offer to the specialty, patients, and population health.

81.4 NURSING: RISING TO THE CHALLENGE AND ADAPTING TO THE CHANGING HEALTHCARE LANDSCAPE

All APRNs have a background as a registered nurse (RN). Registered nurses make up the largest healthcare profession in America, at over four million.[21] In addition, nurses have ranked as the number one profession for honesty and ethics for 20 years in a row.[22] The number of doctorate-prepared nurses tripled between 2010 and 2018 from 10,000 to 33,000[23] Having the foundation of registered nursing prepares APRNs for success when practicing lifestyle medicine. An example of this occurred after the 2020 Surgeon General's Call to Action to Control Hypertension. Nursing leaders from 11 national organizations came together to formulate how nursing could contribute to this call to action.[24] They defined how different sectors of nursing could execute this call to action by utilizing evidenced-based nursing interventions. These included community support to optimize patient care in multiple domains, enumerating roles of registered nurses, advanced practice nurses, QI/population health nurses, schools of nursing, and professional nursing organizations. This example effectively showcases the opportunity that lies within nursing to advance the health of patients and communities. APRNs practicing at the top of their license can interact with the different sectors of nursing and other healthcare disciplines to provide safe, high-quality, equitable care.

The National Academy of Medicine (NAM) (formally National Institute of Medicine) released *The Future of Nursing: Leading Change, Advancing Health* in 2011. Recommendations were made to have nurses included in integral and leadership roles engaged in redesigning healthcare in the United States.[25] In this landmark report, a vision for the future of healthcare in the United States was presented along with the rationale as to why nursing was a key component of realizing this vision. The three areas of necessary change in nursing were practice, education, and leadership. In 2016, a publication was released regarding the progress made on the 2011 report. Areas of opportunity for continued progress included the following: increasing awareness of nurses' capabilities in the areas of practice, education, collaboration, and leadership; the need for diversity in the nursing workforce; and further data collection to continue improvements.[26] To date, the number of nurses with a doctorate has more than doubled since 2011; eight additional states since 2010 have granted APRNs full practice authority; and nurses are holding leadership roles as evidenced by more than 10,000 board seats filled by nurses.[23] As work continues toward the recommendations from the 2011 report, the current Future of Nursing Report for 2020–2030 has been published. This report identifies how nursing ethics, values, and knowledge prepare them to be key stakeholders in addressing social determinants of health (SDOH) and improving health equity.

APRNs are suited to be key stakeholders in expanding access to lifestyle medicine and its pillars to all populations. Bodenheimer and Mason published proceedings of a conference on how nurses, including APRNS, can be partners in transforming primary care and should be able to practice to the full extent of their license.[27] With the projected physician shortages in both primary care and specialties within the next ten years, RNs and APRNs will be asked to fill the gaps in care and improve access to care.[26]

> Allowing APRNs to practice to the full extent of their education and training as recommended in the 2011 The Future of Nursing report would help remediate inequities in access to health care and enable more people to enjoy the benefits of care provided by NPs and other APRNs.[26]

81.5 HOW APRNS CAN ADDRESS THE CURRENT GAPS IN CARE

Building a workforce that is trained in lifestyle medicine can increase accessibility to high-quality care that improves health outcomes. An example could be training CNMs in lifestyle medicine and using their expertise to improve rates of breastfeeding. The American College of Nurse-Midwives (ACNM) Benchmarking Project has been utilizing data from nationally endorsed quality metrics for

quality assurance and quality improvement over the last quarter century.[28] In the 2019 report, they found the average exclusive breastfeeding rate 48 hours after birth among participating midwife practices was 86%. The current reported rate of infants in the United States who are exclusively breastfed at 48 hours after birth is 64.5%[29] This highlights a tremendous opportunity to capitalize on the expertise of CNMs and expand lifestyle medicine across the lifespan.

There is a need for improved data on the cost-effectiveness of both APRN practice and lifestyle medicine. Most data show how APRNs provide high-quality, cost-effective care; however, publications related to evaluating the cost-effectiveness of APRN roles tend to lack quality[30] Abraham et al. conducted a systematic review related to the cost-effectiveness of chronic disease care provided by APRNs compared with physicians.[31] APRNs were cost-effective in the areas of medication management and patient care visits. The findings were not consistent with their cost-effectiveness in laboratory testing and diagnostic procedures. Razavi et al. found that for Medicare beneficiaries, primary care nurse practitioners were more conservative with resource utilization compared with primary care physicians, especially in low-risk populations.[32] A reduction in resource utilization can help with containing costs and additional cost savings in accountable care organizations (ACOs), especially when beneficiaries are not required to see both a physician and an APRN included in the ACO contract. In contrast, Batson, Crosby, and Fitzpatrick found that their 118 advanced practice providers (APPs) within the Hattiesburg Clinic did not perform as well as physician primary care providers in quality metrics, ER utilization, or cost of care provided per member per month (PMPM)[33] The organization concluded that APPs were a critical part of their healthcare delivery and if it were not for the 100-plus APPs employed over 15 years, thousands of patients would have not been able to receive primary care. However, based on the results, APPs were no longer assigned their own patient panels. Veterans Affairs conducted similar studies on patients with diabetes and found lower total healthcare costs for patients with APPs as their primary care provider as compared with physicians.[34] Standardizing the way APRN care is evaluated would be beneficial in determining how to implement their practice into lifestyle medicine. Lopatina et al. recommend utilizing *Guidelines for the Economic Evaluation of Health Technologies: Canada* when evaluating APRN roles.[30] In addition to evaluating APRNs, there are opportunities to expand on the research related to lifestyle medicine interventions and healthcare spending. Livingston et. al expressed the need for lifestyle medicine economic research related to the effects of an intensive therapeutic lifestyle intervention (ITLC), cost savings compared with current disease-related costs, and the impact of lifestyle medicine outcomes on various payment models[35] Training APRNs to practice lifestyle medicine can further improve the cost-effectiveness of the care provided as well as the health of the communities served.

CLINICAL APPLICATIONS

- The foundation of RNs in APRNs prepares them to follow lifestyle medicine practices.
- Strengthening the care team in lifestyle medicine practices can increase high-quality healthcare accessibility and improve health outcomes.
- Increasing the roles of advanced practice providers in lifestyle medicine may lead to cost-effectiveness in healthcare.

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Part XIV

Mental Health and Psychiatry in Lifestyle Medicine



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76 Lifestyle Psychiatry: An Overview

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KEY POINTS

- The budding field of lifestyle psychiatry is being acknowledged and growing within lifestyle medicine.
- The interaction of mental health and physical health is bidirectional and is affected by lifestyle medicine's pillars.
- A compelling body of literature shows that lifestyle interventions significantly benefit chronic medical and mental health conditions.
- Addressing the psychological factors contributing to barriers is key to helping patients reach their lifestyle medicine goals.

76.1 THE TIME IS NOW

Since the first publication of this book in 1999, to the forming of the American College of Lifestyle Medicine in 2004, to the now over 2100 diplomats certified in lifestyle medicine, the growing field of lifestyle medicine has come a long way.[1–3] Notable on this occasion is the inclusion of the "Psychiatry and Mental Health" section in this book for the very first time in this fourth edition. This acknowledgment of the importance of mental health as a part of lifestyle medicine is due in part to the understanding of the bidirectionality of mental health and physical health, as well as the impact of lifestyle factors on these areas. The field of lifestyle medicine builds upon the rich existing literature in the fields of behavioral medicine/health psychology, psychosomatic medicine, and psychophysiology. This budding field of lifestyle psychiatry is more thoroughly addressed in the book that is a part of the Dr. James Rippe's Lifestyle Medicine Series with Taylor and Francis titled *Lifestyle Psychiatry: Through the Lens of Behavioral Medicine*, edited by Drs. Gia Merlo and Chris Fagundes.

Even prior to the onset of the COVID-19 pandemic, the impact of mental health in the United States (and the world) has been significant.[4] Subsequently, the incidence of mental health conditions and the prevalence of substance use has grown, attributed to the worsening of the social determinants of health.[5] Although mental health treatment during the pandemic mostly shifted to a telehealth model, Centers for Medicare and Medicaid Services reports that even more individuals are forgoing mental health treatment or have had their access to treatment severely limited.[6,7] These are alarming statistics, as prior to the pandemic more than 57% of people in the United States did not receive the mental health treatment they needed.[8]

Now is the time to leverage the growing and compelling body of literature that shows how lifestyle medicine significantly benefits chronic medical and mental health conditions. Importantly, poor mental health can inhibit the behaviors needed to obtain goals outlined by the lifestyle pillars (nutrition, sleep, exercise, substance use, stress management, and healthy relationships).[9] Addressing the psychological factors contributing to barriers is key to helping patients reach their lifestyle medicine goals.[10] This synthesis of mental health with lifestyle medicine is the crucial step to treating the whole person.

76.2 WELLNESS, MENTAL HEALTH, AND BRAIN HEALTH

As the World Health Organization (WHO) states, "There is no health without mental health".[41] The terms wellness, mental health, and, more recently, brain health, have been used interchangeably by many. Corbin and Pangrazi in 2001 defined wellness as "a multidimensional state of being describing the existence of positive health in an individual as exemplified by quality of life and a sense of well-being".[57] Individual and environmental factors can lead to impaired wellness and impact the person's overall health. However, optimal individual wellness, through the practice of lifestyle medicine and healthy daily habits, cannot be achieved without addressing *all* aspects of health. Mental health, on the other hand, is defined as "a state of mind characterized by emotional well-being, good behavioral adjustment, relative freedom from anxiety and disabling symptoms, and a capacity to establish constructive relationships and cope with the ordinary demands and stresses of life".[58] Mental health also includes freedom from symptoms of mental illness whether they are a diagnosable mental disorder or subsyndromal. Mental health includes wellness, as well as a capacity to experience emotions, thoughts, and feelings, an ability to problem solve and overcome difficulties, make social connections, and connect with the surrounding world.

While mental health is perhaps a term that is well known by both the public and scientific community, it does not capture the importance of the concept of *brain health*. *Brain health* is defined by the WHO as the fostering of optimal brain development, cognitive health, and well-being throughout the entire lifespan.[56] Indeed, brain health

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encompasses everything we think, do, say, and feel. For this reason, it can be seen that brain health has an ongoing, fluid course. In this way, the lifespan continuum of brain health is in alignment with current evidence regarding neuroplasticity, the ability of the brain to adapt and escape previous genomic restrictions through the formation and reorganization of synaptic connections. This furthers the role of healthy lifestyle habits and brain health factors in the reduction of risk for brain illness progression and related pathologies, as well as overall health, throughout the aging process.

Of note, all three of these concepts—wellness, mental health, and brain health—have well-being in their definitions. Well-being is defined as "a state of happiness and contentment, with low levels of distress, overall good physical and mental health and outlook, or good quality of life".[59] In 2017, the National Academy of Medicine (NAM) rolled out the Action Collaborative on Clinical Well-Being and Resilience.[61] This collaborative has more than 200 organizations in the network focused on reversing clinician burnout. In 2022, NAM continued to create the National Plan for health workforce well-being.[62] While many definitions have been proposed for these complex constructs, for this chapter, we will focus on the three concepts: wellness, mental health, and brain health since well-being is included in the definitions of these three.[63] See Figure 76.1 for a representation of the relationship between wellness, mental health, and brain health.

76.3 THE GUT MICROBIOTA AND MENTAL HEALTH

The brain-gut-microbiota system (BGM) is implicated in the pathology of various diseases, including those within the scope of brain and mental health. The term microbiota describes microorganisms that live in an established environment, whereas microbiomes are the sites of genetic material of microorganisms within particular environments in the human body.[55]

Many factors influence the composition of the microbiota, including stress, exercise, environment, diet, genetics, medicine, pet ownership, and birth mode. Furthermore, the gut microbiota interacts with the brain via multiple pathways, including the neuroanatomical pathway of the gut-brain axis (vagus nerve), the neuroendocrine hypothalamic-pituitary-adrenal axis, the immune response, the intestinal epithelium and the blood-brain barrier, and the microbial production of neurotransmitters such as serotonin.[13] Emerging data shows that mental health disorders, such as depression, are linked to the compositional states of the gut microbiome in a bidirectional manner.[16]

Dysbiosis, the imbalance of the gut microbiome, is the underlying cause of pathology associated with the BGM. For this reason, the role of lifestyle interventions in the interactions between the brain and gut, as well as the facilitation of optimal overall health, is an emerging area worth further consideration for clinical applications.

76.4 HEALTH NEUROSCIENCE

The human brain remains one of the greatest challenges for modern medicine,[11] yet it is one of the most integral and sometimes overlooked aspects of lifestyle medicine. The human brain consists of roughly 100 billion neurons and 100 trillion neuronal connections and consumes about 25% of the body's energy. Recent scientific discoveries (i.e., sequencing the human genome, technology to map neuronal connections and provide higher-quality resolution of imaging technologies,

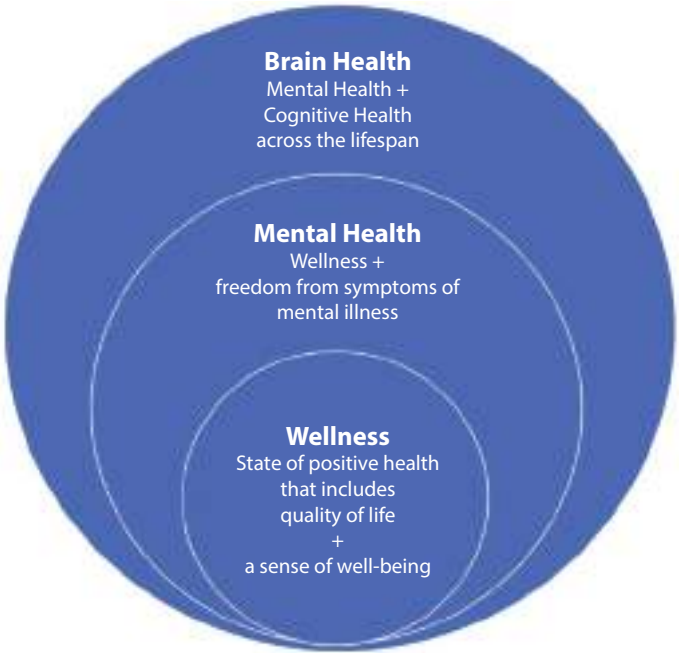


FIGURE 76.1 The relationship between wellness, mental health, and brain health.

and the expanding field of nanoscience) increase the likelihood that the mysteries of the brain will be revealed, particularly as they relate to brain health including neurological and mental and behavioral health disorders. As individuals improve brain health, it will be easier to achieve whole health through implementing lifestyle principles.

To date, these aforementioned technologies have been most successful in diagnosing structural brain deficits, brain tumors, and vascular and inflammatory brain disorders.[12] Currently, there are no established biomarkers for the majority of mental and behavioral health disorders. In their recent review of the current state of imagining and mental and behavioral health diseases, Falkai et al. indicated growing effectiveness in the identification of dementia, particularly Alzheimer's disease (AD), major depressive disorder (MDD), affective psychosis (e.g., bipolar psychosis), and schizophrenia.[12] Specifically, hippocampal volume from structural MRI confirms diagnosis and at-risk populations for AD; for MDD, structural studies are being used to identify potential biomarkers that may help differentiate subcategories of symptoms, like treatment refractory. Individuals with bipolar 1 show a specific pattern of brain anomalies within the temporal lobe, basal ganglia, and ventricular system that can be differentiated from schizophrenia. Finally, for schizophrenia, studies show specific patterns within the hippocampus, amygdala, thalamus, nucleus accumbens, and lateral ventricles that are different from AD, MDD, or bipolar disorder.

Potentially as interesting is the use of functional MRI (fMRI) along with neurofeedback, which shows promise in molding cognition, emotion, thought, and actions as it is able to target specific regions within the brain.[14] In addition to this, there is optimism as new scientific discoveries better explain neurobiological pathways and their correlations with health. For example, in a recent systematic review by Haeger et al, in patients with AD or mild cognitive impairment, aerobic exercise was shown to be the most effective intervention to improve regions prone to neurodegeneration (e.g., hippocampal region, precuneus, anterior cingulate, and the prefrontal cortex). These findings were confirmed by fMRI, diffusor tensor imaging, and cerebral blood flow.[15]

Given the current scientific limitations, Chapman et al. in Chapter 77 propose an assessment tool, the BrainHealth Index. It is a comprehensive survey that combines key aspects of neuroscience and lifestyle medicine, which measures whole brain health: cognition, social functioning, well-being, and real-life functions.[17] This index is not a diagnostic test, however, it is able to detect changes when individuals make adjustments consistent with lifestyle medicine and whole brain health.

76.5 PSYCHIATRIC DISORDERS AND ASSOCIATED MENTAL HEALTH CONDITIONS

Mentions of mental and behavioral health are found throughout early history. Initially, the origins were attributed to supernatural, somatogenic, or psychogenic causes. These varied origins confounded the nature and diagnosis of these mental and behavioral illnesses throughout history. In 1883, German psychiatrist Emil Kraepelin first published a comprehensive collective of psychiatric illnesses around observed symptoms[18] which tried to demystify mental and behavioral health. Unfortunately, unlike other diseases within medicine, there is not a specific laboratory screen test (i.e., checking one-hour post-meal blood glucose), diagnostic test (i.e., cardiac stress test), or radiographic test (i.e., fractured bone) that confirms the diagnosis of mental or behavioral health disease. As such, mental health diagnosis is based on the consensus observations of experts, like in the days of Kraepelin, and their consensus of diagnoses is published in the American Psychiatric Association in the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). It should be noted that not everyone who shares the same mental or behavioral health illness experiences the same degree of functional impairment or severity of symptoms. The DSM provides modifiers to disorders as *mild*, *moderate*, or *severe*. As such, mental and behavioral health illnesses should be thought of as spectrum disorders, which correlate to the severity of symptoms.

As mentioned earlier, there are an alarming number of individuals who have severe mental and behavioral health diseases, which affect the disease burden among communities, regions, and nations.[4] The disease burden includes growing rates of suicide, substance use, dysfunctional homelife, loss of workplace productivity, and propagated trauma. A meta-analysis by Firth et al. shows how individuals with mental health concerns, even schizophrenia, benefit from routine exercise, which is a key component of lifestyle medicine, yet when one has untreated behavioral and mental health symptoms, it is harder to practice lifestyle-promoting health behaviors and receive these benefits.[19]

As the severity and burden of mental health continue to grow, it is hoped that an early detection system can be developed through neuroscientific advancement. The public and healthcare providers need to be aware of subsyndromal symptoms as these early stages may be the most opportune time to start making lifestyle changes.

76.6 RISK AND PROTECTIVE LIFESTYLE FACTORS FOR MENTAL HEALTH AND PSYCHOLOGICAL WELL-BEING

Across the lifespan, mental health and psychological well-being are influenced by many factors, lifestyle behaviors chief among them. The core lifestyle factors addressed in this chapter (the pillars of lifestyle medicine) include the following: diet and eating behaviors, physical activity, sleep, stress management, substance use, and interpersonal relationships. Each of these lifestyle factors and associated behaviors can serve as risk or protective factors for mental health and specific disorders.

For example, research has accumulated on the positive effects of physical activity on mental health, both as a preventative factor and for the treatment or management

of mental health symptoms. Likewise, sedentary behavior has been linked as a risk factor for depression, anxiety, and sleep disturbances. Of note, physical activity and sedentary behavior are two independent target behaviors, not the flip side of the same coin;[20] one can be active and still engage in significant health-hindering stretches of sedentary behavior.

Robust reviews and meta-analyses have highlighted the link between nutrition and mental health as well. The standard American diet has been associated with an increased risk of depression, while a diet resembling a Mediterranean diet (higher in fruits and vegetables) has been associated with a decreased risk.[21] Randomized controlled trials of mixed dietary interventions have also shown improvement in depression and anxiety symptoms.[22]

The above examples are just the tip of the iceberg when it comes to the evidence of lifestyle medicine benefiting mental health. This profound body of evidence should not be ignored for the fee-for-service, treat-the-disease-once-it-is-diagnosable approach to health and wellness prevalent in the United States. In fact, initial widespread approaches have already been implemented in the recommended guidelines of several large professional organizations (notably not in the United States as of yet). In 2010, the position statement on public mental health from the UK Royal College of Psychiatrists highlighted how lifestyle behaviors, namely tobacco use, infrequent exercise, and poor nutrition, are linked to an increased lifetime risk of mental illness.[23] Based on the preponderance of evidence, the European Psychiatric Association's guidelines recommend exercise as a first-line treatment for moderate depression, and as an adjunctive intervention in severe mental illness.[24] And recently, the updated 2020 guidelines for the treatment of mood disorders from the Royal Australian and New Zealand College of Psychiatrists state that "lifestyle changes and psychological interventions are foundational in the treatment of mood disorders. These are both recommended actions—*essentially non-negotiable and to be discussed with all patients*" (emphasis added).[25] Addressing, preventing, and treating mental health concerns in ways that are accessible and affordable, that help reduce stigma, and that have the convenient side effect of better physical health is a win-win for individuals and the public health of any nation.

76.7 BIOPSYCHOSOCIAL IMPLICATIONS AND THE PREVENTION AND MANAGEMENT OF CHRONIC ILLNESSES

The biopsychosocial model, first discussed by George Engel in 1977, refers to the idea that biological, psychological, and social processes are integrally and interactively involved in illness and health.[26] This model expands far beyond earlier models which were reductionist and purely biomedically based. Key in the biopsychosocial model is the interconnection among the factors: that single-factor explanations are likely to be inadequate and that change in one domain necessarily results in changes in other domains. Additionally, it follows that interventions involving all domains produce better results than those grounded on a single domain.[27]

Examples of the biopsychosocial model in the health realm include the overlap between depression and chronic pain. Chronic pain can lead to depression, and depression is known to worsen the experience of pain; the association is bidirectional. In addition, imaging studies have shown an overlap between pain-induced and depression-induced changes in neuroplasticity and neurobiological mechanisms.[28] Treatment for chronic pain is multifaceted and generally begins with non-invasive and non-medication approaches, like lifestyle changes and psychotherapy.[29]

How psychological and social processes affect biological processes can also be seen in the impacts of chronic inflammation on health. Recent research revisits this evidence of how chronic inflammation contributes to the development of chronic disease.[31] This is particularly noteworthy as non-communicable diseases are the leading causes of death and disability in the United States and around the world.[30] Stress, lack of close relationships, and certain health behaviors are known to promote a pro-inflammatory state which in turn contributes to the development and progression of chronic illnesses. In addition, the risk stemming from certain health behaviors may impact inflammation even more when accompanied by psychological risk factors, creating a synergistic effect. Thus, the application of lifestyle medicine's pillars to the prevention and treatment of chronic inflammation and therefore chronic disease has individual and public health implications that reach far and wide. This crucial relationship is further discussed in Chapter 80.

76.8 A BRIEF OVERVIEW OF MENTAL HEALTH AND THE PILLARS

Below is a brief summary of how the individual lifestyle medicine pillars are affected by, and affect, mental health.

76.8.1 Nutrition

For a vast number of people within high-income countries, diets have become a significant contributor to preventable disease and mortality. As important to the nutritional content of the diet (highly processed food, fatty foods, etc.) are the behaviors surrounding eating (binge eating, eating alone, eating while watching electronic media, eating in the car or bedroom, etc.). Dietary habits have been linked to the development of obesity, type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, and forms of cancer. Equally important, dietary habits are linked to attention, mood, behavioral, and anxiety disorders.[32] The development of these disorders is largely through the modification of epigenetic factors and the manipulation of the gastrointestinal microbiome.[33] Thus, attention to nutrition quality is a critical aspect of lifestyle medicine. As nutrition

science advances to include mental health outcomes, there will be more opportunities to implement dietary changes to support mental health.

76.8.2 Substance Use

Substance use, at any level, impacts both mental and physical health. Prior to COVID-19, the death rate from substance use was one of the top public health concerns in the United States. In 2017, the US Health and Human Services declared a public emergency.[34] Among the many consequences of COVID-19, substance use has increased.[35] Continued use of substances makes the practice of other lifestyle pillars challenging and contributes to the growing challenges of psychiatric, cancer, cardiac, and endocrine illnesses. The effectiveness of treatment is challenged by the complexity of the neurobiological underpinnings of these disorders. The use of substances and other unhealthy behaviors quickly hijack the brain's reward, stress, contentment, and focus pathways, which reinforce the brain's wanting of these substances or experiences. SBIRT is a national campaign that encourages all providers to universally screen for substance use disorders and refer for treatment. In the United States, providers currently screen for high blood pressure, a condition that affects approximately 75 million people, and costs about $46 billion in direct and indirect costs; by comparison, substance use affects approximately 100 million people and costs nearly $740 billion in direct and indirect costs.[36,37] Recent randomized control studies have shown that improving lifestyle activities and decreasing substance use leads to improved quality of health.[38]

76.8.3 Physical Activity

Engaging in physical activity has wide-reaching benefits—promoting mental well-being, preventing the potential development of mental disorders, and especially providing sustained benefits for depression, anxiety disorders, attention deficit disorders, and substance use disorders.[39] Exercise in depression may promote increased feelings of self-efficacy and self-esteem as well as promotion of prosocial behaviors.[40] To this end, the Royal Australian and New Zealand College of Psychiatrists promote physical activity as the first line of treatment for mild to moderate depression.[41] Yet, despite the growing evidence, many healthcare providers still default to favoring the traditional use of psychotropic medications as first-line treatment without discussing lifestyle interventions.

76.8.4 Stress

The psychiatric and psychological communities have been studying stress for decades and have developed a robust literature. Since 2007, the American Psychological Association (APA) has been conducting annual surveys regarding the impact of negative stress on residents within the United States. Due to the compounding effects of COVID-19, the economy, racial tensions, and multiple forms of scarcity, the APA reports, "We are facing a national mental health crisis that could yield serious health and social consequences for years to come".[42] Fagundes et al. show that heightened chronic stress leads to imbalances of cortisol and other stress hormones and can cause or contribute to immune system suppression and consequent illness, such as increased risk for psychiatric illness, diabetes mellitus, digestive conditions, and cardiovascular disease.[60] It is also associated with an increased risk for self-destructive behavior like substance use, not taking medications, and not engaging in lifestyle interventions.[43,44]

76.8.5 Interpersonal Relationships

In a recent national study, over one-third of Americans reported being "frequently lonely" or "lonely almost all of the time", with the highest concentration among young adults between the ages of 18 and 25 and mothers of young children.[45] Additionally, a recent meta-analysis highlights the negative effects of loneliness on health outcomes (mental health, general health, well-being, physical health, sleep, and cognition).[46] Equally significant, loneliness has been identified as a risk factor for early death, comparable to other lifestyle diseases.[47] Systematic reviews have shown that individuals with partner support have higher adherence with medications and management of chronic illnesses.[48] Interpersonal relationships are critical to mental and physical health and further understanding is needed in the era of COVID-19 about how our increased reliance on technology and extended periods of social isolation affect health.

76.8.6 Sleep

Despite restorative sleep being crucial for physical, mental, and emotional health,[49] more than one-third of Americans sleep less than seven hours a night and report feeling tired.[50] Multiple studies have shown how sleep deficiency is associated with poor immune function and cardiovascular disorders;[51] it is an independent risk factor for mental health and neurologic disorders and is associated with decreased emotion regulation.[52] Sleep insufficiency leads to cognitive impairments such as vigilance, difficulty thinking, and poor decision-making, leading to greater risk for medical errors among healthcare workers, industrial and vehicular accidents, and risky behaviors.[53] A 2021 meta-analysis of 65 randomized controlled trials showed a dose-response effect between sleep quality and depression and anxiety, where the greater the improvement in sleep quality and duration, the greater the improvement in mental health function.[54]

76.9 WHERE DO WE GO FROM HERE?

As we continue to understand the bidirectionality of mental and physical health, the definition of these constructs becomes all the more important. The concept of brain

health is more inclusive than mental health, or wellness in relation to healthcare provisions. The potential for widespread application of brain health is the basis for its gravity in the scope of lifestyle medicine. Healthcare providers in primary care, psychiatry, and others can and should be primed to regard and assess optimal brain development, cognitive health, well-being, and connectedness as important aspects of standard preventative patient care. With this, it is also essential to continue to further our current understanding of the significant and clinical applications of nutrition and the gut microbiota and their effects on brain and mental health.[64] We have reached a vital pivot point where we can provide a future of hope and healing to our society as we advance our understanding of this important function of lifestyle intervention between the gut microbiota, brain health, and overall health.

CLINICAL APPLICATIONS

- Lifestyle interventions have been shown to be effective in mood disorders.
- Because of the bidirectionality of physical and mental health, encouraging patients to address lifestyle interventions has the potential to affect treatment outcomes.
- Environmental, psychological, and physical stress can lead to immune system responses with increased risk for the progression or worsening of psychiatric illnesses.
- Greater adherence to a biodiverse, whole food, plant-based diet has been linked to better cognitive functioning.

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77 The Neuroscience of Brain Health

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KEY POINTS

- Improving brain health can provide protective benefits on the range of neurological, neuropsychiatric, and age-related and behavioral problems, comparable to the ways a proactive approach to physical health has led to the decline in heart disease.
- Neuroscientific discoveries about the remarkable plasticity of the brain at all ages make the possibility of harnessing the brain's systems to improve overall health scientifically feasible, even when dealing with brain issues.
- Promoting "brain health" as a continuous process, rather than as a fixed diagnostic disease/injury state, is critical to the adoption of practices that promote brain health and strengthen general healthy habits.
- We manage what we measure; brain health can now be measured, monitored, and improved through training at all life stages.
- By recognizing the interdependency of mental health underneath the concept of brain health, this chapter outlines the science of adopting a holistic approach to build brain capacity whatever the starting level by drawing upon a broad range of mind-brain capabilities.

77.1 INTRODUCTION

Improving the health of the human brain has become a pivotal goal to enhance population health. The brain drives all that we do, think, create, overcome, solve, and feel. A healthy brain is essential for developing other healthy habits, elevating well-being, enhancing social connection, increasing years of productivity, and expanding creativity to deal with challenges across the entire lifespan.[1]

Unlike well-accepted preventive practices for the heart such as exercise and nutrition, the brain is typically only considered after a person begins to manifest noticeable changes in cognitive, psychological, social, or motor functions. Diagnosis and treatment are sought primarily when significant deficits emerge in normal interactions, responsibilities, emotional responses, and mobility. Brain health, however, is much more than the absence of disease and damage.[2] Preventive and restorative approaches to improve brain wellness, akin to those available for physical well-being, are urgently needed. Such a development offers the promise of extending the average level of brain performance well beyond its current peak in the late 20s and early 30s.[3,4]

Brain health has been elusive to clinical practitioners not for lack of interest, but rather due to limited knowledge as to the best practices for translating neuroscience discovery into brain health promotion and care. Reasons for this include:

- Lack of a widely accepted *definition* of brain health.
- Absence of validated multi-dimensional, biopsychosocial *measurements* of brain health.[1]
- Dearth of *access* to brain health-enhancing methods using scalable protocols and technologies.
- Limited medical school *training* about the rapidly emerging discoveries related to neuroplasticity and its application to building brain health.
- Paucity of *reimbursement models* for interventions that prevent deficits and build brain health—in other words, a sort of "preventive neurology", "preventive psychiatry", or "preventive neuroradiology".[5]

This chapter addresses the first three issues and outlines current state-of-the-art research offering the foundations for medical practice guidelines for advancing brain health.

77.2 BACKGROUND

Discoveries in neuroscience over the past two decades have radically revised our understanding of the brain's lifelong ability to change, adapt, and improve its function.[6–10] Longstanding beliefs still prevail in medical practice that the brain's "plasticity" is confined to development (such as within the first few years of life) and recovery (a limited time interval post brain insult, typically three to six months). These beliefs are wrong, yet their persistence means that efforts to improve brain function over extended periods are woefully underexplored.

Emerging evidence shows that comprehensive, multidimensional measures of brain function can reliably assess gains in brain health in response to a number of

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interventions—training in strategic thinking and attention, for example—and lifestyle changes such as improved sleep.[11] Healthcare practice has the potential to target brain health (also referred to as brain wellness) rather than focus almost exclusively on detecting problems and charting cumulating age-related losses over time. As with all preventive medicine, intervention before disease onset is much easier to achieve and more effective than after onset. Progress is being made in identifying potential biomarkers, such as gains in neural network synchrony, brain blood flow, and network modularity, which correspond with improved cognitive health.[6,10,12] As these biomarkers become better established and validated in larger populations, the opportunities for effective and individually targeted preventive interventions grow even more urgent.

77.3 DEFINITION OF BRAIN HEALTH

The concept of brain health was introduced in 1999 by scientists at the Center for BrainHealth at The University of Texas at Dallas. The Center for BrainHealth is the first research institute focused almost exclusively on developing and testing measures and protocols to evaluate and enhance brain skills in populations ranging in age from early teens to late life.[13] Since that time, the term "brain health" has become widely used but still with a major bias toward brain injury and disease.

There are many definitions for brain health. It is essential to establish consensus for stakeholders regarding what the concept of "brain health" means. We recommend and adapt the definition set forth by the World Health Organization (WHO). The WHO defines brain health as the promotion of optimal brain development, cognitive health, and well-being across the life course[14] adapted herein to also include the element of *connectedness to people and purpose*.[11] Brain health is viewed as a continuous process rather than a fixed state, which corresponds to the evidence for lifelong neuroplasticity.

One key issue that commonly arises is the relationship of brain health to the term "mental health". The term *brain health* comprises mental health, while not replacing it, whereas the term "mental health" also includes the idea of wellness and is associated with emotional and behavioral deficits such as depression, anxiety, suicidality, and addiction. Unlike brain health, mental health does not usually embrace cognitive and social domains. For example, training cognitive strategies shown to promote brain health, such as strategic attention and innovative thinking, have been shown to reduce symptoms of depression and stress and improve real-life performance.[9]

Brain health may open new horizons to advance more global public health policies that have generalized applications to all patients. This makes brain health highly relevant for lifestyle medicine for several reasons. First and foremost, brain health is more inclusive than mental health across care providers. A multitude of healthcare professionals (e.g., lifestyle medicine, pediatrics, internal medicine, gynecology, family practice, psychiatry, gerontology, and more) can and should be trained to pay more attention to addressing optimal brain development, cognitive health, well-being, and connectedness as routine targets of preventive healthcare.

Second, the term mental health does not typically address cognitive abilities or "cognitive capital", i.e., the summated cognitive capacities of a population. This is important because greater cognitive capital has been shown to predict higher levels of health generally, both physical and mental.[15] The cognitive capital of a community, city, state, or country is also crucial for its economic prosperity because it enables populations to pivot more adaptively in the face of economic shocks, rapid technological change, and environmental challenges.[16,17] An absence or reduction of a flexible mindset contributes to economic and social deterioration that will worsen mental and physical well-being.[18,19]

A third reason that brain health is more policy and lifestyle medicine-ready as a concept than mental health is that it integrates aging-related brain diseases, which are predicted to be one of the greatest health challenges facing the world, one that particularly impacts low- and middle-income countries.[20] In particular, there is a spiraling prevalence of dementia linked to the accelerating proportion of older people in all countries in the world, secondary to the impressive lengthening of life expectancy.[21] Additionally, impaired well-being is a risk factor for dementia but is often overlooked in dementia treatment.[22] Mental health, as a concept, does not afford policy implications for this enormous health challenge that, if unchecked, will overwhelm the resources and finances of health providers and services. Brain health, on the other hand, is ready to be tested, with clear implications for health promotion policy.

Fourth, the concept of brain health has positive connotations centered around capacity-building principles of neuroplasticity that avoid the stigma attached to mental health, as the latter focuses largely on diagnosing deficits rather than considering individual potential. Therefore, it affords considerable opportunities for policymakers to advance population-scale interventions to millions of people and focus on individual empowerment. Brain health offers a positive message that is similar to successful heart-healthy interventions such as those advocating the value of aerobic exercise.[23,24]

77.4 MEASURING BRAIN HEALTH

The lack of a clear index of brain health is a major void for healthcare practice and public policy.[11] Most primary care doctors *rarely* evaluate brain health with any objective measures during regular health exams. Even in cases where brain functions are assessed, the assessment time is minimal and the measures are typically cursory, including very simple tasks such as list memory, naming, or simple figure drawings. These measures were designed to detect significant problems and quantify compromised brain function, not to identify pathways to optimize brain systems.

The National Institutes of Health's definition of brain health is provided by the National Institute on Aging,[25] thus

mistakenly linking brain health solely to advancing age. This age focus ignores the centrality of brain health to well-being, social connection, and physical health in teens and young adults, defining brain health only in the four domains of cognitive health, motor, emotional, and tactile function. Whereas these are important in an aging population, they overlook other crucial dimensions including social interaction (social support, social engagement, compassion), daily life (nutrition, exercise, mindset, sleep, responsibilities), and aspects of well-being (resilience, mood, quality of life).

77.4.1 BrainHealth Index

Brain health is a complex concept demanding an easy-to-understand presentation. A number of groups are developing multi-dimensional measures (e.g., Bassetti et al.[1]), including the Barcelona Brain Health Initiative,[26] the "cognitive clock",[27] and the Human Brain and China Brain Projects.[28,29]

Another significant international effort is the telehealth-delivered BrainHealth Project (https://centerforbrainhealth.org/project/world-class-team), which aggregates multiple dimensions into a BrainHealth Index,[11,30] a composite of 22 gold standard, change-sensitive measures collected with a range of MRI neural markers applied repeatedly over time to a population ranging in age from 18–95. The Project is led by the authors of this chapter and is sponsored by research funding from the Center for BrainHealth. The index assesses *cognition* (e.g., executive functions, memory, innovative thinking, and complex abstraction), *social functioning* (e.g., social support, social engagement, and compassion), *well-being* (e.g., depression, stress, anxiety, quality of life), and *real-life functions* (e.g., exercise, nutrition, sleep, mindset, and responsibilities).[11]

The novel development in the BrainHealth Index was the identification of at least three measurable components, uncovered through factor analysis.[11] These components are the very same factors included in the definition of brain health set out in this chapter. Moreover, longitudinal follow-up of brain health performance in light of these factors reveals dynamic targets for individuals that can contribute to cumulative gains in the holistic Index over time.[30] The Index was not developed to establish a diagnostic label.

These factors are as follows: (a) *clarity* (*cognitive health*), (b) *connectedness*, and (c) *emotional balance* (*well-being*) and are being validated by functional brain imaging measures to chart continued brain change over time (see Figure 77.1).

- *Clarity* measures abstraction, big-picture thinking, memory, sleep, and compassion.
- *Emotional balance* measures mood, stress, and sleep.
- *Connectedness* measures social support, compassion, engagement, happiness, resilience, satisfaction, and meaningful activities.

MRI and other neural correlates of training-related improvements in these factors have revealed increased connectivity in the central executive and the default mode networks, with corresponding gains in brain blood flow.[10,31] Studies are underway to further understand and validate the corresponding dynamic changes over time linking behavioral and neural domains following telehealth-delivered brain health training (https://centerforbrainhealth.org/project). These data will serve to identify the structural and functional brain changes that support the upward potential for building stronger brain health over the life span.

By aggregating brain health measurement across multiple, hitherto disparate, domains, we can evaluate with hopes of eventually predicting how different components interact and influence brain health over time. For example, emotions such as anxiety and depression affect cognitive health,[32–35] whereas strong cognitive functions—particularly executive and attention processes—aid emotional regulation and build social resilience.[36,37] Social isolation has negative effects on emotional well-being and cognitive function[38] Sleep,[39] diet,[40–42] and physical activity[43,44] all mutually interact and affect emotional, cognitive, and social functions. Furthermore, these different processes both depend on and influence the constantly changing structure and function of brain networks and systems.[45,46]

77.5 ACCESS TO INTERVENTIONS PROMOTING BRAIN HEALTH

Achieving optimal brain health demands interventions developed and tested to enhance the multi-faceted aspects of brain health across the age spectrum, rather than a fragmented, siloed approach. To our knowledge, limited consensus exists regarding scalable, evidenced-based interventions delivered either using a face-to-face approach or are capable of being scaled through telehealth. Both approaches are vital. The most prominent and successful attempt at a scalable multi-faceted intervention was directed at older individuals at risk of dementia, known as the Finnish "FINGER" trial. The FINGER trial showed how a multi-modal intervention delivering vascular risk monitoring, cognitive training, and dietary and exercise advice could significantly improve cognition,[47] and has seeded a worldwide network of similar trials (see an overview at https://alz.org/wwfingers/overview.asp).

The FINGER studies are limited in two ways, however. First, the intensive, face-to-face nature of the intervention makes it extremely expensive, labor-intensive, and hence not scalable to millions of people worldwide. Second, it is focused only on older people, yet we know that brain health is a lifelong process with cumulative effects over decades and requiring a whole-life approach.

Our work complements and builds on decades of positive findings for enhancing cognitive and emotional function using verbal and/or procedural protocols ranging from teaching strategies aimed at improving the efficiency of frontal-lobe-based executive networks[48] to enhancing mood and reducing anxiety through methods such as cognitive behavior therapy.[49] The ability to scale such methods

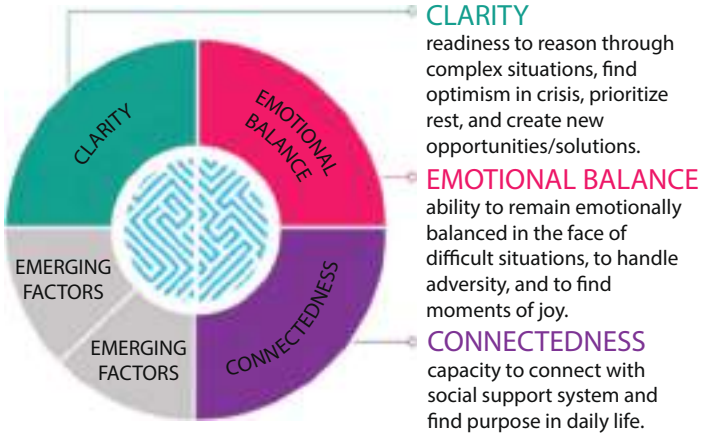


FIGURE 77.1 BrainHealth Index.

using web-based technology enables availability entirely remotely, potentially accessible to millions of users across the globe once language and cultural appropriateness are addressed.

Most online offerings of "brain training" do not have strong published evidence of their efficacy. A review by Owen and colleagues concluded that most online brain training programs improved the specific processes trained but did not generalize to real-life functions.[50] One exception is the BrainHQ (www.brainhq.com) online training programs that have shown positive cognitive effects in a range of populations across many studies.[51,52] One study showed impressive gains in certain cognitive processes of older adults with real-life benefits maintained up to ten years later with just a few booster sessions.[53] Their work has also been shown to be associated with lowering driving accidents in older adults, and improvements in daily life independence.[54,55] Other evidenced-based online training programs include NeuroRacer[56,57] and ACTIVATE,[58,59] both of which have been shown to improve learning and behavior outcomes across populations. Another exception is SMART training, described in the next section. At present, both BrainHQ and SMART are offered through the online BrainHealth Project, which aims to test the extent to which participants can achieve gains on the holistic BrainHealth Index year by year as the study's enrollment is expanded and followed over longer intervals.

Today more than ever, healthcare practitioners need a global brain health strategy translatable and sustainable across the lifespan.[42,60] Heart health lays out a roadmap for how to scale prevention over whole populations based on the Framingham epidemiological study of heart health coupled with lifestyle advice for maintenance.[61] The BrainHealth Project applies and adapts this approach for brain health, helped by advances in e-health, technology, and big data analytics to yield population-scalable interventions.

77.5.1 The BrainHealth Project Intervention

The US National Academy of Sciences published an expert review on the most promising methods for preventing cognitive decline (and by implication improving brain health): blood pressure control, increased physical activity, and cognitive training. The expert panel concluded that the evidence was strongest for cognitive training.[62]

The Center for BrainHealth has developed a method of cognitive training called Strategic Memory Advanced Reasoning Training (SMART). SMART is unique among such methods internationally because of (a) its focus on strategic and tactical control of attention; (b) its use of everyday materials in training; and (c) its proven ability to improve cognitive health, well-being, connectedness, and real-life functions.[10,11,13] SMART improves not only cognition but also emotions, e.g., mood and anxiety,[9,63] making this scientifically supported program unique. Recognizing the range of lifestyle and other factors shown to contribute to brain health such as nutrition, sleep, and exercise, discussed elsewhere, the BrainHealth Project also incorporates interventions and advice aimed at improving these on its web platform by exercising tactical thinking skills as provided by SMART.

The first phase of the larger and longer-term BrainHealth Project study enrolled 180 healthy adults (ages 18–87 years) who took the BrainHealth Index pre and post a 12-week online training period. The training was self-paced and augmented by 30-minute coaching calls with clinicians after the first Index, at six weeks, and again after the second Index at 12 weeks. Seventy-five percent of participants had at least a five-point gain on their BrainHealth Index. The more training modules individuals completed, the higher their gains on the Index. Comparable gains were seen for older and younger adult participants, and across gender and educational levels, with improvements attributable to different combinations across the clarity, emotional balance, and connectedness factors. For example, one participant improved due to increased clarity and decreased stress, while another participant prioritized sleep and social relationships. The effects of the training will be assessed in larger and longer-term follow-up studies for at least ten years.

77.6 GUIDELINES FOR BRAIN HEALTH

The first two principles for brain health in lifestyle medicine include[1] empowering patients to take steps toward building stronger brain skills and[2] inspiring them to get an annual brain health check-up to motivate continued adoption of healthy habits.

77.6.1 General Principles

Empower your patients. By helping patients realize the immense control they have to strengthen their own brain health, lifestyle medicine practitioners are uniquely positioned to promote brain health, particularly when there are no diagnosed brain issues.[64] Despite the fact that many people worry about age-related changes to their brains, or fear future changes, the vast majority do not talk to their physicians about these concerns.[65]

Emphasize the importance of metrics in health. Establish routine methods of objectively assessing and tracking—even in the absence of complaints—patients' brain health, with individuals serving as their own comparison over time. The goal year by year is to achieve "You, but better". The metrics should be framed as dynamic targets, rather than as fixed diagnostic categories, and yield realizable goals for improvement across clarity, emotional balance, and connectedness elements. They also provide practitioners with a compass for when and where to direct patients for specialized medical intervention, as indicated.

Evidenced-based guidance for improving brain health. There is strong evidence to support the effectiveness of certain forms of cognitive training in improving brain wellness with generalization to everyday function such as driving and independent living skills,[53,54] and an expert panel of the National Academies of Sciences and Medicine came to a similar conclusion. There are many different biologically plausible mechanisms by which purely behavioral interventions can modify the brain's physiology and link to improved cognition, hence improving brain health. These can be broadly divided into "bottom-up" and "top-down" interventions.

Bottom-up approaches aim to "force" neural networks to improve the quality and speed of their functioning using adaptive training, where the difficulty of the tasks increases or decreases with performance. The most well-supported of such methods is the suite of programs offered by BrainHQ, mentioned above.[66–68] Many different neural mechanisms likely underpin the observed improvements, such as stimulation-induced white matter changes caused by improved myelination. This benefit to neural systems purportedly is brought about by training-induced oligodendrocyte activity, a type of neuroglia supporting the insulation of axons in the brain. These better-insulated axons increase the fidelity and speed of information passing through neural networks.[69] A second example of these bottom-up effects is the stimulation of norepinephrine activity in the locus coeruleus. Norepinephrine has remarkable neuromodulatory properties, including strengthening of networks needed for the current task in hand while inhibiting neural networks not needed for the current task. Cognitive challenges of the type offered by certain bottom-up cognitive training programs activate this system, strengthening the neural networks that are activated.[70,71]

Top-down approach. The strongest evidence for a "top-down" method is SMART training, described above. This showed significant gains across a wide range of healthy and clinical populations in complex reasoning, innovative thinking, memory, and executive functions as well as generalized benefits such as reduced symptoms of depression and stress[9,10,72] and gains in real-life function such as daily responsibilities, medical decision-making more in line with a personal value system, and improved learning skills[9,13,73] and academic performance.[74,75]

Clinical trials with SMART showed neural benefits, including improved synchrony of pivotal frontoparietal neural networks that act as a "flexible hub". These networks support the ability to rapidly take in and sort the massive amounts of incoming new information and resolve conflicts to guide adaptive behaviors. This complex network supports agility of thinking in conjunction with the ability to focus on tasks to optimize performance.[10,76,77] SMART training trials show significant increases in global and regional cerebral blood flow in healthy adults, as well as those with mild long-term residual brain injury[9] and bipolar disorder.[78] These neural changes were correlated with gains in complex cognition.

77.6.2 Specific Guidelines

Evidence shows global brain health can be enhanced to support an individual's ability to thrive in their context through multiple pathways: clarity, connectedness, and emotional balance.

77.6.2.1 Strengthening Clarity of Thinking

Clarity of thinking represents the readiness to adeptly reason through complex situations and create new solutions/opportunities.[11,79] Brain trainings that teach tactical thinking skills also generalize to making more logical decisions and reasoned health choices.[73,80] Patients can learn to actively orchestrate brain networks in ways that help them escape from habitual, and sometimes toxic, thinking habits such as constant distractions, multi-tasking, and negative ruminations. Such training improves the efficiency of frontal-lobe-based executive networks, which are critical to brain health across the lifespan. Additionally, becoming more critical problem solvers and active decision makers through broader, bigger-picture thinking skills can be practiced and honed. Learning to calm the brain can help reduce information overload, which often leads to poor decision-making. Other contributors to strong clarity are healthy sleep habits and practicing acts of compassion.

Specific tips include:

- Carve out dedicated time of 30 to 45 minutes for your top two tasks, avoiding any distractions and interruptions. Make sure to define tasks that can be completed in this time slot.

- Synthesize key ideas or bottom-line messages from readings, conversations, or meetings to increase deeper-level thinking, as this helps strengthen the brain's frontal networks.[13]
- Innovate and generate a multitude of actionable best next steps when reflecting on failures, challenges, and disappointments. Our brain is uniquely wired and strengthened by innovative thinking across our life span.[72]

77.6.2.2 Maintaining Emotional Balance

Chronic stress has been shown to impair memory function and shrink the hippocampus[81,82] It also impairs prefrontal cortex function because of a variety of mechanisms, including excessive norepinephrine interfering with efficient brain network performance.[83] Reframing challenging situations by evaluating pros and cons, putting forth effort to identify lessons learned, and identifying alternative solutions can all contribute to emotional stability in the face of adversity. Goal setting can serve to help individuals take small steps toward daily success. Achieving even small goals elevates mood and reduces anxiety because perceived success activates the brain's dopamine-fueled reward network. Success can be largely defined by individuals and the goals they set for themselves. SMART training offers systematic methods for structuring brain effort in a way that prevents overloading the brain while promoting mood-enhancing success.

Specific tips are:

- Take regular brain breaks every day of five minutes, five times a day to calm and recalibrate the brain.
- Embrace "Living in the Moment" by savoring the present moment and acknowledging small things for which to be grateful.
- Structure daily life around clearly defined mini goals that are neither too difficult nor too easy. Micro-antidepressant task completions can deliver success-related dopamine-linked activity to increase mood and reduce anxiety.

77.6.2.3 Prioritizing Connectedness

Connectedness (to people and purpose) reflects continually being driven by a bigger purpose and maintaining meaningful relationships and activities. Encouraging individuals to find purpose in their actions and with the people in their lives helps to fortify brain health and is a strong driver of cognitive reserve.[84] Having meaningful interactions, engaging in new activities, meeting new people, mentoring and volunteering, and participating in hobbies are ways to establish a quality social support system and engage in meaningful life activities, as well as provide stimulating cognitive challenges that are critical for resilience across the lifespan.

Specific tips are:

- Contact a friend each day. Initiate outings with others. Be present to focus on quality conversation.
- Volunteer for a cause that is personally motivating and connects with new people.
- Move out of the status quo and participate in activities that are different, out of the ordinary, and/or challenging.
- Seek ways to show compassion (to family and friends, strangers, those with whom you have conflict, other living things) and value yourself by doing simple things you enjoy.

Promote the lifestyle principles and guidelines above combined with other healthy habits that support brain health. These include sleep, physical exercise, nutrition, and controlled heart-healthy factors such as blood pressure and cholesterol, covered elsewhere in this book. Specialized medical interventions are warranted in cases of worsening psychiatric concerns, cognitive slippage, and other social changes so that timely diagnoses and treatments can be provided. Presently, only medical diagnoses and prescription medications have addressed these issues. Greater gains in brain health are shown when these medical interventions are combined with lifestyle interventions and guidance where individuals learn strategies that intentionally shift how they view negative situations to curiosity-seeking solutions. A combined approach may increase efficacy and drive habit change.[85,86]

77.7 CONCLUSION

Our brain is our most valuable resource. Brain health plays a major role in how well individuals embrace opportunities and manage the challenges of life. Improving brain wellness has been shown to help people enhance decision-making, adopt healthier life patterns, find purpose, build grit to overcome adversity, improve learning effectiveness, connect meaningfully with others, and expand emotional balance to better deal with adversity. Unfortunately, brain healthcare and health promotion have not received the attention they deserve, and the dramatic decline of neural health starting in young to middle adulthood is our greatest cost burden.

Boosting individual brain health will do more to help economies around the world flourish than can be captured by GDP.[87] The key source for building better lives and more vibrant communities is building stronger brain health and wellness to support well-being, connectedness, and possibility thinking. We cannot afford to wait another generation to focus a concerted effort on maintaining brain fitness throughout the life cycle.

CLINICAL APPLICATIONS

Some of the clinical applications include:

- Patient education regarding healthy lifestyle habits should include information on brain health, for those with and without brain concerns, as more

can be done to build reserves in health than after brain-related issues are detected.
- Annual assessments of brain health that measure its upward potential can reduce the stigma of brain problems and motivate people to take timely proactive steps toward building brain capacity.
- Clinicians can and should address mental health problems from a higher, more holistic category of brain health since strategies that improve social connectedness and/or cognitive clarity can reduce mental health symptoms, either alone or when combined with appropriate medications.
- Complaints of brain fog (e.g., worsening concentration, memory, speed of processing, innovative thinking, or mental stamina to mention a few) need to be taken seriously and contributing factors addressed with lifestyle changes before difficulties worsen. Brain fog is one of the most common symptoms with a multitude of causes indicating the brain's neural systems are not working at normal capacity and efficiency.
- Empowering a person's role and self-agency in daily tending to their personal brain healthy habits will help people to improve their quality of life at all ages.

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78 Diet and Exercise Interventions in the Management of Psychiatric Disorders: Mechanism and Efficacy

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KEY POINTS

- Diet and exercise are pluripotent interventions that simultaneously sustain cardiometabolic and mental health.
- Diet and exercise are evidence-based treatments for core symptoms of psychiatric disorders, including depression, anxiety, PTSD, ADHD, schizophrenia, and cognitive disorders.
- Mechanisms for diet impacting psychiatric disorders are substrates and cofactors in the production of neurotransmitters, the reduction of oxidative stress and neuroinflammation, the reduction of homocysteine, and the improvement of cerebral blood flow
- Diets that reduce processed foods and increase traditional natural foods with an emphasis on plant polyphenols appear to be most effective (e.g., the Mediterranean diet)
- A mechanism for exercise impacting psychiatric disorders is brain-derived neurotrophic factor restoring brain volume with a reduction of inflammation
- Higher doses of cardiovascular exercise (i.e., frequency × intensity) appear to be most effective

78.1 INTRODUCTION

In a certain sense, it is unimaginable that lifestyle behaviors would not impact mental health. Our nervous system evolved under the same conditions as the rest of our biological system, intimately entrained by the foods we eat and the activities we perform. It becomes an intriguing hypothesis that the same diets, behaviors, and physical activities that sustain cardiovascular and metabolic health would also sustain mental health.

Indeed, the Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines have expanded the bio-psycho-social model to the bio-psycho-social-lifestyle model and now recommend adjuvant diet and exercise interventions as part of the standard of care for people with mood disorders.[1] The European Psychiatric Association has produced a position paper that concluded that cardiovascular exercise is an evidence-based treatment for core symptoms of severe mental illness.[2] The American Psychiatric Association has begun to explore the topic of lifestyle interventions for psychiatric disorders with a recent textbook dedicated to the subject.[3]

Insight into the link between lifestyle behaviors and mental health was initially prompted by epidemiological studies that noticed a co-clustering of cardiometabolic diseases with psychiatric disorders. It was proposed that cardiometabolic diseases and psychiatric disorders might share common etiologies and treatments that are mutually impacted by our choices of foods and our balance of movement and rest.[4] Indeed, a host of epidemiologic, mechanistic, and randomized controlled trials (RCTs) have demonstrated associations, rationale, and efficacy of lifestyle interventions in the management of core symptomology of psychiatric disorders.

78.2 DIET AND PSYCHIATRY

78.2.1 Diet and Psychiatry Mechanisms

Given that diet provides the atomic constituents of our bodies, arguably, there may be no psychiatric mechanism that diet would not impact. Several core mechanisms include nutrients as essential cofactors in the production of neurotransmitters; oxidative stress and neuroinflammation in the CNS[5,6] and the microbiome in the gut-brain axis.[7,8] Thus, diets that contain adequate nutrition provide the substrates necessary to produce sufficient neurotransmitters, and diets that contain significant amounts of antioxidants—or upregulate the production of endogenous antioxidants—reduce oxidative stress and neuroinflammation. Likewise, diets that contain a varied amount of plant ingredients, which may be complemented by fermented foods, produce biodiversity within the microbiome, which subsequently also reduces inflammation.[9,10]

78.2.2 Dietary Depression RCTs

One of the earliest RCTs examining how dietary intervention could impact depression was by Merrill and colleagues

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in 2008. Having served over 40,000 participants at the time, the Coronary Health Improvement Project (CHIP) was originally designed as a cardiovascular health intervention. However, CHIP facilitators noticed the improved mood of their participants and formally tested this hypothesis with a six-month 348-person RCT. The initial intervention was a 40-hour health education program, given over four weeks with an emphasis on plant-based, minimally processed foods, such as whole grains, legumes, vegetables, and fresh fruits with lower intakes of fat, sugar, salt, and animal-based protein. At six-week and six-month follow-ups, compared with the waitlist control, the intervention group significantly improved on the Beck Depression Inventory (−2.4 points vs −0.7 points, $p < 0.0001$) and −2.2 points vs −0.8 points, $p < 0.0001$, respectively.[11]

In 2017, Jacka and colleagues published the results of their dietary RCT (n = 67) that was designed for patients with moderate-to-severe major depressive disorder. In addition to receiving standard of care, patients were randomized to receive seven hours with a dietitian recommending a Mediterranean diet vs seven hours with social support as the control group. At 12 weeks, compared with the control group, the intervention group had significantly decreased depression scores with a large effect size (Cohen's d = 1.6) and a between-group difference of seven points on the Montgomery–Åsberg Depression Rating Scale ($p < 0.001$). Additionally, there was a four-fold increased rate of remission from depression in the dietary group compared to the control group ($p = 0.028$).[12]

In 2019, Francis and colleagues completed an RCT (n = 100) evaluating a dietary intervention for college students with depression. Using a 13-minute video, combined with handouts on diet, supplemented by free olive oil and nut butter for the students, the dietary intervention was impressively efficient. At three weeks follow-up, compared with the habitual diet control group, the dietary intervention group significantly decreased depression, as measured by the Center for Epidemiological Studies Depression Scale (CES-D) with a moderate effect size ($p = 0.007$, Cohen's d = 0.65). In fact, when evaluated by the average CES-D score of the group, the dietary intervention group no longer met the criteria for major depressive disorder.[13]

78.2.3 Schizophrenia and Diet

The provocative association between gluten and psychosis was first proposed in 1966 when Dohan evaluated rates of schizophrenia during wartime as countries altered wheat policy to meet martial demands which was mirrored by changes in incidence rates of schizophrenia.[14] As time progressed, DB-RCTs for treating schizophrenia with a gluten-free diet were inconclusive. Some early trials demonstrated significant improvement in psychotic patients,[15–17] whereas other trials demonstrated no improvement.[18] However, ongoing epidemiology, mechanistic understanding, and further case reports[19–21] have evolved to predict which subgroup of patients with schizophrenia might respond to a gluten-free diet. A robust case-control study using subjects from the large Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study found six to eight times more antigliadin antibodies in patients with schizophrenia compared with matched controls.[22] These antigliadin antibodies stimulate downstream inflammatory cascades, as well as increase the metabolism of tryptophan into kynurenine which converts to kynurenic acid in the central nervous system, an endogenous NMDA receptor antagonist that is associated with the negative symptoms of schizophrenia.[23] In 2019, the first modern feasibility DB-RCT (n = 16) re-evaluated a gluten-free diet in patients with schizophrenia, specifically those with elevated anti-gliadin antibodies. Kelly and colleagues found significant improvements in the Clinical Global Impression Scale and negative symptoms in the Scale for the Assessment of Negative Symptoms, with large and moderate effect sizes, respectively.[24] A larger follow-up trial is ongoing.[25]

Additional dietary interventions might be inferred from nutrient studies as interventions for people with schizophrenia. Levine and colleagues completed a six-month double-blind, randomized crossover trial (n = 42) utilizing folate, B12, and B6 for patients with co-morbid elevated homocysteine levels.[26] Homocysteine is relevant to schizophrenia, given that it is an inflammatory cytotoxin that readily passes through the blood–brain barrier and degrades the prefrontal cortex and hippocampus,[27] two areas of reduced volume in schizophrenia. Compared with placebo, Levine and colleagues found that reducing homocysteine through folate, B12, and B6 supplementation rendered significant improvements in PANSS total symptoms and trend-level improvements in positive, negative, and general symptoms ($p = 0.02$ to 0.08). It stands to reason that diets that reduce homocysteine would likewise prevent the brain volume loss that elevated homocysteine would otherwise cause.[26]

78.2.4 Diet and ADHD

Successful dietary interventions for ADHD have focused on the few foods diet, consisting of rice, turkey, lamb, vegetables (lettuce, carrots, cauliflower, cabbage, beet), pears, and water, plus potatoes, fruits, corn, and wheat eaten on prescheduled days and doses. In 2011, Pelsser and colleagues published the results of a five-week DB-RCT (n = 100) comparing the few foods diet vs a generally healthy diet control group. Compared with the control group, the intervention group demonstrated remission from ADHD symptoms according to the ADHD Rating Scale and Abbreviated Conners' Scale ($p < 0.0001$). The results were predominantly due to the 64% of patients in the few foods diet that were clinical responders, defined as at least a 40% reduction of symptom burden.[28] These results were largely confirmed in a meta-analysis of the published literature by Sonuga-Barke and colleagues in 2013.[29] One possible mechanism underlying the few foods diet could be the elimination of artificial food additives. As confirmed in a large DB-RCT (n = 297) by McCann and colleagues

in 2007, artificial food additives produced statistically or trend-level significant worsening of attention in children.[30]

78.2.5 Diet and Cognition

Analogous to VO_2 max of the heart, a major factor contributing to acute and chronic cognitive abilities is blood flow to the brain. Acutely, foods that increase the production of nitric oxide increase blood flow to the brain.[31] Chronically, diets that reduce the risk of arterio- and atherosclerosis, such as carotid artery stenosis, increase blood flow to the brain and help to maintain brain volume over a lifetime.[32–34] Although many polyphenol-rich foods, such as green tea, berries, and grapes stimulate the production of nitric oxide, chocolate has demonstrated the most robust results in clinical trials for improving cognition. Desideri and colleagues and Mastroiacovo and colleagues completed two nearly identical eight-week DB-RCTs (n = 180) evaluating the impact of high vs intermediate vs low flavanol chocolate on cognitive performance. In a dose-dependent manner, chocolate flavanols improved cognitive performance on the Mini Mental Status Exam, verbal fluency, and trail making A and B tests ($p \leq 0.005$).[35,36] An impressive three-month DB-RCT (n = 37) by Brickman and colleagues demonstrated that high-flavanol chocolate improved cognitive scores and increased blood flow to the hippocampus, specifically the dentate gyrus of the hippocampus, which is the area of the brain most correlated to age-related cognitive decline and is the only area of the brain capable of producing stem cells in adults ($p \leq 0.005$). With three months of chocolate, cognitive scores improved equal to three decades of age reversal. Of note, to produce double-blinding with chocolate, chocolate processed with alkali, aka Dutch-processed chocolate, was used as the placebo. Alkali binds to the polyphenols of the chocolate, rendering them physiologically inert.[37] Therefore, unprocessed chocolate is essential for beneficial effects.

The efficacy of comprehensive dietary changes in the prevention and attenuation of mild cognitive impairment has been demonstrated in several RCTs. In 2015, Valls-Pedret and colleagues evaluated a subgroup (n = 477) of the very large 7400-person PREDIMED RCT, demonstrating that a Mediterranean diet produced statistically and trend-level significant improvements in memory, executive function, and global cognition over an average of 4.1 years compared with a low-fat control group.[38] In 2015, Ngandu and colleagues completed a large two-year RCT multidomain lifestyle intervention (n = 1260) combining diet, exercise, and cognitive training to prevent cognitive decline in elderly people, as part of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Compared with the healthy advice control group, the intensive lifestyle intervention demonstrated statistically significant improvements in executive function, processing speed, and total neuropsychological test battery score ($p < 0.03$).[39]

A diet that demonstrates promise in the prevention of cognitive impairment is the MIND diet (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay).[41] The MIND diet is a Mediterranean-style diet with particular emphasis on high polyphenol content through leafy greens and choosing berries as the primary source of fruit. Arjmand and colleagues completed an RCT evaluating the MIND diet vs calorie reduction in 40 obese middle-aged women. At three-month follow-up, compared with calorie reduction alone, the MIND diet demonstrated statistically significant improvements in working memory, verbal recognition, and attention.[40] A large 600-person three-year follow-up RCT of the MIND diet is currently underway.[41]

78.3 EXERCISE AND PSYCHIATRY

78.3.1 Exercise and Psychiatry Mechanism

An appreciation of how exercise intervenes with psychiatric disorders requires an understanding of the neurotrophic hypothesis in psychiatry.[42] The neurotrophic hypothesis relates to brain-derived neurotrophic factor (BDNF) and dendritic arborization—arbor as in tree branches. When there is sufficient BDNF and dense dendritic arborization, neurons have extensive branches, interconnecting neurons with other neurons in a rich web. When there is reduced BDNF and dendritic arborization, neurons have limited branches and the neural pathways that exist are restricted. Compared to a rich web of neurons, restricted neural pathways produce rigid patterns of thought and emotion. Rigid patterns in depression produce thoughts and emotions of personal deficiency.[43,44] In anxiety and trauma, rigid inputs produce worry and fear when there is no active objective concern.[45] In cognitive disorders, reduced neural pathways limit access to memories.[46] In psychotic disorders, the reduced brain volume of the prefrontal cortex and hippocampus limits the ability to discriminate reality from aberrant beliefs and perceptions and contributes to negative symptom burden.[47]

In contrast, cardiovascular exercise increases dendritic arborization by increasing BDNF. A partial misnomer, BDNF is produced in the brain but is also a contraction-induced protein generated by vascular smooth muscle, where it works in conjunction with nitric oxide to regulate vasodilatation.[48] As blood vessels expand and contract to accommodate each stroke volume of cardiac output, BDNF is released into systemic circulation, whereupon it passes through the blood–brain barrier and regrows the brain through its neurotrophic action.

78.3.2 Cardiovascular Exercise and Depression

Schuch and colleagues completed a systematic review and meta-analysis of 25 RCTs with a total of 1487 patients evaluating the effects of cardiovascular exercise on depression. After accounting for publication bias, cardiovascular exercise had a statistically significant and large effect size on depression. Moderate and high-intensity exercise produced an even larger effect as did supervised exercise ($p \leq 0.003$).[49]

Exercise appears to be an effective treatment for depression at any age and health status. Wegner and colleagues completed a systematic review and meta-analysis of 30 RCTs with a total of 2110 children and adolescents, demonstrating that cardiovascular exercise has a statistically significant and moderate effect size on depression ($p \leq 0.01$).[50] Herring and colleagues demonstrated the efficacy of cardiovascular exercise as a treatment for depression by evaluating 90 RCTs with 10,534 patients who were older, sedentary, and chronically ill, albeit the effect size was smaller at 0.3 ($p < 0.001$).[51]

Particular attention should be given to an RCT (n = 121) by Murri and colleagues who demonstrated that combining progressive exercise with antidepressants for six months produced an 81% remission from depression, nearly doubling the effect of antidepressant treatment alone ($p < 0.001$).[52]

78.3.3 Cardiovascular Exercise and Schizophrenia

In 2015, Firth and colleagues completed a systematic review and meta-analysis of four RCTs that evaluated moderate-to-vigorous exercise as a treatment for patients with schizophrenia and found significant improvements with moderate-to-large effect sizes for positive, negative, and total symptoms ($p \leq 0.01$).[53] In 2016, Dauwan and colleagues completed a systematic review and meta-analysis of 29 RCTs examining the effects of aerobic exercise and yoga on 1109 patients and found significant improvements in positive, negative, and total symptoms with small to moderate effect sizes ($p \leq 0.05$).[54] In 2017, Firth and colleagues completed a second systematic review and meta-analysis on seven RCTs that evaluated the effect of aerobic exercise on cognitive performance in 385 patients with schizophrenia. Exercise improved global cognition and working memory with small effect sizes, but moderate effect sizes on social cognition and attention ($p \leq 0.24$). Again, greater amounts of exercise produced stronger effects in subgroup analysis.[55]

78.3.4 Cardiovascular Exercise and ADHD

Cardiovascular exercise is known to enhance executive function and working memory,[56] so may have special relevance to patients with ADHD. Liang and colleagues completed a systematic review and meta-analysis of 15 RCTs that evaluated exercise in 493 children and adolescents with ADHD. Exercise had a moderate-to-large effect size on overall executive function (g = 0.611), inhibitory control (g = 0.761), and cognitive flexibility (g = 0.780) ($p < 0.001$). In a subgroup analysis, moderate-intensity exercise was superior to light exercise, and ongoing regular exercise produced nearly double the effect size when compared with acute exercise ($p < 0.05$).[57]

78.3.5 Cardiovascular Exercise and Cognitive Impairment

In 2006 and 2011, Colcombe and colleagues and Erickson and colleagues, respectively, published landmark RCTs demonstrating that cardiovascular exercise could reverse age-related cognitive impairment and brain volume loss. In Colcombe's study (n = 59), after six months, the cardiovascular exercise group increased both gray and white matter brain volume with the largest changes in the frontal lobe, whereas the stretching and toning group continued to lose brain volume ($p < 0.05$).[58] In Erickson's study (n = 120), after 12 months, the cardiovascular exercise group regrew 2% of brain volume in the hippocampi, whereas the stretching control group hippocampi continued to lose 1.4%. The cardiovascular exercise group increased hippocampi volume equal to being three years younger than their stretching group peers in terms of brain volume ($p < 0.001$).[59]

In 2018, Northey and colleagues completed a systematic review and meta-analysis of 39 RCTs with 12,800 older adults and evaluated the efficacy of exercise on cognitive function. Exercise had a small effect size overall (g = 0.29), however, when exercise was completed five to seven days per week, the effect size increased to a moderate-to-large effect (g = 0.69) ($p < 0.01$).[60] Similarly, Liu and colleagues completed a systematic review and meta-analysis of 22 RCTs with 1647 patients with a formal diagnosis of Alzheimer's disease which found that exercise improved scores on the Mini Mental Status Exam ($p < 0.0001$) and the Alzheimer's Disease Assessment Scale-Cognitive ($p = 0.04$) with small and large effect sizes, respectively.[61]

78.3.6 Exercise, Anxiety, and Post-Traumatic Stress Disorder

In 2017, Stubbs and colleagues published a systematic review and meta-analysis of six RCTs with 262 patients evaluating the efficacy of exercise for anxiety, finding a statistically and clinically significant benefit with a moderate effect size ($p = 0.02$).[62] Likewise, in 2021, Björkman and colleagues completed a systematic review and meta-analysis of 11 RCTs with 605 patients with post-traumatic stress disorder (PTSD). Exercise produced statistically significant improvements in core symptoms of PTSD with moderate effect size. In subgroup analysis, symptoms of depression, sleep, substance use, and quality of life all improved ($p \leq 0.05$).[63]

78.4 CLINICAL CONSIDERATIONS

With this formidable evidence base supporting the utilization of diet and exercise interventions in the management of psychiatric disorders, it would be wise to temper expectations with regard to implementation within current healthcare systems. Well-designed clinical trials often provide a level of support and multifaceted interventions that may be untenable for most clinical practices. There are few comprehensive lifestyle interventions covered by insurance,[64] and those usually require a recent acute cardiac event.[65] Therefore, providers generally must

integrate lifestyle interventions within their visits with a range of other agendas. Dietary interventions are possibly the most complicated lifestyle intervention with new skills required for shopping, storing, cooking, and selecting ingredients to create healthy, delicious, and balanced meals. Cardiovascular exercise, as well as other lifestyle interventions, such as meditation and sleep, may be easier to implement given that a single skill is being taught, but even these interventions are more sustainable with guided support. Additionally, in well-designed clinical trials, the number needed to treat is rarely below four.[1,4] Hence, clinicians should reasonably expect that intensive lifestyle interventions may improve psychiatric symptoms in some patients, whereas other patients may not experience benefits. Nevertheless, given the low side effect burden and the global health benefits of improving lifestyle choices, it is reasonable to include lifestyle recommendations as part of a medical and therapeutic treatment plan for most patients.

78.5 CONCLUSION

Although diet and exercise highlight specific mechanisms in psychiatric disorders, there is significant cross-pollination and synergy between lifestyle habits. For instance, BDNF—intervening on the neurotrophic hypothesis of psychiatric disorders—is robustly produced by cardiovascular exercise and is also produced by certain foods high in polyphenols, such as chocolate, tea, and berries.[66,67] Nitric oxide produced by food increases blood flow to the brain and also improves VO_2 max of the heart, exercise intensity, and exercise endurance.[68–71] Although foods rich in antioxidants reduce oxidative stress and inflammation, exercise is likewise anti-inflammatory via cytokines produced by muscular contraction.[72] Other lifestyle interventions, such as sleep, meditation, and yoga, increase BDNF and decrease inflammation[73–75] producing an orchestra of complementary mechanisms building upon each other for optimum effect.

The evidence on lifestyle interventions for psychiatric disorders is considerable with detailed understanding of mechanisms and a consistent demonstration of efficacy in clinical trials. It is reasonable to include lifestyle interventions as a major component of treatment recommendations for fostering optimum mental health in both primary and secondary prevention. Additionally, lifestyle interventions for mental health may be a deft ally in encouraging lifestyle interventions for cardiometabolic diseases. Whereas patient populations may have a conceptual understanding of the long-term risks of heart disease and diabetes, all patients have a palpable understanding of what it is to feel better and have clearer thinking in their day-to-day lives. Hence, the encouragement of lifestyle interventions for improved mental health may be a leverage point for improving global health for individual patients and public health.

CLINICAL APPLICATIONS

Diet and depression	• Mediterranean diets appear to improve depression and increase rates of remission from depression in patients with baseline poor diets.
Diet and schizophrenia	• In a subset of patients with schizophrenia with high gliadin antibodies, gluten-free diets may improve negative and general symptoms. • B vitamins that reduce homocysteine may improve core symptoms of schizophrenia in patients with baseline elevated homocysteine.
Diet and ADHD	• Diets with a complete abstinence from processed foods and artificial ingredients may improve ADHD.
Diet and cognitive disorders	• Foods (chocolate, berries) improve acute cerebral blood flow via the production of nitric oxide, thus improving cognition. • Chocolate processed with alkali aka "Dutch processed" is used as a placebo. Alkali renders active ingredients physiologically inert. • Diets that prevent carotid artery stenosis sustain chronic blood flow and reduce the risk of cognitive impairment and dementia.
Cardiovascular exercise and depression	• CV exercise improves depression in pediatric, adult, and older adult populations. • Combining CV exercise with antidepressants may produce up to 81% remission from depression over a six-month period, double the effect of antidepressants alone.
Cardiovascular exercise and schizophrenia	• CV exercise may improve negative and cognitive symptoms of schizophrenia.
Cardiovascular exercise and ADHD	• CV exercise may improve executive function and working memory in ADHD with moderate-to-large effect.
Cardiovascular exercise and cognitive disorders	• CV exercise restores brain volume in the hippocampus and prefrontal cortex, which may ameliorate, prevent, and/or reverse age-related cognitive decline.

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79 Risk and Protective Factors for Mental Health

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KEY POINTS

- Lifestyle factors can be protective of, or be detrimental to, mental health.
- Lifestyle interventions can be utilized to prevent and treat mental health conditions and optimize psychological well-being.
- Risk and protective factors can be briefly assessed with brief, validated screening measures to inform lifestyle interventions for mental health.

79.1 INTRODUCTION

Mental health is inextricably tied to lifestyle factors and quality of life across the lifespan. Mental health is defined as "a state of mind characterized by emotional well-being, good behavioral adjustment, relative freedom from anxiety and disabling symptoms, and a capacity to establish constructive relationships and cope with the ordinary demands and stresses of life".[1] In short, mental health includes both an absence of pathology as well as an overall sense of well-being. Lifestyle factors, including diet, physical activity, sleep, stress, interpersonal relationships, and substance use, can each support mental health and serve as a protective factor or be detrimental to mental health.[2,3] Specifically, suboptimal lifestyle behaviors, such as poor nutrition or inadequate sleep, may influence the onset and progression of many health conditions.[4,5] Those who meet clinical criteria for mental illness have higher rates of mortality and morbidity related to a number of direct and indirect factors, such as poor health behaviors and stigma affecting healthcare.[6] Fortunately, several lifestyle factors, such as regular exercise and vegetable-rich diets, are health-promoting and have been shown to improve mental health.[4,5]

A lifestyle medicine approach to addressing risk and protective factors for mental health is especially relevant to primary care practitioners, as most mental health conditions are diagnosed and treated in a primary care setting.[7] Table 79.1 outlines recommendations for brief, validated measures to assess primary lifestyle factors in clinical settings. The current chapter will outline the key areas of lifestyle medicine and address how lifestyle can positively influence mental health or increase risk for poor mental health. While a thorough discussion of sociocultural influences is beyond the scope of this chapter, each of the risk and protective factors outlined below should be considered from a biopsychosocial perspective, including the influence of social determinants of health on lifestyle behaviors, health beliefs, and access to resources.

79.2 RISK AND PROTECTIVE LIFESTYLE FACTORS

79.2.1 Diet and Nutrition

Across the lifespan, diet, gastrointestinal (GI) health, brain health, and mental health have been shown to have a complex and tightly related association.[8,9] Research suggests dietary patterns that prioritize fruits, vegetables, and whole grains are associated with a lower incidence of depression and anxiety disorders when compared with "Western" diets that include large quantities of processed foods, refined grains, and sugar.[10] Another study found that moderate adherence to a plant-rich Mediterranean diet demonstrated a 27% reduction in depression risk, while high adherence was associated with a 32% reduction.[11]

Research is still emerging on the exact ways by which diet impacts mental health, but various mechanistic and clinical data offer potential mechanisms. GI microbiota diversity, which refers to the number of different species of organisms in the gut, has been shown to be important to physical, and now, mental health. Research has found less GI microbiota diversity in individuals with social stress, anxiety, depression, bipolar disorder, and schizophrenia.[12,13] Diet plays an essential factor in determining GI microbiota diversity, with diets high in fiber, polyphenols, and unsaturated fatty acids promoting more diversity, while diets low in fiber and high in refined carbohydrates, sugar, and alcohol result in less diversity.[14,15] A healthy, diverse GI microbiota may contribute to mental health in part through the production of tryptophan, the precursor to serotonin, as well as other neurotransmitters, such as GABA and norepinephrine.[8,14]

Additionally, micronutrient intake may play a role as several nutrients are essential cofactors for neurotransmitter production.[15] Deficiencies of nutrients, such as vitamins C and B, have been linked to the risk of mental health conditions.[12,16–18] Vitamin B12 supplementation has demonstrated benefits for stress and depression.[12,18] Studies

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TABLE 79.1
Validated Brief Measures to Assess Risk and Protective Lifestyle Factors for Mental Health

Lifestyle Factor	Validated Assessment Measure	Measure Details
Diet	Short-form Food Frequency Questionnaire (SF-FFQ)	Twenty-five-item measure of diet quality provides a diet quality score.[75]
	Mediterranean Diet Adherence Screener (MEDAS)	Fourteen-item assessment of food consumption of the 12 main aspects of the Mediterranean diet.[76]
Physical activity	International Physical Activity Questionnaire-Short Form (IPAQ-SF)	Seven-item questionnaire assessing time spent doing various levels of physical activity and spent sedentary. Can be self-administered. Available in multiple languages.[77]
Stress	Perceived Stress Scale (PSS)	Ten-item questionnaire assessing the perception of stress, not stress itself.[78] Results and utility are dependent on an individual's ability to identify and report stress.
Substance use	The Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool (TAPS Tool-I and Tool-II)	TAPS-I is a four-item screen for substance use. For those who screen positive, nine-item TAPS-II can used for additional screening of substance use over the past three months.[79, 80]
Sleep	Insomnia Severity Index (ISI)	Seven-item measure with clinical insomnia cut-off.[81]
	STOP-Bang	Eight-item measure for risk of obstructive sleep apnea.[82]
Social support	Multidimensional Scale of Perceived Social Support (MSPSS)	Twelve-item measure of perceived support across family, friends, and significant other domains.[83]

have also shown that omega-3 deficiency is associated with increased risk for the development of depression, bipolar disorder, substance use disorders, schizophrenia, attention deficit disorder, and neurocognitive disorders, as well as low mood and hostility.[13,19,20]

Diet may also affect mental health through immune-modifying and epigenetic mechanisms.[9,21] Pro-inflammatory Western diets have been shown to cause neuro-oxidative stress and inflammation that can result in neuronal damage,[22] lesser well-being, and greater risk for anxiety and depression symptoms.[23] While research continues to elucidate the ways by which diet impacts mental health, current evidence shows there is an opportunity to address dietary risk factors for mental health and encourage dietary patterns that can protect mental health.

79.2.2 Physical Activity

Many studies have demonstrated a link between physical activity and mental health. Sedentary behavior, defined as activities done in a seated or reclined position requiring low energy expenditure,[24] has been associated with increased depression and stress, as well as poorer self-image and life satisfaction among adolescents and adults.[24,25] Conversely, physical activity requiring high energy expenditure has been associated with improved mental health across the lifespan in a healthy population as well as among adults with a variety of physical health comorbidities, including cancer and autoimmune conditions.[26–30] Physical activity also has a role in the prevention and management of mental illness, as benefits have been demonstrated for mood disorders, anxiety disorders, attention deficit disorders, substance use disorders, and schizophrenia.[10]

The precise mechanisms by which physical activity impacts mental health are unclear, though several hypotheses have been suggested. Exercise has been demonstrated to impact brain structure (e.g., hippocampal volume) and result in neurogenesis, angiogenesis, and synaptogenesis.[10] Additional potential biological mechanisms include neurotransmitter release and mediation of the inflammatory response.[31] Psychologically, exercise may impact mood by increasing self-esteem, self-efficacy, and social connectedness.[32] By incorporating physical activity into a treatment plan, including for those with or at risk for mental illness, there is an opportunity to simultaneously improve mental and physical health.

79.2.3 Sleep

Both quality and quantity of sleep play a key role in overall health, including mental health. Sleep, more specifically insomnia (difficulty initiating or maintaining restful sleep) is an independent risk factor for mental and neurological disorders.[11] Specific sleep disorders, such as obstructive sleep apnea, have also been associated with cognitive impairments, mood dysregulation, and worse immune function.[33] Yet, some of the strongest evidence for the impact of sleep on health points to the relationship between insomnia and depression, with insomnia as a key predictor of the development of depression.[34]

Accordingly, managing sleep issues is an essential part of preventing and treating mental health issues. A 2021 meta-analysis of randomized controlled trials indicated greater improvement in sleep was associated with improvement in overall mental health, depression, anxiety, and rumination.[35] Interventions to address sleep and sleep disorders often include sleep hygiene, which emphasizes behavioral and environmental factors that can influence sleep quality.[36] For those who need more intervention than sleep hygiene, cognitive behavioral therapy for insomnia (CBT-I), is the

gold-standard and first-line treatment for insomnia and is also a promising treatment for comorbid depression and insomnia.[37] CBT-I is an important treatment option as a standalone treatment or combined with other treatments as a common side effect of psychiatric medications is interference in sleep onset and maintenance, thus potentially exacerbating underlying mood and cognitive symptoms.[38] Identifying and treating sleep issues, either in conjunction with mental health treatment or independently, is a critical opportunity for primary and secondary prevention of mental health symptoms and disorders.[39]

79.2.4 Stress

Stress can affect mental health at all stages of life, and successful treatment of stress may reduce symptoms of mental illness.[3] Even before birth, parental stress is thought to lead to epigenetic alterations in offspring which can profoundly influence mental health throughout the lifespan.[40] A preponderance of evidence suggests that stressful early life experiences, sometimes called adverse childhood events, contribute to mental health pathology later in life.[3] Demographic and sociocultural factors, such as race, ethnicity, and social determinants of health, have also been associated with increased risk for chronic stress.[41] It has been posited that the epigenetic inheritance of stress contributes to the racial disparities in cardiovascular disease.[42] Research on social determinants of health also suggests that those who live in unsafe and under-resourced neighborhoods are more likely to experience the physiological effects of stress (i.e., allostatic load), though this relationship is partially mediated by health behaviors (e.g., smoking).[43]

Stress can manifest cognitively, behaviorally, and physiologically, and these different expressions of stress may be independent or interrelated. Recognizing how an individual's stress presents can be the key to effective treatment.[44]

Screening for stress is vitally important and should include attention to physical signs of stress (e.g., GI symptoms), as many individuals struggle to articulate stress when screened.[45] People experiencing stress may have a difficult time making and sustaining changes, including changes to health behaviors that could mitigate stress. For example, research shows those experiencing stress are less likely to change their behaviors than those not experiencing stress,[46] and that stress affects the brain in ways that negatively impact future-oriented planning.[47] While it is impossible to know with certainty which treatment for stress will work best for an individual,[48] screening for stress and identifying manifestations of stress are both critical to effective lifestyle change and health behavior maintenance.

79.2.5 Substance Use

Tobacco, alcohol, marijuana, illicit substance use, and prescription medication misuse are all bidirectionally related to mental health.[3] Many individuals report relying on substances to cope with symptoms of shame, depression, anxiety, and other mental illnesses.[49–52] Rates of alcohol use disorder and other substance use continue to increase, and data continues to emerge regarding the concerning rates at which individuals have relied on substances to cope with the stress of the COVID-19 pandemic.[52–54] Not only does experiencing mental distress increase the likelihood of substance use, but research also shows substance use increases the risk of various mental health issues. For example, research suggests causal links between both alcohol use disorder and illicit substance use and risk for major depression and anxiety disorders.[55,56] Similarly, marijuana use has been shown to predict greater risk for a substance use disorder, while abstinence has been associated with fewer symptoms of anxiety and less alcohol and nicotine use.[52,57]

Cigarette use has a bidirectional relationship with mental health. Smoking has been associated with an increased risk of depression, anxiety, panic disorder, and schizophrenia.[58–60] In a meta-analysis of more than 50,000 adults, smoking significantly increased the prospective risk of depression over six years.[61] Anxiety symptoms have been shown to contribute to the onset of smoking and contribute to smoking behaviors.[60] Though the causal relationship between mental illness and smoking remains unclear, individuals with serious mental illness, such as schizophrenia, smoke at much higher rates than the general population.[62] Tobacco cessation is an important modification to reduce risk for mental disorders, as it has been associated with decreased symptoms of anxiety, depression, self-reported stress, improved mood, and overall quality of life.[63,64] Overall, substance use tends to increase risk for worse mental health, and interventions that support cessation have the opportunity to support mental and physical health and related outcomes.

79.2.6 Relationships and Social Support

Healthy and supportive interpersonal relationships are a protective factor for the prevention of mental health symptoms and disorders and optimal quality of life. Both enacted and perceived social support are important predictors of satisfaction with life.[65] For example, the well-known 75-year longitudinal Grant study found close relationships to be the single most impactful predictor of life satisfaction.[66] Good social support has been associated with better ability to cope with stress, and even less mental decline among older adults.[67] The effects of social support have also been studied across the lifespan, with protection from depression based on parental support for children and adolescents.[68] Research has also indicated the importance of intimate partner relationships, with the quality of a long-term partnership, often in the form of marriage, associated with greater physical and mental health.[67]

Alternatively, there are several relational risk factors for poor mental health, including unhealthy relationships that include harm or abuse, trauma, and social isolation. Intimate partner violence (IPV) is well understood to

adversely impact mental health and has been associated with increased risk for depression, anxiety, and post-traumatic stress disorder (PTSD).[69] Social isolation has been associated with a greater decline in mental health and an increase in symptoms such as loneliness, helplessness, and worse mood.[70] Lack of social connectivity has even been associated with greater degrees of inflammation and worse immune function.[70] Even after controlling for lifestyle and socioeconomic factors, lesser social connection is associated with a higher risk of mortality.[70]

The COVID-19 pandemic exacerbated social isolation and the cascade of mental and physical health implications, such as greater depression and anxiety, and worse sleep quality.[71] Fortunately, social support can be leveraged to positively influence lifestyle interventions and, for example, to improve adherence to lifestyle and pharmacological treatment of type 2 diabetes mellitus.[72] Thus, identifying insufficient social support and providing appropriate referrals to local organizations and social services can reduce risk, protect mental health, and improve the efficacy of lifestyle interventions.[73,74]

79.3 CONCLUSION

The current chapter provided an overview of each of the primary lifestyle factors and their impact on mental health, as well as the utility of associated clinical interventions. As indicated by both well-established and emerging areas of science, health behaviors such as engaging in daily physical activity and managing stress can support mental health, prevent and reduce mental distress, and complement treatment for mental illness. However, other lifestyle behaviors such as insufficient sleep and social isolation are risk factors for worse mental health and increased risk for mental illness. Utilizing brief, accessible, and empirically based screening measures (Table 79.1) within clinical contexts can allow for the assessment of risk factors and lay a foundation for the development of lifestyle medicine interventions to support mental health. While considering social determinants of health, attention to these risk and protective lifestyle factors for mental health can foster opportunities for lifestyle interventions to prevent and treat mental health symptoms and illnesses effectively.

CLINICAL APPLICATIONS

- Lifestyle interventions, including nutrition, physical activity, sleep, social connectedness, substance use, and stress management, impact the risk of developing a mental disorder.
- Lifestyle interventions may complement psychotherapy and medication for the management of mental disorders.
- Evaluations of patients should include a comprehensive lifestyle assessment, which also includes a discussion of the barriers to implementing lifestyle changes (see Table 79.1 for helpful tools).
- Monitor individuals with a diagnosis of mental illness for cardiometabolic risk factors, including side effects of psychotropic medications.

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80 Biopsychosocial Implications and the Prevention and Management of Chronic Illnesses

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KEY POINTS

- Chronic low-grade systemic inflammation underlies most chronic illnesses.
- Psychological stress, troubled close relationships, and poor health behaviors contribute to an overactive pro-inflammatory state and chronic illness risk.
- Lifestyle interventions that target the "six foundational pillars of lifestyle medicine" can slow and sometimes prevent chronic illnesses; lifestyle interventions also reduce systemic inflammation, indicating a possible mechanism of action.

80.1 INTRODUCTION

Thanks to decreased infant mortality, better nutrition, and extraordinary advances in healthcare, life expectancies have increased dramatically in the United States and globally.[1] People in the United States can expect more than 30 additional years of life than their ancestors born at the dawn of the 20th century. As a result, 16% of the population is older than 65, the age at which people are considered "older adults". Indeed, if someone reaches age 65, they can expect to live another 20 years[1]

Chronic illnesses emerge at a much greater frequency as people age. Accordingly, chronic illness (i.e., noncommunicable diseases) has replaced infectious diseases as the leading cause of death and disability in the United States and globally.[2] More than three-fourths of those over 65 have at least one chronic illness[3] or condition.[4] All six foundational pillars of lifestyle medicine (i.e., diet, exercise, stress management, substance use, sleep, and close relationships) contribute to chronic illness development and progression[5] In this chapter, we consider how stress, close relationships, and health behaviors "get under the skin" to impact the development and progression of chronic illnesses. Toward this end, we take a biopsychosocial approach to understanding the etiology and management of chronic illnesses. We commence by reviewing how molecular processes and cellular alterations associated with aging contribute to the emergence and progression of chronic illnesses. Then, we consider how stress, close relationships, and health behaviors impact the molecular and cellular underpinnings of chronic illness by contributing to age-related changes in chronic low-grade systemic inflammation. Finally, we describe a growing literature showing it is possible to target biological mechanisms through lifestyle interventions.

80.2 INFLAMMATION AS A COMMON PATHOGENIC MECHANISM UNDERLYING CHRONIC ILLNESSES

Age-related alterations in cellular and molecular processes play a critical role in the development and progression of most chronic illnesses.[6,7] Given that the immune system dynamically remodels in older adulthood, gerontologists have become particularly interested in the cellular and molecular processes that promote age-related changes in the immune system (i.e., immunosenescence)[8] As a result of immunosenescence, older adults are less likely to mount an adequate immune response when vaccinated and more susceptible to infection, latent herpes virus reactivation, and an overactive inflammatory network.[9]

Chronic low-grade systemic inflammation is a common pathogenic biological mechanism underlying most chronic illnesses[10] It is necessary and adaptive for the immune system to mount an acute pro-inflammatory response when someone is infected or injured. Yet, chronic low-grade inflammation, revealed by elevated levels of inflammatory biomarkers such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α), is involved in many age-related diseases[10]

Inflammaging is an emerging term characterizing the low-grade, chronic, systemic inflammation in aging that is an important indicator of morbidity and mortality.[7,11] There is a plethora of epidemiological evidence that a mild chronic inflammatory state is predictive of an aging phenotype[11,12] Pro-inflammatory cytokines, such as IL-6 and TNF-α, are predictive of cardiovascular disease, some cancers, type II diabetes, arthritis, osteoporosis, Alzheimer's disease, and periodontal disease[13–16] Chronic inflammation is an essential biological mechanism that promotes waning physical function leading to frailty, disability, and, ultimately, death[17] Inflammation is also associated with

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muscle wasting, cognitive decline, and increased disease vulnerability[18]

80.3 MECHANISMS OF LOW-GRADE INFLAMMATION: PATHWAYS TO CHRONIC ILLNESSES

Given the role of chronic low-grade inflammation in the development and progression of chronic illnesses, it is critical to understand the origins and mechanisms that underlie an overactive pro-inflammatory state to create targeted and tailored interventions[12] The origins of a pro-inflammatory phenotype are multifactorial. This chapter focuses on those related to the six pillars of lifestyle medicine[12,19] First, we describe how the stress-response system can promote acute and chronic inflammation. Then, we explain how past and current close relationships can buffer and exacerbate stress's negative impact. Finally, we describe how key health behaviors (i.e., diet, tobacco use, and exercise) promote inflammation while considering how the stress-response system can interact with these health behaviors in additive and possibly synergistic ways.

80.3.1 Stress-Response System

The stress-response system involves alterations in the autonomic nervous system and the hypothalamic-pituitary axis (HPA axis) within the neuroendocrine system in response to stress. When the stress-response system is activated, catecholamines are released as part of the sympathetic nervous system response.[20] Norepinephrine-dependent adrenergic stimulation triggers NF-KB, an intracellular signaling molecule that regulates pro-inflammatory cytokine gene expression.[20] Cortisol, the glucocorticoid produced by the HPA axis in response to stress, also impacts pro-inflammatory activity[21] Although cortisol is anti-inflammatory, chronically elevated cortisol promotes desensitization of the glucocorticoid receptor, thereby promoting glucocorticoid resistance. When the glucocorticoid receptor is desensitized to the anti-inflammatory impact of cortisol, the body cannot regulate the magnitude of inflammatory responses, thus allowing a pro-inflammatory state[22]. There is growing evidence that the parasympathetic branch of the autonomic nervous system is also involved in the regulation of chronic low-grade systemic inflammation[23] Acetylcholine, the principal neurotransmitter of the parasympathetic nervous system, is secreted under conditions of rest and restoration and inhibits systemic inflammation via the "cholinergic anti-inflammatory pathway".[23]

When negative emotions, such as depression, loneliness, and grief, are present over a prolonged period, the stress-response system is "primed" to mount a robust inflammatory stress response[24–28] For example, in 111 recently widowed older adults, my group recently tested the hypothesis that widow(er)s experiencing more profound grief would have a greater pro-inflammatory response to an experimental stressor than those with less grief. After intravenous catheter placement, we took a small amount of blood to obtain levels of IL-6 in serum at baseline. Then, we administered a well-established standardized laboratory stressor designed to elicit a stress response. Blood was taken 45 minutes and two hours after the stressor. Our results indicated that widow(er)s who exceeded the cut-point for grief complications exhibited more significant stress-induced elevations in the pro-inflammatory cytokine, IL-6, than individuals who experienced less grief. Importantly, this finding persisted even after accounting for depressive symptomology.[29] This finding illustrated relational loss's unique impact on the inflammatory stress response. As discussed below, relationships can positively impact pro-inflammatory cytokine production and chronic illness risk[30]

80.3.2 Social Processes

One of the fundamental tenets in lifestyle medicine is that close social relationships impact physical health across the lifespan; elegant theoretical frameworks from the social psychological literature have clearly articulated that human beings have a need to belong. Although this need is universal, not everyone experiences health benefits from social relationships.[31] In fact, social relationships are a source of strain and sorrow, across the lifespan, for a considerable amount of the population.[31] Indeed, those who have stronger social relationships have a 50% greater likelihood of survival than those who report low social support, according to a meta-analysis of 148 studies.[24] Indeed, social integration impacted mortality rates at a level equivalent to smoking and physical activity[24] A meta-analysis of 41 studies revealed that those who reported more social support and social integration had lower systemic inflammation than those who reported less social support and social integration[32]

There has been considerable research to show that objective social isolation and loneliness enhance the risk of poor quality of life and disease.[26,27,33,34] Nevertheless, there is strong evidence that loneliness primarily mediates the link between objective social isolation and mental and physical health outcomes; thus, it is the perception of social isolation (i.e., loneliness), rather than one's objective reality that largely impacts health[28,33] This is important because if one is able to understand when and why people perceive isolation or loneliness, interventions can be designed to alleviate this negative emotion. In an 18-year study of 6729 individuals from the National Health and Nutrition Examination Survey assessing social isolation and multiple markers of chronic inflammation, chronic inflammation explained the link between social isolation and mortality[26] Healthy adults exposed to acute stress exhibited more significant increases in the pro-inflammatory cytokines, TNF-α, and IL-6, than their less lonely counterparts[35] Similarly, lonelier posttreatment breast cancer survivors exposed to acute stress exhibited more significant IL-6 and IL-1β than their counterparts who felt more socially connected[29]

Not only are current interpersonal relationships linked to immune dysregulation, but past relationships are as well. There is considerable evidence that children who were abused have dysregulated immunity.[30,36,37] In a longitudinal prospective study of adults with an average age of 32, more than 10% of adult low-grade inflammation was attributable to child maltreatment. Further, in a study of healthy older adult family dementia caregivers and non-caregivers, children who had experienced emotional, physical, or sexual abuse as children were more likely to have higher IL-6 and TNF-α levels than those who were not abused as children[38] Perceived social status might alter the impact of having troubled relationships with parents. Widow(er)s who reported troubled relationships with their parents, and being of lower social status, produced more robust pro-inflammatory cytokines; however, this was not the case for widow(er)s who reported troubled relationships with their parents as children but high social status.[39]

80.3.3 Health Behaviors: Diet, Exercise, Sleep, and Tobacco Use

Health behaviors are adopted by individuals or groups to prevent illness or injury and maintain health status. Poor diet, lack of exercise and sleep, and tobacco use are modifiable risk factors for morbidity and mortality that impact chronic low-grade inflammation.[40] Ischemic heart disease is the leading cause of death for men and women; scientists estimate that up to 80% of cardiovascular and coronary heart disease events can be attributed to *poor-quality diet*, *excess calorie intake*, physical inactivity, and smoking[41].

Although the risks associated with health behaviors are profound in their own right, recent evidence suggests they may impact inflammation more if accompanied by psychological risk factors (e.g., stress and poor close relationships)[42] Consider how comfort foods high in saturated fat are consumed more frequently during stress. Recent work suggests that these high saturated fat foods may promote greater risk when consumed in times of high stress compared with when they are consumed in times of low stress. For example, triglycerides, which increase after a high saturated fat meal, provoke monocytes to produce pro-inflammatory cytokines;[43] Multiple labs have shown IL-6, TNF-α, and CRP increases following a single meal high in saturated fat.[44–46] Recent work has demonstrated that stress potentiates the adverse repercussions of eating high saturated fat comfort foods because the post-prandial (post-meal) response of lipids and pro-inflammatory cytokines is exaggerated when one experiences frequent stress[47,48] Psychological stress can also promote lipemia (high lipid content in the blood) by enhancing triglyceride responses to a high saturated fat meal and inhibiting clearance[49] For example, in one study, total triacylglycerol and very low-density-lipoprotein-TG areas under the curve were 50% or higher during a stressful condition than in a control condition.[50] This finding was not related to pre-meal levels. Increased post-prandial changes were independent of baseline triacylglycerol levels[50] In another study, acute stress slowed triglyceride clearance.[51] Compared with the non-stress session, clearance of an exogenous fat load took 14% longer on average following a laboratory stressor.[51]

80.4 INTERVENTIONS

Although many health recommendations exist to reduce chronic illness risk, knowing which constructs to prioritize is critical to most effectively and efficiently guide intervention, development, and ultimately reduce risk. For example, if the synergistic impact of diet and psychological stress predicting post-prandial increases in triglycerides and inflammation is robust, this information will guide intervention components above and beyond general dietary recommendations.[42]

Regular physical activity is associated with lower levels of pro-inflammatory cytokines.[51] In addition to its physiological benefits, intervention studies have demonstrated that regular exercise reduces psychological distress and enhances psychological well-being, which may serve as an indirect pathway to reduced inflammation.[52–54] While much of the literature has focused on cardiovascular training, positive effects are also found with a variety of other activity interventions; for example, the flexibility/strength training control group in one study showed a significant decrease in TNF-α,[55] while a tai chi intervention produced positive alterations in varicella-virus specific immunity.[56]

Data from well-controlled randomized clinical trials have demonstrated mindfulness as an important tool to reduce stress, improve sleep, and improve adherence to good health behaviors (e.g., diet, exercise, substance use cessation). Mindfulness reflects an intentional awareness of internal and external stimuli occurring in the present moment.[57] That is, individuals can allow distressing cognitions, emotions, perceptions, and sensations to occupy awareness without necessarily trying to change them and without becoming engaged in their content. These thoughts and feelings are viewed simply as passing mental events that may or may not reflect reality. Mindfulness-based interventions, such as the eight-week Mindfulness-based Stress-Reduction Protocol (MBSR), have been implemented to target various health problems. In a community-based sample of employed adults, MBSR participants reported significantly less anxiety and negative affect after treatment than the control group. In a randomized control trial, those who received a mindfulness-based intervention exhibited a reduced stress response to experimental stress than participants in the control condition.[58] MBSR may be a powerful tool in reversing the physical consequences of a dysregulated stress response.

In addition to interventions that require commitment and behavior change, there is work to suggest a role for supplements and medications. In a clinical trial designed to reduce inflammation in older adults, randomized assigned to receive omega-3 polyunsaturated fatty acid supplementation

showed a modest decrease in the pro-inflammatory cytokine, IL-6, compared with placebo controls.[59] In another trial examining the impact of omega-3 polyunsaturated fatty acid supplementation in medical students, those who received the supplement exhibited a 14% decrease in IL-6 production and a 20% decrease in anxiety symptoms.[59] Medications such as statins, fibrates, and niacin can also be effective, yet these interventions have monetary costs and physical health side effects.[60–65]

80.5 CONCLUSION

Overactivation of the stress-response system is strongly predictive of chronic illness occurrence.[66] A lifetime of elevated levels of low-grade inflammation (sometimes called *inflammaging*) predicts chronic illness incidence, typically occurring in older adulthood.[67] A biopsychosocial approach to systemic inflammation highlights the variety of lifestyle factors that promote chronic illnesses or protect against them. For instance, loneliness, poor social support, childhood maltreatment, high-fat diets, sedentary lifestyles, and tobacco use are all risk factors for chronic illnesses through elevated low-grade inflammation.[66,67] Successful intervention research has demonstrated that systemic inflammation can be reduced by targeting the six pillars of lifestyle medicine.[68] Practitioners and researchers alike may apply these findings to promote healthy aging.

CLINICAL APPLICATIONS

- Behavior change interventions that reduce tobacco use, increase healthy eating, and/or improve exercise may be more helpful when combined with stress-reduction interventions.
- Clinicians should consider assessing patients' social networks, including loneliness and childhood maltreatment.
- Medications such as statins, fibrates, and niacin can be effective for reducing inflammation, but the monetary costs and physical health side effects may make behavior change interventions more appealing to patients.

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Part XV

Preventive Neurology



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81 The Influence of Lifestyle on Parkinson's Disease Management

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KEY POINTS

- Parkinson's disease (PD) is the second-most prevalent neurological condition worldwide and is associated with aging.
- Many low-risk and potentially high-yield recommendations for lifestyle modification could be made to decrease the risk and progression of PD.
- A healthy dietary pattern has been shown to contribute to a lower risk of PD.
- Lack of sleep has a substantial impact on the development of neurodegenerative illnesses and inhibits the body's ability to eliminate neurotoxic substances.
- Physical activity is a key component of rehabilitation programs for patients with PD.
- PD is influenced by both acute and chronic stress.

81.1 INTRODUCTION

Parkinson's disease (PD) is the second-most prevalent neurological condition worldwide and in the United States, almost a million people have PD. By 2030, it is anticipated that this number will reach 1.2 million.

In patients with PD, pathologic processes are already advanced at the time when the clinical diagnosis is made, particularly as the prodromal period may span up to two decades or more. This late timing is likely the reason why it has been challenging to slow the disease progression in patients. There has been increasing evidence from observational studies for the role of several lifestyle factors in modulating the risk for PD at individual and population levels.

In the past decade, additional evidence has been published that enhances our understanding of the complexity of these associations. Despite the caveats of observational studies, a number of low-risk and potentially high-yield recommendations for lifestyle modification could be made to minimize the individual and societal burdens of Parkinson's disease, including dietary modifications, increasing physical activity, and head injury avoidance. The most promising and best-studied factor for disease prevention is exercise. Indeed, studies have shown that regular aerobic exercise is associated with improved preservation of the basal ganglia network, and human studies have corroborated these findings, demonstrating advanced neuroplasticity in the basal ganglia circuitry. Other lifestyle factors such as nutrition, regular consumption of caffeine, reduction of alcohol, prevention of concussions and head trauma, and reduction of environmental exposure to pesticides have been associated with risk reduction. In this chapter, we will explore lifestyle factors that have been linked to the prevention of PD.

81.2 NUTRITION

A healthy dietary pattern has been shown to contribute to a lower risk of PD. Despite the challenges of studying nutrition over a long period of time, many dietary patterns have been studied for their association with PD risk, and the results are a variation of a theme that highlights the importance of improving dietary patterns rather than myopically focusing on specific macro or micronutrients. The dietary pattern most extensively associated with a lower risk of PD is essentially a plant-based dietary pattern with a high intake of fruits, vegetables, legumes, whole grains, nuts, and fish, and a low intake of sources of saturated fat from meat and dairy products, refined carbohydrates, and alcohol. The Mediterranean dietary pattern has been associated with a reduced risk of PD development in multiple cohorts.[1,2] In populations from the Center for Parkinson's Disease at Columbia University, in New York (n = 209), and the Washington Heights–Inwood Columbia Aging Project (n = 48), a higher adherence to a Mediterranean-type diet was associated with 14% reduced odds for PD after adjustment for all covariates (OR, 0.86; 95% CI, 0.77–0.97; P = 0.010). People with lower Mediterranean-type diet scores had a higher risk for earlier PD age at onset (β = 1.09; P = 0.006).[1] In 47,679 participants from the Nurses' Health Study and Health Professional Follow-up Study, adherence to a Mediterranean-style diet, especially among those who scored in the top 20%, were one-third less likely to develop multiple early Parkinson's symptoms over 20 years, compared with people in the bottom 20%. Higher adherence to this dietary pattern was inversely associated with features such as constipation, excessive daytime sleepiness, and depression.[3] In a study from a population-based cohort of older adults (Hellenic Longitudinal Investigation of Aging and Diet) in Greece, high adherence to the Mediterranean

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diet was associated with a lower probability for prodromal PD ($P < 0.001$), represented by non-motor markers of prodromal PD, depression, constipation, urinary dysfunction, and daytime somnolence. Each unit increase in Mediterranean diet score was associated with a 2% decreased probability for prodromal PD ($P < 0.001$). Compared with participants in the lowest quartile of Mediterranean diet adherence, those in the highest quartile had approximately 21% lower probability for prodromal PD.[2]

Recently, the MIND Diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) has also been studied with regard to its association with PD, as it has been shown to lower the risk of Alzheimer's dementia and overall dementia. The MIND dietary pattern emphasizes the consumption of leafy greens, berries, vegetables, whole grains, nuts, seeds, and extra virgin olive oil as the main source of cooking oil, and fish as a source of long-chain n-3 polyunsaturated fatty acids (PUFAs) while minimizing the consumption of meat, high-fat dairy, and sources of saturated fats. In a cross-sectional study involving 167 PD patients and 119 controls, adherence to the MIND diet was most strongly related to a later age of onset specifically in the female subgroup, reflecting differences up to 17.4 years ($P < 0.001$). The study found a strong correlation between dietary habits and the age of PD onset, suggesting nutritional habits can play a crucial role in delaying PD progression.[4] In addition, there has also been a link between early changes in gut microbiota and PD.[5]

Gut microbial dysbiosis and alteration of microbial metabolites in PD have been increasingly reported. Alterations in the composition and abundance of gut microbiota can affect both the enteric nervous system and the central nervous system (CNS), indicating the existence of a microbiota-gut-brain axis and thereby contributing to neurodegenerative diseases, including PD. This alteration in the gut microbiota may be related to the cause or effect of motor or non-motor symptoms in PD, but the specific pathogenic mechanisms are unclear. Case-control studies show changes in gut microbiota composition in PD patients compared with healthy individuals, and there are suggestions of a link between microbiota alterations and disease progression. Indeed, in a randomized clinical trial, probiotic products consisting of *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum* were administered to PD patients over a 12-week period, which resulted in beneficial effects on MDS-UPDRS, C-reactive protein, blood glutathione, and insulin metabolism, pointing to a potential association between modification of the gut microbiome and its long-term effect on PD pathophysiology.[6] A recent systematic review of 64 studies showed a strong Mediterranean diet was associated with a lower risk of AD and PD, and due to its high fiber natures, a change in the gut microbiota was observed, where one family, eight genera, and three species had an inverse relationship with the Mediterranean diet and PD. Conversely, weak Mediterranean diet adherence, gut dysbiosis, and PD were suggested to be in a chain of causality.[7] However, the exact mechanism remains to be elucidated, and more studies are needed to investigate the characteristics of microbiota composition with the aim of discovering new biomarkers for the prevention, early diagnosis, or monitoring the disease progression.

There is a strong association between dairy consumption and PD. In a large prospective study of the association between intake of dairy products and risk of PD among 57,689 men and 73,175 women from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort, dairy product consumption was positively associated with risk of PD. Meta-analysis of all prospective studies confirmed a moderately elevated risk of PD among persons with high dairy product consumption. Compared with the lowest quintile of consumption, those with the highest consumption of dairy had a 60% higher risk of developing PD (95% CI: 1.3, 2.0) for both sexes, 80% for men (95% CI: 1.4, 2.4), and 30% for women (95% CI: 0.8, 2.1). These data suggest that dairy consumption may increase the risk of PD, particularly in men.[8] Recently, Mendelian randomization indicated a causal relationship between dairy intake and higher PD risk, not biased by confounding or reverse causation[9]

81.3 SLEEP

One of the most common non-motor symptoms of PD is sleep disturbance, which is experienced regardless of the disease stage and has a major impact on the quality of life of patients.[10] Sleep disturbances can occur in some cases over two decades before the diagnoses of PD such as REM behavioral disorder (RBD).[11] PD affects the control of sleep and wakefulness, which results in the development of disorders such as insomnia and excessive daytime sleepiness (EDS). On the other hand, sleep disturbances can be iatrogenic due to medications.[12]

With the prevalence ranging from 30–80%, insomnia is the most common sleep disorder in such patients. An individual with insomnia finds it difficult to initiate, maintain, or consolidate sleep or to generate a good quality of sleep overall. Patients report sleep interruption and early awakening more than sleep initiation problems. Furthermore, insomnia is associated with nocturnal hypokinesia, dystonia, mood disorder, and pain which can disrupt sleep.[13] Identifying possible causes of insomnia in PD is the first step in managing it, for this, patients should be evaluated for potential nocturnal motor symptoms and mood disorders as well.

EDS is defined by difficulty staying awake and alert during the day, resulting in unintentional episodes of sleep or drowsiness. Its prevalence ranges from 20–75% among PD patients and increases with the disease progression. Dopamine agonists are the most often responsible medications and have been widely connected to EDS and sleep attacks. Physicians should also consider polysomnography to screen or test for comorbid sleep disorders such as obstructive sleep apnea, restless leg syndrome (RLS), and RBD.

RLS is a common sleep disorder found in PD with the prevalence estimated to range from 8–24%. RLS is defined as an urge to move the legs due to sensory discomfort. It may be associated with iron deficiency or exacerbated with medications used to treat motor and non-motor symptoms of PD including antidepressants with serotonergic activity and antihistamines; however, there is not a consensus statement yet.[14] Therefore, it is essential to look for low serum ferritin or medications potentially responsible.

RBD is a parasomnia that arises out of the REM stage, leading to skeletal muscle paralysis which causes patients to act out their dreams. RBD prevalence is estimated to be 2% in the general population[15] and up to 23.6% in PD patients.[16] The underlying pathophysiology for loss of REM atonia is believed to be the accumulation of alpha-synuclein in pontine nuclei. RBD is linked to a worse prognosis for PD and there is a chance of more severe cognitive impairments, hallucinations, and motor dysfunctions in patients with concomitant RBD.[13]

There is no doubt that sleep contributes to the maintenance of physical and neurological health. Neurologic function may be negatively impacted by sleep disturbances, which can range from circadian misalignments to high levels of day-to-day variability in sleep schedule to sleep disorders[17] The discovery that sleep deprivation impairs the elimination of potentially neurotoxic chemicals (such as beta-amyloid and tau) has significance for the etiology of neurodegenerative diseases.[18] In order to improve the neurologic health and function of patients, not only insufficient quantity but also insufficient quality of sleep must be managed.

81.4 EXERCISE

For the first time in 2005, Praag et al. discovered that exercise could boost cognition, spatial learning, and neurogenesis in old mice.[19] Since then, it has now been demonstrated that exercise, even low-commitment exercise programs, has a wide range of positive impacts on the human brain, including memory, mood, cognitive functioning, plasticity, and learning capacities.[20–22]

Physical activity is a key component of rehabilitation programs for patients with PD, currently recommended as a strategy to manage the disability induced by the disease. Exercise is an important therapy technique for managing PD's motor and non-motor symptoms.[23] Various types of exercise-based interventions including aerobic and strength training have been extensively studied through clinical trials. The review of these studies suggests that conventional exercise training positively impacts disease severity, motor disorders, activity performance, and non-motor impairments.[24] In recent studies, novel forms of exercise such as aquatics, tai chi, dance, Nordic walking, and other complementary therapies have shown promising health effects on PD.[25] According to the World Health Organization (WHO), older adults (age >65 years) should complete a minimum of 150 minutes of moderate or 75 minutes of vigorous-intensity aerobic exercise per week. However, a great majority of healthy older adults do not engage in this weekly minimum activity level. As we know, following PD, activity levels abruptly decline and are much lower than those of healthy peers. Patients should consult with their healthcare provider before beginning any exercise plan to be sure they can safely engage in and continue any exercise intervention.

Due to movement disorders attributed to PD, there is a need for an adjusted guideline for the patients. Yet, little is known about the modality, frequency, and intensity required to control symptoms. Guidelines for obtaining the possible disease-modifying effects of exercise have been published by the SPARX2 and Park-in-Shape trials.[26,27] Based on these protocols, PD patients should exercise three times a week; however, it is unknown if exercising more frequently will produce better results. One should consider that after four weeks of inactivity, the short-term exercise-induced improvements in motor symptoms subside. Like anti-parkinsonism drugs, exercise must be included in patients' routines to have long-term effects. Regarding the intensity, patients are recommended to exercise at a level between 70 and 85% of their maximal heart rate. To put that in context, the level of exercise should be raised if a person is able to talk while exercising. In addition, exercise sessions should last 30 to 40 minutes to be sufficient for the primary exercise set. Walking and stationary cycling are the two forms of aerobic exercise that are most frequently mentioned in PD studies. In a setting where most people show gait and balance impairments early in the disease process, stationary cycling could be a safer alternative and lessen the risk of falling.

Since every individual with PD requires specific treatment, it is likely that every patient should have a different prescription for a successful training schedule. Therefore, if exercise is to be used as medication, we need to give each patient a precise "dosage" that may have recognized consequences.

81.5 STRESS MANAGEMENT

Neurodegenerative diseases such as PD are influenced by both acute and chronic stress. Aside from repetitive chronic stressors, single acute stressors can cause structural and functional alterations in neurons. The brain is vulnerable to oxidative stress because it uses chemically varied reactive species to fulfill heterogeneous signaling activities.[28] Acute stress exacerbates motor symptoms such as tremors, freezing, and dyskinesia and reduces the effects of dopaminergic drugs. On the other hand, depression and anxiety disorders are more likely to happen during chronic stress. There is data suggesting an increase in cortisol levels in PD patients, indicating these patients are more vulnerable to stress effects.[29] Recently the COVID-19 pandemic has been a significant stressor worldwide and PD patients with higher COVID-related stress load exhibited more severe motor and non-motor dysfunctions, which is likely due to psychological distress and lack of physical activity. In a recent online

survey performed on a large PD population, stress reduction strategies especially mindfulness have been studied[30] Mindfulness is defined as moment-to-moment non-judgmental awareness. The effects of mindfulness-based interventions (MBI) on psychological distress reduction and symptom improvement in several chronic conditions have been demonstrated. Patients were evaluated in terms of how often they used mindfulness in their daily lives, as well as the self-reported effects that mindfulness had on their symptoms. Mindfulness was practiced by 38% of patients who reported improvement in their motor and non-motor symptoms. They concluded mindfulness may influence PD symptom severity with the greatest effects on depression and anxiety.

A review study consisting of eight articles evaluating the effects of MBI on the clinical symptoms of PD patients was published in 2020. Surprisingly, six out of eight studies reported a decrease in depression and four out of seven showed a reduction in anxiety scores. Only three trials studied motor symptoms and two of those found a substantial improvement following MBI. Two out of eight studies found a significant effect on quality of life in patients.[31]

Impaired self-awareness for motor symptoms in PD is related to lower therapy adherence, higher caregiver burden, and mortality rate. Buchwitz et al. developed a protocol for a newly designed MBI to raise self-awareness in PD. "Insight into Parkinson's Disease Symptoms by Using Mindfulness" or IPSUM is an eight-week program exclusively planned for PD patients. It is expected that this new method can improve self-awareness for both motor and cognitive symptoms. There are a number of criteria necessary for mindfulness training to be a successful method of raising self-awareness in PD patients. For instance, patients' perceptions of their own bodies may change if they are taught how to express their perceptions rather than judge them. As individuals begin to pay more attention to the here and now (during mindfulness exercises), they ought to become more conscious of their bodily movements, posture, and other interior feelings (thoughts and emotions). By being more accepting of oneself and their condition, consistent mindfulness meditation practice, increased management of negative emotions, and attention training, this perceptional shift may be easier to achieve and sustain.[32]

81.6 COGNITIVE-BASED INTERVENTIONS

Compared with the general population, PD patients have an up to six times higher prevalence of cognitive impairment.[33] They may experience a complete spectrum of impairment, from subjective cognitive decline to dementia.[34] Despite increased research over the past two decades, cognitive difficulties in PD remain poorly understood; however, there are interventions designed to improve or maintain patients' cognition commonly called cognition-based interventions (CBI).[35] CBI is divided into three categories: cognitive training, cognitive rehabilitation, and cognitive stimulation. For instance, cognitive stimulation provides a variety of enjoyable activities that stimulate general thinking, concentration, and memory, usually in a small group of people.

A recent systematic review including 11 randomized clinical trials (all with cognition therapy) reported encouraging findings. Nine out of 11 studies showed positive impacts on cognition, particularly on various executive functions and attentional performance.[35]

One of the interesting stimulations investigated is playing chess. Research shows a link between playing chess and reducing the risk of dementia[36] Five cognitive domains are covered by this practice mind sport: math, visual-spatial skills, critical thinking, and short- and long-term memory use. An experiment performed on 500 patients over five years showed those who regularly played board games had a nearly 35% lower risk of dementia compared with individuals who did so sometimes or never. In fact, those over 75 who engaged in brain-stimulating hobbies like chess had a lower risk of developing dementia[37] Chess appears to be a treatment that works to prevent or protect before disease onset; however, there is limited information on chess' advantages once an illness has been recognized and diagnosed.

CLINICAL APPLICATIONS

- The main risk factor for the onset and progression of Parkinson's disease is age and numerous cellular processes predisposed to neurodegeneration are affected by aging.
- A number of low-risk and potentially high-yield recommendations for lifestyle modification could be made to minimize the individual and societal burdens of Parkinson's disease, including dietary modifications, increasing physical activity, and stress management.
- A healthy dietary pattern has been shown to contribute to a lower risk of PD.
    - The dietary pattern most extensively associated with a lower risk of PD is essentially a plant-based pattern with a high intake of fruits, vegetables, legumes, whole grains, nuts, and fish, and a low intake of sources of saturated fat from meat and dairy products, refined carbohydrates, and alcohol.
    - The Mediterranean dietary pattern has been associated with a reduced risk of PD development.
    - Alterations in the composition and abundance of gut microbiota can affect both the enteric nervous system and the central nervous system, indicating the existence of a microbiota-gut-brain axis and thereby contributing to neurodegenerative diseases, including PD.

- Meta-analysis of all prospective studies confirmed a moderately elevated risk of PD among persons with high dairy product consumption.
- One of the most common non-motor symptoms of PD is sleep disturbance, which is experienced regardless of the disease stage and has a major impact on patients' quality of life.
  - Identifying possible causes of insomnia in PD is the first step in managing it, for this, patients should be evaluated for potential nocturnal motor symptoms and mood disorders.
  - The discovery that sleep deprivation impairs the elimination of potentially neurotoxic chemicals (such as beta-amyloid and tau) has significance for the etiology of neurodegenerative diseases.
- Physical activity is a key component of rehabilitation programs for patients with PD, currently recommended as a strategy to manage the disability induced by the disease. Frequency of exercise is three times a week and each session should last 30 to 40 minutes.
  - Novel forms of exercise such as aquatics, tai chi, dance, Nordic walking, and other complementary therapies have shown promising health effects on PD.
  - Walking and stationary cycling are the two forms of aerobic exercise that are most frequently mentioned in PD studies.
  - In a setting where most people show gait and balance impairments early in the disease process, stationary cycling could be a safer alternative and lessen the risk of falling.
- Acute stress exacerbates motor symptoms; however, depression and anxiety disorders are more likely to happen during chronic stress. The effects of mindfulness-based interventions on psychological distress reduction and symptom improvement in PD have been demonstrated.

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82 Sleep and Lifestyle Medicine

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KEY POINTS

- Restorative sleep is a cornerstone of lifestyle medicine and contributes to our physical, mental, emotional, and spiritual well-being.
- Sleep disorders are increasingly common, and pharmacological interventions have proven insufficient to treat sleep disorders in the long term.
- Our sleep is significantly influenced by daytime habits like the consumption of caffeine, alcohol, and tobacco, as well as diet, light exposure, and exercise.
- With age, sleep becomes less restorative; hence, it is essential to address unhealthy lifestyle habits to ensure restorative sleep and promote optimal health and healing.
- Sleep disturbances result in mental, emotional, and physical fatigue and are associated with disease and illness ranging from cellular damage to organ malfunction.
- Insufficient sleep increases the risk of obesity and heart disease, especially in patients with diabetes.
- Sleep disturbances accelerate the progression of neurodegenerative disorders, have the potential to trigger seizures, and increase the risk of stroke.
- Bidirectional relationships exist between sleep disorders and psychiatric conditions like depression and anxiety. Sleep is a common comorbidity in patients with ADHD.

82.1 INTRODUCTION

Sleep is critical for maintaining health, especially brain health. As with nutrition and physical activity, sleep is among the cornerstones of lifestyle medicine for optimal physical, mental, and emotional well-being.

There is plenty of data demonstrating the bidirectional relationship between sleep and health; poor sleep increases the risk of disease and illness, and conversely, many diseases disrupt sleep. This can lead to a vicious cycle culminating in worsened morbidity and mortality. Research has demonstrated that a minimum of seven hours of deep restorative sleep is essential for memory consolidation, and much of the cleansing is done through a remarkable system called the glymphatic system.[1] Furthermore, there is significant evidence that individuals who have insufficient depth or quantity (seven to eight hours) of sleep are susceptible to cognitive decline, depression, and anxiety, and are at greater risk of developing dementia.[2–5] Cumulative effects of disordered sleep include early mortality, cardiovascular disease, hypertension, obesity, metabolic syndrome, diabetes and impaired glucose tolerance, immunosuppression, inflammation, cancer, cognitive impairment, and psychiatric disorders, with anxiety and depression being the most common.[6] Despite our greater awareness, it is apparent that the prevalence of sleep disorders is increasing, which may speak to our worsening lifestyles.

To date, we have many tools in our armamentarium to address sleep disorders such as insomnia, restless legs syndrome, sleep apnea, and other conditions. Nevertheless, our approaches, whether pharmaceutical, for insomnia or restless legs syndrome, or appliance-based, for sleep apnea, have been nominal and often fail to reverse the underlying causes of the conditions and do not address the preventive component of these conditions.[7,8]

In this chapter, we hope to provide insight into the tremendous impact of lifestyle on our sleep and its role in avoiding sleep disorders, which are devastating millions worldwide.

82.2 SLEEP DEFINITION AND ITS STAGES

A healthy sleep architecture consists of repeated cycles of around 90 minutes of rapid eye movement (REM) and non-REM stages of sleep through the night. Healthy restorative sleep typically consists of approximately four to six of these cycles. All stages do not need to occur in every sleep cycle; however, optimal sleep needs all stages to occur throughout the night. Each sleep stage in any given sleep cycle contributes to physiological changes that promote brain health. On average, most adults require about seven to eight hours of sleep, although this range varies based on age and genetic predisposition.

Non-REM sleep consists of a continuum of three separate stages (stage 1, stage 2, and stage 3), with each stage progressively "deeper" from a neurophysiological perspective. In non-REM, each "deeper" stage of sleep leads to further reductions in blood pressure and heart rate while rhythmic breathing patterns and heart rate continue. In stage 3 of sleep, there is increased blood supply to muscles, while the energy in the form of adenosine triphosphate (ATP) is restored, and growth hormone is released to promote growth, development, and repair.[9–11]

Sleep patterns change as people age, and sleep disorders become more common as we get older. As many as 57% of older adults have reported complaints of poor sleep.[12–15]

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Changes in sleep architecture also occur with aging. In particular, sleep tends to become less restorative as older adults spend an increasing percentage of sleep in stages 1 and 2 and a decreasing percentage of time in deep sleep (stage 3) and dream (REM) sleep.[16–18] Thus, awareness of sleep disorders and lifestyle factors that can potentially disrupt sleep is critical.

Insufficient sleep is often termed sleep deprivation and leads to sleep debt (also called sleep deficit). Sleep debt often results in varying expressions of mental, emotional, and physical fatigue, ultimately leading to difficulties in daily activities, especially those requiring high-level cognitive functions. Similar to ethanol, sleep deprivation leads to impaired judgment and reduced insight. Beyond reduced alertness and insight, symptoms of sleep deprivation include lapses in attention, poor short-term memory, errors by omission, reduced ability to multitask, irritable mood, aggressive behavior, or daytime sleepiness. Physical manifestations of sleep debt include impaired coordination, reaction time, muscle fatigue, hand tremors, lowered body temperature, increased blood pressure, increased stress hormone levels, and increased heart rate variability. Sleep debt tends to accumulate; about two weeks of less than six hours of sleep per night reduces alertness and performance to a level equivalent to 24 hours of sleep deprivation. A week or more of only four hours of sleep each night creates errors in attention-oriented tasks equivalent to two to three days without any sleep.[19] Only sleep reverses the harmful effects of sleep deprivation. Therefore, recovery from sleep loss depends on the consistency of proper restorative sleep.

82.3 COMMON SLEEP DISORDERS

Nearly all of us will experience some sleep disorder during our lifetime. There are over 100 different types of sleep disorders ranging from difficulty sleeping at night to problems with excessive daytime sleepiness. This chapter will focus on the most common lifestyle-responsive sleep disorders.

Sleep apnea is estimated to be prevalent in 15–30% of males and 10–15% of females in North America.[20,21] There are two types of sleep apnea (obstructive and central), with the most common type (>85%) being obstructive sleep apnea (OSA). OSA is characterized by complete or partial collapse of the upper airway for ten seconds or longer repeatedly throughout the night. Although all persons are subject to relative relaxation of the soft tissues in the airway during sleep, in OSA, these tissues create a blockage of the upper airway sufficient to limit airflow and disrupt sleep-related breathing. Moreover, when the airway is blocked, the drop in oxygen levels in the blood leads to arousal and disturbed sleep architecture. Because these awakenings or alterations of sleep state are often brief, there is often no awareness that they occur during sleep. The awakenings repeat during the night, and in severe sleep apnea, 30 or more awakenings occur per hour over one night of sleep. Even though the awakenings are usually very short, the fragmentation and interruption of sleep along with the reduction of oxygenation have a significant and negative impact on health.[22–24] In central sleep apnea (CSA), prolonged breathing pauses lead to hypoventilation and hypoxemia syndromes. These are due to dysregulation and lack of cueing from the central nervous system that would otherwise continue involuntary breathing. As a result, there is no drive to initiate and complete a breath for ten seconds or longer. This process fragments sleep quantity and quality similar to OSA even though the mechanisms are different.[25]

Periodic limb movement disorder (PLMD) is a sleep disorder characterized by the rhythmic movements of the limbs that possibly fragment the quantity but more often disrupt sleep quality. A type of PLMD is *Willis-Ekbom Syndrome* (previously referred to as restless legs syndrome). This sleep disorder is characterized by sensorimotor discord when resting or lying down to sleep, resulting in discomfort, aching, jerking, twitching, tingling, or creeping-crawling sensations, thereby leading to an irresistible urge to move or shift the legs, arms, or torso. Etiologies include iron and vitamin B12 deficiency, third trimester of pregnancy, abnormal blood sugar, thyroid disorders, renal disease, and Parkinson's disease.[26,27]

Insomnia is the most common of all sleep complaints. It is a sleep disorder characterized by difficulty falling asleep, staying asleep, or experiencing restorative sleep for at least one month, ultimately leading to daytime dysfunction or disturbance. Etiologies include poor sleep habits such as late-night eating, stress, medical comorbidities, psychiatric comorbidities including anxiety and depression, medication effects, caffeine, nicotine, or another sleep disorder.[28,29]

82.4 ASSOCIATION OF DISRUPTED OR DISORDERED SLEEP WITH DISEASE AND ILLNESS

Building upon the appreciation of the underlying physiology of sleep and its inherent opportunities, the importance of sleep relates not only to the public's health but also to individuals' health and wellness. Sleep is associated with health and healing, whereas disrupted and disordered sleep is associated with disease and illness. The majority of medical literature has drawn associations between premature all-cause mortality and both shorter (less than seven hours) and longer sleep (more than eight hours).[30,31] Research connects health and sleep by demonstrating the impact of sleep spanning the continuum of cellular health to organ systems. Moreover, sleep impacts health and healing not only on the physical level but also on the mental and emotional levels.

82.4.1 Endocrine System and Sleep

Poor sleep impacts the neurochemistry of hunger[32] as well as hormonal health. Sleep deprivation alters the pattern of growth hormone release, and the timing of cortisol rise can be disrupted by sudden changes in the sleep-wake cycle.[33]

82.4.2 Obesity and Sleep

Adults with shorter sleep durations and sleep loss are at increased risk of becoming obese.[34–36] This association can be explained by the neuroendocrine functions modulated by sleep, which when disrupted, lead to increased levels of ghrelin, decreased levels of leptin, increased appetite, decreased glucose tolerance, and insulin sensitivity, ultimately leading to increased fat accumulation.[35]

82.4.3 Heart Disease and Sleep

Short sleep durations increase the risk of cardiovascular disease, hypertension, and myocardial infarctions. Long sleep durations, on the other hand, are not associated with these risks.[37] Among the common sleep disorders, obstructive sleep apnea is an independent risk factor for hypertension, ischemic heart disease, and even stroke.[38] In patients with type 2 diabetes, disturbances to sleep quality or quantity significantly increase the risk of cardiovascular disease and all-cause mortality.[39]

82.4.4 Autoimmune Disorders and Sleep

Sleep disorders are associated with autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and systemic sclerosis.[40]

82.4.5 Neurological Disorders and Sleep

Poor sleep accelerates the progression of major neurodegenerative disorders like Parkinson's disease and Alzheimer's disease, possibly by impairing the clearance of misfolded neurotoxin proteins involved in the pathogenesis of these disorders.[41,42] Epilepsy is another neurological disorder linked to sleep. Sleep deprivation decreases GABA-mediated inhibition, thereby reducing the seizure threshold and triggering epileptic seizures.[43] Importantly, clinically induced sleep deprivation is of high diagnostic utility in epilepsy.[43] In addition to neurodegenerative disorders and epilepsy, stroke is also linked to sleep. Sleep disturbances, including sleep-disordered breathing and disrupted sleep durations, increase the risk of stroke and are also worsened post-stroke.[44] For instance, insomnia patients have a 54% increase in stroke risk, and conversely, half of stroke patients suffer from insomnia. [44,45]

82.4.6 Psychiatric Disorders and Sleep

Many psychiatric conditions are linked to sleep disturbances including depression, anxiety, and ADHD. A bidirectional relationship exists between sleep disturbances and depression. In patients with depression, comorbid insomnia increases the severity and duration of depressive episodes and increases risk of relapse.[46] In patients without depression, having insomnia increases their risk of developing depression.[46]

Similar to depression, sleep disturbances are known to be cardinal symptoms of anxiety disorders. Sleep disruption in the short term increases stress responsivity and anxiety, and has been shown to increase risk of substance abuse.[47,48]

Patients with ADHD commonly have comorbid sleep disorders which lead to significant functional impairments that affect day-to-day functioning.[49] Childhood ADHD that persists into adulthood is significantly associated with poor sleep quality.[50]

82.5 INTERVENTIONS AND TREATMENTS FOR DISRUPTED AND DISORDERED SLEEP

82.5.1 Treatment of Sleep-Related Breathing Disorders

Given the complex nature of sleep apnea, as it pertains to its causes and especially treatments, our approach needs to be detailed and personalized. First, a thorough clinical evaluation with an interdisciplinary team and sleep testing is required so patients are ensured appropriate treatment options. Treatment options can be divided into non-surgical and surgical approaches. By convention, non-surgical approaches are thoroughly reviewed before considering surgical intervention.[51]

Non-surgical approaches for obstructive sleep apnea begin with treating underlying medical conditions, positional therapy, and lifestyle modifications, focusing on nutrition and exercise. Pharmacotherapy directed toward underlying allergic rhinitis or hypothyroidism may be helpful in combination with other therapies.[52, 53] For central sleep apnea, narcotic medications may be a contributor, and thus it is necessary to review medications and propose alternative regimens. Depending on polysomnogram results, positional therapy such as avoiding the supine sleep position can be efficacious.[54–58] Such an approach may improve snoring and resolve or reduce the severity of sleep apnea. A typically helpful lifestyle discussion prioritizes healthy body weight and judicious intake and timing of alcohol.

Nasal dilators and mandibular advancement devices demonstrate promising results for mild and positional sleep apnea. Nasal dilators are particularly helpful for patients suffering from uncomplicated snoring and nasal obstruction. Mandibular advancing devices contract the genioglossus and anteriorly forward the mandible and hyoid bone to increase the oral airway during sleep.[59]

Positive airway pressure (PAP) is the treatment of choice for moderate and severe sleep-related breathing disorders, including obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation. The most common form—continuous positive airway pressure (CPAP)—maintains a constant level of PAP in a spontaneously breathing patient. Other forms that provide non-invasive positive pressure ventilation include auto-adjusting PAP (autoPAP), bilevel positive airway pressure (Bilevel PAP), adaptive servoventilation (ASV), and volume-assured pressure support (VAPS)[60].

82.5.2 Treatment of Periodic Limb Movements (Willis-Ekbom Disease)

Therapeutic interventions for Willis-Ekbom disease, a neuro-sensorimotor disorder (better known by its previous name, restless legs syndrome), are contingent on the underlying etiology. The challenge lies within the varied causes of genetics and environmental factors. Willis-Ekbom disease is a continuous spectrum with a significant genetic contribution at one end and a major environmental or comorbid disease contribution at the other. Previous research suggests that the involved genes are significantly expressed in the primary form of the disease (idiopathic) and the comorbidities that are the roots of the secondary forms of RLS (Trenkwalder et al., 2016). In up to 42% of cases, genetic factors contribute to the etiology of Willis-Ekbom Disease.[61]

The most common secondary forms are linked to iron deficiency, pregnancy, Parkinson's disease, and end-stage renal disease.[62] Other associations include vitamin and mineral deficiencies, thyroid disorders, cardiovascular disease, arterial hypertension, diabetes, neuropathy, erectile dysfunction, arthritis, rheumatic illnesses, multiple sclerosis, migraine, fibromyalgia, mood disorders, attention-deficit hyperactivity disorder, liver disease, obesity, narcolepsy, and other sleep disorders.[63] Ultimately, most presentations of Willis-Ekbom disease are treated with pharmacology (dopamine agonists, gabapentin, or low-potency opioids).[64] Additional options seek to reduce the excessive periodic limb movement and their arousals by treating an accompanying sleep disorder if present. A newer approach uses a medical device to enhance peripheral circulation with pneumatic compression or introduce counter-stimulation by vibration.[65]

82.5.3 Treatment of Insomnia

Although more than half of primary care patients may experience insomnia, only about one-third report this problem to their physicians,[66] and only 5% seek treatment.[67] As a result, most persons with insomnia remain untreated.[68] Given the fast pace of primary care visits, it is not surprising that two-thirds of patients with insomnia report a poor understanding of treatment options, and many turn to alcohol (28%) or untested over-the-counter remedies (23%) [67]. Given the limited time available for each patient visit in the primary care setting, treatment approaches may rely primarily on pharmacological interventions. This approach takes away the opportunity to help patients live whole lives by discussing underlying issues that contribute to their insomnia. Non-benzodiazepine receptor agonists such as eszopiclone, zolpidem, and orexin antagonist suvorexant may improve short-term global and sleep outcomes for adults with insomnia. However, pharmacotherapies' comparative effectiveness and long-term efficacy for insomnia are unknown. Benzodiazepine hypnotics, melatonin agonists, and antidepressants may be helpful in general populations and for most pharmacologic interventions in older adults in select individuals. However, there is insufficient data about the potential of these medications to be widely helpful. In general, pharmacotherapy is intended for short-term use. Hypnotics may be associated with dementia, fractures, and significant injury. The Food and Drug Administration warns about cognitive and behavioral changes, iatrogenic illness or accidents, including driving impairment, and other harms, and advises lower doses for females and older adults.[8,69]

The therapy paradigm starts with etiology: comorbid insomnia due to another sleep disorder or a medical disorder that requires treatment of the underlying process, or the more common psychophysiological insomnia requiring cognitive and behavioral approaches. Herein set the opportunity for cognitive behavioral therapy for insomnia (CBT-I), which has been well-established and evidence-based as an efficacious treatment for insomnia.[52,70–72] CBT is commonly prescribed for depression, but clinical trials have shown it is the most effective long-term solution for those with insomnia. The positive effects of CBT-I on sleep quality are robust over time.[73] In addition, CBT-I has been found to be efficacious in populations with a variety of comorbid medical conditions, including persons with comorbid insomnia,[74] comorbid psychiatric conditions,[75] and chronic pain.[76–80] CBT-I helps identify the negative attitudes and beliefs that hinder sleep and replaces them with positive thoughts, effectively "unlearning" the negative beliefs.[81] The behavioral aspect of CBT focuses on helpful sleep habits and avoids unhelpful sleep behaviors, as well as managing lifestyle and environmental issues. Behavioral techniques that may be recommended include stimulus control,[82] sleep restriction,[57] systematic desensitization,[83] sleep hygiene, sleep environment improvements, relaxation training,[84] paradoxical intention,[85] hypnosis,[86] and biofeedback.[87] CBT-I throughout six to eight weekly sessions[88–90] for most adults in either individual or group-based administration is effective,[79,91,92] yet vastly underutilized in comparison with pharmacological approaches.

82.6 INTEGRATIVE AND PREVENTIVE APPROACHES

First, the awareness and continued appreciation of the importance of sleep are essential for the best health and critical for preventing sleep disorders. In our ever more complex lives, we seek to expand the hours of the day, and as a result, sleep is treated as a mere luxury when it must be prioritized. Educating the public and our patients about the fundamental need for adequate sleep cannot be overstated. Like nutrition and exercise, restorative sleep is a prerequisite for optimal health and healing. Sleep not only positively impacts the physical body, but also promotes mental and emotional health.

Furthermore, it is essential to note that healthy sleep supports healthy eating and physical activity. Therefore, sleep both directly and indirectly benefits health. Conversely,

disrupted and disordered sleep negatively impacts health and healing opportunities. In this chapter, we have presented sleep and its connection with both public health and personal wellness. Sleep strongly correlates with cardiovascular disease, obesity, metabolic syndrome, diabetes, immune status, cancer, memory, pain control, and mental and emotional health. Although restorative sleep on its own may not be sufficient to prevent the development of these diseases entirely, it plays an essential role in reducing their severity and slowing their progression.

82.6.1 The Link between Nighttime and Daytime

Sleep quality is impacted by time spent in bed and the entire 24 hours of the day; this means that our daytime lives impact our ability to fall asleep, stay asleep, and wake up refreshed for the new day. Many lifestyle interventions can be implemented to achieve a greater quality of sleep; these relate to caffeine, alcohol, tobacco, unhealthy eating patterns, excessive light exposure, and lack of exercise.

82.6.2 Sleep and the Digital Environment

The world as we know it has expanded with artificial light and electronics. Despite the significant advancement, this has been at the cost of sleep quantity and quality. Exposure to light, mainly blue light, acts upon several non-image-forming (NIF) functions of the visual system. They impact sleep by directly acting on the sleep-wake cycle and indirectly by influencing body temperature, hormonal balance, alertness, and cognitive processing—these, in turn, negatively impact sleep.[93] NIF functions are maximally sensitive to blue wavelengths (460–480 nm), which are involved in melatonin suppression, vigilance, and stimulating mental activity.[94,95] Blue light exposure one to two hours before bed reduces sleep onset, REM duration, and overall perception of sleep quality. Sources of blue light include artificial lighting and digital screens (televisions, computers, tablets, and phones). Herein lies the opportunity to honor the benefits that lighting and electronics have added to our lives. However, limiting light exposure to specific times is a new opportunity to ensure healthy sleep.

82.6.3 Sleep and Caffeine

Caffeine is a standard part of many of our lives, as witnessed by morning coffee and tea rituals and the surge in energy drinks among younger adults. Unfortunately, caffeine has a discernible impact on sleep that can significantly affect restorative sleep.[96] Caffeine blocks the adenosine receptor in the central nervous system, which is involved in sleep induction and deep sleep regulation. Caffeine has a half-life of three to seven hours, depending on an individual's cytochrome p450 1A2 genotype expression. Despite the recognized antioxidant benefits of coffee and tea, the timing and quantity of caffeine consumption are essential to consider when it comes to sleep quality. According to the 2001 *Sleep in America* poll by the National Sleep Foundation, 43% of Americans are "very likely" to use caffeinated beverages to combat daytime sleepiness. This, in turn, creates a vicious circle of poor sleep leading to daytime sleepiness, which leads to increased caffeine consumption. The opportunity is to focus on the timing and quantity of caffeine consumption in our daily lives so that it can be a promoter and not a disruptor of our best sleep.

82.6.4 Sleep and Alcohol

Alcohol is commonly used worldwide as a sleep aid.[97] Regrettably, this is neither helpful nor recommended based on its effects on sleep. Whereas in the short term, it helps induce sleep, this effect tapers in a series of days and weeks depending on the individual's hepatic clearance. The impact of ethanol on sleep staging demonstrates a reduction in sleep quality in the second half of the sleep night. Alcohol has physiological effects on sleep, such as airway relaxation and narrowing, negatively impacting sleep-related breathing, such as obstructive sleep apnea. Ethanol demonstrates a dose effect on both its impact on sleep staging and the physiology of breathing during sleep. As with caffeine, the opportunity is to balance the timing and quantity of ethanol in our daily lives so that it does not interfere with healthy sleep.

82.6.5 Sleep and Tobacco

Tobacco has multiple hazards to optimal health. In addition to its addictive potential, tobacco adversely affects the quantity and quality of sleep. Nicotine shifts the circadian rhythm by altering the expression of clock genes.[98] People who smoke tobacco are more than twice as likely to have obstructive sleep apnea. The airflow limitation is partly due to the inflammatory effect on the nasal and oral airways.[99] Tobacco use leads to difficulty initiating sleep due to its stimulant and withdrawal effects.[100] Those who smoke tobacco are more likely to experience restless sleep due to more time spent in the light sleep stages than the deep and REM sleep stages.[101] It is thus critical to universally promote the idea that tobacco cessation is vital for public health and for restorative sleep.

82.6.6 Sleep and Nutrition

Eating patterns and food choices influence overall health as well as sleep health. Individuals consuming an excessive number of calories report short sleep time and quality.[102] Refined carbohydrates such as sugars act as stimulants in the body and influence a wide range of neurotransmitter shifts that make falling asleep and staying asleep more difficult.[103] Individual variance in food tolerance to spicy foods and dairy also impacts the ability to physically be soothed to be able to sleep. Large meals eaten close to bedtime typically disrupt sleep onset and quality. As discussed earlier, poor sleep creates the hormonal and neurochemical basis for food cravings. Again, we see the vicious circle of poor

sleep leading to overconsumption and poor food choices limiting restorative sleep. The opportunity to support healthy nutrition also supports healthy sleep.

82.6.7 Sleep and Exercise

National Sleep Foundation's 2013 Sleep in America poll highlighted the association between exercise and better sleep. A physically robust daytime utilizes our ATP resources such that the cleaving of the phosphate bonds results in a higher amount of adenosine by bedtime. Again, adenosine promotes sleep induction and deep sleep stages. Exercisers, compared with non-exercisers, are more likely to report restorative sleep. Poor sleep makes us less likely to exercise, which in turn leads to relative difficulty falling asleep, falling back asleep in the middle of the sleep night, and waking up too early.[104–107] Thus, there is a vicious circle of reduced physical activity and reduced sleep. Although the timing of exercise has been widely debated, it is likely based on individual experience.

82.6.8 Sleep and Lifestyle Medicine

Lifestyle changes have been relatively easy to state but not always easy to translate into the context of people's lives. Lifestyle interventions go above and beyond by seeing our patients physically, mentally, emotionally, and spiritually. Ultimately, it is understood and appreciated that these dimensions do not reside in different silos of thought or experience but are integrated into our daily lives. With this approach, we can address not only what is helpful but an opportunity to address how and why the current habits are in place. It is this approach that helps people enhance their sleep and their lives. Sleep is a key to health, and lifestyle is an essential path to health and sleep.

82.7 SUMMARY

Restorative sleep is among the cornerstones of lifestyle medicine for optimal health. Lifestyle medicine incorporates the full spectrum of factors that contribute to the quality of sleep relating to all aspects of our daily lives—physical, mental, emotional, and spiritual. The prevalence and incidence of sleep disorders, which adversely affect health in the short and long term, are rising. Although effective in the short term, pharmacological interventions are insufficient on their own for the treatment of sleep disorders. Given that our sleep quality is impacted by the entire 24 hours of the day, it is crucial to address our daytime habits that may reduce our sleep quality. Lifestyle medicine focuses on lifestyle habits while also considering underlying medical conditions to prevent disease and illness.

CLINICAL APPLICATIONS

- Sleep tends to become less restorative as we age; therefore, seeking opportunities to maintain healthy sleep and address lifestyle factors that disrupt sleep is crucial.
- Sleep debt results in mental, emotional, and physical fatigue, causing difficulties in daily activities requiring high-level cognitive functions.
- Our awareness of our cognitive and physical deficits resulting from sleep debt often fades with continued sleep deprivation, leading to reduced alertness and functionality.
- Disordered sleep is associated with disease and illness, and the effects range from cellular damage to organ system malfunction. Sleep impacts health and healing not only on the physical level but also on the mental and emotional levels.
- Insomnia is the most common sleep disorder and is associated with lifestyle factors such as poor sleep hygiene and stress. Other common sleep disorders include sleep apnea (obstructive and central) and periodic limb movement disorder (PLMD) like Willis-Ekbom syndrome (aka restless legs syndrome).
- Given that research has shown that lifestyle interventions are essential to achieve a greater quality of sleep, it is vital to pay special attention to our daytime habits relating to caffeine, alcohol, tobacco, eating patterns, light exposure, and exercise:
  - Frequently consumed to combat daytime sleepiness, caffeine leads to poor nighttime sleep by impairing proper sleep induction and regulation of deep sleep. Poor sleep caused by caffeine consumption ultimately worsens daytime sleepiness, leading to a vicious circle.
  - Alcohol, a common sleep aid, may induce sleep but can significantly affect sleep quality. Alcohol also alters the physiology of breathing, which worsens sleep-related breathing disorders.
  - It is crucial to restrict the quantity and schedule the timing of alcohol and caffeine consumption to prevent these substances from disrupting sleep.
  - Nicotine leads to difficulty initiating sleep and increases time spent in light sleep stages by altering the expression of clock genes that regulate the circadian rhythm.
  - Consumption of spicy foods, sugar and dairy, large meals close to bedtime, or excessive calories leads to stimulant effects, making it difficult to fall asleep and stay asleep. This leads to short sleep time and reduced sleep quality. The resultant poor sleep increases unhealthy food cravings through hormonal and neurochemical mechanisms.
  - Blue light exposure from artificial lighting and digital screens close to bedtime reduces sleep onset, REM duration, and overall perception of sleep quality. Blue light exposure also disrupts

the visual system's non-image-forming functions, resulting in melatonin suppression, vigilance, and stimulating mental activity.
- Physical exercise in the daytime promotes restorative sleep by increasing the amount of adenosine in the body, which induces sleep and prolongs the duration of deep sleep stages. Conversely, poor sleep makes individuals less likely to exercise, leading to difficulty falling asleep, staying asleep, and early wake times.

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83 Headache and Lifestyle Medicine

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KEY POINTS

- Headaches are one of the most common and disabling conditions experienced globally.
- The most common primary headaches experienced are migraines, tension headaches, and cluster headaches.
- These various types of headaches can often be triggered by environmental and lifestyle factors.
- Increased levels of inflammatory markers in the body disrupt the body's homeostasis and thereby contribute to increased onset, frequency, and severity of headaches.
- Preventive treatment through lifestyle modifications is one of the most powerful tools to improve the quality of life for patients who experience chronic headaches.
- Leading a healthy lifestyle, exercising regularly, and abstaining from smoking can help prevent and reduce headaches.
- Foods with higher levels of omega-3 such as those from a plant-based diet like nuts, seeds, tofu, Brussels sprouts, and avocado help reduce inflammatory levels in the body
- Secondary headaches are rarer in comparison with primary headaches but include conditions such as brain tumors, cervical spine disorders or injuries, concussions, aneurysms, and meningitis.
- Supplements such as magnesium, riboflavin (B2), melatonin, feverfew, and vitamin D have been shown to be helpful for headache management.
- Management of medical conditions such as hypertension, high cholesterol, and insulin resistance/diabetes may help reduce the frequency and severity of headaches.

83.1 BACKGROUND

Despite headache disorders being one of the most common causes of functional

disability experienced by nearly all ages worldwide, headaches continue to be both underdiagnosed and undertreated throughout the world. In the United States, 35 million individuals annually suffer from migraines alone, an often severe and debilitating type of headache. Migraines affect about 18% of American women and 6% of American men. Women, especially those between 18 and 55 years old, are three times as likely as men to have a migraine.[1]

In comparison, nearly 75% of the population worldwide experienced a headache in the past year alone.[2] To date, we have developed several treatments for the various headache types, yet we have not been able to reduce the prevalence of these conditions tremendously. With headache diagnosis and pharmaceutical treatment being difficult and complicated, the focus on lifestyle change and management becomes all the more necessary, as there is growing evidence that lifestyle intervention can have a profound influence on most headaches.

In general, headaches are delineated into primary headaches, which are not caused by another condition, and secondary headaches, which are caused by other conditions such as brain tumors, aneurysms, meningitis, and or brain and neck injuries. The most common primary headaches are migraines, tension headaches, and cluster headaches. Although we currently have many pharmaceutical treatments for many of the headaches, we have also learned that many of the headaches have a significant lifestyle component that is often not addressed. In this chapter, we have reviewed the extant literature related to lifestyle and headaches and how healthcare providers can incorporate the following recommendations into their practice.

83.2 PRIMARY HEADACHES

The most common types of primary headaches include migraine, cluster headaches, and tension-type headaches.

83.2.1 Migraine

Migraines are the fourth leading cause of all emergency room visits reported in the United States.[3] Migraine headaches typically tend to affect women more than men and can be exacerbated by stress, physical exertion, fluctuations in hormone levels (i.e., use of oral contraceptives or during a woman's menstrual cycle), and certain types of food (dairy, cheese, meat, chocolate). For many patients, migraines can occur either episodically or up to several times per month. In 60% of migraine cases, patients report having a unilateral headache described as a moderate to severe pulsating sensation with accompanying symptoms such as nausea, vomiting, or sensation to light or sound.[4]

83.2.2 Tension-Type Headaches

These are the most common types of headaches and are known to affect women more than men. They are typically

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described as a bilateral, dull constant "band-like" pain and can be triggered by symptoms of anxiety, stressful situations, depression, poor sleep, physical exertion, and poor posture. Patients typically report feeling a tightness in the back of their neck but do not report symptoms of nausea, vomiting, or aura. These headaches can sometimes accompany symptoms of either increased sensitivity to sound or light but usually do not report both (unlike patients with migraines). Oftentimes, tension-type headaches last anywhere from 30 minutes upwards to seven days, with frequencies varying from occasional to daily, and are usually mild to moderate in intensity.[5]

83.2.3 Cluster Headaches

While migraines and tension-type headaches are known to affect predominantly females, cluster headaches affect mostly adult men aged 20–40 years of age. Patients often report experiencing severe, agonizing pain with unilateral or periorbital headaches. These episodes tend to arise within minutes and are usually short with frequent reoccurrence in a "cyclical" pattern, where the headaches can last weeks to months and then go into remission. In some patients, they can have upwards to eight attacks in 24 hours with pain piercing enough to wake them from sleep. Alcohol may be a trigger for these episodes. Other accompanying symptoms to be aware of include ipsilateral nasal congestion or discharge, lacrimation, ptosis, miosis, or conjunctival injection.[6]

83.3 PROPOSED PATHOPHYSIOLOGICAL MECHANISMS

Despite significant advancement in our knowledge regarding the pathophysiology behind headaches, headaches remain a complex set of disorders to treat. For most of history, headaches, especially migraines, were thought to be a form of a vascular disorder where extracranial vessels become dilated leading to the classical throbbing pain experienced by patients. It is only in the last couple of decades that we have learned about the many different mechanisms that could be propagating the different types of headaches.

83.4 Migraines

Recent evidence has illustrated that a cascade of events occurs during a migraine attack. Multiple potential pathways, including those related to channelopathies, vascular anomalies, and a disorder of sensory processing may occur.[7] Part of the process involves triggers, which can sometimes be instigated by environmental and lifestyle factors.

83.4.1 Lifestyle

Headaches can be both a cause and a consequence of an unhealthy lifestyle. Studies have shown that your lifestyle can directly impact the onset, frequency, and severity of headaches, most notably affecting tension headaches and cluster headaches. Three specific unhealthy behaviors can significantly contribute to having headaches: smoking, being overweight, and exercising less than two times per week. In fact, smoking was associated with an 80% increase in migraines, being overweight with a 60% increase in migraines, and an increase of 50% in those who did not regularly exercise at least three to four times per week.[8] All three of these unhealthy behaviors directly promote inflammation in the body, thereby triggering downstream changes in the brain leading to headaches. It is clear that leading a healthy lifestyle, exercising regularly, and abstaining from smoking can help both prevent and reduce headaches.

83.4.2 Central Nervous System

In biology, homeostasis is defined as the tendency to maintain a steady state despite the influence of external factors. Inflammatory changes caused by living a poor lifestyle can directly affect our body's homeostasis due to changes in the hypothalamus (our brain's control center).[9] The elevated levels of various inflammatory markers mediate a propensity for central sensitization.[10] Studies have shown patients with chronic headaches tend to have more elevated levels of various neurotransmitters and neuropeptides such as interleukins and calcitonin gene-related peptide (CGRP) in comparison with the general population.

83.4.3 Treatments of Migraines

83.4.3.1 OTC Treatments

Some examples of non-pharmacologic treatments for migraines include adequate hydration, resting in the dark, meditation and deep breathing exercises, and physical activity. Common over-the-counter (OTC) therapies include acetaminophen, aspirin, or ibuprofen. However, overusing these medications can result in rebound headaches.

83.4.3.2 Triptans

In patients who experience moderate to severe headaches, triptans are one of the medications initially used for abortive treatment. Triptans work as serotonin agonists. Triptans are contraindicated in patients with vascular disease (i.e., heart attack, stroke, uncontrolled hypertension) because of the medication's effects on vasoconstriction.[13]

83.4.3.3 Ditans

A more recent development in the treatment of migraines includes the class of ditans. Ditans are selective 5-HT1F receptor agonists that act on the trigeminal pathway. The vascular effect of this class of medications is still under investigation.[14]

83.4.3.4 Gepants

The newest classes of migraine treatments are the gepants, CGRP receptor antagonists. This class of migraine treatment blocks the activity of the CGRP molecule to bind to its receptor, which helps both abort and reduce how often

migraines occur. Gepants do not cause vasoconstriction, which makes them safe to use in patients who have underlying cardiovascular conditions.[15]

83.4.3.5 Neuromodulation

An alternative to pharmacologic treatment has been non-invasive neuromodulation devices. These devices are placed directly on the skin and cause electrical impulses. They have limited but noteworthy results in the literature.[16]

83.4.4 Preventive Migraine Treatment

Successful preventive treatment provided to migraine sufferers is one of the most powerful tools available to drastically improve their quality of life. When it comes to migraines and most headaches, there are two types of preventive measures, pharmaceutical and lifestyle modifications.

The pharmaceutical treatment approach has been most effective in reducing the frequency and intensity of headaches;[17] however, despite the benefits of preventive migraine treatment, studies have found that compliance to preventive pharmacological treatment is as low as 25%.[18] It must also be noted that in patients who are compliant with preventive medical treatment, medication needs to be trialed. All medications do not work well for everyone and depending on genetics, compliance, and severity of headaches, there is a phase of trial and error that the patient has to go through to find the right fitting medication.

Although there may be significant trial and error associated with finding individualized pharmaceutical treatments for patients, positive lifestyle changes are often directly correlated with the prevention and reduction of headache episodes.[19] Lifestyle changes can be universally applied with a low risk of associated side effects and are also cost-effective. A healthy lifestyle with adequate hydration, regular exercise, stress reduction, and alcohol and smoking cessation can be an incredibly powerful management strategy alongside pharmaceutical treatments for headache sufferers.

83.4.4.1 Preventive Pharmacologic Drugs

Various classes of drugs have been used as a form of preventive pharmacologic treatment for migraines. Among these include the following: antidepressant drugs such as serotonin norepinephrine reuptake inhibitors (venlafaxine) and tricyclic antidepressants (amitriptyline and nortriptyline); antihypertensive drugs such as beta-blockers (propranolol) and calcium channel blockers (verapamil); and antiepileptic drugs such as valproic acid and topiramate, which have been found to have a great side-effect profile. Recent studies have also shown medications such as lisinopril (angiotensin-converting enzyme inhibitors) and candesartan (angiotensin receptor blockers) to be effective in the prevention of headaches.[20] CGRP monoclonal antibodies have also been found to be effective treatments in reducing monthly headaches and may also have a faster onset compared with other oral preventive treatments.

Overall given the challenges with compliance, the potential for side effects of medications, and the phase of trial error to find the right medication, it is important to institute a combination of pharmacological and non-pharmacological treatments (lifestyle modifications) that may be beneficial to the overall health of the patient.

83.4.4.2 Lifestyle

Headaches can be both a cause and a consequence of an unhealthy lifestyle. Studies have shown that one's lifestyle can directly impact the onset, frequency, and severity of headaches. Common culprits such as smoking and lack of exercise have been shown to contribute to increased headache severity and frequency.[21] It is clear that leading a healthy lifestyle, exercising regularly, and abstaining from smoking can help both prevent and reduce headaches.

83.5 TENSION HEADACHES

As mentioned earlier on in the chapter, tension headaches are the most common headaches to occur in most epidemiological studies. These headaches are typically described as a dull ache occurring in a band-like pain around the head.

The most common pharmaceutical medications used to relieve this common headache include NSAIDs (such as ibuprofen and aspirin) or acetaminophen. In patients who tend to have more frequent tension headaches, a prophylactic medication such as amitriptyline may be considered as well; however, certain medications such as triptans and opioids should be avoided in this headache group.[22]

Non-pharmacological therapy for tension-type headaches is focused on addressing the various exacerbating factors for tension headaches. These include but are not limited to poor sleep and diet, stress, anxiety, depression, and head injury. It is important to implement lifestyle modifications such as proper sleep hygiene, a healthy lifestyle, and exercise. Additionally, patients may also consider cognitive behavioral therapy and relaxation training to address psychiatric root causes.

83.6 Cluster Headaches

One of the most painful types of headaches is the cluster headache. Although these are rarer compared with tension headaches, they are often easier to identify due to the classic one-sided, brief, recurring episodes that occur in a cyclical pattern.

Acute episodes can be treated either with triptans or high-flow oxygen therapy; however, medications such as acetaminophen or ibuprofen are typically not recommended as they can lead to overuse headaches. Verapamil may also be considered for prophylactic treatment.

Various lifestyle changes can help with cluster headache prevention, these include smoking cessation, limiting alcohol, and adhering to a regular sleep routine.[23]

83.7 SECONDARY HEADACHES

Headaches that occur due to an underlying medical condition are known as secondary headaches. These headaches are rarer in comparison to primary headaches but include conditions such as brain tumors, cervical spine disorders or injuries, concussions, aneurysms, and meningitis. Treatment of secondary headaches requires mostly medical management as opposed to lifestyle modification.

83.7.1 Tumors

Any space-occupying lesions in the brain, such as brain tumors, typically present as a dull headache that seems to be side-locked, i.e., the location of the pain tends not to move, unlike primary headache disorders. Over time, patients will experience symptoms of increased pressure that may significantly worsen in weeks to months.[24]

83.7.2 Aneurysms

The clinical presentation of brain aneurysms is highly variable. About one-third of those with aneurysms report having sudden, severe headaches, which present as either dull, sharp, or throbbing.[25] Prevention and minimizing the risk or extension of aneurysms centers around implementing various lifestyle factors. Studies have shown that limiting tobacco products, consuming a healthy diet, regular exercise, and managing blood pressure (low salt diet), cholesterol (reducing saturated fats), and diabetes can play a positive role in prevention. Imaging modalities such as CT scans or MRI can be used to screen for brain aneurysms. Early detection is absolutely imperative in preventing further extension along with utilizing proper lifestyle changes.

83.7.3 Meningitis

Meningitis is a disease due to inflammation of the meninges (fluid and membranes in the brain and the spinal cord). This inflammatory disease can occur as a result of a viral, bacterial, or fungal infection. It typically presents with a triad of symptoms: fever, headache, and neck stiffness/rigidity. Vaccines are widely available to prevent the most common types of meningococcal infections. Proper hygiene, such as regular hand washing, can also help further reduce the risk of meningitis.[26]

83.7.4 Cervical Spine Disorders/Injuries

Cervicogenic headaches are headaches that occur due to problems in the cervical spine. They can be caused by conditions such as disk degeneration or arthritis. Typically, these headaches are accompanied by neck pain and can also appear similarly to migraine headaches. Injuries from sports or motor vehicle accidents can also contribute to these types of headaches. Avoiding injury to the head and neck can help prevent cervicogenic headaches.[27]

83.8 Lifestyle Modifications in General

Although there is evidence that headaches have been present throughout history, there is also evidence that the prevalence and influence of headaches have significantly increased in our modern life. Headaches are not only occurring more frequently but are also occurring in younger patients when compared with the past.[28] This may be due to more stringent epidemiological studies or because we are now looking more for people with headaches. Factors such as increasing stress and anxiety, new physical stressors, lack of physical activity, poor sleep, inadequate nutrition, and increased screen time are all contributing to all types of headaches.[29]

Lifestyle modifications such as improving sleep quality, obtaining proper nutrition, limiting alcohol and caffeine, participating in regular physical activity, and reducing digital technology have been found to be effective in migraine management. Our increased use of technology has significantly contributed to the rise of headache incidence. Studies have shown that more than eight hours of computer use in adults and over four hours of video game play in children have been correlated with headache frequency.[30]

83.8.1 Sleep

Patients with migraines can also modify their triggers through lifestyle modifications. According to the *Cleveland Clinic Journal of Medicine*, SEEDS (sleep, exercise, eat, diary, and stress) is an evidence-based structured approach to help patients manage migraines.[30] In regard to sleep, patients are recommended to optimize both the quality and the amount of sleep they obtain. Most adults require at least eight hours of sleep per night and are recommended to sleep in a dark, cool (around 68°F), and quiet room. Our body produces melatonin (a chemical our brain uses to help us fall asleep), which increases in levels when it starts to become dark. If we regularly keep bright lights on until we sleep, this resets the circadian rhythm of melatonin and inhibits melatonin production. To help maintain an adequate circadian rhythm, dimming the lights in the evening and following good sleep hygiene have been found to be helpful.

Patients with primary headache disorders have been found to experience sleep comorbidities such as obstructive sleep apnea (OSA) or insomnia, which can further exacerbate headaches. Studies have shown that 29% of individuals with OSA experience awakening headaches, 15% experience tension-type headaches, and 8% experience migraines.[31] OSA is treated with the use of continuous positive airway pressure (CPAP) machines, which often results in better sleep quality, thereby resulting in reduced frequency, duration, and pain associated with migraines.[32]

83.8.2 Exercise

In patients with migraines, levels of beta-endorphins were found to be decreased in their cerebrospinal fluid compared

with the general population; however, activities such as exercise can be a way to combat these lower levels. Most patients are recommended to exercise 30–60 minutes at least three to five times per week. Engaging in exercise has been found to be beneficial in patients with headaches due to the natural release of endorphins causing pain relief, thereby resulting in decreased frequency and severity of headaches. On the other hand, a sedentary lifestyle with minimal physical activity has been found to be associated with migraines.[33]

83.8.3 Nutrition

Diet can play a significant role in both the prevention and treatment of headaches. Studies have shown that eating regularly along with maintaining a balanced healthy diet (with plenty of fruits and vegetables) can help reduce headaches. In particular, patients who followed a low-fat diet reported decreased medication use and also had less frequent headache episodes. Additionally, it is important to eat consistently as skipping meals can cause the body to experience stress due to the spikes or sudden drop in glucose levels, which can be a risk factor for headaches. Consuming a high-fiber, plant-based/predominant, low-fat diet was also found to reduce the severity of headaches in women who experience menstrual-related headaches.[34]

It is no surprise that the average American diet promotes an inflammatory state. According to the WHO, approximately 42% of adults in the United States are obese. It has been thought that a hypothetical relationship may exist between obesity and headaches. In patients who suffer from obesity, headaches may be attributed to higher levels of systemic inflammation (i.e., increased levels of CGRP) due to increased body fat percentage or irregular hypothalamic function. In these patients, focusing on dietary changes and weight loss has been found to decrease levels of inflammation, thereby decreasing the frequency and severity of headaches.[35]

Although there is no specific recommendation for a "migraine diet" per se, various studies have shown that certain diets, such as the modified Atkins diet and the ketogenic diet, may play a role in decreasing levels of neuroinflammation, decreasing CGRP levels, improving mitochondrial function, and offering neuroprotection. Also, improving the balance of omega-3 and omega-6 has been found to show a reduction in the levels of inflammatory markers, which may reduce and prevent the onset of headaches in patients.[35] Foods with higher levels of omega-3 include fish, nuts, seeds, tofu, Brussels sprouts, and avocado. In some patients, certain foods can trigger headaches such as chocolate, caffeine, artificial sweeteners, nitrate-containing meats, processed meats, beans, and dairy. Patients are often recommended to keep a headache diary to help monitor which foods, if any, may be triggers for their headaches. Overall, a healthy lifestyle is essential for proper headache management.

83.9 STRESS MANAGEMENT

According to the American Migraine Foundation, stress is a significant inducing factor in approximately 70% of patients who experience migraines. In this patient population, it is vital to implement lifestyle changes for stress reduction. For example, studies have shown that deep breathing exercises, relaxation techniques, and social support can be used to provide stress relief and thereby alleviate headaches. These lifestyle changes can be significantly impactful in improving the quality of life for headache sufferers.[36]

83.9.1 Hydration

A vital component of maintaining a healthy lifestyle is achieving adequate daily hydration. Headaches can be triggered by temperature changes and drinking enough water can help reduce the stress experienced by the body. An average healthy adult requires about eight 8-ounce glasses of water per day, this is often referred to as the "8 × 8" rule.[37]

83.10 MANAGEMENT OF MEDICAL CONDITIONS

Studies have shown that there is a high prevalence of hypertension in patients with both episodic headaches and those with chronic headaches. According to the International Classification of Headache Disorders, headaches are one of the most common symptoms reported in patients with hypertension.[38] Additionally, patients with headaches, especially migraines, are at an increased risk of developing hypertension.[39] Additionally, high cholesterol is another medical condition that has been found to have an association with headaches.[40] In fact, some studies have shown that patients with high low-density lipoprotein (LDL) levels tend to report experiencing more severe migraines in comparison with those with lower LDL levels. Other metabolic conditions such as diabetes have been shown to be associated with more headaches as well, especially during hypoglycemic states. Insulin resistance has also been shown to increase migraine episodes due to increased levels of inflammatory markers like free fatty acids and lipids in the blood (LDL). [41]

83.10.1 Supplements

Herbal and nutritional supplements have also been used for the prevention of migraine. More recent systematic reviews have shown to support the use of magnesium and riboflavin (vitamin B2). The herb feverfew, which is also a commonly used supplement, was found to have more mixed and inconclusive evidence.[42] Magnesium and feverfew have been studied to be helpful in the treatment of the aura phase of the migraine cycle. Currently, the use of melatonin and vitamin D is being studied for migraine prevention. In a randomized controlled trial, the combination of simvastatin and vitamin D was found to reduce the frequency of headaches in patients.[43] Another study was found to show the use

of the synthetic cannabinoid nabilone to be beneficial in the treatment of patients with chronic migraines and rebound headaches due to medication overuse.[44] Another herbal supplement found to be helpful in preventing migraines is butterbur, which is derived from the leaves of *Petasites japonicus*. This herbal supplement was given a level A recommendation by the American Headache Society, but due to its adverse effects resulting in liver toxicity, it was removed from the US market.

83.11 SUMMARY

Headaches are one of the most common reasons for emergency room visits in the United States and one of the ten most common causes of functional disabilities worldwide. Although we now have a better understanding of some of the causes and currently have an armamentarium of treatments for these headaches, unfortunately, there is not as much effort being applied to preventive aspects of these headaches. There is tremendous data that for most of these headaches, preventive measures may have a profound effect on the incidence, prevalence, and burden impact. In order to reduce the burden of those suffering from headaches, it is imperative we close any knowledge gaps by educating others on the influence of lifestyle factors. Nutrition, exercise, stress reduction, sleep optimization, and better medical and lifestyle management of chronic diseases such as diabetes, high blood pressure, and high cholesterol, as well as reduction and better yet elimination of alcohol and cigarette use, can profoundly aid in our fight against onset, maintenance, and reversal of these headaches.

CLINICAL APPLICATIONS

Headaches are underdiagnosed and undertreated throughout the world. Although we have developed several treatments for various headache types, we have not been able to reduce the prevalence of these conditions. In fact, the prevalence and influence of headaches have significantly increased in our modern life. Increasing stress and anxiety, new physical stressors, lack of physical activity, poor sleep, inadequate nutrition, and increased screen time have all significantly contributed to the increased prevalence of headaches worldwide.

Successful preventive headache treatment is one of the most powerful tools available to drastically improve these patients' quality of life. Studies have shown that one's lifestyle can directly impact the onset, frequency, and severity of headaches. Leading a healthy lifestyle, exercising regularly, and abstaining from smoking and alcohol can help both prevent and reduce headaches.

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84 Stroke and Vascular Brain Diseases

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KEY POINTS

- Stroke is the fourth leading cause of mortality in the United States and the leading cause of disability, however, optimal strategies, including lifestyle factors, can prevent up to 80% of strokes.
- A myriad of modifiable risk factors such as hypertension, hyperlipidemia/atherosclerosis, diabetes, atrial fibrillation (AF), smoking and other drug use, alcohol, diet, and physical activity need to be addressed and optimized to lower the chance of developing strokes.
- Effective strategies, including the use of novel oral anticoagulants for AF, antiplatelet therapy, and intensive lowering of atherosclerosis risk factors, can serve as both primary and secondary prevention of strokes.
- Adherence to DASH, Mediterranean, and prudent dietary patterns reduced the risk of stroke, whereas the Western dietary pattern has been associated with increased stroke risk. Low-fat diets have not been found to have a protective effect.

84.1 INTRODUCTION

Stroke places a tremendous burden on the healthcare system worldwide. In the United States, it is the fourth leading cause of mortality, with an estimated 795,000 incidences of stroke each year. It is one of the leading causes of serious disability.[1,2] According to the Global Burden of Disease, Injuries, and Risk Factors Study (GDB 2019), stroke was ranked as the most common cause of death after ischemic heart disease.[3] The global burden of stroke based on disability-adjusted life years lost and the absolute number of people affected every year is still on the rise, with the highest burden seen in low-income and middle-income countries. As age is one of the main risk factors for stroke, and with the elderly population expected to double to more than 70 million by the year 2030, reducing the incidence of stroke has become a central healthcare policy concern.[4] Treatment costs associated with chronic disease constitute three-fourths of US healthcare expenditures, and of this, $400 billion per year is spent on heart disease and stroke.[5] It is, thus, imperative to identify and implement healthcare policies that can reduce the risk of stroke.

Implementing a national stroke prevention approach can serve as a complementary strategy to reduce the increasing global burden of stroke and subsequent disability.[6] Risk factors associated with stroke have been divided into two main categories: non-modifiable and modifiable. Advanced age, gender, race, and genetic susceptibility are the most prominent non-modifiable risk factors, while lifestyle risk factors such as diet, exercise, and use of tobacco and alcohol are considered modifiable risk factors.[7] By addressing the modifiable risk factors, it is estimated that stroke prevalence can be reduced by as much as 80%.[6] Thus, primary prevention of stroke takes central importance. Substantial research has been done over the past decades to advance the understanding of stroke mechanisms and therapies. Despite a large body of data supporting specific pharmaceutical agents, such as antiplatelets, antithrombotics, and statins, as preventive measures for stroke, diet remains a focus of extensive epidemiological research for stroke prevention. This chapter reviews major advances in stroke prevention in the last few years, pertaining to the modifiable medical and behavioral stroke risk factors.

84.2 PATHOPHYSIOLOGY OF STROKE

The brain microcirculation ensures the proper distribution of oxygen and glucose in tissue while also removing the byproducts of cellular metabolism. The delicate endothelial monolayer of cerebral blood vessels, as part of its normal function, inhibits platelet aggregation and thrombosis to ensure smooth blood flow. Stroke is a devastating process caused by impaired blood flow that results in irreversible damage to the brain by disturbing the cerebral microcirculation. Within seconds after the start of cerebral ischemia, there is a loss of aerobic metabolism causing local acidosis, dysfunction of the ion channels causing accumulation of sodium and calcium within the cell leading to cell swelling, and a release of excitotoxic neurotransmitters, lipase, and proteases, all culminating in neuronal apoptosis.[8]

84.3 MODIFIABLE RISK FACTORS

84.3.1 Hypertension

Hypertension is the most important modifiable risk factor for both cerebral infarction and intracerebral hemorrhage (ICH). Per the most recent guidelines, hypertension is defined as a blood pressure greater than 130/80 mm Hg. Studies have consistently demonstrated a strong, continuous, and independent positive relationship between blood pressure (BP) and stroke, such that the higher the BP, the

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greater the risk of stroke throughout the usual range of BP, including the non-hypertensive range.[9–13]

Though the awareness and subsequent treatment of hypertension in the United States has increased over the years, the prevalence of hypertension has remained stable at approximately 29%.[14] Regular medical check-ups and screening are essential in identifying hypertension early and initiating treatment with lifestyle interventions and medications in order to prevent progression and minimize future complications. Other complementary strategies such as population-wide approaches to reduce BP have also been endorsed as more effective than individual approaches for the detection and treatment of high BP, that is, the high-risk approach.[12] There is strong evidence that supports the treatment of hypertension to a goal of less than 150/90 mmHg in those aged ≥60 years and to a goal of diastolic BP less than 90 mmHg in those aged 30–59.[15] Blood pressure control is associated with a lower risk of stroke and cardiovascular events and generally improves health outcomes, especially in older adults, however, in certain high-risk patients, lower BP goals (SBP <120) were associated with hypotension, syncope, increased medication burden, and at times an increase in all-cause mortality.[16–21] Therefore, the management and treatment of hypertension in any individual should be tailored according to their characteristics and the comorbidity burden.

The management of hypertension for secondary stroke prevention is probably the most important intervention and has been studied repeatedly in the past. Studies have shown antihypertensive medication may be initiated or resumed after an acute ischemic stroke within the first 24 hours for patients who have pre-existing hypertension, and who are neurologically stable. For patients who have already experienced a stroke or TIA, treatment to an SBP goal <130 is recommended to decrease risk of recurrent stroke.[22–28] Current guidelines show no definitive evidence supporting specific classes of antihypertensive therapy over others as a means to prevent stroke. Further hypothesis-driven trials are needed to delineate the efficacy of individual agents in specific subpopulations.

84.3.2 Hyperlipidemia and Elevated CRP

Lowering blood cholesterol in patients at elevated cardiovascular risk has been a significant strategy in stroke prevention.[29–31] Several studies have discovered the benefits of statins in reducing stroke risk as both primary and secondary prevention strategies.[32–34] In addition to elevated cholesterol and LDL, high-risk CRP has also been found to predict risk of ischemic stroke, and in patients with a history of stroke, could serve as a potential biomarker to predict risk of recurrent stroke.[35–38] In healthy patients, without a prior history of stroke, there appears to be a benefit in starting statin if hs-CRP levels are found to be elevated despite normal LDL levels.[39] Although high levels of cholesterol and low-density lipoprotein predispose to ischemic stroke (especially of atherosclerotic mechanism), low levels have been associated with an increased risk of intracerebral hemorrhage.[40]

84.3.3 Type 2 Diabetes

Diabetes is a known risk factor for stroke, especially in women and patients younger than 65 with a 74% increased rate if the duration of diagnosis is longer than three years.[41–44] Studies have shown that a hemoglobin A1c goal of less than 7% is optimal for stroke prevention, however, below that does not confer an inverse relationship in terms of stroke prevention.[45]

84.3.4 Atrial Fibrillation

Atrial fibrillation is a common cause of disabling stroke, resulting from embolism of stasis-precipitated thrombi formed in the left atrium, left atrial appendage, or both.[46] There have been advances including the development of new anticoagulants, evidence of the benefits of long-term monitoring, and appreciation of the potential role of atrial disease in cryptogenic stroke, even in the absence of AF. These new anticoagulants can be broadly divided into the direct factor Xa inhibitors, such as rivaroxaban, edoxaban, and apixaban, and the direct thrombin inhibitors, particularly dabigatran, and have demonstrated greater efficacy as well as minimal side effects of bleeding when compared with warfarin.[47–56] One of the challenges in the care of patients with cryptogenic strokes and TIA is the detection of covert paroxysmal AF, which constitutes about 30% of all ischemic strokes.[57,58] Extended cardiac rhythm monitoring of up to 30 days via cardiac telemetry or insertable cardiac monitor in such patients has revealed evidence of AF in a significant proportion of patients, with longer periods of monitoring increasing the yield.[58–60] There is no convincing evidence that anticoagulation protects against recurrent stroke among patients without a definite source of cardiac embolism or in cases of cryptogenic stroke. However, large aortic arch atheroma and complex plaques were associated with a higher risk of stroke over a period of two years.[61] N-terminal pro-B-type natriuretic peptide (NTproBNP) is a serum biomarker associated with cardiac dysfunction that predicts the development of AF and studies have shown that in patients with elevated levels above the 95th percentile who were randomized to warfarin had a reduction in their risk of stroke or death compared with patients allocated to aspirin.[62–64] Further trials of the use of NTproBNP and other biomarkers associated with AF in the risk stratification of patients with cryptogenic stroke are needed.

84.3.5 Chronic Kidney Disease

Chronic kidney disease is an independent risk factor for stroke. A TA analysis of 21 studies has shown that an eGFR<60 ml/min, high albuminuria, and proteinuria are associated with an increased risk of stroke.[65–70] This is especially true in patients requiring dialysis. In a large study in

Taiwan comprising nearly 80,000 dialysis patients, it was found that there was a nearly three-fold increase in ischemic stroke and a six-fold increase in hemorrhagic stroke.[71] Another study titled Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) revealed a nearly ten-fold increase in stroke incidence in dialysis patients when compared with the general population.[72] However, it has also been found that among patients with CKD, there are higher instances of prior strokes, atrophy, and white matter disease when compared with the general population.[73–80] In CKD patients especially, control of blood pressure is one of the most important modifiable risk factors in primary and secondary prevention of strokes.[81]

84.3.6 Obstructive Sleep Apnea

Sleep apnea is becoming an increasingly common condition due to the increased prevalence of obesity and is an established risk factor for stroke.[82–87] It is common among post-stroke patients as well. Managing and treating this condition can serve as both primary and secondary prevention of stroke.[82] Sleep apnea drives a pathological increase in sympathetic activity, which in turn causes the development of or worsens already existing secondary stroke risk factors such as hypertension, dyslipidemia, cardiac dysrhythmias, and glucose tolerance.[83] Therefore, tools such as the Epworth Sleepiness Scale, Berlin Questionnaire, or STOP-Bang can be used to screen patients in the clinical setting to evaluate for possible sleep apnea.[88–90] In patients found to have sleep apnea, weight loss through healthy diet and exercise must be encouraged along with avoidance of provoking factors such as alcohol, smoking, and hypnotic drugs. Treatment of sleep apnea with positive airway pressure ventilation has been shown to improve patient's cognition, neurological function, and disabilities faced post-stroke. Other strategies such as surgical intervention may be employed to reduce the risk of future vascular events.[91–94]

84.4 DIET

There is an increasing interest in the relationship between diet and stroke. However, owing to intrinsic methodological limitations of diet research, there is a trend to study dietary patterns as opposed to single macro- or micronutrients.

84.4.1 Fruits and Vegetables

There is ample evidence that a diet high in fruits and vegetables is associated with reduced stroke risk in a dose-response manner.[95–98] Higher consumption of plant-based foods, namely cruciferous vegetables, green leafy vegetables, citrus fruits, vitamin C-rich fruits, and whole grains reveal an inverse relationship with and incidence of cerebrovascular disease, ischemic stroke, and IH, however, this association was not seen with potatoes and legumes.[95–97,99,100–103] After adjustment for age, sex, BMI, family history of stroke, and other confounding factors intakes of total fat, plant fat, calcium, potassium, vitamin B1, vitamin B2, vitamin B6, niacin, and folate were negatively correlated with the risk of stroke.[103]

84.4.2 Fish

There have been several studies ranging from prospective cohort and case-control studies that have assessed the relationship between fish intake and stroke risk. Overall, the relationship is not entirely clear, however, studies have shown that overall a dose-dependent relationship exists between fish consumption and overall ischemic stroke risk at higher quantities of greater than five times per week, however, in mild quantities of a few servings per month, there appeared to be some protection against first-time stroke, mostly seen in females and the Black population, especially with the intake of fatty fish such as tuna or broiled fish.[104–109] This may be likely due to the atheromatous plaque-stabilizing quality of omega-3 fatty acids and their putative anticoagulant effects.[110,111] However, the anticoagulant effect can only be observed at high levels of fatty fish intake, which may ultimately lead to an increased risk of hemorrhagic stroke but no significant correlation was found between fish consumption and hemorrhagic stroke.[112] The risk of ischemic stroke mainly increased with the consumption of fried and salted fish, with effects seen greater in men.[114]

84.4.3 Meats, Eggs, and Dairy

Animal products, mainly eggs, dairy, and meats, have gathered attention due to concerns that they may increase stroke risk.

The relationship between egg consumption and stroke is of interest due to the presence of both potentially harmful constituents (cholesterol) and healthful nutrients (B vitamins, folate, and monounsaturated fatty acids) in this food. Multiple large prospective studies have examined this relationship and have found no association between stroke at any level of intake, after adjustment for age, gender, BMI, smoking, high blood pressure, diabetes, serum cholesterol, race/ethnicity, and educational status.[115–117]

Milk consumption was not associated with incident stroke mortality. As compared with subjects who consumed milk below the medium intake, those who drank milk at or above the medium intake were at lower risk of ischemic stroke after adjustments were made for age, smoking, total energy, and social class.[118] Although, compared with milk drinkers, non-milk drinkers were more likely to drink alcohol.[119] Whole-milk intake was associated with an increased risk of intracranial hemorrhage and yogurt intake with an increased risk of subarachnoid hemorrhage. The highest quintile of cream intake was associated with a slight decrease in cerebral infarct risk and intracranial hemorrhage, yet no association was found for total dairy intake, ice cream, cheese, low-fat milk, butter, or sour milk and stroke risk[120]

Consumption of meat with a frequency greater than four times per week was positively correlated with risk of all strokes as well as first-incident strokes.[121] However, some preliminary evidence suggests that specific amino acids, such as taurine and arginine, found in animal protein may modulate vasoactivity, resulting in reduced blood pressure.[122] Therefore, low intakes of animal fat and protein may have a stronger association with intracranial hemorrhage as compared with ischemic stroke. Increased risk of intracranial hemorrhage has been observed among women who consume low levels of animal protein and saturated fat, with the latter among hypertensive women only.[123]

84.4.4 Soy

Soy provides an abundance of nutrients including fiber, antioxidants, and phytochemicals and is an especially important food group in the vegetarian food guide pyramid.[124,125] Soy isoflavones can act as antioxidants, reducing the formation of oxidized lipoproteins like low-density lipoproteins. Several studies have examined the relationship between soy and stroke. The highest tertiles of intake of dried soybeans, tofu, soymilk, and total soy foods were each associated with a significantly reduced risk of stroke after adjustment for confounders, as compared with the lowest tertiles of consumption.[126] A protective effect of soy and isoflavone intake against risk of ischemic stroke and myocardial infarction (MI) has also been observed. Evaluation of soy and isoflavone intake revealed a strong inverse association between risk of stroke and MI in women, primarily postmenopausal women, with consumption five times per week, as compared with zero to times per week. However, a weak inverse association was identified between consumption of miso soup, beans, and isoflavones and CVD mortality among men.[127]

84.4.5 Whole Grains

The relationship between grain intake and stroke has been studied. A significant inverse relationship between whole-grain consumption and ischemic stroke risk was observed across all quintiles of intake, which remained unchanged after adjustment for other CVD risk factors.[128] However, no association between total grain intake and incidence of ischemic stroke risk was observed.[129]

84.4.6 DASH Diet

The DASH diet, which emphasizes a high intake of fruits, vegetables, grains, low-fat dairy products, nuts, chicken, and fish and a low intake of red meat, sweets, and refined carbohydrates, has demonstrated great efficacy in reducing blood pressure and low-density lipoproteins, which are known risk factors for CVD.[130] Higher adherence to the DASH diet was significantly associated with reduced risk of stroke.[131]

84.4.7 Mediterranean Diet

The Mediterranean diet has been touted for its health benefits and has been found to decrease risk of vascular deaths, myocardial infarction, and stroke in a dose-dependent manner.[131–134] The Mediterranean diet has also been shown to be effective in reducing risk and mortality for a number of chronic diseases including CVD, cancer, and neurodegenerative disease.[135] It is consistent with the American Heart Association's dietary guidelines, as it is high in fruits, vegetables, monounsaturated fat, fish, whole grains, legumes, and nuts, and recommends moderate alcohol consumption and a low intake of red meat, saturated fat, and refined grains.

84.4.8 Other Dietary Patterns

Research on low-fat diets, particularly low trans fats and cholesterol, and replacing saturated fats with polyunsaturated and monounsaturated fats, have demonstrated reduced risk of cardiovascular disease, however, there was no statistical association with specific types of fat (total, animal, vegetable, saturated, monounsaturated, polyunsaturated, and trans fat) and stroke risk.[134–137]

84.5 EXERCISE

Physical inactivity has been proven as a risk factor for stroke and it has been demonstrated that moderate to vigorous intensity aerobic exercise for at least 30 minutes, three to four times a week can cut the incidence of stroke.[138–140] Multiple trials have been able to demonstrate the protective effects of physical activity for both men and women. In the Northern Manhattan Study, individuals in the upper quartile of increased level of physical activity had lower risk of silent brain infarcts, compared with those who did not exercise.[141] A preliminary study of the California Teachers Study Cohort, postmenopausal women on hormone therapy who exercised moderately to strenuously in the three years before enrollment had a 20% reduced risk of stroke; physical activity appeared to counteract the high risk of stroke associated with hormone therapy.[142]

84.6 SMOKING

Smoking has been strongly associated with a two to four times increased incidence of stroke, worse outcomes post-stroke, and increased risk of recurrent strokes.[143,144] This relationship has not been established for ICH, perhaps owing to the small sample size of patients in that group.[144] Exposure to environmental tobacco smoke (passive cigarette smoke, or "secondhand" tobacco smoke) is an established risk factor for heart disease.[145] One way to reduce the risk of stroke is by a combination of counseling and medication, including medications such as nicotine patches, bupropion, and varenicline.[143] Recent observational studies provide evidence that smoking bans in communities can

reduce the risk of stroke. After Arizona enacted a statewide ban on smoking, for example, there was a 14% reduction in strokes in counties that had not previously had a ban in place.[146]

84.7 ALCOHOL USE

Studies showing the relationship between alcohol and stroke risk have revealed somewhat of a protective effect with low intake of alcohol (one drink per day for women, two or fewer drinks per day for men), however, it is not recommended to start drinking alcohol for stroke prevention if previously abstinent.[147] There is also a dose-dependent relationship between alcohol consumption and risk for hemorrhagic stroke.[148,149]

84.8 SUMMARY

Stroke is a devastating condition that is one of the leading causes of disability in the United States and abroad. Although this condition can be managed with acute treatments and secondary prevention, an increasing amount of evidence through recent research shows that there is potential to drastically decrease the incidence of stroke by over 80% with lifestyle factors alone. In addition to managing traditional stroke risk factors such as hypertension, diabetes, hyperlipidemia, chronic kidney disease, and sleep apnea, research has shown tremendous benefit in lifestyle changes through healthy diets such as DASH, the Mediterranean diet, and plant-based diets which have been shown to decrease stroke risk. Regular exercise, abstinence from smoking, and limited quantities of alcohol have also been strategies for stroke prevention. Moving forward, it is imperative that health policy and public health facilities put a larger amount of focus on the prevention of stroke through lifestyle management.

CLINICAL APPLICATIONS

Modifiable Risk Factor	Summary of Findings
Hypertension	• There is a strong, continuous, and independent positive relationship between blood pressure (BP) and stroke.[9-13] • Regular medical check-ups and screening are essential in identifying hypertension early and initiating treatment with lifestyle interventions and medications in order to prevent progression and minimize future complications. • After a patient suffers from a stroke or TIA, treatment to a SBP goal <130 is recommended to decrease risk of recurrent stroke.[22–28] • Current guidelines show no definitive evidence supporting specific classes of antihypertensive therapy over others as a means to prevent stroke.
`Hyperlipidemia	• Lowering blood cholesterol in patients at elevated cardiovascular risk has been a significant strategy in stroke prevention.[29–31] • Several studies have discovered the benefits of statins in reducing stroke risk as both a primary and secondary prevention strategy.[32–34] • In addition to elevated cholesterol and LDL, high-risk CRP has also been found to predict risk of ischemic stroke, and in patients with a history of stroke, could serve as a potential biomarker to predict risk of recurrent stroke.[35–38] • In healthy patients, without a prior history of stroke, there appears to be a benefit in starting statins if hs-CRP levels are found to be elevated despite normal LDL levels.[39] • Although high levels of cholesterol and low-density lipoprotein predispose to ischemic stroke (especially of atherosclerotic mechanism), low levels have been associated with an increased risk of intracerebral hemorrhage.[40]
Type 2 diabetes mellitus	• Studies have shown that a hemoglobin A1c goal of less than 7% is optimal for stroke prevention, however, below that does not confer an inverse relationship in terms of stroke prevention.[45]
Atrial fibrillation	• Factor Xa inhibitors and direct thrombin inhibitors have demonstrated greater efficacy and decreased risk of bleeding when compared with warfarin.[47–56] • [56]Extended cardiac rhythm monitoring of up to 30 days via cardiac telemetry or insertable cardiac monitor has revealed evidence of AF in a significant proportion of patients, with longer periods of monitoring increasing the yield.[58–60] • There is no convincing evidence that anticoagulation protects against recurrent stroke among patients without a definite source of cardiac embolism or in cases of cryptogenic stroke. • Large aortic arch atheroma and complex plaques were associated with a higher risk of stroke over a period of two years.[61] • N-terminal pro-B-type natriuretic peptide (NTproBNP) levels predict the development of atrial fibrillation and studies have shown that patients with elevated levels above the 95th percentile who were randomized to warfarin had a reduction in their risk of stroke or death compared with patients allocated to aspirin.[62–64]
Chronic kidney disease	• Chronic kidney disease is an independent risk factor for stroke, especially in patients dependent on dialysis.[71] • An eGFR<60 ml/min, high albuminuria, and proteinuria are associated with an increased risk of stroke.[65–70] • Control of blood pressure is one of the most important modifiable risk factors in primary and secondary prevention of strokes in patients with CKD.[81]

Obstructive sleep apnea	• Management and treatment of sleep apnea can serve as both primary and secondary prevention of stroke.[82] • Tools such as the Epworth Sleepiness Scale, Berlin Questionnaire, or STOP-Bang can be used to screen patients in the clinical setting to evaluate for possible sleep apnea.[88–90] • In patients found to have sleep apnea, weight loss through healthy diet and exercise must be encouraged along with the avoidance of provoking factors such as alcohol, smoking, and hypnotic drugs. • Treatment of sleep apnea with positive airway pressure ventilation has been shown to improve patient's cognition, neurological function, and disabilities faced post-stroke.[82] • Other strategies such as surgical intervention may be employed to reduce the risk of future vascular events.[91–94]
Diet	• Higher consumption of plant-based foods, namely cruciferous vegetables, green leafy vegetables, citrus fruits, vitamin C-rich fruits, and whole grains reveal an inverse relationship with and incidence of cerebrovascular disease, ischemic stroke, and IH, however, this association was not seen with potatoes and legumes.[95–97,99,100–103] • Intakes of total fat, plant fat, calcium, potassium, vitamin B1, vitamin B2, vitamin B6, niacin, and folate were negatively correlated with the risk of stroke.[103] • The relationship between fish consumption and stroke risk is unclear. A dose-dependent relationship has been shown to exist at higher quantities of greater than five servings per week, however, in mild quantities of a few servings per month, there appeared to be some protection against first-time stroke mostly seen in females and the Black population, especially with the intake of fatty fish such as tuna or broiled fish.[104–109] The risk of ischemic stroke mainly increased with consumption of fried and salted fish, with effects seen greater in men.[114] • Studies have found no association between stroke at any level of egg consumption after adjustment for age, gender, BMI, smoking, high blood pressure, diabetes, serum cholesterol, race/ethnicity, and educational status.[115–117] • Milk consumption was not associated with incident stroke mortality. Whole-milk intake was associated with increased risk of intracranial hemorrhage and yogurt intake with an increased risk of subarachnoid hemorrhage.[120] • The highest quintile of cream intake was associated with a slight decrease in cerebral infarct risk and intracranial hemorrhage, yet no association was found between total dairy intake, ice cream, cheese, low-fat milk, butter, or sour milk and stroke risk.[120] • Consumption of meat with a frequency greater than four times per week was positively correlated with risk of all strokes as well as first-incident strokes.[121] • Some preliminary evidence suggests that specific amino acids, such as taurine and arginine, found in animal protein, may modulate vasoactivity, resulting in reduced blood pressure.[122] Therefore, low intakes of animal fat and protein may have a stronger association with intracranial hemorrhage as compared with ischemic stroke. • Increased risk of intracranial hemorrhage has been observed among women who consume low levels of animal protein and saturated fat, with the latter among hypertensive women only.[123] • The highest tertiles of intake of dried soybeans, tofu, soymilk, and total soy foods were each associated with a significantly reduced risk of stroke after adjustment for confounders, as compared with the lowest tertiles of consumption.[126] • A protective effect of soy and isoflavone intake against risk of ischemic stroke and myocardial infarction (MI) has also been observed in women, primarily in postmenopausal women.[127] • A significant inverse relationship between whole-grain consumption and ischemic stroke risk has been observed but the same was not seen with total grain intake.[128,129] • Higher adherence to the DASH diet was significantly associated with reduced risk of stroke.[131] • The Mediterranean diet has been found to decrease risk of vascular deaths, myocardial infarction, and stroke in a dose-dependent manner.[131–134] • There was no statistical association between specific types of fat (total, animal, vegetable, saturated, monounsaturated, polyunsaturated, and trans fat) and stroke risk.[134–137]
Exercise	• Physical inactivity has been proven as a risk factor for stroke and it has been demonstrated that moderate to vigorous intensity aerobic exercise for at least 30 minutes, three to four times a week can cut the incidence of stroke.[138–140]
Smoking	• Smoking has been strongly associated with a two to four times increased incidence of stroke, worse outcomes post-stroke, and increased risk of recurrent strokes.[143,144] • A combination of counseling and medication, including medications such as nicotine patches, bupropion, and varenicline, is a strategy to decrease stroke risk.[143]
Alcohol	• There is somewhat of a protective effect against stroke with low intake of alcohol (one drink per day for women, two or fewer drinks per day for men), however, it is not recommended to start drinking alcohol for stroke prevention if previously abstinent.[147] • There is also a dose-dependent relationship between alcohol consumption and risk for hemorrhagic stroke.[148,149]

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85 Alzheimer's Disease
Pathophysiology and Prevention

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KEY POINTS

- Alzheimer's disease affects people of all ethnicities, all over the world. It is the fourth leading cause of morbidity and mortality globally and creates a huge social and financial burden on worldwide healthcare systems.
- To date, pharmaceutical therapies directed at targeting early-onset Alzheimer's disease pathologies have been largely unsuccessful, further emphasizing the role of preventive measures through lifestyle change.
- The amyloid and tau theories are the prevalent disease models for Alzheimer's dementia and are driven by inflammation. This inflammation is caused by systemic problems such as diabetes, hyperlipidemia, oxidative stress, head trauma, and tobacco and alcohol use.
- The conventional Western diet promotes neuroinflammation through the consumption of excess fat, cholesterol, and sugar/fructose. Furthermore, this diet pattern negatively affects beneficial intestinal bacterial populations. Diets with more anti-inflammatory effects include the DASH diet, the Mediterranean diet, the MIND diet, and in some cases, the ketogenic diet.
- In addition to diet, key influencers in preventing dementia include exercise, stress reduction, sleep optimization, and addressing hearing loss.
- Strategies for reducing the incidence of dementia largely involve early lifestyle interventions at a population level. More comprehensive models that aim to improve the quality of life for people with dementia involve patient care teams as well as interventional training at the clinic level.

85.1 BACKGROUND

One of the most devastating and fastest-growing epidemics affecting the world is dementia, currently affecting approximately 57 million people and potentially 152.8 million by 2050.[1] Dementia disproportionally affects certain subsets of the population including women, African Americans, and Hispanics, especially those living in low to middle-income communities.[2] Many people are led to believe that the disease is part of normal aging, or are diagnosed when it is too late for any preventive interventions. According to the World Health Organization, dementia is currently the fourth leading cause of mortality and morbidity globally, and the top leading cause of morbidity in the United States; one American is diagnosed every 64 seconds.[3]

There are several types of dementia, including Parkinson's dementia, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, Huntington's dementia, mixed dementia, and dementia secondary to underlying conditions such as traumatic brain injury (TBI). The most common type is Alzheimer's dementia (AD), representing 60–80% of all dementias. While many public health interventions and medical treatments have been successful in reducing mortality in people living with diabetes, HIV, cancer, and heart disease, AD-related mortality has risen by a staggering 145.2% in the last 20 years. Though the human cost is immeasurable, the direct cost to the healthcare system of AD is estimated to be $321 billion. The indirect cost to families as a result of time lost from work and the cost of out-of-pocket support is more than $271.6 billion per year.[1] Heart disease, the highest leading cause of mortality globally, comparatively averages $378 billion annually.[4] The yearly cost of AD is expected to rise to $1.1 trillion solely in the United States and $20 trillion worldwide by 2050.[5]

AD research has been targeting two early-onset pathologies that play an important role in the onset of disease: amyloid-beta (Aβ) peptide and hyperphosphorylated tau (p-tau).[6] However, despite high trial expenditure, the US Food and Drug Administration (USFDA) has approved only six drugs, including three cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and one N-methyl-d-aspartate (NMDA) receptor antagonist (memantine). Though heavily used in the AD population, their effectiveness can be questioned as they are not disease-modifying therapies and are expensive. One of the previously mentioned drugs per patient can cost $1800 annually or $5 per day.[7] These drugs improve symptoms at a certain snapshot of time but neglect the progression of this deadly disease.

Aduhelm (aducanumab-awa) is the most recent drug, approved by the FDA in 2021, and is designed to alter disease progression by removing amyloid-beta (Aβ) peptide which accumulates and forms plaques.[6] Two studies have shown that intravenous infusion of Aduhelm in patients decreased the amount of "amyloid fibril", confirmed with positive emission tomography (PET) scans. However, the same two clinical

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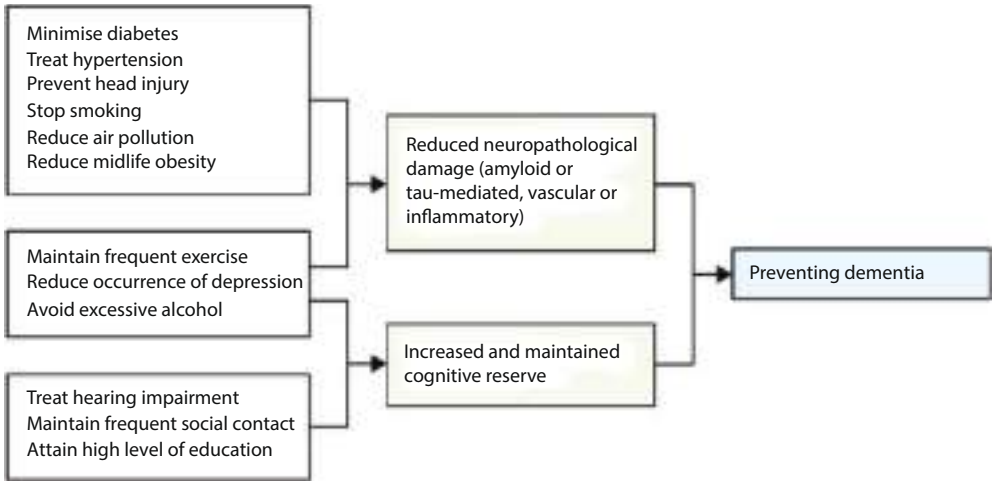


FIGURE 85.1 Preventing dementia.

studies did not reproduce these clinical benefits and could not confirm a positive relationship between reduction in amyloid burden and improved clinical outcome.[7] Though the drug was approved on the basis of its significant therapeutic benefit in certain situations, it has not produced any clinically substantial results in subsequent AD trials.

Although risk factors such as insulin resistance, high cholesterol, elevated blood pressure, and high body mass indexes increase with age, many normal functioning processes such as inflammation, oxidation, glucose and insulin regulation, and lipid dysregulation become less efficient with age. These can accelerate various disease processes in individuals.[8] However, there has been significant research that "successful cognitive aging" involves strategies at both the individual and community levels[9] Early diagnosis of risk factors and comprehensive lifestyle change is the most powerful approach in reducing mortality and incidence of dementia. Higher adherence to a healthy lifestyle score, characterized by nutrition, exercise, stress management, restorative sleep, and mental and social optimization is related to decreased risk of AD incidence.[10]

85.2 PROPOSED PATHOPHYSIOLOGICAL MECHANISMS

85.2.1 Amyloid Theory

Amyloid precursor protein (APP) is a cell surface receptor most densely found in neuronal synapses, regulates neuronal plasticity and nutrient transport, and supports the development of new synapses. APP is cleaved by an enzyme called alpha-secretase, producing neuronal transmembrane peptides that reduce intracellular calcium in neurons, preventing apoptosis. When APP is instead cleaved by beta- or gamma-secretase, this produces dysfunctional transmembrane proteins that allow more intracellular calcium (leading to apoptosis). These cleaved fragments also "clump" together and oligomerize.[11]

The amyloid theory was proposed 25 years ago when it was discovered that mutations in APP, presenilin 1, and/or presenilin 2 genes (PSN1/PSN2) were associated with increased amyloid-beta protein production. It was first found to aggregate in key processing areas of the brain, reducing synaptic transmission, forming "plaques", and activating local microglial inflammatory responses. Although beta-amyloid is normally found in the aging brain, disruption in neuronal metabolism was found to lead to increased phosphorylation of amyloid-beta, further stabilizing these plaques which interfere with neurotransmission,[11] triggering inflammation, leading to synaptic dysfunction, and eventually, cause gradual apoptosis leading to dementia. However, with the failure of several anti-amyloid medications, more recent hypotheses now posit that beta-amyloid may instead be a trigger for the hyperphosphorylation of tau protein, which may be the active cause of Alzheimer's disease. In essence, beta-amyloid may be thought of as laying the groundwork for tau protein to cause pathology.[12]

85.2.2 Tau Theory

The tau theory suggests that aggregations of tau protein strings form neurofibrillary tangles inside of cells, leading to inflammation and cell death. Deposition of tau protein is often seen ten or more years prior to the deposition of beta-amyloid protein and has been a more consistent predictor of AD later in the disease.[12] Tau protein stabilizes microtubules in cells. When it undergoes phosphorylation, this destabilizes the microtubule which can develop into neurofibrillary tangles. This becomes pathologic as neuronal cells with impaired microtubule formation have impaired axonal transport and are unable to undergo normal reparative and supportive processes.[13] Several anti-tau therapeutics have been proposed, however, these have not yet shown clinical benefit.[14]

85.2.3 Diabetes and Insulin Resistance

The brain is an extremely glucose-sensitive and by extension an insulin-dependent organ. Among other brain

structures, both insulin receptors and insulin-like growth receptors are expressed in the hypothalamus, hippocampus, and cortex, structures that are primarily involved in metabolic regulation, memory, and executive function. Unsurprisingly, insulin plays a large role in synaptic plasticity, and insulin signaling is often impaired in the brains of patients with diabetes and Alzheimer's disease[15] due to hyperinsulinemia as a response to hyperglycemia. For this reason, Alzheimer's disease is sometimes referred to as "type III diabetes"[16] Specifically, as glucose crosses the blood–brain barrier, peripheral hyperglycemia causes glial-mediated inflammation, leading to increased neuronal insulin resistance. Over time, this results in synaptic failure and degradation as the blood–brain barrier also becomes more permeable through insulin resistance

85.2.4 High Cholesterol

Since the identification of the ApoE4 gene (which encodes the ApoE4 protein, responsible for lipid transport) and its correlation with a predisposition for Alzheimer's disease in 1993, elevated cholesterol has been a target in the prevention of dementia. Increased low-density lipoprotein leads to increased production of the cholesterol metabolite, 24-hydroxycholesterol exclusively generated in neurons. Although not pathologic by itself, increased production was observed in patients with early development of Alzheimer's disease. Furthermore, increased glial-mediated inflammation, as also seen in diabetes, was also noted with increased cholesterol levels.[17]

85.2.5 Inflammation

The brain's macrophage, microglia, have several critical roles including synapse organization, debris removal via phagocytosis, cellular protection and repair, control of neuronal signaling and excitability, and turnover of myelin. They produce inflammatory signals as a part of the brain's innate immune response. Sustained activation of this inflammatory response has been shown to exacerbate the role of both beta-amyloid accumulations and neurofibrillary tangles, which in turn enhance microglial activation.[18] ApoE4 expression is increased in activated microglia, as is the expression of NLRP3. NLRP3 acts as a sensor of neuronal environment irritants, a critical component of immune homeostasis. When activated, it creates what is known as the NLRP3 "inflammasome", which releases a cascade of pro-inflammatory cytokines.[19] Another genetic marker of interest is triggering receptor expressed on myeloid cells 2 (TREM2).[20] It was discovered that mutations in this gene have also been associated with a higher likelihood of developing Alzheimer's disease. Normal TREM2 maintains the metabolic function of microglia, especially during stress, however, its mutated form inhibits this protective ability.[21] Therefore, continually sustained activation of these components creates an environment of perpetuated inflammation in the brain.

85.2.6 Oxidation

Oxidative stress refers to an imbalance between the production of reactive oxygen species and antioxidant production. This results from increased protein oxidation, lipid peroxidation, and end-glycosylation products, all of which are molecular processes that produce byproducts that increase oxidation at the cellular level. The antioxidant defense mechanism primarily includes the production of intracellular low molecular weight glutathione, which decreases with age.[22] Furthermore, reactive oxygen species (peroxyl radicals) and reactive nitrogen species directly damage proteins and DNA bases, leading to aldehyde byproducts that deplete glutathione.[23] Therefore, the cumulative effect of increased oxidation production overwhelms the already reduced potential from antioxidant production.

85.2.7 Head Trauma

Although the exact mechanism supporting the relationship between the development of dementia and the incidence of traumatic brain injury is not well described, many studies have found a positive correlation between head injury with or without loss of consciousness and the later development of dementia. A single head injury (regardless of loss of consciousness) is associated with a 1.25 increase in risk of developing dementia over the next 25 years. In the case of two or more head injuries, that risk increases to 2.14.[24]

85.2.8 Alcohol

Alcohol consumption has long been associated with major impacts on health and is a significant contributor to global disease burden. This has previously been discussed in relation to "heavy" alcohol use (an average of four standard drinks daily) and its effects on cognition, cardiovascular disease, nutrition, and cancer. The effects on cognition are assessed by measuring global brain volume, and both gray and white matter volume. While studies in the early 2000s touted that small quantities of alcohol, specifically containing resveratrol (a compound found in red wine) conferred health benefits,[25,26] recent research does not support this practice. In several large population studies, one standard drink daily was enough to result in overall damage to the frontal lobes, hippocampus, and cerebellum. These subjects were found to have decreased gray matter volume in critical structures of the prefrontal cortex, insula, superior temporal gyrus, striatum, thalamus, and hippocampus when compared with healthy, alcohol-abstinent controls.[27] Regular consumption of alcohol also downregulates structural proteins necessary to maintain the integrity of the blood–brain barrier (zona occludins-1, VE-cadherin, and occludin), which leads to damage by neurotoxic agents.[28] Increased iron deposition in the brain has also been noted with moderate alcohol intake, leading to both Alzheimer's and Parkinson's disease.[29] Therefore, it is no longer accurate to suggest that any level of alcohol consumption is beneficial for health.

85.2.9 Smoking

Smoking is associated with increased production of reactive oxygen species, therefore, leading to increased oxidative stress. As previously discussed, damage caused by free radical species incites a systemic inflammatory response that has profoundly damaging effects on neuronal tissue through increased production of superoxide radicals and hydrogen peroxide.[30] A large body of epidemiological research has demonstrated a dose-dependent but increased risk for Alzheimer's disease and dementia in association with cigarette smokers,[31] a risk that persists even years after tobacco cessation.

85.3 NUTRITION AND ITS EFFECT ON RISK

Several studies have aimed to assess the relationship between dietary composition and Alzheimer's disease. A 2002 study in Finland suggested that elevated total cholesterol and high blood pressure contributed to a greater risk of Alzheimer's disease than the ApoE4 gene mutation or any familial risk.[32] A 2.2–2.4 times increase in risk was seen in patients with a high intake of saturated and trans-unsaturated fats.[33] More recent associations with all components of a typical "Western diet", consisting of refined sugars, simple carbohydrates, salt, saturated fatty acids, and cholesterol (and poor in grain, fiber, and mono- and polyunsaturated fatty acids), have been made with impaired cognition, learning, and memory specifically through changes in gut microbiota.[34] Changes to the population of gut microbiota, referred to as "dysbiosis", have been linked to a propensity toward developing obesity and diabetes among other metabolic disorders.

85.3.1 The Effect of the Western Diet

The Western diet pattern has demonstrated an association with decreased overall hippocampal volume, and more concerning, may also be transmitted from mother to child through epigenetic mechanisms. Increased accumulation of amyloid-beta protein, increased levels of neuroinflammatory markers (such as TNF-alpha, IL-6, IL-1 beta), and increased blood–brain barrier permeability has been demonstrated in consumers of high fat, cholesterol, and sugar/fructose diets.[34] However, just as the Western diet has been studied in connection with inducing all of these neurodegenerative changes, several diets have also been shown to modify intestinal bacteria populations in ways that prevent the development of type 2 diabetes and other known neuroinflammatory disorders.[35]

85.3.2 Risk Reduction through Diet

Popular dietary models that have been associated with overall Alzheimer's dementia risk reduction include the DASH (Dietary Approaches to Stop Hypertension) diet, Mediterranean diet, and ketogenic diet. Perhaps the most well-known of these is the Mediterranean diet. The Mediterranean diet is rich in olive oil, vegetables, fruit, nuts, cereals, legumes, fish, and seafood. Overall, it consists of a high ratio of monounsaturated to saturated lipids. A four-year trial found that a sustained Mediterranean diet led to a reduction in inflammatory markers, such as VCAM-1, ICAM-1, IL-6, and CRP. Lowering inflammation reduces all-cause mortality including cancer, cardiovascular, and cerebrovascular causes.[36]

The DASH diet consists of mostly whole grains, with protein coming from lean meats, fish, poultry, nuts, and beans. It is rich in fruit and vegetables, and low-fat dairy products, resulting in a high fiber to low/moderate fat ratio. The diet overall proposes reduced sodium intake for the control and reduction of high blood pressure (daily sodium intake is typically <2400 mg). It excludes or proposes reducing saturated fats, total fat, cholesterol, refined grains, and sweets. More recently, a hybrid of the DASH and Mediterranean diets has been proposed, called the MIND diet, alluding to its clear benefit with regard to neurological health.[36,37] It promotes a plant-based diet, limiting meat, salt, and dairy products. In the Rush University Memory and Aging Project, strict adherence to the MIND diet resulted in a 53% risk reduction in the development of Alzheimer's disease for subjects aged 58–98 years old. Importantly, even moderate adherence to the diet resulted in a 35% risk reduction.[37]

Finally, the ketogenic diet proposes a high fat, moderate protein, and low carbohydrate intake. Ketogenic diets have been shown to improve neuroinflammatory markers and amyloid/tau deposition, resulting in short-term cognitive improvements in humans.[38] It should be noted, however, that there exists very little evidence that this diet plan can be sustained by most patients for longer than three months.[39]

85.4 OTHER LIFESTYLE INFLUENCES

85.4.1 Exercise

For decades, physical exercise has been shown to have a positive correlation with health as a whole. Exercise can be broken down into four categories: aerobic, anaerobic, agility training, and stretching and flexibility.[40] However, not all exercise provides equal benefits in improving vascular health and growth, psychological processes, and the development of new neuronal connections. Extended periods of regular, high-intense aerobic exercise dramatically reduce rates of AD. LADIS, a European multicenter study, revealed that in three years, physical activity reduced the risk of cognitive impairment and dementia by 40%.[41] Another study revealed that when comparing intensive aerobic exercise with stretching on those diagnosed with mild cognitive impairment (MCI), the participants who engaged in the intensive aerobic exercise exhibited better executive function due to greater blood flow to the frontal lobe and an increase in brain size, regardless of their genetic disposition to AD.[42]

Anaerobic exercise such as strength training also resulted in an inverse relationship with cognitive decline. A 2010 meta-analysis consisting of 15 studies with 34,000 participants further demonstrated that strenuous exercise resulted in a 38% reduction in cognitive decline.[43] Another type of anaerobic exercise, resistance training, improved cognition to normal in 47% of subjects with MCI; greater leg strength as a result of this exercise also proved contributory to better brain quality.[44] Therefore, any exercise, but especially regular aerobic exercise to one's daily regimen, is crucial for maintaining brain functioning and improving brain health.

85.4.2 Stress

Environmental threats and adversity increase systemic cortisol production, which in turn upregulates the production of pro-inflammatory cytokines. Via the limbic-hypothalamic-pituitary-adrenal axis (HPA axis),[45,46] the brain regulates and processes emotional responses to stimuli. If perceived as a negative stressor, it induces the hypothalamus to release corticotropin-releasing factor (CRF). This causes a release of multiple pituitary hormones, including ACTH, which then act on the adrenal glands to secrete both mineralocorticoids and glucocorticoids such as aldosterone and cortisol.[47] This flood of steroid hormones results in the dampening of higher cognitive processing. Under evolutionary circumstances, this is useful for making quick responses focused on an immediate threat. However, similar threat responses are generated over increasingly "smaller" matters today and occur much more often. This creates elevated baseline levels of circulating cortisol and other pro-inflammatory cytokines, leading to neuronal atrophy and cell loss in the limbic system and prefrontal cortex.[48] This atrophy occurs through glucocorticoid suppression of brain-derived neurotrophic factor (BDNF), which typically promotes the growth and maturation of neuronal cells.[49]

The sympathetic pathway also activates a similar response, together with the HPA, resulting in increased glucocorticoid release. Microglia, which compromise the main component of the brain's immune system, are inhibited by glucocorticoids and noradrenaline, which is released through the activation of the sympathetic nervous system. Curiously, both glucocorticoids and noradrenaline can also enhance the activity of microglia under acute stress conditions but have deleterious effects under severe, continued stress conditions.[50] The sympathetic nervous system also perpetuates systemic vasoconstriction under stressful conditions. Acutely, this decreases the involvement of the medial prefrontal cortex, which can lead to neuronal loss in this area as well as the insula and parietal cortex under chronic stress conditions.[51]

One such proposal for stress reduction that has been shown to result in meaningful structural change is meditation. Several studies have linked regular meditation practice with reduced brain atrophy, increased neuroplasticity, and improved cognition. Specifically, MRI findings demonstrated increased thickness of the outer (cortical) layer used in higher cognitive processes, and this effect was most pronounced in older subjects.[52]

85.4.3 Sleep

The amount and, more importantly, the depth of sleep are associated with corresponding changes in memory consolidation, cognition, and appetite. Sleep is an anti-inflammatory process. Similar to a stress state, sleep deprivation results in dysfunction of the hypothalamic-pituitary-adrenal axis, and excessive daytime sleepiness from inadequate sleep is associated with a decreased response to chronically elevated baseline cortisol.[53] This results in attenuation of microglial activity by pro-inflammatory cytokines, adenosine, and interferons.[54] Microglia are responsible for the normal maintenance and "pruning" of neurons during sleep. A structure located in the area of the rostral pons, known as the locus coeruleus, is a key part of the reticular activation system and mediates wakefulness through the secretion of norepinephrine. It continually secretes norepinephrine throughout the brain except during REM (rapid eye movement) sleep and just before NREM (non-rapid eye movement) sleep.[55] These pauses allow for the incorporation of new information via synaptic plasticity into memory circuits.

The "dual process hypothesis" of sleep has suggested that non-REM or NREM sleep, which takes place typically during the first half of the sleep cycle, is necessary for the consolidation of declarative memory, while REM sleep in the second part of the sleep cycle is for implicit (procedural) memory[55] It therefore follows that a dysfunctional HPA axis, leading to elevated cortisol and therefore a pro-inflammatory chronic state, creates an environment for the development of chronic disease. Furthermore, chronic stimulation of the brain by norepinephrine in the absence of the deeper sleep phases creates a chronically sleep-deprived state.

Addressing sleep deprivation requires a multidisciplinary approach that takes many of the above factors into account: lowering baseline stress levels, optimizing an exercise routine, and making dietary changes to maintain a healthy weight. Obstructive sleep apnea, most often caused by obesity, leads to periodic hypoventilation throughout the night, which, over time, leads to increased neuronal stress and inflammation.[56] Other behavioral interventions for optimizing sleep include decreased intake of caffeine, as well as establishing sleep hygiene routines.

85.4.4 Diminished Hearing

Age-related hearing loss is another modifiable risk factor that is linked to cognitive decline and dementia. According to the 2018 meta-analysis by Loughrey et al.,[57] hearing loss can affect the clinical outcomes of dementia. Though easily amenable with hearing aids, only one in five Americans with hearing loss acquire these devices;[58] some reasons

include lack of access to a primary care provider, unsupportable insurance, or high costs. However, further clinical trials are needed to determine the causal relationship between hearing loss and cognitive decline.

85.5 IMPLEMENTING RISK REDUCTION GUIDELINES

Community involvement is a key sector to be utilized to tackle this and other public health concerns. A study published by the Flemish Ministry of Welfare[59] reported that a mass media public health campaign involving social media and an interactive online assessment increased 80.5% of the participants' motive to engage in healthier activities by exercising and eating healthier meals. The feedback from post-campaign also revealed that more than half of the subjects were unaware of the strategies to reduce dementia risk, followed by a lack of motivation, financial constraints, and a shortage of time. With strong efforts in public awareness, people may feel empowered to take control of disease, rather than be fearful, improving their quality of life.[60] Another study conducted in Saudi Arabia reported positive attitudes toward people with AD but lacked the required knowledge to understand the disease.[61] This further echoes a similar conclusion that more educational programs via video clips or in-person presentations at a community level such as churches, dance centers, gyms, and movie theaters are needed.

85.5.1 Early Diagnosis and Prevention

Healthy lifestyle changes have been the gold standard in controlling hypertension, type 2 diabetes, and their effects on systemic disease. However, the effect of disease on brain health has not been emphasized. Most neuroimaging with MRI and EEG occurs when individuals present with abnormal cognitive functioning that significantly affects their daily life, and often are left with limited options in the further prevention of progression of the disease.[62]

The importance of primary care in early and ongoing cognitive testing has been studied. A study conducted in China explored the importance of using several tests due to the varying sensitivity and specificity. The Clinical Dementia Rating (CDR) has 74% accuracy in screening patients for dementia—more significant than the Brief Elderly Cognitive Screening Inventory (BECSI), the Quick Cognitive Screening Scale for Elderly (QCSS-E), the Mini-Mental State Examination (MMSE), and the Core Neurocognitive Test (CNT).[63] Another study conducted in Hong Kong compared the efficacy of using a digital cognitive test to screen for MCI and dementia with the conventional Montreal Cognitive Assessment. The EC-Screen uses a platform that reads the test instructions for the various tasks, which can be completed in approximately five minutes. Unlike the MOCA, which is dependent on education level, the EC-Screen has made an alternative version adapted for individuals with a lower education level.[64] It can be administered by any staff, family member, or personally, which can improve efficiency in primary health and community areas.

In addressing brain health, recognizing the disease is equally important as maintaining a management plan with a collaborative team of providers including nurses, pharmacists, nursing home staff, and caregivers.[62,64]

85.5.2 Comprehensive Intervention Models

Several studies have been conducted where intervention models were designed to help dementia patients both maintain and improve their daily living ability.[65] One study conducted in 2019 in China involved a five-part model that incorporated self-care training (dressing, preparing food), exercise, cognitive training (matching games, concentration), social interest (calligraphy, painting, reading), and nursing (directed toward caregivers' understanding of health knowledge and behavior processing).[66] Compared with standard medication management (control), the intervention group improved in self-care ability, housework, communication, and leisure activity domains. Although this did improve patient quality of life, this study as well as a similar study in 2016 (focused solely on caregiver education and interventions), did not lead to slowed disease progression nor improvements in their memory or directivity.[67]

This highlights the importance of multimodal interventions that not only improve the quality of life in existing dementia but also in the prevention of the multiple risk factors that have been shown to slow disease progression. This is best demonstrated by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) model.[68] Patients in this randomized control trial were assigned to either a control group or an intervention group that received dietary counseling, physical exercise, cognitive training, and the monitoring of metabolic and vascular risk factors. This model resulted in an average of 25% improvement in global cognition, executive function, processing speed, and complex memory tasks even at several years follow-up post-study compared with the control group.

85.5.3 Clinic-Based Intervention Protocols

Since 2001, at least seven studies lasting anywhere between one to four years have been conducted to examine the outcomes of collaborative, outpatient primary care models. They are listed below with their respective outcomes:

- Healthy Aging Brain Center (HABC, 2004): Reduced ER usage and need for acute hospitalization.
- Aging Brain Care Medical Home (ABC, 2012–2014): Decreased severity of cognitive, functional, and psychological impairment.
- Alzheimer's and Dementia Care (ADC, 2012–2014): Patients passed 92% of specific "dementia care quality" indicators such as degree of mental

status changes and usage of acetylcholinesterase inhibitor medications.
- Alzheimer's Disease Coordinated Care for San Diego Seniors (ACCESS, 2001–2002): Of several findings, there was more support group engagement, more usage of acetylcholinesterase inhibitor medications, and more adherence to dementia care guidelines.
- Centre for Family Medicine Health Team (2008–2011): Decreased wait time to access psychoeducation and greater satisfaction with education received.
- Dementia Life- and Person-Centered Help in Mecklenburg-Western Pomerania (DeLPHi, 2012–2016): Increased chance of receiving antidementia drug treatments.
- DementiaNet (2015–2017): Earlier dementia diagnosis and better coordination of care.

All of the above studies noted improvements across multiple surveys assessing the severity of dementia symptoms and quality of life. Benefits to patient caregivers and financial burden were also noted for certain studies.[69]

85.5.4 Population-Based Intervention Protocols

At a population level, the focus on minimizing the risk of dementia is based on prevention. Specifically, addressing many of the aforementioned risk factors at all stages of life—avoiding head injury, decreasing alcohol intake, cessation of both active and passive smoking, a sustained exercise routine, social life, and the maintenance of systolic blood pressure throughout the midlife years ≤130 mmHg.[68]

85.6 SUMMARY

The development of Alzheimer's disease is attributable to a culmination of different risk factors, often both lifestyle- and environmentally based, most of which are modifiable. In summary, the prevention of chronic vascular disease (through cessation of smoking, cholesterol control, blood glucose control, etc.) aids in reducing cumulative systemic inflammation, which overall lowers the risk of developing dementia. Addressing environmental and external risk factors, such as sleep hygiene, stress levels, and head trauma are also key factors in preventing Alzheimer's disease. Just as the approach to reducing the incidence and burden of dementia is multifactorial, interventions at the clinic and population level must also be multi-pronged, with the ultimate goal focused on disease prevention in the early years through midlife.

CLINICAL APPLICATIONS

- *Prevention through early life and midlife*
  - Control of hypertension, diabetes (type II), and hyperlipidemia.
  - Avoidance of head trauma.
  - Avoiding tobacco use and alcohol use, or early cessation.
  - Implementing anti-inflammatory dietary changes.
  - Development and maintenance of regular varied exercise.
  - Addressing sleep hygiene
- *Diagnosis*
  - Early and ongoing cognitive testing has been found to screen patients with dementia with high efficacy.
  - Early neuroimaging may be considered depending on cognitive screening.
- *Intervention*
  - Different models exist that address dementia at both the clinical level and the multidisciplinary level (involving physical therapists, dietitians, nursing staff, and caregivers). All of these emphasize a multi-pronged approach to delaying the progression of dementia and improving symptom management through exercise, dietary changes, social enrichment, caregiver involvement, and cognitive challenges.

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Part XVI

The Practice of Lifestyle Medicine



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86 Definition of Lifestyle Medicine*

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KEY POINTS

- Lifestyle medicine is a relatively new medical specialty being defined as the prevention and treatment of appropriate disease states by changing the personal habits and behavioral choices of individuals in such a way as to address the underlying cause
- Practitioners of lifestyle medicine see it as part of allopathic medicine and neither complementary nor alternative but foundational to treating chronic lifestyle-caused disease.
- Lifestyle medicine can be effective in the treatment and, in some cases, the complete reversal of the manifestations and possibly even the cure of many chronic non-infectious diseases.

86.1 LIFESTYLE MEDICINE: THE HISTORY OF A DEFINITION

The phrase "lifestyle medicine" appears to have been first used by the epidemiologist Ernst Wynder in a discussion of the effects of smoking on lung cancer risk around 1988.[1] Wynder used the phrase in a symposium title in 1989.[2] Hans Diehl reports hearing Wynder use the term, being enamored with the phrase, and seeking to copyright it in the United States in 1988.[3] The request was denied by the authorities because the individual words were of widespread common use and the combination was not distinct. James Rippe published the first text entitled "Lifestyle Medicine" in 1999.[4] Gary Egger, A. Binns, and S. Rossner published "An Introduction to Lifestyle Medicine" in 2007.[5] PubMed references to the phrase rose from 208 in January 2018[6] to 859 in November 2022[7] and reflect continued interest (see Figure 86.1).

Within the medical community, the phrase "lifestyle medicine" has variations in implications/meanings. Those early users of the paired-word phrase seemed to be focusing on how the personal behaviors of individuals affect their health and well-being. As noted above, the first documented use was referring primarily to the effect of smoking on the risk of emphysema/COPD pathology. Hans Diehl was the founder of the Coronary Health Improvement Project (CHIP) program, and his efforts for lifestyle change in the treatment of coronary heart disease focused on nutrition, exercise, and other modifiable risk factors to help reverse atherosclerotic pathology. The CHIP program promoted the newly added credibility proffered when Dean Ornish published his randomized controlled trial (RCT) demonstrating the reversibility of the disease.[8] Early implications center on personal behavior change and have invoked significant reference to behavioral change techniques.

Rippe's initial 1999 text defined lifestyle medicine as, "The integration of lifestyle practices into conventional medicine to lower the risk for chronic disease and, if disease is already present, to serve as an adjunct to therapy".

In 2008, the leadership of the American College of Preventive Medicine, Mark Johnson and Mike Barry, defined lifestyle medicine as, "A defined scientific approach to decreasing disease risk and illness burden by utilizing lifestyle interventions such as nutrition, physical activity, stress reduction, smoking cessation, avoidance of alcohol abuse, and rest."

In his 2008 textbook, Eggers addressed the definition in this way: "The therapeutic use of lifestyle interventions in the management of disease at all levels to help manage the growing number of cases presenting to doctors now with a lifestyle-based cause of disease such as obesity and type 2 diabetes". He then added a sentence that lessens the personal "guilt" for an individual disease sufferer and admits to important societal forces (now popularly referred to as "Social Determinates of Health) active in deciding individual behavioral choices. "The application of environmental, behavioral, medical and motivational principles to the management of lifestyle related health problems in a clinical setting".

The American College of Lifestyle Medicine and American College of Preventive Medicine prepared an overview of lifestyle medicine in 2009 that sought to gather into one place the current thinking on the area from a medical perspective. Unfortunately, it is no longer posted online.

Lifestyle medicine core competencies were published in *JAMA* (2010) to help define the discipline within medicine.[9] These were organized into six Accreditation Council for Graduate Medical Education and American Board of Medical Specialties (ACGME/ABMS) categories. The final list consisted of 34 competencies in the six ACGME/ABMS categories. A recent update[10] expands the list to 88 and is available at https://journals.sagepub.com/doi/epub/10.1177/15598276221121580.

In the fall of 2012, ACLM convened a task force to draft the official standards for ACLM and the field of lifestyle medicine that focused primarily on the clinician-patient relationship.

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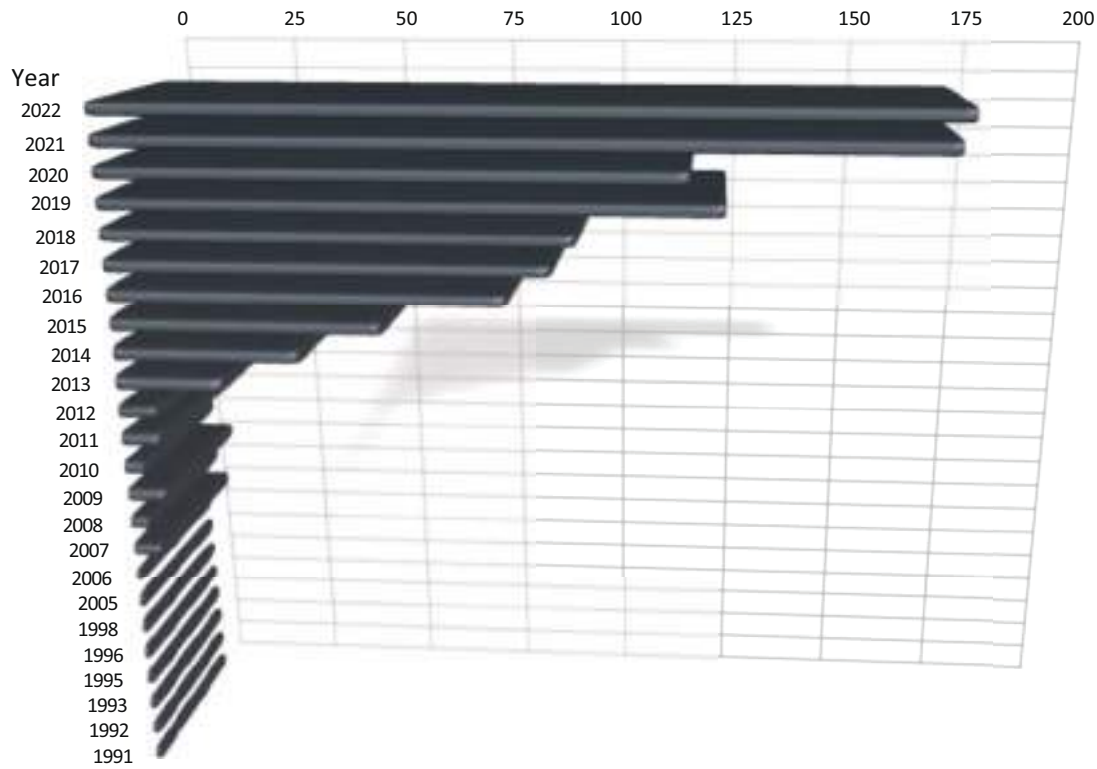


FIGURE 86.1 PubMed references to "lifestyle medicine" by year (https://pubmed.ncbi.nlm.nih.gov/?term=%22Lifestyle%20medicine%22&timeline=expanded).

> Lifestyle Medicine is the therapeutic use of evidence-based lifestyle interventions to treat and prevent lifestyle related diseases in a clinical setting. It empowers individuals with the knowledge and life skills to make effective behavior changes that address the underlying causes of disease.[11]

A similar definition appeared in late 2014 in the *International Journal of Clinical Practice* that included a community focus.

> Lifestyle Medicine is the evidence-based practice of helping individuals and communities with comprehensive lifestyle changes (including nutrition, physical activity, stress management, social support, and environmental exposures) to help prevent, treat, and even reverse the progression of chronic diseases by addressing the underlying cause.[12]

In their 2016 book, *Lifestyle Medicine: A Manual for Clinical Practice*, Mechanick and Kushner hinted at the concept of a specialty within medicine when they defined lifestyle medicine as

> a branch of medicine focused on preventive healthcare and self-care dealing with research, prevention, and treatment of disorders caused by lifestyle factors and preventable causes of death such as nutrition, physical inactivity, chronic stress, and self-destructive behaviors including the consumption of tobacco products and drug or alcohol abuse.[13]

The website of the American College of Lifestyle Medicine continues to provide a definition that has now morphed to include an allopathic specialty status. It is an expansion of previous definitions that focused primarily on modalities and evidence-based science as well as the prevention and reversal of disease.

> Lifestyle medicine is a medical specialty that uses therapeutic lifestyle interventions as a primary modality to treat chronic conditions including, but not limited to, cardiovascular diseases, type 2 diabetes, and obesity. Lifestyle medicine certified clinicians are trained to apply evidence-based, whole-person, prescriptive lifestyle change to treat and, when used intensively, often reverse such conditions. Applying the six pillars of lifestyle medicine—a whole-food, plant-predominant eating pattern, physical activity, restorative sleep, stress management, avoidance of risky substances and positive social connections—also provides effective prevention for these conditions.[14]

In Egger's 2017 edition, the definition expanded to include, "The application of environmental, behavioural (sic), medical and motivational principles to the management (including self care and self-management) of lifestyle-related health problems in a clinical and/or public health setting."[15] As it did in its earlier rendition, the current Australasian Society for Lifestyle Medicine (ASLM) webpage definition

goes on to endorse the social and policy dimensions of the basic six pillars earlier defined by the American College of Lifestyle Medicine.[16]

86.2 THE AMERICAN BOARD OF LIFESTYLE MEDICINE

In early 2016, the American Board of Lifestyle Medicine[17] (ABLM) was formed as an independent not-for-profit company (501c6) to identify lifestyle medicine clearly within the "house of medicine". This was shortly followed by the formation of the International Board of Lifestyle Medicine (IBLM). Because of the desire to eventually be accepted as a subspecialty by the American Board of Medical Specialties, the focus was on evidence-based medicine. Established pathways were followed.[18] As of June 2022, there are over 2009 ABLM physicians and 3234 worldwide physician diplomats in 72 countries.[19] The test questions and board review materials have gone a long way toward collecting, categorizing, and developing standards from the peer-reviewed evidence while creating a foundation on which the practical "definition" of lifestyle medicine will continue to expand (Figure 86.2).

To facilitate the teaching of lifestyle medicine, the American College of Lifestyle Medicine has created curricula for colleges, medical schools, and graduate medical education. The Lifestyle Medicine Residency Curriculum (LMRC) is to be available as a standardized curriculum virtual learning tool that is updated continually on a three-year cycle. When completed and verified by participating residency leadership, the virtual presentations and corresponding required activities make the resident board eligible. Its adoption has primarily been in preventive medicine, internal medicine, and family medicine residencies around the United States.

86.3 THE UNIQUE ROLE OF LIFESTYLE MEDICINE WITHIN ALLOPATHIC MEDICINE

There is a growing interest from the political realm influencing various professional organizations to address environmental and social determinants of health, society, and agribusiness disease-modifying factors. While lifestyle medicine has focused more on health professionals working to modify the behaviors of individuals to prevent disease, improve health, and even reverse disease, there is a recognition that these larger factors are important. Effectiveness in creating change in society is often perceived as in the realm of public health. Additionally, many lifestyle medicine practitioners are also schooled and even boarded in this specialty. Lifestyle medicine and public health in many ways share the task of engendering positive change in the slightly different but overlapping responsibilities.

In recent years, various professional organizations have begun to emphasize the importance of lifestyle medicine and have taken steps to increase the visibility of lifestyle interventions within the various specialties. This reflects a practical response to the growing body of evidence for the effectiveness of lifestyle interventions. An example of this includes a 2021 consensus report acknowledging

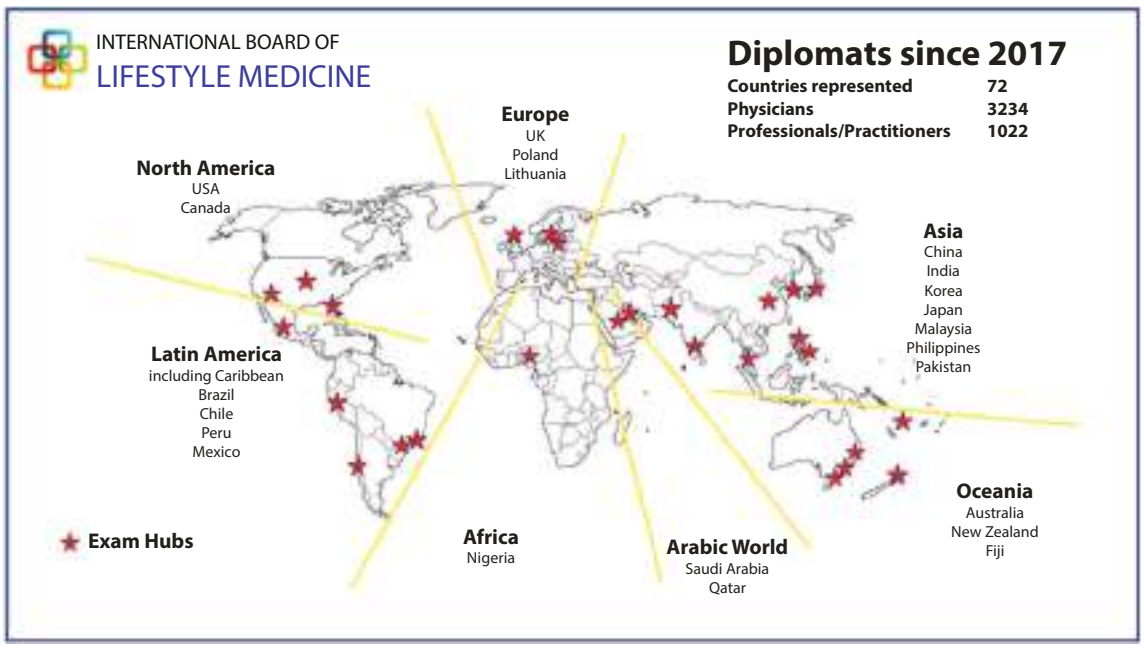


FIGURE 86.2 Report of total number of diplomats between when the first board was offered and June 2022. Received as PowerPoint slide from Stephan Hertzog, Executive Director, American Board of Lifestyle Medicine, International Board of Lifestyle Medicine (received June 12, 2022.) Used with permission.

the possibility of the potential remission of type 2 diabetes through lifestyle changes prepared by the American Endocrine Society, the European Association for the Study of Diabetes, Diabetes UK, and the American Diabetes Association and published in *Diabetologia*,[20] *Diabetes Care*,[21] *The Journal of Endocrinology and Metabolism*,[22] and *Diabetes Medicine*.[23]

Lifestyle medicine plays an important role within standard allopathic medicine. Its focus is primarily on individual lifestyle behaviors. Its success depends more on patient motivation and coaching than on physician prescription. The inclusion of cognitive behavioral therapies in lifestyle change and motivational counseling coaches patients to become more involved and responsible for their own outcomes. By nature, "coaching" applies to every lifestyle medicine practice and patient interaction within the context of a collaborative care model and may make significant use of allied healthcare professionals to provide much of the direct counseling. Prescriptive lifestyle interventions for specific diseases are best done with a multidisciplinary healthcare team. The evidence for the effectiveness of these prescriptions is strong and growing and is being included in many national guidelines for use in both prevention and treatment.[24]

There are a growing number of clinicians who wish to practice lifestyle medicine as the key driver of their medical practice. One might well identify these as lifestyle medicine specialists. There are efforts underway for the introduction of standards as well as additional board certification for the advanced lifestyle medicine specialist.

This should create three levels on which practitioners include lifestyle medicine in their practice. For those practicing more traditional allopathic medicine, lifestyle medicine remains central to practice as evidenced by its presence in the national guidelines for virtually every metabolic disease. Second, some desire to include a special lifestyle focus into their primary care practices, the lifestyle medicine specialist who, while not ignoring effective techno-therapies, gives primary, real, and effective attention to the behavioral, environmental, and societal factors of chronic disease prevention and management. Third, there remains a conceptual need for the advanced lifestyle medicine specialist with the skill to coordinate the clinical teams addressing resistant cases to instruct and manage intensive lifestyle care programs (both inpatient and outpatient) and guide communities, healthcare institutions, and government policy in the appropriate application of lifestyle medicine within their appropriate cultural spheres.

86.4 DIMENSIONS OF THE DEFINITION

A definition of a field of study must, of necessity, lay out in broad strokes the meaning. In applying the definition to practice, the dimensions and application are more fluid, reflecting the expansion and application of medical knowledge and experience in how lifestyle practices affect health and well-being. These are key concepts of lifestyle medicine:

- Primary prevention, secondary prevention, and tertiary prevention are included. This means that lifestyle change may be effective for the full spectrum of chronic disease treatment and even remission or cure.[25] It appears from the evidence that lifestyle medicine can often be more effective than tertiary techno-therapies such as cardiac bypass surgery or stenting for heart disease[26–30] and pharmaco-therapies for diabetes.[31]
- Lifestyle medicine is an essential component of the treatment of most chronic diseases and is incorporated into many national disease management guidelines. These should be a part of every practicing physician's thinking and practice. Unfortunately, when the guidelines are applied in "usual" clinical practice, the recommendations are given a modicum of lip service but lack an adequate application of the necessary evidence-based changes to the individual patient's present behavioral practices.[32] Recognizing the importance of dealing with the underlying cause, lifestyle medicine practitioners apply the principles and techniques of behavior change to effectively address the lifestyle determinants of chronic diseases.
- As a practical clinical discipline, lifestyle medicine incorporates clinicians working with a team of other healthcare professionals to develop patient-specific interventions. Nutritionists, behaviorists, coaches, exercise physiologists, nurses, and others should be included. A range of health professionals working as a team is needed to prevent, manage, and treat the estimated 70% of modern health problems that have a lifestyle-based etiology.
- The process of medical education should both introduce and expand the student's awareness of the ability of lifestyle change to positively affect outcomes as well as teach the skills of behavior change. Movement in this area is reflected by the 2020 American Heart Association's revision and update of its 2016 statement emphasizing the importance of medical education to achieve competency in lifestyle counseling.[33]
- Lifestyle medicine bridges the gap between health promotion, behavior change, and conventional medicine. The scientific disciplines come together to create effective behavior change. One might view lifestyle medicine as inhabiting a space somewhere between behavioral psychology and primary care. This perspective calls for the lifestyle medicine physician and the caregiver team to rely more on modern coaching techniques and less on expert- or dictatorial-toned interactions.
- While allopathic medicine requires overt treatment directives (and even demands) in critical

care, trauma, and other acute situations, the lifestyle medicine approach recognizes that the patient is ultimately in control of the journey away from disease and into well-being. The lifestyle medicine clinician, of necessity, must provide direction, education, and motivation rather than simply being a coach encouraging the individual to set his/her own goals.

- One must recognize that it is not possible to solve health problems by "doing the wrong thing better". The "right thing" (best or evidence-based way) must be identified and made plain even if the individual can only see himself or herself making small steps in that direction.
- The lifestyle medicine clinician will also find cognitive behavioral therapy practices of benefit in helping the individual overcome barriers to improving behaviors. Helping to identify cognitive distortions and reframe behavioral decisions from the vantage point of "truth" can lead to more efficient and long-lasting behavioral health changes.
- Sound scientific evidence from diverse health-related fields coalesce to assist clinicians in the process of treating disease and promoting good health. In practice, lifestyle medicine is most effective when a well-informed primary care provider coordinates a team-based application. While medical sub-specialists should be knowledgeable in the lifestyle dimensions of their system specialty, they are often lacking in the practical application of the evidence as well as the skills needed for successful application.
- Many healthcare workers do not practice in their own lives what they know to be the healthiest lifestyle practices and often have a difficult time instructing their patients to do something they "do not think anyone will actually do" (see Chapter 91). When there is a cognitive dissonance between personal practice and the best scientific evidence, the clinician's personal biases interfere with the proffering or even the acknowledgment of the best evidence. This problem is not unique to lifestyle medicine but is common to any application of the scientific process.
- Measuring a biometric more consistently (lipids or A1C) or prescribing appropriate drugs may prolong life but do not adequately address the behavioral and complex biochemical interactions that cause and/or accelerate the lifestyle-caused disease process. In order to deal with the root cause of chronic non-infectious diseases, patients are required to change high-risk health behaviors to behaviors that will help to reverse the pathology and/or reduce the likelihood of disease progression. Even as effective evidence-based health technologies are applied, lifestyle behavioral changes are usually required to stop or reverse the underlying pathophysiology.
- As the medical profession has developed over time, physicians have often functioned as experts in diagnosis and treatment. As holders of the knowledge and skills, they prescribe the appropriate technology to the recognized disease pattern and expect the patient to comply. The evidence is that compliance with pharmaco-technology is rather low (for example, around 50% at one year for hypertension medications[34]) and the cause is multi-factorial.[35] A patient's calculation of the risks and benefits is often different than that of the clinician. A study of cardioprotective drug interventions suggests that informing patients of the actual percentage chance (not relative risk) of the benefit from preventive drug strategies will substantially reduce the actual use of such drugs. For the individual, this is unlikely to be detrimental. However, there is concern for the population at large as reduced uptake of the drug will lead to an increased prevalence of the target event and clinicians are used to managing treatments at this level.[36] The same compliance issues are present with the lifestyle medicine approach. Directly addressing the patient's fears and perceptions and shifting the "control" to the patient is required, as it is the patient who must make the behavior change. Indeed, taking the necessary steps to place the patient in control of their disease is likely to significantly increase behavioral compliance. Certainly, just the perception that the physician has understood the patient and that the patient understood what the clinician was communicating, termed "concordance" in the literature, has been reported as one of the strongest determinants of compliance.[37] Societal, legal, and public health interventions will also need to focus on making it easier for the public to make the right personal choice. Lifestyle medicine changes the emphasis to an approach in which the patient becomes increasingly involved in his or her care and moves the physician toward being a coach-educator and less of a dictator.
- Lifestyle medicine is not simply about prolonging life, it is about ensuring people can enjoy their later years with less pain and disease. As David Katz, one of the more prolific lifestyle medicine communicators of recent years, is often heard to say, lifestyle medicine is about "adding years to life and life to years".
- Lifestyle medicine relies heavily on the scientific process but also embraces evidence-based creative thinking as the first step of the scientific process. While recognizing the importance of blinded and randomized controlled trials for minimizing bias, it is clear that these studies are not easily applied universally to the diversity of individual human

experience. Due to a focus on limited hypotheses and relatively larger expense, RCTs have a significant and inherent inefficiency. Well-designed and run prospective epidemiological trials have the capacity to bring larger volumes of high-quality evidence while more effectively addressing the complexities and nuances of biological diversity and individual behaviors, and should be accepted as actionable evidence on an equal, but separate, basis with the RCT.

- The scientific process focuses on probabilities in populations but each patient as an individual has unique characteristics of physiology and perspective that require adaption to the best evidence of the individual. Reductionism is incompetent to address this diversity and uniqueness. While there are certainly exceptions, researching and applying healthy lifestyle patterns are usually of more practical use than focusing on one particular nutrient or behavior.[38]
- There is much to be learned from the scientific process despite its inherent weaknesses and slowness. Humility and the desire to discover more are keys to progress. The lifestyle medicine clinician will welcome honest scrutiny and seek to broaden both understanding and practical application. This concern has been addressed in a review of research tools that builds on several approaches to suggest a strength of evidence approach entitled Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM).[39] It provides a framework through which to identify actionable recommendations where evidence has not or cannot reach the level of a randomized control trial.
- Changing individual behaviors is a challenging task in the best of circumstances but it is made even harder by a culture and subculture that encourages unhealthy behaviors. From the ubiquitous advertising of unhealthy value-added dietary and drink choices to a work and commuting environment that discourages physical activity, hundreds of cultural practices and environmental pressures undermine the health of individuals and communities. These may include structural interventions such as:
  - Increasing bike commuting, green space, and walking trails
  - Making it easier to take the stairs in buildings
  - Subsidizing whole plant food to make it more easily available in "food deserts"
  - Establishing farmer markets for the sale of local produce
  - Implementing a system in grocery stores for rating food healthfulness and quality to assist those seeking to make healthier choices
  - Limiting food stamps use to healthier foods
  - Cigarette taxes and banning advertising

  Those things that improve the context in which people are making choices will promote sustainability and may be included within the realm of lifestyle medicine. There is a tendency to place blame on individuals for their unhealthy practices, but commonly, at least a portion of the guilt belongs to unintended consequences or even the profit-driven actions or intent of capitalists within Western society. An expanded understanding of lifestyle medicine will necessarily expand the focus to include the improvement of society, culture, environment, and even government in ways that make it easier for everyone to make healthier choices. The real win in lifestyle medicine is a cultural win that makes the best lifestyle choices easy.
- Lifestyle medicine practitioners should be reimbursed for outcomes. The current payment system rewards procedures, putting the lifestyle physician at a disadvantage.[40] While the system is moving in that direction, its focus is more on screening and prevention rather than decreasing the per-member-per-month cost or quality of life.

86.5 DEFINITION CONSTRUCTS

Over the years, those active in the field have developed constructs with which to communicate and operationalize lifestyle medicine. They become the structure for patient education and programming. There are a variety of emphases ranging from nutrition and exercise to interpersonal relationships, stress management, and optimizing social relationships. While a complete listing is not possible here, a selected chronological listing may be helpful in understanding the dimensional complexity of lifestyle medicine as it has been developing through the years (Table 86.1).

86.6 SUMMARY

Lifestyle medicine is a relatively new term that has been adopted widely by the allopathic medical community. Its definition has expanded from beginnings that focused on health behaviors to include a clinical team, a branch of medicine, a medical specialty, and the social determinants of health within a society. The American College of Lifestyle Medicine defines lifestyle medicine as the following:

> Lifestyle medicine is a medical specialty that uses therapeutic lifestyle interventions as a primary modality to treat chronic conditions including, but not limited to, cardiovascular diseases, type 2 diabetes, and obesity. Lifestyle medicine certified clinicians are trained to apply evidence-based, whole-person, prescriptive lifestyle change to treat and, when used intensively, often reverse such conditions. Applying the six pillars of lifestyle medicine—a whole-food, plant-predominant eating pattern, physical activity, restorative sleep, stress management, avoidance of risky

TABLE 86.1
Lifestyle Medicine through the Years

NEWSTART[41] (circa 1982)	Ornish[42] 1990 Spectrum/Undo It	CREATION Health[43] 1994	Katz 2010[44, 45] True Health Initiative	American Board of Lifestyle Medicine[46] 2017
Nutrition	Nutrition	Choice	Forks (nutrition)	Nourishment
Exercise	Exercise	Rest	Fingers (not smoking)	Movement (exercise)
Water	Stress management	Environment breathing, hydration	Feet (exercise)	Resilience (emotional health)
Sunshine	Social support	Activity	Stress management	Connectedness (social)
"Temperance"—avoid harmful substances or excesses		Trust	Sleep	
Air		Interpersonal relationships	Love	
Rest				
Trust				

substances and positive social connections—also provides effective prevention for these conditions.

CLINICAL APPLICATIONS

- Lifestyle medicine involves significant evidenced-based changes in behaviors that affect health by a multidisciplinary team whose members have adopted healthy lifestyles.
- Ideally, every physician should offer lifestyle therapies to their patients with amenable disease states.
- There is a place for lifestyle medicine specialists to manage more challenging cases.
- The intent of lifestyle medicine is to increase both the quality and quantity of life with lower personal and societal costs.
- Interventions are based on the best quality evidence available from randomized controlled trials and well run epidemiologic observational trials.
- Lifestyle medicine seeks to change the cultural environment by working with businesses, communities, and governments to bring effective structural and social changes that encourage healthy behavior choices.

Those in lifestyle medicine see themselves as within the house of medicine, practicing evidence-based allopathic medicine that focuses on improving individual and societal behaviors that address the underlying cause of disease with the intent to both prevent and reverse disease.

NOTE

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87 Health Provider Core Competencies in Lifestyle Medicine

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KEY POINTS

- In 2009, a national panel of health professionals convened by the American College of Lifestyle Medicine (ACLM) and the American College of Preventive Medicine (ACPM) recommended 15 core competencies for providers to practice high-quality lifestyle medicine.
- The original competency domains covered leadership, knowledge, assessment skills, management skills, and use of office and community support.
- The refined and updated domains include the topics of practitioner's personal health, community advocacy, nutrition science, physical activity, sleep health, treating tobacco use disorder and managing other toxic exposures, key clinical processes, health behavior change fundamentals, emotional and mental health, and connectedness and positive psychology.
- The fundamentals of lifestyle medicine emphasize maximal use of science-based interventions, minimal use of medications and/or supplements, clinical approaches that leverage shared medical appointments, team-based care, behavioral science, and clinical patient and family/caregiver support enhanced with community resources.
- Key application areas of lifestyle medicine include nutrition and physical activity prescriptions, sleep hygiene guidance, facilitating health behavior change, assisting tobacco cessation and avoidance of risky substance use, stress management, promoting emotional well-being, and weight management.
- Provider self-care is an essential competency area that is shown to enhance providers' lifestyle counseling.
- The competencies have been refined during the development of national training programs of the ACLM and ACPM and the certification requirements and examination questions set forth by the American Board of Lifestyle Medicine.
- A dedicated committee of international lifestyle medicine experts will continue to update the competencies regularly to reflect the latest science and the advancing practice of the field.

87.1 INTRODUCTION: BACKGROUND AND DRIVING FORCES FOR CORE COMPETENCIES

The term "lifestyle medicine" has been used by a small group of practitioners and frontrunners in the field since 1988. However, it has not been used broadly across medical settings. Healthcare practitioners have been either unaware of the term or have used it to refer to different practices. No standard definition existed, leading to a lack of effective communication about the key elements of the field and what constitutes high-quality lifestyle medicine clinical practice and training.

By 2009, leaders of the *American Journal of Lifestyle Medicine*, the American College of Lifestyle Medicine (ACLM), and the American College of Preventive Medicine (ACPM) had developed their own definitions, overlapping, but slightly different. These definitions are reviewed in Chapter 86. Clearly, in order to advance the field with effective communication, research, training, and practice, consistency in terminology was necessary. Therefore, in 2009, the ACLM and the ACPM, with assistance from a special grant, convened a panel of representatives from an array of medical specialty societies that would develop a standard definition. The panel was also tasked with identifying the knowledge and skill competencies that physicians need in order to offer high-quality lifestyle medicine services.

87.2 NATIONAL CONSENSUS PANEL: BREAKTHROUGH FOR THE FIELD OF LIFESTYLE MEDICINE

The consensus panel gathered for a one-day meeting in 2009 led by Mark Johnson, representing ACPM, and Liana Lianov, representing ACLM, and facilitated by Mike Parkinson, a former ACPM president. The remainder of the panel consisted of representatives from the American Academy of Family Physicians, the American Medical Association, the American College of Physicians, the American Osteopathic Association, the American Academy of Pediatrics, and the American College of Sports Medicine. The panelists continued their discussion electronically for the ensuing year until they agreed on a definition for lifestyle medicine and 15 core lifestyle medicine competencies for primary care physicians. The panel also

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agreed that the initial focus should be on physicians, with the alignment that competencies for other health professionals and healthcare team members were necessary and would be developed subsequently.

The definition of lifestyle medicine that the panel developed is, "The evidence-based practice of helping individuals and families adopt and sustain healthy behaviors that affect health and quality of life". As reflected in this definition, the panelists clearly resonated with the fact that the role of supporting patients with behavior change is at the root of the practice to secure improved health outcomes. Much discussion was ignited about the types of behaviors a lifestyle medicine practitioner should aim to support. In the end, the panel decided to keep it open-ended with: "Examples of target patient behaviors include but are not limited to eliminating tobacco use, improving diet, and increasing physical activity".

The panel aligned around the basic constructs for a competent lifestyle medicine practitioner. These constructs require the ability to 1) perform comprehensive lifestyle assessments including risk factors and patient's readiness to change modifiable risk factors, 2) use national guidelines in lifestyle prescriptions, 3) use a team approach and establish effective patient and caregiver relationships, 4) make referrals when appropriate, 5) use information technology to maximize continuity of care, 6) personally practice a healthy lifestyle, and 7) promote healthy behaviors as the foundation for clinical care and lifestyle medicine. One can easily recognize how all of the outlined competencies can apply to primary care and other medical specialty practitioners. The key difference is in the focus area of using lifestyle change to, not only prevent but also treat diseases. Table 87.1 provides the complete list of the competencies, as worded by the consensus panel.

Unlike many other competency topics, which required discussion, the recommendation that physician personal health be a competency received immediate unanimous agreement by the panel. Physicians must aim to practice healthy lifestyles to maintain their own health and more effectively work with patients.

These recommendations of the national consensus panel were immediately seen as a breakthrough for the field of lifestyle medicine. The new set of core competencies that were developed in alignment with representatives from diverse physician and health organizations signaled the birth of a new field to the modern medical community, the knowledge and skills of which are relevant to any physician aiming to offer standard, quality services that leverage lifestyle change to achieve health outcomes. The statement of the consensus panel was published as a commentary in the *Journal of the American Medical Association* on July 14, 2010.[1,2] This article was the first circumstance in which the term "lifestyle medicine" was mentioned in the journal, outside of book reviews. The commentary aimed to nudge the general medical community to adopt these competencies.

87.3 REFINING THE ORIGINAL LIFESTYLE MEDICINE CORE COMPETENCIES

As seen in Table 87.1, the competencies developed in 2010 are worded succinctly and have led to much discussion about

TABLE 87.1
Original Lifestyle Medicine Core Competencies Identified by National Consensus Panel

Competency Domain	Core Competencies
Leadership	Promote healthy behaviors as foundational to medical care, disease prevention, and health promotion.
	Seek to practice healthy behaviors and create school, work, and home environments that support healthy behaviors.
Knowledge	Demonstrate knowledge of the evidence that specific lifestyle changes can have a positive effect on patients' health outcomes.
	Describe ways that physician engagement with patients and families can have a positive effect on patients' health behaviors.
Assessment skills	Assess the social, psychological, and biological predispositions of patients' behaviors and the resulting health outcomes.
	Assess patient and family readiness, willingness, and ability to make health behavior changes.
	Perform a history and physical examination specific to lifestyle-related health status, including lifestyle "vital signs" such as tobacco use, alcohol consumption, diet, physical activity, body mass index, stress level, sleep, and emotional well-being.
	Based on this assessment, obtain and interpret appropriate tests to screen, diagnose, and monitor lifestyle-related diseases.
Management skills	Use nationally recognized practice guidelines (such as those for hypertension and smoking cessation) to assist patients in self-managing their health behaviors and lifestyles.
	Establish effective relationships with patients and their families to effect and sustain behavioral change using evidence-based counseling methods and tools and follow-up.
	Collaborate with patients and their families to develop evidence-based, achievable, specific, written action plans such as lifestyle prescriptions.
	Help patients manage and sustain healthy lifestyle practices and refer patients to other healthcare professionals as needed for lifestyle-related conditions.
Use of office and community support	Have the ability to practice as an interdisciplinary team of healthcare professionals and support a team approach.
	Develop and apply office systems and practices to support lifestyle medical care including decision support technology.
	Measure processes and outcomes to improve quality of lifestyle interventions in individuals and groups of patients.
	Use appropriate community referral resources that support the implementation of healthy lifestyles.

their detailed interpretation. For example, some lifestyle medicine leaders expressed concern over the competency that discusses the use of national guidelines. In Chapter 86, lifestyle medicine was described as using treatments that have a basis in science. Yet some experts expressed concern that national guidelines can be influenced by commercial sectors, not always abiding by science.

Most hotly debated has been the issue of whether a whole food, plant-based diet should be the standard diet in lifestyle medicine interventions. To address some of these concerns, ACLM brought together the Lifestyle Medicine Standards Task Force, chaired by Jennifer Rooke, to review the literature and develop standards for the field. The Task Force's final standards released in 2013 confirm the National Blue Ribbon Panel's core competencies and enhance them with details. The Task Force concluded that the current scientific evidence favors a whole food, unprocessed, plant diet. The Task Force added two modality domains to the three in the consensus panel definition: stress management and "interpersonal-community-group relationships". They acknowledged that lifestyle medicine core competencies are essential to all physicians as a basic approach to managing chronic diseases. They also noted that a deeper set of knowledge and skills is required to offer lifestyle medicine as a specialized service.

87.4 LIFESTYLE MEDICINE CORE COMPETENCIES TRAINING

After the publication of the lifestyle medicine core competencies in *JAMA* in 2010, practitioners began to request training in these competencies. ACLM and ACPM successfully secured funding and in 2013 began the development of an online training program that was tested as a webinar series in 2014 and released in 2015. In the process of developing the training with learning objectives, the faculty further refined the core competencies. In addition, key modalities were covered, including nutrition, physical activity, sleep, avoiding risky substance use, stress management, and emotional well-being.

Principles highlighted in this training included maximal use of science-based interventions, minimal use of medications and/or supplements, clinical approaches that leverage shared medical appointments, team-based care, behavioral science, and clinical patient and family/caregiver support enhanced with community resources. Settings in which lifestyle medicine services can be integrated include primary care, specialty care, solo practitioner and team-based care, and virtual/telemedicine practices.

Additional organizations and partners, such as the Institute of Lifestyle Medicine, have contributed to training physicians in the core competencies through live and online training. Incorporating training early in a medical career is essential, as medicine builds a healthcare community of the future that fully integrates lifestyle medicine principles. An initiative, LMed, is offering online access to a variety of lifestyle medicine training modules geared for medical students and residents.[3,4]

87.5 REFINING THE COMPETENCIES FOR LIFESTYLE MEDICINE CERTIFICATION

As practitioners began training in lifestyle medicine, interest grew in establishing a certification process. In 2016, the field took another leap forward with the establishment of the American Board of Lifestyle Medicine for which Wayne Dysinger is the founding chair and Liana Lianov is the founding vice-chair. The founding board further refined the list of competencies upon which a certification exam is based.

87.6 UPDATING THE COMPETENCIES

In 2022, an update of the refined competencies list that was developed by a committee of lifestyle medicine experts from several different nationalities was released. The committee members met virtually over several months and made changes based on a consensus process. These updated competencies will serve as the foundation for lifestyle medicine training and education and board certification examinations. A committee with oversight by the Lifestyle Medicine Global Alliance will continue the updating process on a regular basis.

The updated competencies were reorganized, condensed where there was overlap, and reworded for clarity, and a few new competencies were added. Otherwise, the overall intent and content remained the same (Table 87.2). One new competency related to the prevalence and cost burden of lifestyle-related diseases was added. Several competencies on the therapeutic alliance and competency regarding the comparison of lifestyle medicine with medication treatment were added. Also, the role of lifestyle medicine in promoting personal practitioner resiliency and reducing burnout was specifically called out. The topic of sleep hygiene assessment became a separate competency and a competency was added to activities that increase physical, mental, and emotional flourishing.

Applicants for certification need to define lifestyle medicine, understand the difference between this field and related fields, and describe its unique role. They must understand the importance of lifestyle interventions in treating lifestyle-related diseases, describe the role of behavioral determinants in achieving positive health outcomes, and cite the scientific evidence for behaviors and lifestyle changes that impact health outcomes and disease pathophysiology.

The core of successful lifestyle medicine interventions is enabling patients to achieve health-appropriate behavior change. Hence, practitioners need to skillfully assess each patient's change-readiness stage and offer stage-matched responses. Empathetic interactions with patients and their families and caregivers are required to build effective

TABLE 87.2

2022 Updated Core Competencies[5]

A. Introduction to Lifestyle Medicine	1. Discuss lifestyle medicine and its unique role in healthcare practice 2. Describe the lifestyle medicine core competencies as identified by a national consensus panel 3. Compare and contrast lifestyle medicine with other fields of health and medicine 4. Summarize the scientific evidence that shows health behaviors are associated with key health outcomes 5. Describe the evidence showing that lifestyle interventions effectively impact disease pathophysiology 6. Describe the priority of lifestyle medicine in the spectrum of treatment algorithms for chronic, lifestyle-related diseases across the lifespan 7. Discuss the prevalence and associated cost burden of lifestyle-related diseases, such as hyperlipidemia, cardiovascular disease, prediabetes, diabetes, hypertension, obesity, and cancer 8. Explain the impact of lifestyle choices on planetary health and sustainable living
B. The Role of the Practitioner's Personal Health and Community Advocacy	1. Examine scientific evidence that suggests practitioners who practice healthy lifestyles are more likely to offer counseling, serve as role models, and improve patient outcomes 2. Develop a culture of leadership by modeling personal health behaviors 3. Describe strategies for incorporating personal wellness for practitioners into clinics, medical offices, or other healthcare settings, including wellness programs 4. Examine essential practitioner characteristics and practices that increase the capacity and impact of the therapeutic alliance 5. Integrate personal readiness assessments and lifestyle action plans into sustainable life patterns for practitioners 6. Explore the role of lifestyle medicine in promoting personal practitioner resiliency and reducing burnout 7. Advocate for lifestyle medicine directly with patients and their families, as well as policy and decision-makers within the community
C. Nutrition Science, Assessment, and Prescription	1. Assess food intake patterns and nutrients of deficit and excess 2. Analyze food labels for the health impacts of ingredients 3. Discuss commonalities and key messages of global dietary guidelines. 4. Summarize the health impact of prominent dietary patterns, including plant predominant and non–plant predominant patterns 5. Describe how the level of processing in a food affects health and discuss the evidence base for these effects 6. Describe the practice of culinary medicine and its role in sustainable healthy eating behavior 7. Summarize the major studies of nutrition in the prevention, treatment, and reversal of hyperlipidemia, cardiovascular disease, prediabetes, diabetes, hypertension, obesity, and cancer 8. Apply nutrition prescriptions based on science that shows how nutrition can address the pathophysiology of most chronic diseases, including inflammation, oxidation, glycosylation, epigenetic expression, and the microbiome* 9. Demonstrate the ability to write evidence-based nutrition prescriptions* 10. Describe indications for referral to a lifestyle medicine trained registered dietician to translate and further personalize nutrition prescriptions
D. Physical Activity Science, Assessment, and Prescription	1. Discuss the aerobic, strength, flexibility, and balance components of physical activity 2. Examine the evidence and pathophysiology between physical activity components and health outcomes 3. Describe the benefits of physical activity in preventing or treating disease in special populations, such as healthy older adults, pregnant women, children and adolescents, persons with obesity or disability, cardiovascular disease, diabetes, cancer, disability, and stroke 4. Summarize the role of physical activity guidelines 5. Integrate key physical activity assessment tools into clinical practice 6. Define fitness terminology relevant to writing exercise prescriptions 7. Integrate evidence from relevant physical activity literature into treatment protocols for management, remission, or reversal in patients with diabetes, cancer, cardiovascular, and cerebrovascular disease* 8. Describe indications for referral to health fitness professionals 9. Develop physical activity prescriptions appropriately modified for special populations, such as healthy older adults, pregnant women, children and adolescents, persons with obesity or disability, cardiovascular disease, diabetes, cancer, disability, and stroke*
E. Sleep Health Science and Interventions	1. Describe sleep's role in health and chronic disease pathophysiology 2. Perform sleep assessments to identify patients with insufficient or poor-quality sleep 3. Summarize lifestyle-based interventions that can improve sleep health 4. Assess the risk for common sleep disturbances, such as obstructive sleep apnea, chronic insomnia, and restless legs syndrome, and refer to sleep specialists when applicable 5. Describe the indications for referral to a sleep specialist or for a sleep study to assess for sleep apnea 6. Describe indications for referral to a program or specialist in cognitive behavior therapy for insomnia

(*Continued*)

TABLE 87.2 (CONTINUED)

2022 Updated Core Competencies[5]

F. Treating Tobacco Use Disorder and Managing Other Toxic Exposures (Including Vaping, Alcohol Use, and Other Illicit Substances)	1. Describe the health effects of tobacco, alcohol, and other frequently used substances and the benefits of cessation 2. Apply patient screening tools for substance use 3. Create patient-centered substance use treatment plans using practice guidelines and behavioral interventions* 4. Summarize the diagnostic criteria for common substance use disorders 5. Integrate behavior therapy with pharmacotherapy for tobacco and other substance use disorder plans, and refer to a substance use disorder specialist when indicated* 6. Apply the United States Preventive Services Task Force guidelines for patients with tobacco use disorder
G. Key Clinical Processes in Lifestyle Medicine	1. Integrate lifestyle vital signs into components of the patient history and physical exam 2. Analyze and implement evidence-based clinical practice guidelines relevant to lifestyle medicine for prevention, treatment, and reversal of chronic diseases* 3. Describe the treatment of disease with the lifestyle medicine pillars as compared with medication 4. Demonstrate how to screen, diagnose, treat, and monitor a lifestyle-related disease and provide lifestyle medicine–focused anticipatory guidance* 5. Discuss strategies for a clinical practice to access and implement use of local, national, and global resources 6. Describe the key strategies for leveraging inter-professional teams to enhance health behavior change interventions 7. Examine how group visits and telehealth can optimize lifestyle medicine treatment encounters 8. Create and utilize data from office systems, such as electronic health records with lifestyle medicine guidance, in clinical decisions and care, including tracking screening frequency, test results, referrals, and recommended follow-up 9. Analyze the evidence for collaborative and chronic care models on improved lifestyle outcomes 10. Discuss successful primary care and office-based models for lifestyle modification 11. Design a quality improvement project for lifestyle medicine clinical practice, using tools, such as Plan-Do-Study-Act (PDSA) cycles 12. Explain principles of evidence-based medicine and their application to lifestyle medicine 13. Describe methods of assessing effectiveness of interventions, such as patient activation measures and therapeutic alliance measures
H. Fundamentals of Health Behavior Change	1. Summarize health behavior change theories, such as the health belief model, the social learning theory, and the transtheoretical model (TTM), and their application to lifestyle medicine practice 2. Demonstrate key elements of conducting a patient assessment within the TTM and collaborate to develop stage-matched responses 3. Apply the process of building effective and therapeutic alliances with patients that foster their personal growth 4. Explain how to collaborate with your patients to promote health behavior changes 5. Apply motivational interviewing, cognitive behavioral, health coaching, and positive psychology techniques 6. Summarize the evidence to support the use of behavior change techniques in clinical practice 7. Use the skills of open inquiry, reflections, and empathy to develop and maintain a therapeutic alliance 8. Describe the impact of positive emotions on the success of health behavior change 9. Develop patient-centered, written action plans based on the appropriate stage of change of the TTM 10. Summarize the process of follow-up for ongoing lifestyle change progress, including building patient self-efficacy and relapse prevention 11. Describe the factors that support sustained behavior change 12. Explain the role of family and other support to initiate and maintain health behavior change 13. Manage disruptions to the therapeutic alliance 14. Identify patient resources for sustainable behavior change in relation to the pillars of lifestyle medicine
I. Emotional and Mental Health Assessment and Interventions	1. Apply screening tools for stress, depression, and anxiety in clinical practice 2. Explain the relationship and pathophysiology between emotional and physical health 3. Summarize the nature of stress, the role of stressors, such as adverse child experiences, and identify manageable elements of pathogenic stress reactions 4. Describe and utilize evidence-based and patient-centered mental and emotional health, including self-management and resilience-building techniques 5. Analyze the clinical relevance and evidence base for mindfulness-based stress reduction (MBSR) and related stress management strategies 6. Manage treatment plans for lifestyle-related mental health diseases, such as depression and anxiety* 7. Describe indications for referral to mental health professionals (versus when clinically indicated) 8. Apply mindfulness skills to enable presence, clarity, and curiosity in the clinical encounter
J. The Role of Connectedness and Positive Psychology	1. Apply positive psychology in health behavior change counseling 2. Describe how positive psychology strategies support achieving and sustaining healthy behaviors 3. Compare and contrast eudaimonia and hedonia, and explain their effect on physical health, including longevity 4. Describe how social connectedness and social networks influence emotional well-being, physical health, and longevity 5. Summarize the deleterious and positive effects social media has on emotional well-being and flourishing 6. Explain the relationship among the lifestyle pillars, positive emotions, and flourishing 7. Describe positive psychology activities that can boost emotional well-being and flourishing

*Indicates competencies that might be beyond the scope of practice for some health professional groups. The lifestyle medicine board examination includes additional questions for physicians/health care providers.

relationships that support successful outcomes. Skills in motivational interviewing and cognitive behavioral and (see also Chapter 22 on Motivational Interviewing and Lifestyle Change) positive psychology techniques (see also Chapter 24 on The Impact of Positive Psychology on Behavioral Change and Healthy Lifestyle Choices) also enhance relationships with patients that support behavior change.

Practitioners must not only be able to make lifestyle treatment prescriptions but also assist patients who are in the action stage to develop written feasible, individualized action plans.

For patients who achieve action plans, providers must be able to help patients maintain those healthy behaviors. Effective use of motivation and confidence scales is essential. Also, an understanding of health behavior change theories (see also Chapter 21 on Applying Psychological Theories to Promote Healthy Lifestyles by Gholami et al.), including the key construct of self-efficacy and frameworks, such as the five As (ask, advise, assess, agree, assist) model[6] how to incorporate these techniques into the office visit and how to apply the elements of sustainable self-management is essential. Skills to support behavior change include coaching skills appropriate to patient readiness, culture, and personality, offering follow-up strategies for ongoing lifestyle change progress, and relapse prevention planning.

- Describe the process of building effective relationships with patients.
- Apply motivational interviewing, cognitive behavioral, and positive psychology techniques.
- Develop a written action plan based on the treatment prescription adjusted for the appropriate stage of change.
- Describe strategies for helping patients maintain healthy behaviors.
- Cite at least three health behavior change theories and their potential application to practice.
- Understand the five As and how to incorporate them into the office visit.
- Identify two key constructs for effective, sustainable self-management.
- Describe the process of follow-up for ongoing lifestyle change progress, including building patient self-efficacy.
- Demonstrate the use of readiness, importance, and confidence scales.
- List components of relapse prevention planning.
- Cite the evidence base for effective coaching that promotes health behavior change and improves health outcomes.
- Describe how to create relationships with patients that foster their personal growth.
- Describe the role of self-motivation and self-confidence in effective coaching for health behavior change.
- Describe the main stages of the coaching process.
- List the coaching questions for each stage of change.

The ability to conduct key clinical processes of a successful lifestyle medicine practice includes taking a patient history and conducting a physical examination with emphasis on lifestyle risk factors, ordering appropriate screening and diagnostic tests relevant to lifestyle-related diseases, interpreting the tests using scientifically based criteria, and referring to local community resources. Additional crucial lifestyle medicine practice skills involve collaborating with other health professionals, such as dieticians, health educators, fitness trainers, and psychologists outside of the practice, as well as leveraging an interdisciplinary team in the practice (where available) to enhance health behavior change interventions.

In fact, the refined competencies were adapted for an array of health professionals beyond the initial target groups of physicians. Hence, a number of the competencies are distinguished with an asterisk as ones that may be outside of the scope of practice for some health professional groups.

A clinical practice that optimally supports lifestyle modification must work with office systems and tools that track screening frequency and test results and proactively prompt follow-up, incorporate planned and group visits, maintain information about local community resources, and design office flow to assure consistent and up-to-date referrals. The provider should be able to cite the evidence for successful collaborative chronic care and primary care office-based models for lifestyle modification.[7] As with any healthcare practice, lifestyle medicine providers should be able to apply healthcare service quality improvement processes, including the Plan-Do-Study-Act (PDSA) cycles.[8] But these processes should focus on how best to implement lifestyle interventions.

As noted in a prior section, one area on which the national consensus panel for the core competencies unanimously agreed is the physician's personal health practices. Providers eligible for certification should be able to cite scientific studies demonstrating that physicians who practice healthy lifestyles are more likely to offer counseling and improve patient outcomes. (see also Chapter 24 on The Impact of Positive Psychology on Behavioral Change and Healthy Lifestyle Choices). Lifestyle medicine clinicians should be able to implement strategies for incorporating healthcare team wellness activities into clinics, medical offices, or other healthcare settings. Moreover, since a healthy lifestyle is more likely to be achieved and maintained in supportive environments, lifestyle medicine practitioners should conduct effective advocacy and lend their expertise in healthy lifestyles to policy-makers and decision-makers within the community.

The single modality area with the greatest attention and focus in a healthy lifestyle, due to its spectrum of approaches and controversy across health professionals, is nutrition. A foundation for nutrition prescriptions is to first understand the Dietary Guidelines for Americans and why they are important. But the field of lifestyle medicine also requires going beyond the guidelines to the latest science, with the acknowledgment that dietary guidelines can have

limitations. Criteria to determine which foods are healthiest and which are least health-promoting should be based on this science. Providers need to be able to list the food components most Americans get too much of and in which foods they are found, as well as the

shortfall of nutrients that Americans are failing to sufficiently consume and in which foods they are found.

Lifestyle medicine practitioners should be able to summarize the major nutrition studies and the evidence base for nutrition prescriptions. They need to demonstrate the ability to perform a basic nutrition assessment and make nutrition prescriptions to address basic disease processes such as inflammation, and prevent and treat the most common chronic diseases including hyperlipidemia, diabetes, hypertension, cardiovascular disease, and cancer. An understanding of macronutrients in various dietary patterns, food types that contain important micronutrients, and the oxidative impact of food preparation methods are key knowledge areas. Providers must also be knowledgeable in effective community programs and digital applications, such as the Complete Health Improvement Program,[9] and refer patients to them appropriately. An understanding of the avoidance of medication side effects through appropriate intensive nutritional interventions, and the role of epigenetics in healthy nutrition, are additional core knowledge areas. The ability to manage medications during the transition to a healthy lifestyle in diabetes and other chronic diseases is an essential skill.

Knowledge of the science supporting physical activity and skill in prescribing physical activity constitute the second major lifestyle medicine modality. Practitioners need to define physical activity and exercise, list the most recent Physical Activity Guidelines for Americans (PAGA) (see also Chapter 16 on Exercise Prescription for Apparently Healthy Individuals and for Special Populations) and the recommendations for healthy adults, children, pregnant individuals, and individuals with various chronic illnesses. (See Chapter 16). They must be able to describe the key scientific evidence that links physical activity and health that supports the physical activity components (aerobic, strength, flexibility, and balance) and the use of physical activity in contrast to medication to treat chronic disease and manage weight.[10,11] They also must identify the minimum and maximum levels of exercise, list key physical activity assessment tools, have the ability to use METS in assessing fitness, and be proficient at developing exercise prescriptions, including the basic components of the prescription (frequency, intensity, type, and time) (see Chapter 15 on Physical Fitness Evaluation). As with other modalities, effective practitioners must understand the role of personal behavior and role modeling.

MDs/DOs

- Thirty hours of online CME
- Ten hours of in-person CME
- A case study outlining your personal experience with lifestyle medicine

PhD/master's Level

- Thirty hours of online CME
- Ten hours of in-person CME

While the ABLM sets the certification competencies and lifestyle medicine standards, it is left up to the participants to acquire the necessary knowledge, skills, and experience from reputable sources. The ABLM accepts CMEs of the following programs/providers:

Online content:

- ACLM/ACPM Lifestyle Medicine Core Competencies (LMCC)
- Institute of Lifestyle Medicine (Harvard) online courses
- Cornell certificate in plant-based nutrition

In-person learning:

- ACLM conferences and workshops (CME)
- Institute of Lifestyle Medicine (Harvard) conferences (CME)
- Food as Medicine conferences (CME)
- International Plant Based Nutrition Healthcare Conferences (CME)
- ACPM conference, lifestyle medicine stream (CME)

Rules:

- CMEs must be no older than 36 months at the time of registration
- Proof of CMEs, credentials, and case study must be submitted at least 30 days prior to the certification exam
- To certify as a Lifestyle Medicine physician
  - You must be an ABMS board-certified MD or DO
  - Your certification will be issued by the ABLM
- To certify as a Lifestyle Medicine professional
  - You must hold a PhD or master's degree in a health or allied health discipline, or
  - You must be a Doctor of Nursing Practice, or
  - You must be a certified and licensed physician assistant, or
  - You must be a Doctor of Optometry, or
  - You must be a Doctor of Podiatry, or
  - You must be a Doctor of Chiropractic, or
  - You must be a Doctor of Psychotherapy, or
  - You must be a Doctor of Exercise Physiology, or
  - You must be a Doctor of Occupational Therapy, or

- You must be a Doctor of Pharmacy, or
- You must be a Doctor of Physiotherapy, or
- You must be a Doctor of Psychology, or
- You must be a Doctor of Dentistry
- Your certification will be issued by the ACLM

Demonstrate key elements of conducting patient readiness assessment and stage-matched responses

Describe the relationship between physical activity (PA) and health:

- Develop an exercise prescription
- Describe the major evidence for the physical activity components (aerobic, strength, flexibility, and balance)
- Define physical activity and exercise
- List the components of exercise
- Describe the US Physical Activity Guidelines for Americans (PAGA)
- Understand the role of personal behavior and role modeling
- Understand the use of METS in assessing fitness
- Describe the impact of exercise on weight
- Identify the minimum and maximum levels of exercise
- Describe the major evidence for the physical activity components (aerobic, strength, flexibility, and balance)
- List key physical activity assessment tools
- Describe how to collaborate with your patients to promote physical activity change
- Identify resources for sustainable behavior change
- List the components of writing the exercise prescription
- Describe the treatment of disease with exercise as compared with medication
- List evidence-based PA recommendations for healthy older adults, pregnancy, obesity, heart disease, diabetes, cancer, disability, and stroke

Emotional and mental well-being is at the heart of a person's ability to achieve and maintain healthy lifestyles. Emotional distress and mood disorders are frequent comorbidities of common chronic illnesses, such as diabetes and cardiovascular diseases, and have direct physiologic effects, which impact health outcomes directly in addition to lowering attention to and capacity for health behaviors. Lifestyle medicine providers must maintain knowledge of these associations and the latest science, including the role of stress and the physiologic impact and effectiveness of interventions, such as mindfulness-based stress reduction. They need to be able to conduct assessments, offer appropriate interventions, manage depression and anxiety as comorbidities, and refer to mental health professionals when indicated. They must be skilled at applying screening tools for stress, depression, and anxiety, assisting patients with self-management, implementing principles of positive psychology, and referring to emotional well-being programs. Providers who engage in effective patient relationships are able to identify the benefits of physician empathy, attunement, and resonance in the clinical encounter, and practice it consistently.

Sleep is another fundamental component of a healthy lifestyle (see Chapter 82). Lifestyle medicine practitioners must understand sleep's role in health and chronic disease and be able to recommend physical activity, dietary, environmental (such as light exposure), and coping behaviors that can improve sleep health. Also essential to the lifestyle medicine practice is knowing how to assess for key factors that differentiate patients with insufficient or poor-quality sleep and the ability to recommend lifestyle adjustments related to light exposure and meal composition and timing to support improved sleep.

Understanding sleep's role in health and chronic disease:

- Identify lifestyle-based activity, dietary, environmental, and coping behaviors that can improve sleep health
- Identify at least two lifestyle adjustments related to light exposure and meal composition and timing that support improved sleep
- Identify key factors that differentiate patient subpopulations with insufficient or poor-quality sleep
- Understand the role of light exposure and endogenous melatonin in sleep health
- Identify two to three lifestyle adjustments related to light exposure that support improved sleep
- Identify one to two lifestyle adjustments related to meal composition and timing that support improved sleep

Assisting patients with tobacco cessation (see Chapter 97) and managing risky alcohol (see Chapter 98) are additional skills critical to a high-quality practice. The practitioner needs to describe the evidence-based literature on the health effects of tobacco, the role of avoiding excessive alcohol intake in preventing and treating chronic disease, and effective tobacco cessation and alcohol misuse interventions. He must demonstrate the ability to screen for tobacco use and alcohol misuse and assist patients to develop and implement plans for tobacco cessation plans and avoiding risky alcohol use.

Weight management is an important focus area for lifestyle medicine due to the current obesity epidemic. The practitioner must understand the medical risks associated with overweight and obesity and the complex etiology of obesity (see Chapter 42). He needs to use evidence-based weight management guidelines, such as those released by national organizations, including the Endocrine Society, the American Heart Association, the American Gastrological Association, and the Obesity Society[12] to design successful intervention plans and programs. He also needs to be able to implement the four main components of weight management skills within clinical practice: behavior change, nutrition, physical activity, and psychosocial support.

87.7 THE ONGOING EVOLUTION OF LIFESTYLE MEDICINE COMPETENCIES

As described in this chapter, the knowledge and skill competencies of practitioners in the field of lifestyle medicine have been identified, expanded, and refined in the years since the term was first used. Innovators in the field began defining the practice in the 1980s. The field came into its own with the release of a definition and core competencies by the National Consensus Panel in 2010. Training programs for continuing education, as well as for students and residents, and the development of a certification program have further defined and refined these knowledge and skills areas required for competent lifestyle medicine practitioners. The application of the competencies was expanded for use by a variety of health practitioners beyond the initial target group of physicians and certain competencies may be relevant only for physician or other health provider groups. The competencies were updated in 2022 and will need ongoing updates. With the growing interest of physicians in focusing on lifestyle medicine as an area of specialization, competencies for physicians specializing in lifestyle medicine have been developed.[13] A set of competencies for lifestyle medicine intensivists whose practices are dedicated to intensive lifestyle medicine interventions are soon to be released.

The field is continuing to evolve, as the science and evidence that supports it expands.

Opportunities to study and implement new clinical applications will influence the competency requirements (Table 87.3). However, the core basis of the field will remain focused on lifestyle interventions for treating disease based on scientific evidence.

Website Resources

American Board of Lifestyle Medicine: https://ablm.org
American College of Lifestyle Medicine: https://lifestylemedicine.org/certification

TABLE 87.3
Clinical Applications

Competency Area	Key Clinical Applications
Personal Health/Self-Care	Model healthy behaviors for patients
	Discuss with patients behavior change challenges and solutions from personal experience, as appropriate
Health behavior change	Assess patients' readiness to change
	Engage in empathetic interactions with patients/families
	Apply evidence-based coaching techniques, such as motivational interviewing, cognitive behavioral and positive psychology techniques
	Help patients develop relapse prevention planning
Effective clinical processes	Take a patient history, conduct a physical examination, and order and interpret appropriate screening and diagnostic tests relevant to lifestyle-related diseases
	Refer to local community resources and collaborate with other health professionals,
	Work in an interdisciplinary team
	Incorporate planned and group visits
Healthy nutrition	Perform a basic nutrition assessment
	Make nutrition prescriptions to prevent and treat the most common chronic diseases
	Manage medications during the transition to a healthy diet and lifestyle
Physical activity	Use physical activity in contrast to medication in treating chronic disease and managing weight
	Use METS to assess fitness
	Develop exercise prescriptions, including the basic components of the prescription (frequency, intensity, type, and time)
Mental and emotional well-being	Apply screening tools and assess for stress, depression and anxiety, and general emotional well-being
	Manage mood disorders and refer to mental health professionals when indicated
	Assist patients with self-management and refer to emotional well-being programs
	Consistently practice physician empathy, attunement, and resonance in the clinical encounter
	Recommend positive psychology-based activities
Sleep Health	Recommend physical activity, dietary, and coping behaviors that can improve sleep health.
	Assess for key factors that differentiate patients with insufficient or poor quality sleep
	Recommend lifestyle adjustments related to light exposure and meal composition and timing to support improved sleep
	Understand sleep's role in health and chronic disease
Tobacco cessation and managing risky alcohol use	Screen for tobacco use and alcohol misuse
	Assist patients in developing and implementing plans for tobacco cessation plans and avoiding risky alcohol use
Weight management	Use evidence-based weight management guidelines
	Design successful intervention plans and programs
	Implement the four main components of weight management: behavior change, nutrition, physical activity, and psychosocial support

Positive psychology science for health and in healthcare—Global Positive Health Institute: https://positivehealth.world
Healthy People 2030: https://health.gov/healthypeople
Institute for Health Care Improvement: https://www.ihi.org
National Survey on Drug Use and Health: https://nsduhweb.rti.org
Prescription for Health: http://www.prescriptionforhealth.org/
US Preventive Services Task Force: www.uspreventiveservicestaskforce.org

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88 Lifestyle Medicine Clinical Processes

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88.1 INTRODUCTION

What sets a traditional clinical practice apart from one that has a foundation in lifestyle medicine? Practicing lifestyle medicine (LM) in the clinic first entails placing the patient at the center of the encounter. Patients are the experts of their own lives, necessary to every aspect of care, and treatment depends on their consent. Second, the patient's lifestyle is assessed, and positive change is supported throughout the encounter. The treatments and follow-ups are prescribed according to the patient's engagement level in lifestyle change. Education, referrals, and community resources are provided with respect and in line with the patient's goals, values, and need for further care.

In this chapter, we explore four perspectives of clinical processes:[1] the clinical encounter,[2] interdisciplinary team-based care,[3] office systems and processes, and quality improvement,[4] and how each is essential to forming and sustaining a lifestyle medicine practice.

88.2 LIFESTYLE MEDICINE IN THE CLINIC

The clinical practice of LM necessitates a comprehensive approach that identifies underlying lifestyle-related risk factors through vital signs, history, physical examination, and screening and diagnostic tests (Figure 88.1). Once lifestyle risk factors are identified, lifestyle medicine treatments can be prescribed at a high enough intensity to affect health outcomes, while systematically tracking and documenting patient outcomes. As lifestyle-related diseases improve, some medications may need to be reduced or discontinued, making LM one of the few fields of medicine where deprescribing is a routine part of practice.

88.2.1 Lifestyle-Focused History

The process of taking an LM history includes an assessment of behavioral risk factors, such as physical activity level, nutrition, stress and well-being, social relationships, sleep, and substance use, as well as environmental and occupational factors, that predispose one to developing preventable lifestyle-related diseases. The 2010 foundational JAMA article, *Physician competencies for prescribing lifestyle medicine*,[1] labeled these brief assessments done at the point of care lifestyle "vital signs". Implementing lifestyle vital signs is considered a key proficiency for the LM practitioner.

88.2.1.1 Lifestyle Medicine Vital Signs

Traditional vital signs, like temperature and heart rate, are measurements of the body's most basic functions. They must be within a certain range to sustain life. Following a similar logic, lifestyle medicine vital signs assess a range of behaviors at which a "healthy" life is sustainable.

The Physical Activity Vital Sign described by Coleman et al was the prototype that other LM vital signs followed.[2] This simple two-question screening could quickly let clinicians know if a patient was inactive, insufficiently active, or appropriately active. Physical fitness is now recognized as both a current measure of health and a surrogate marker of future disease.

The ongoing challenge has been clearly identifying the fundamental behavioral pillars of health and how best to assess them. Useful lifestyle medicine vital signs may differ between practices and locations around the world. The goal remains for providers and patients to efficiently identify the presence of helpful or harmful lifestyle behaviors.

As seen in Figure 88.2, the American College of Lifestyle Medicine has produced a Lifestyle Assessment Short Form to assist clinicians in delivering a brief assessment to evaluate several of these key components with a brief series of questions.

Given the expanse of potential questions and responses in an LM-focused history, it is valuable to have both brief and expanded measures for LM risk factors, creating a more efficient delivery mechanism and the ability to target counseling to those areas in which the individual is receptive to change or has greater need. A more in-depth version of the Lifestyle Assessment Form[3] has been developed for a detailed analysis of these components and can be found in Figure 88.3.

Some providers chose to use a long form at an initial patient assessment as an exhaustive evaluation of all potential lifestyle-related health behaviors. Others chose to evaluate behaviors briefly, identify the key areas of interest, and then provide appropriate longer assessments at the subsequent visits or for the patient to complete on their own time. Below, brief and in-depth methods are discussed to evaluate individual pillars of health.

88.2.1.2 Physical Activity Assessment

The relationship between physical activity and health outcomes is generally curvilinear so marked health benefits can be seen with relatively minor increased amounts of physical activity. Exercise is safe for most people and has many associated health and fitness benefits (Table 88.1).[4]

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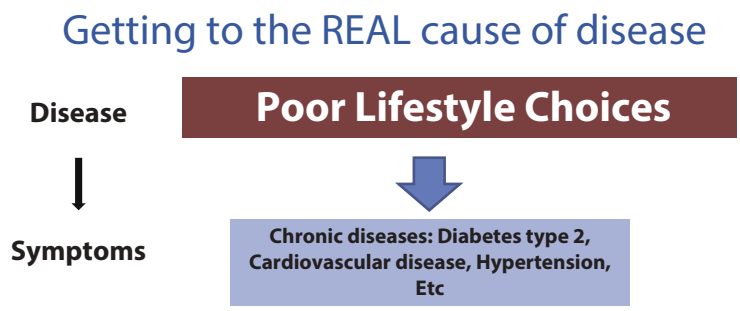


FIGURE 88.1 Real cause.

A helpful tool to assess who is safe to begin exercise and who is not is the Physical Activity Readiness Questionnaire (PARQ).[12]

88.2.1.3 Nutrition Assessment

Nutrition assessments and interventions very often demand the most attention but may also yield the highest benefit. An unhealthy diet can be closely correlated with an increased risk of chronic conditions, including overweight, obesity, diabetes, hypertension, and hyperlipidemia (Table 88.2).[13,14]

When measuring dietary habits, appropriately train your team and prepare educational materials that clarify terms like serving size, food groups, complex versus simple carbohydrates, and "processed" meat. Heavy attention has been given to the macronutrients (carbohydrates, protein, and fat), however, it may be more meaningful to assess for dietary patterns, looking for things such as 1) the presence of whole foods rather than select nutrients (e.g., whole grains rather than selenium), 2) foods associated with health and disease resistance (e.g., vegetables, fruits, whole grains, legumes, nuts and seeds), and 3) foods associated with disease (e.g., processed meats, red meats, fried foods, added sugars, refined grains).

Encourage self-monitoring, for example, measurement of nutrition and caloric intake has shown a consistent association with successful weight loss.[30] Advanced smartphone apps may also encourage weight loss.[31]

88.2.1.4 Stress Assessment

A national study on stress estimated that 60 to 80% of primary care visits were associated with stress-related complaints (headache, back pain, migraines), therefore, making it crucial to assess stress (Table 88.3).[32]

88.2.1.5 Well-Being Assessment

Well-being measures include the presence of positive emotions and moods (e.g., contentment, happiness), the absence of negative emotions (e.g., depression, anxiety), satisfaction with life, fulfillment, and positive functioning.[37] Well-being can be challenging to assess in the clinic as it addresses the sensitive areas of mental and emotional health.

If possible, allow the patient to answer this type of question in a more private setting such as surveys administered on paper, mobile phone, or tablet at the time of visit rather than directly asking the questions. Paper screening and e-screening both appear to have similar benefits and risks from disclosure.[38]

As in nutrition, digital tools may offer utility not only in the evaluation and monitoring phases but also in planning and implementing the interventions. Apps for emotional and mental self-help were found to increase motivation and the desire to set goals, confidence, control, and intentions to be mentally and emotionally healthy, with association with perceived change in behavior.[48] These mobile health technologies have the potential utility of incorporation into the electronic record for an efficient clinical practice.

88.2.1.6 Social Support Assessment

A 75-year cohort study on adult development that compared male Harvard students to similar men from inner-city Boston concluded that the single most important predictor of happiness and longevity is social connectedness.[49] Social support and optimism can help negate the typical health effects of a disadvantaged childhood.[50] Gaining an understanding of a person's social support system may be essential to behavior change.

88.2.1.7 Sleep Assessment

Sleep is one of the least appreciated pillars of lifestyle medicine. It is considered almost heroic by some in American culture if one can function continuously on a small amount of sleep. However, evidence seems to indicate that no one really functions well in a sleep-deprived state. Chronic sleep deprivation increases the risk of cardiovascular disease, obesity, and type 2 diabetes.[53] Sleeping less than six hours a night increases a driver's risk of crashing by 33%. [54]

88.2.1.8 Substance Use

Substance use is already a part of the social history asked in most medical clinics. The harms of tobacco, alcohol, and illicit drug use are well known. We continue to learn more about the health impacts of recreational marijuana. Prescription drug misuse and overprescribing continue to rise. Getting an idea of how often and how much your patients use these substances can help gauge their health risks.

88.2.1.9 Risk Factors

National and international guidelines and risk factor assessments may also be used to evaluate disease risk.

AMERICAN COLLEGE OF
Lifestyle Medicine

LOMA LINDA UNIVERSITY
HEALTH
Produced in collaboration
with Loma Linda University

Lifestyle Assessment Short Form

OVERALL HEALTH

1. Please circle your overall LEVEL of HEALTH

0 Very poor health 1 2 3 4 5 6 7 8 9 10 Excellent health

SLEEP

2. OVER THE LAST TWO WEEKS, how many hours of sleep did you average in a 24-hour period?

a. Less than 4 hours
b. 4-5 hours
c. 6 hours
d. 7-8 hours
e. 9 or more hours

3. OVER THE LAST TWO WEEKS, how often did you feel tired or have difficulty staying awake during routine tasks in the day?

a. Not at all
b. Several days
c. More than half the days
d. Nearly every day

NUTRITION

5. OVER THE LAST TWO WEEKS, how often have you eaten fast food, sugary drinks (e.g., soda, sports drinks, juice) or packaged foods (e.g., chips, candy, crackers, cookies)?

a. Not at all
b. Several days
c. More than half the days
d. Nearly every day

6. ON AN AVERAGE DAY, how many servings of whole fruits and vegetables do you eat (1 serving is about a handful and does not include fruit juice)?

a. Less than 2 servings
b. 2-3 servings
c. 4-5 servings
d. More than 5 servings

WEIGHT MANAGEMENT

4. What do you think about your current weight?

a. I want to gain a lot of weight
b. I want to gain a little weight
c. I am happy with my weight
d. I want to lose a little weight
e. I want to lose a lot weight

EXERCISE

7. OVER THE LAST TWO WEEKS, how many days did you exercise at a moderate to strenuous intensity (e.g., brisk walking or enough movement to break a light sweat)?

a. Less than 1 time per week
b. 1-2 times per week
c. 3-4 times per week
d. 5 or more times per week

8. DURING AN AVERAGE SESSION, how many minutes do you exercise at a moderate to strenuous intensity (e.g., brisk walking or enough movement to break a light sweat)?

a. Less than 10 minutes
b. 10-29 minutes
c. 30-49 minutes
d. 50 minutes or more

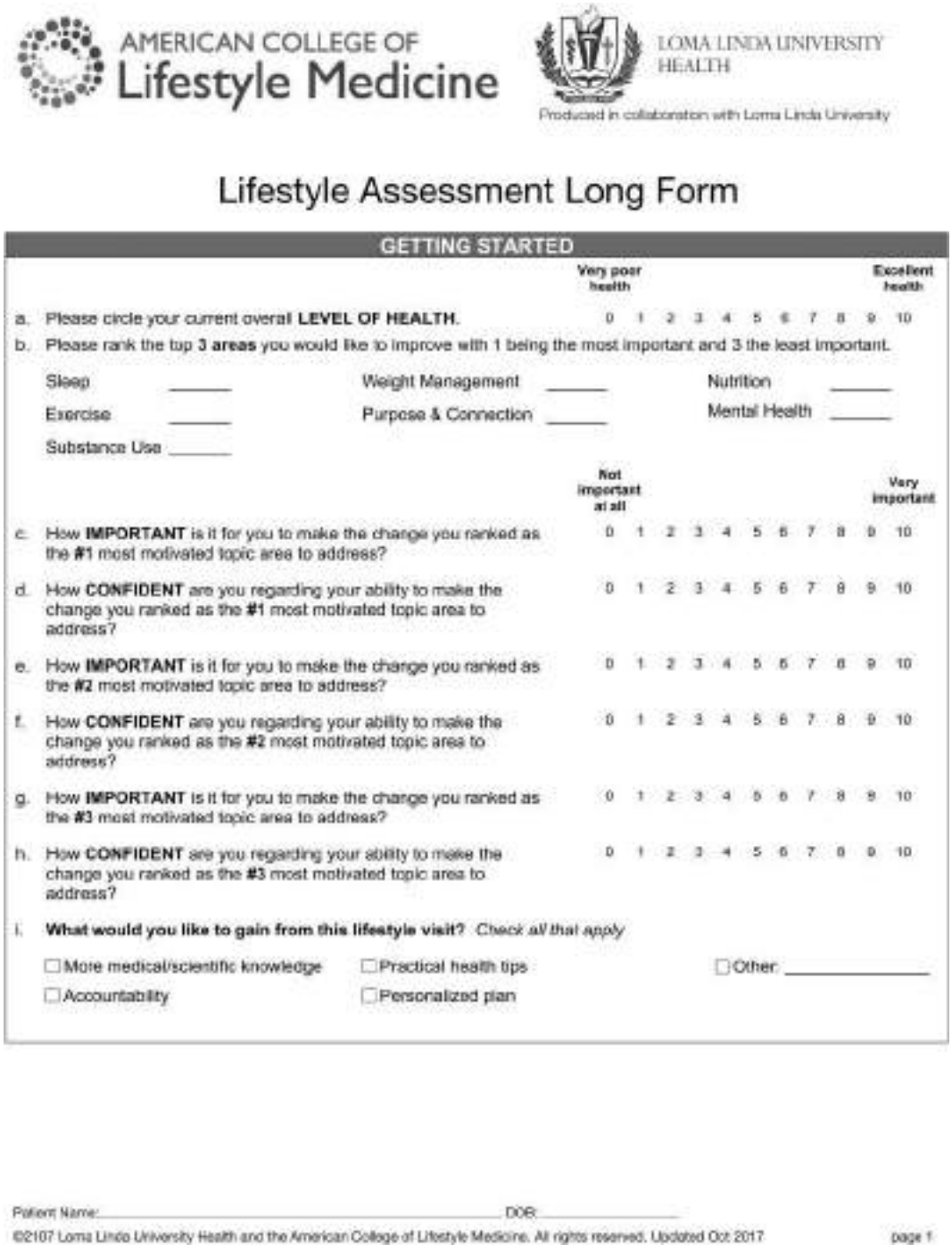
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FIGURE 88.2 American College of Lifestyle Medicine Lifestyle Assessment short form.

88.2.1.10 USPSTF Preventive Services

The US Preventive Services Task Force (USPSTF) has created peer-reviewed recommendations also relevant to an LM evaluation that include recommended disease screening and counseling services. The electronic Preventive Services Selector (ePSS) is an application designed to guide clinicians in providing screening, counseling, and other preventive medicine services according to specific patient



AMERICAN COLLEGE OF Lifestyle Medicine

LOMA LINDA UNIVERSITY HEALTH

Produced in collaboration with Loma Linda University

Lifestyle Assessment Long Form

GETTING STARTED

		Very poor health									Excellent health
a.	Please circle your current overall **LEVEL OF HEALTH.**	0	1	2	3	4	5	6	7	8	9	10

b. Please rank the top **3 areas** you would like to improve with 1 being the most important and 3 the least important.

Sleep _____ Weight Management _____ Nutrition _____

Exercise _____ Purpose & Connection _____ Mental Health _____

Substance Use _____

		Not important at all									Very important
c.	How **IMPORTANT** is it for you to make the change you ranked as the **#1** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10
d.	How **CONFIDENT** are you regarding your ability to make the change you ranked as the **#1** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10
e.	How **IMPORTANT** is it for you to make the change you ranked as the **#2** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10
f.	How **CONFIDENT** are you regarding your ability to make the change you ranked as the **#2** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10
g.	How **IMPORTANT** is it for you to make the change you ranked as the **#3** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10
h.	How **CONFIDENT** are you regarding your ability to make the change you ranked as the **#3** most motivated topic area to address?	0	1	2	3	4	5	6	7	8	9	10

i. **What would you like to gain from this lifestyle visit?** *Check all that apply*

☐ More medical/scientific knowledge ☐ Practical health tips ☐ Other: _____

☐ Accountability ☐ Personalized plan

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FIGURE 88.3 American College of Lifestyle Medicine long form.

characteristics, such as age, sex, and selected behavioral risk factors. Incorporating the ePSS into an LM clinical assessment ensures that appropriate preventive services are included within the encounter and helps exclude those that should not be incorporated.

Resources:

www.uspreventiveservicestaskforce.org/webview/#!/

and

www.uspreventiveservicestaskforce.org/apps/.

88.2.1.11 Risk Factor Assessment Tools

88.2.1.11.1 Cardiovascular Disease Assessment

For evaluating an individual's risk for developing cardiovascular disease, particularly for having a heart attack in the next ten years, the ASCVD Risk Estimator from the American College of Cardiology and the American Heart Association can be used.[69] This risk estimator is also intended for use in patients who are at risk for atherosclerotic disease and ASCVD-related events, especially due to



SLEEP					
Please answer based on your sleeping patterns OVER the LAST TWO WEEKS	Never	Seldom	Sometimes	Often	Always
a. How often have you had difficulty staying awake during routine tasks?	1	2	3	4	5
b. How often have you had difficulty staying awake while driving?	1	2	3	4	5
c. How often have you felt fatigued or needed to nap during the day?	1	2	3	4	5
d. How often has it taken you more than 30 minutes to fall asleep at night?	1	2	3	4	5
e. How often have you woken up at night?	1	2	3	4	5
f. How often have you unintentionally woken up early in the morning?	1	2	3	4	5
g. How often do you look at a screen within 2 hours of sleeping (i.e. TV, computer, iPad, or Phone)?	1	2	3	4	5
h. How often have your legs or arms jerked during sleep?	1	2	3	4	5
i. How often have you experienced "creeping" or "crawling" feelings in your legs?	1	2	3	4	5
j. How often have you snored loudly, gasped, choked, or stopped breathing during sleep?	1	2	3	4	5
k. How often have you used sleeping aids (i.e. tobacco, alcohol, over-the-counter medications, or prescription medications) to help you fall asleep?	1	2	3	4	5
l. Do you have a job that requires night shifts?	1	2	3	4	5
m. Do you have a medical condition or chronic pain that interferes with your sleep?	1	2	3	4	5
n. On an average weekday do you get at least 7-8 hours of sleep in a 24-hour period?	1	2	3	4	5
o. On an average weekend do you get at least 7-8 hours of sleep in a 24-hour period?	1	2	3	4	5

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

dyslipidemia, hypertension, and personal history of diabetes and smoking. The estimates apply to African American and non-Hispanic white men and women 40 through 79 years of age and are available online and through an application.[69] Lifetime risk can be estimated for adults 20 to 59 years of age. The goal is to facilitate physician-patient discussion and support decision-making to optimize care and lower the risk for ASCVD. These tools can help create quantitatively driven discussions that compare normal and optimal risk levels and identify those factors contributing to the elevated ten-year and lifetime risk.

88.2.1.11.2 Metabolic Syndrome Assessment

Metabolic syndrome is a combination of multiple risk factors that arises from insulin resistance accompanying abnormal adipose deposition and function. The metabolic syndrome is accompanied by a two-fold increase in the risk of cardiovascular disease and a five-fold increase in the risk of type 2 diabetes. A clinical diagnosis of the metabolic syndrome is useful because it affects therapeutic strategy in patients at higher risk, whether to single out and treat each risk separately or to implement therapies that will reduce all of the risk factors simultaneously with an LM



NUTRITION

EATING PATTERNS
Please answer based on your typical eating habits

a.	On average, how many cups (8 oz.) of caffeinated beverages do you drink **per day** (tea, soda, coffee, or energy drinks)?	0	1	2	3	4+
b.	On average, how many servings of alcohol do you drink **per day**?	0	1	2	3	4+
c.	On average, how many cups (8 oz.) of sugary drinks (soda, sports drinks, juice) do you drink **per day**?	0	1	2	3	4+
d.	On average, how often do you snack on convenience or "junk" food **per day**? (i.e. chips, candy, granola bars, crackers, cookies, etc.)	0	1	2	3	4+
e.	On average, how many meals do you buy from a restaurant or fast food **per week**?	0	1	2	3	4+
f.	On average, do you drink at least 8 glasses of water **per day**?		No		Yes	
g.	On average, do you eat at least 5 handfuls of nuts **per week**?		No		Yes	
h.	Do you use natural or artificial sweeteners? (i.e. Equal, Stevia, Splenda, Sweet & Low, honey, agave, etc.)		No		Yes	
i.	Do you add salt to most of your meals?		No		Yes	
j.	Do you eat processed meats (i.e. sausage, hot dogs, salami, bacon)?		No		Yes	

k. Do you have any bad reactions (sensitivities or allergies) to food? If yes, please list here: _____

l. Do you avoid any particular foods? If yes, please list here: _____

m. Do you have foods that you crave? If yes, please list here: _____

n. Are you currently following a particular diet or nutrition plan? If yes, please list here: _____

o. During the last 3 months, did you have any episodes of excessive overeating? If yes please explain here: _____

p. Are you concerned about making the wrong food choices? If yes, please explain here: _____

q. Have you ever had an eating disorder? If yes, please list here: _____

Do you use any of the following VITAMINS or SUPPLEMENTS? *Check all that apply*

❑ Vitamin D ❑ Calcium ❑ Vitamin B12
❑ Probiotics ❑ Omega 3 ❑ Multivitamin
Other: _____

Do you use any of the following OILS with your meals or cooking? *Check all that apply*

❑ Olive Oil ❑ Canola Oil ❑ Vegetable Oil
❑ Coconut Oil ❑ Butter ❑ Lard
Other: _____

FOOD RECALL: *Please record below what AND how much you ate and drank yesterday (or the last typical day)*

Breakfast: _____ Time: _____
Lunch: _____ Time: _____
Dinner: _____ Time: _____
Snacks: _____ Time: _____
Drinks/Beverages: _____ Time: _____

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

approach focused on weight reduction, increased exercise, and improved nutrition. [70]

According to guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least three of the following five conditions:[71]

- Glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
- Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)
- Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
- HDL-C <40 mg/dL in men or <50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
- Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women



WEIGHT MANAGEMENT

BEHAVIOR PATTERNS	Never	Seldom	Sometimes	Often	Always
a. How often do you skip meals?	1	2	3	4	5
b. How often do you snack in between meals?	1	2	3	4	5
c. How often do you eat while watching TV?	1	2	3	4	5
d. How often do you eat while in bed?	1	2	3	4	5
e. How often do you have difficulty sleeping?	1	2	3	4	5
f. How often do you lack physical activity or exercise?	1	2	3	4	5
g. How often do you feel a lack of purpose or meaning in your life?	1	2	3	4	5

Which of the following factors apply to your eating habits and current lifestyle? ***Check all that apply***

❑ Like healthy food	❑ Don't like healthy food	❑ Know how to cook healthy foods
❑ Fast eater	❑ Eat slowly	❑ Read nutrition labels
❑ Rely on packaged or fast foods	❑ Dislike cooking	❑ Prepare meals at home
❑ Do not plan meals	❑ Eat a variety of foods	❑ Always hungry
❑ Late night eater	❑ Negative relationship to food	❑ Erratic eater
❑ No time to prepare healthy food choices	❑ Don't know how to cook	❑ Live alone or eat alone often

Do any of the following situations or emotions cause you to eat? ***Check all that apply***

❑ Sadness	❑ Pain	❑ Insomnia	❑ Anxiety
❑ Fatigue	❑ Social or Family Situations	❑ Boredom	❑ Stress

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

88.2.1.11.3 Diabetes Risk Assessment

The American Diabetes Association has developed a risk assessment tool to assist in screening for diabetes. Using age, gender, medical history, family history, activity level, and weight category, the algorithm can be used to identify those who score five or higher and are at increased risk for having diabetes.[72] Other resources include the International Diabetes Federation online type 2 diabetes risk assessment, which is designed for people without a current diagnosis of diabetes and is intended to highlight a person's risk of developing type 2 diabetes in the next ten years.[73]



WEIGHT MANAGEMENT (continued)

WEIGHT HISTORY

a.	Have you ever been overweight or obese? If yes, answer below:	No	Yes
	Were you overweight as a child?	No	Yes
	Were you overweight as a teenager?	No	Yes
	Were you overweight between the ages of 20-29?	No	Yes
	Were you overweight between the ages of 30-39?	No	Yes
	Were you overweight above the age of 40?	No	Yes
b.	Are you currently trying to lose or gain weight?	No	Yes
	If yes, please circle your goal: Lose weight Gain weight		
c.	Have you ever intentionally lost or reduced your weight by more than 5 lbs.?	No	Yes
	If yes, did you regain weight within 1 year?	No	Yes
d.	Have you had weight loss surgery?	No	Yes
	If yes, please list the type of surgery you had: _____		

Have you ever used weight loss medications? *If yes, circle which ones you have used? If other, please list.*

❑ Acutrim ❑ Alli ❑ Amphetamines ❑ Anorex ❑ Belviq ❑ Byetta ❑ Contrave
❑ Desatrim ❑ Didrex ❑ Fastin ❑ Fenfluramine ❑ Mazanor ❑ Meridia ❑ Obalan
❑ Phendiet ❑ Fen-Phen ❑ Phentermine ❑ Plegine ❑ Plegine ❑ Prozac ❑ Pondimin
❑ Qsymia ❑ Redux ❑ Sanorex ❑ Tenuate ❑ Tepanil ❑ Vyvanse ❑ Wechlesa
❑ Wellbutrin ❑ Xenical ❑ I don't remember the name of the medication
❑ Other _____

WEIGHT LOSS STRATEGIES

Have you tried any of the following alternative therapies or programs? *Check all that apply. If other, please list.*

❑ Acupuncture	❑ Acupressure	❑ Nutritionist/Registered Dietitian
❑ Residential Programs	❑ Hypnosis	❑ Physical Activity/Exercises

❑ Other _____

Which commercial or fad diets have you tried in the past? *Check all that apply. If other, please list.*

❑ Atkins Diet	❑ Low Fat	❑ Calorie Counting	❑ Paleo
❑ CHIP	❑ South Beach	❑ DASH	❑ Vegan
❑ Mediterranean Diet	❑ Elimination Diet (Allergy)	❑ Gluten Free	❑ Vegetarian
❑ Jenny Craig	❑ Weight Watchers	❑ Low Carb	❑ Slim Fast/Meal Replacement

❑ Other _____

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

88.2.2 Lifestyle-Focused Physical

88.2.2.1 Biometric data, Physical exam, Fitness, and Laboratory Testing

88.2.2.1.1 Overweight and Obesity Identification

In addition to measuring weight and height for body mass index (BMI), the addition of the waist circumference is of value to help screen for possible health risks associated with increased abdominal adiposity. This is a component of the screen for metabolic syndrome, as increased waist circumference increases the risk of developing heart disease and type 2 diabetes.[74,75] The combination of weight and waist circumference data provides simple and accessible markers for measurement in ongoing clinical evaluations and helps individuals recognize their health risk categories, ranging from normal to extremely high.



EXERCISE

EXERCISE HABITS: AEROBIC/CARDIO TRAINING

a. During the average week, how many **days** do you exercise at a moderate to strenuous intensity (i.e. brisk walking or enough to break a light sweat)? _____days

b. During an average session, how many **minutes** do you exercise at a moderate to strenuous intensity (i.e. brisk walking or enough movement to break a light sweat)? _____min

_____ total min/week (days x min)

c. List types of aerobic activities you do (i.e. walking, jogging, swimming, bicycling, dancing, etc.): _____

_____

EXERCISE HABITS: STRENGTH/RESISTANCE TRAINING

a. During the average week, how many **days** do you do strength/resistance training? _____days

b. How many **minutes** do you exercise with strength/resistance training? _____min

_____ total min/week (days x min)

c. List types of activities you do (i.e. weightlifting, Pilates, kettle ball, resistance machines, exercise bands, etc.):____

_____

What MOTIVATES you or would motivate you to exercise? *Check top three*

❑ Nothing would motivate me ❑ Family or partner ❑ Improve mood ❑ Weight reduction
❑ Control Blood glucose ❑ Body Image ❑ Increase Energy ❑ Reduce blood pressure
❑ Decrease stress ❑ Prevent heart disease ❑ Prevent Bone loss ❑ Improve sleep
❑ Increase self-esteem ❑ Other:_____

Are there any BARRIERS or PROBLEMS that limit exercise? *Check all that apply*

❑ No barriers ❑ Depression ❑ Work Responsibility ❑ Cost
❑ Life Transition Period ❑ Time ❑ Fear ❑ Other
❑ Family Responsibility ❑ Apparel ❑ Energy

EXERCISE SAFETY

a. Do you have any injuries that would make it difficult to exercise? No Yes
If yes, please explain: _____

b. Do you have any joint, muscle, or bone problems that might get worse with exercise? No Yes
If yes, please explain: _____

c. Do you have any breathing problems while exercising? No Yes
If yes, please explain: _____

d. Do you have any balance problems or have had a fall in the last 6 months? No Yes
If yes, please explain: _____

e. Do you have any difficulty completing your activities of daily living (i.e. showering, dressing, toileting)? No Yes
If yes, please explain: _____

Do you have any of the following health problems? *Check all that apply*

❑ Arrhythmia or irregular heartbeat ❑ Uncontrolled diabetes ❑ Recent heart attack
❑ Arthritis or significant joint pain ❑ Severe or uncontrolled heart failure ❑ Chronic or unusual fatigue/tiredness
❑ Chest pain/angina ❑ Uncontrolled asthma ❑ Difficulty breathing with activity
❑ Other

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

88.2.2.1.2 Blood Pressure

The 2017 American College of Cardiology and American Heart Association (AHA) guidelines updated the definition of high blood pressure to account for complications that can occur at lower numbers and to allow for earlier intervention.[76]

For an adult 45 years of age without hypertension, the 40-year risk for developing hypertension is 93% for African Americans, 92% for Hispanics, 86% for whites, and 84% for Chinese adults. A 20 mm Hg higher SBP and 10 mm Hg higher DBP are each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease. In persons ≥30 years of age, higher SBP and DBP are associated with increased risk for CVD, angina, myocardial infarction (MI), heart failure (HF), stroke, peripheral arterial disease, and abdominal aortic aneurysm.[77]

Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients



MENTAL HEALTH

PERCEIVED STRESS

	Never	Seldom	Sometimes	Often	Always
a. How often have you felt that you were unable to control the important things in your life?	1	2	3	4	5
b. How often have you felt **lack of** confidence about your ability to handle your personal problems?	1	2	3	4	5
c. How often have you felt that things were **not** going your way?	1	2	3	4	5
d. Have often have you found it hard to let go of things that upset you?	1	2	3	4	5

How do you COPE with stress? *Check all that apply*

❑ Meditation	❑ Food (too much, too little)	❑ Gambling	❑ Distraction
❑ Exercise/Physical Activity	❑ Spirituality/Faith	❑ Journaling	❑ Hurting yourself (i.e. cutting, etc.)
❑ Counseling/Psychotherapy	❑ Sex	❑ Massage/Body work	❑ Pet therapy
❑ Socializing with friends or family	❑ Recreational drugs (i.e. marijuana, cocaine, etc.)	❑ Prayer	❑ Other
❑ Art	❑ Television and/or video games	❑ Substance (tobacco, alcohol)	

RESILIENCE

When I am under extreme stress	Never	Seldom	Sometimes	Often	Always
a. I find a way to learn from my experience.	1	2	3	4	5
b. I find a way to take action.	1	2	3	4	5
c. I find it easy to prioritize what is important in my life.	1	2	3	4	5
d. I look at a stressful situation as an opportunity to grow.	1	2	3	4	5
e. I meet the goals I set for myself.	1	2	3	4	5
f. I believe that there are a lot of ways around a problem.	1	2	3	4	5
g. I feel motivated to pursue my goals.	1	2	3	4	5
h. I know I can get through it.	1	2	3	4	5

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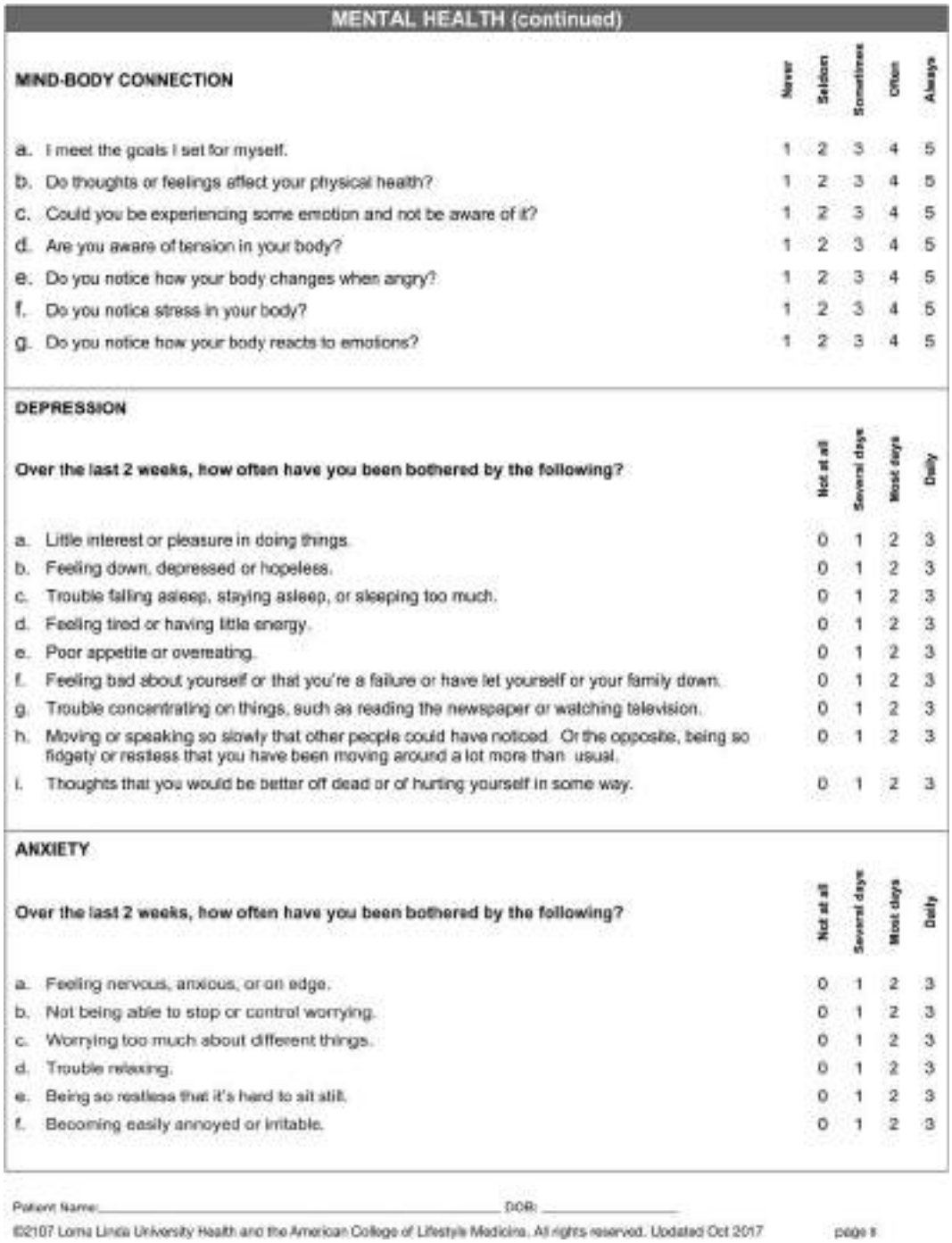
FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

with clinical CVD and an average SBP ≥130 mm Hg or a DBP ≥80 mm Hg, or for primary prevention in adults with no history of CVD but with an estimated ten-year ASCVD risk of ≥10% and SBP ≥130 mm Hg or DBP ≥80 mm Hg. Use of BP-lowering medication is also recommended for primary prevention of CVD in adults with no history of CVD and with an estimated ten-year ASCVD risk <10% and an SBP ≥140 mm Hg or a DBP ≥90 mm Hg.[77]

The goal of the new guidelines is to increase hypertension awareness, encourage lifestyle modification, and focus antihypertensive medication initiation and intensification on US adults with high CVD risk. [77]

88.2.2.1.3 Fitness Measures

Multiple options are available for body composition assessments, including skinfold measurements, bioelectric impedance analysis (BIA), and dual-energy x-ray absorptiometry (DXA). Although not always paid for by insurance, these measurements help differentiate whether weight is due to either fat mass or lean tissue, which is of value when



MENTAL HEALTH (continued)

MIND-BODY CONNECTION	Never	Seldom	Sometimes	Often	Always
a. I meet the goals I set for myself.	1	2	3	4	5
b. Do thoughts or feelings affect your physical health?	1	2	3	4	5
c. Could you be experiencing some emotion and not be aware of it?	1	2	3	4	5
d. Are you aware of tension in your body?	1	2	3	4	5
e. Do you notice how your body changes when angry?	1	2	3	4	5
f. Do you notice stress in your body?	1	2	3	4	5
g. Do you notice how your body reacts to emotions?	1	2	3	4	5

DEPRESSION Over the last 2 weeks, how often have you been bothered by the following?	Not at all	Several days	Most days	Daily
a. Little interest or pleasure in doing things.	0	1	2	3
b. Feeling down, depressed or hopeless.	0	1	2	3
c. Trouble falling asleep, staying asleep, or sleeping too much.	0	1	2	3
d. Feeling tired or having little energy.	0	1	2	3
e. Poor appetite or overeating.	0	1	2	3
f. Feeling bad about yourself or that you're a failure or have let yourself or your family down.	0	1	2	3
g. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
h. Moving or speaking so slowly that other people could have noticed. Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3
i. Thoughts that you would be better off dead or of hurting yourself in some way.	0	1	2	3

ANXIETY Over the last 2 weeks, how often have you been bothered by the following?	Not at all	Several days	Most days	Daily
a. Feeling nervous, anxious, or on edge.	0	1	2	3
b. Not being able to stop or control worrying.	0	1	2	3
c. Worrying too much about different things.	0	1	2	3
d. Trouble relaxing.	0	1	2	3
e. Being so restless that it's hard to sit still.	0	1	2	3
f. Becoming easily annoyed or irritable.	0	1	2	3

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

combined with the basic measurements of weight, BMI, and waist circumference.[78]

88.2.2.1.4 Cardiorespiratory Fitness Testing

Fitness testing options are numerous and need to be adapted to the LM practice setting based on the availability of clinical staff members, resources, and timing constraints. Cardiorespiratory fitness testing defines how well the body can perform dynamic activity using large muscles at a moderate to high intensity for a period of time, which is valuable in evaluating overall fitness and determining functional capacity as well as any underlying cardiorespiratory abnormalities that are due to cardiovascular disease. The maximum volume of oxygen (VO_2 max) consumed during exercise, also known as aerobic power, is an indirect marker of cardiorespiratory fitness.



PURPOSE AND CONNECTION

How often do you agree with the following:	Never	Seldom	Sometimes	Often	Always
a. I live a purposeful and meaningful life	1	2	3	4	5
b. I have a spiritual community that I can turn to in times of need	1	2	3	4	5
c. I have a source of inner strength and meaning	1	2	3	4	5
d. I am satisfied with my current belief system	1	2	3	4	5
e. I have people who care about what happens to me	1	2	3	4	5
f. I have people who accept me at my worst and best	1	2	3	4	5
g. I have people I trust at home or work who I can talk to about my problems	1	2	3	4	5
h. I get help when I'm sick	1	2	3	4	5

SMOKING AND SUBSTANCE HISTORY

NICOTINE/TOBACCO (i.e. cigarettes, e-cigarettes, e-cigarettes/vaping, cigars, chew, snuff)

a. Do you use any of the nicotine products listed above? No Yes
If yes, do you want to quit using the nicotine/tobacco products? No Yes
If yes, answer the questions below:

b. How soon after you wake up do you use nicotine/tobacco?
❑ After 60 minutes ❑ 31-60 minutes ❑ 6-30 minutes ❑ Within 5 minutes

c. How many cigarettes do you smoke per day?
❑ 10 or less ❑ 11-20 ❑ 21-30 ❑ 31+

d. What age did you start smoking? _____
e. What is the longest time period you have stayed quit? _____
f. What made you start smoking again? _____
g. Which of the following people smoke around you? *Check all that apply*
❑ Friends ❑ Family ❑ Partner
❑ Co-Workers ❑ Other: _____

h. How many times have you seriously tried to quit? ___
i. For your most recent quit attempt, how long did it last? _____
j. Who is supporting you to quit smoking? _____
k. What is your most important reason to quit smoking? _____

l. Are you currently using or have used any medications to help you quit smoking? No Yes
If yes, check with of the following medications you have used:
❑ Nicotine Patch ❑ Nicotine Gum ❑ Nicotine Lozenge
❑ Wellbutrin/Bupropion Pill ❑ Chantix/ Varenicline Pill ❑ Other: _____

m. If you used any of the medication listed above, did they help? No Yes
If yes, list which ones helped: _____

Patient Name: _____ DOB: _____

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

88.2.2.1.5 Muscular Fitness Testing

Muscular fitness testing includes both muscular strength and muscular endurance. Muscular strength is difficult to test in a clinic unless the clinic has the hardware to measure an applied load to certain movements (e.g., a bench press or leg press). Muscular endurance testing measures the ability of a muscle group to perform repeated or sustained contractions to sufficiently evoke muscular fatigue, thus providing an evaluation of the ability to perform activities of daily living. Muscular endurance tests include push-ups, curl-ups, and body weight squat tests. The total number of correctly performed repetitions is then evaluated based on established age and sex norms. These tests may be best performed by a fitness professional as part of an



SMOKING AND SUBSTANCE (continued)

n. Have you used any methods in the past other than medications to try to quit? No Yes

If yes, check which of the following methods you have used:

❑ Self-help ❑ Gradual reduction ❑ Cold turkey ❑ Hypnosis

❑ Acupuncture ❑ Special filters ❑ Vaping/e-cigarettes ❑ Other: _____

ALCOHOL

a. Do you drink alcohol? No Yes

If yes, please answer the questions below:

b. What type of alcohol do you prefer? _____

c. On average, how many servings do you drink per day/week/month/year on average? _____

If yes, please answer the questions below:

d. Have you ever felt you should "**Cut** down" on your drinking? No Yes

e. Have people **Annoyed** you by criticizing your drinking? No Yes

f. Have you ever felt **Guilty** about your drinking? No Yes

g. Have you ever had a drink in the morning to steady your nerves or to get rid of a handover (**eye opener**)? No Yes

h. Do you binge drink (more than 5 drinks for men or 4 drinks for women within 2 hours)? No Yes

Have you used any of the following substances in the past year?

Recreational drugs (cocaine, heroin, meth, etc.) No Yes

If yes, what level of concern do you have regarding use of the substances? No Concern 0 1 2 3 4 5 High Concern

If yes, how much substance do you usually use? _____

Marijuana No Yes

If yes, what level of concern do you have regarding use of the substances? No Concern 0 1 2 3 4 5 High Concern

If yes, how much substance do you usually use? _____

TREATMENT HISTORY

Have you ever received treatment for a mental health problem? No Yes

Have you ever received treatment for drug or alcohol use? No Yes

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

interdisciplinary LM clinical team, as the proper technique is paramount in evaluations of muscular endurance and strength to avoid injury.

Some basic movement patterns assessing activities of daily living, hip hinge evaluations, air squats, and push-pull-press motions with the upper body, can be incorporated into the clinical musculoskeletal exam and addressed through prescribed fitness programs. Patients can be encouraged to track their own fitness level over time through simple tracking. If they are unable to complete certain activities, help patients with modifications to make fitness safe. As an example, if unable to do a push-up on the floor because of knee pain, have the patient start with wall push-ups.

MEDICAL SYMPTOM QUESTIONNAIRE (MSQ)

This questionnaire identifies symptoms that help to identify the underlying causes of illness, and helps you track your progress over time. Rate each of the following symptoms based upon your health profile for the **PAST 30 DAYS**. If you are taking after the first time, record your symptoms for the LAST 48 HOURS ONLY.

Point Scale

0 = Never or almost never have the symptom
1 = Occasionally have it; effect is not severe
2 = Occasionally have, effect is severe
3 = Frequently have it, effect is not severe
4 = Frequently have it; effect is severe

DIGESTIVE						**EMOTIONS**					
Diarrhea	0	1	2	3	4	Mood swings	0	1	2	3	4
Constipation	0	1	2	3	4	Anxiety, fear, nervousness	0	1	2	3	4
Bloated feeling	0	1	2	3	4	Anger, irritability, aggressiveness	0	1	2	3	4
Belching, passing gas	0	1	2	3	4	Depression	0	1	2	3	4
Heartburn	0	1	2	3	4	**Total points**_____					
Intestinal/stomach pain	0	1	2	3	4	**ENERGY/ACTIVITY**					
Nausea or vomiting	0	1	2	3	4	Fatigue, sluggishness	0	1	2	3	4
Total points_____						Apathy, lethargy	0	1	2	3	4
EARS						Hyperactivity	0	1	2	3	4
Itchy ears	0	0	1	2	3	Restlessness	0	1	2	3	4
Earaches, ear infections	0	1	2	3	4	**Total points**_____					
Drainage from ear	0	1	2	3	4	**EYES**					
Ringing in ears, hearing loss	0	1	2	3	4	Watery or itchy eyes	0	1	2	3	4
Total points_____						Swollen, reddened or sticky eyelids	0	1	2	3	4
HEAD						Bags or dark circles under eyes	0	1	2	3	4
Headaches	0	1	2	3	4	Blurred or tunnel vision *(does not include near or far*	0	1	2	3	4
Faintness or lightheadedness	0	1	2	3	4	*sightedness)*					
Dizziness	0	1	2	3	4	**Total points**_____					
Insomnia	0	1	2	3	4	**NOSE**					
Total points_____						Stuffy nose	0	1	2	3	4
HEART						Sinus problems	0	1	2	3	4
Irregular or skipped heartbeat	0	1	2	3	4	Sneezing attacks	0	1	2	3	4
Chest pain	0	1	2	3	4	Excessive mucous formation	0	1	2	3	4
Rapid or pounding heartbeat	0	1	2	3	4	Hay fever	0	1	2	3	4
Total points_____						**Total points**_____					
JOINTS/MUSCLES						**SKIN**					
Pains or aches in joints	0	1	2	3	4	Acne	0	1	2	3	4
Arthritis	0	1	2	3	4	Hives, rashes, dry skin	0	1	2	3	4
Stiffness or limitations of movement	0	1	2	3	4	Hair loss	0	1	2	3	4
Pain or aches in muscles	0	1	2	3	4	Flushing or hot flushes	0	1	2	3	4
Feeling of weakness or tiredness	0	1	2	3	4	Excessive sweating	0	1	2	3	4
Total points_____						**Total points**_____					
LUNGS						**WEIGHT**					
Chest congestion	0	1	2	3	4	Binge eating/drinking	0	1	2	3	4
Asthma, bronchitis	0	1	2	3	4	Craving certain foods	0	1	2	3	4
Shortness of breath	0	1	2	3	4	Excessive weight	0	1	2	3	4
Difficulty breathing	0	1	2	3	4	Water retention	0	1	2	3	4
Total points_____						Underweight	0	1	2	3	4
MIND						Compulsive eating	0	1	2	3	4
Poor memory	0	1	2	3	4	**Total points**_____					
Confusion, poor comprehension	0	1	2	3	4	**OTHER**					
Poor concentration	0	1	2	3	4	Frequent illness	0	1	2	3	4
Poor physical coordination	0	1	2	3	4	Frequent or urgent urination	0	1	2	3	4
Difficulty making decisions	0	1	2	3	4	Genital itch or discharge	0	1	2	3	4
Stuttering or stammering	0	1	2	3	4	**Total points**_____					
Learning disabilities	0	1	2	3	4						
Slurred speech	0	1	2	3	4	**GRAND TOTAL** _____					
Total points_____											

KEY: Add individual scores and total each group. Add each group score to give a grand total.
*Optimal is <10; Mild Symptoms: 10-50; Moderate Symptoms: 50-100; Severe Symptoms: over 100

Patient Name:_____ DOB:_____

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

88.2.2.2 Resources

Exercise is Medicine (EIM) was started through a Global Health Initiative and is overseen by the American College of Sports Medicine.[85] Their goal is to make physical activity assessment and promotion a standard part of clinical care. EIM has created several helpful resources such as individual exercise prescriptions based on one's diagnosis (i.e., diabetes, hypertension, fibromyalgia). These resources can be found on the website (www.exerciseismedicine.org) under "Rx for Health Series".[86]



PREVENTIVE SERVICES

a. Have you had a physical exam and/or "Wellness" Visit in the past 12 months? No Yes I don't know
If yes, list date and outcome: _____

b. Have you had a dental exam and teeth cleaning in the past 12 months? No Yes I don't know
If yes, list date and outcome: _____

c. Have you been screened for diabetes with blood work? No Yes I don't know
If yes, list date and outcome: _____

d. Have you had your cholesterol, lipids or triglycerides measured? No Yes I don't know
If yes, list date and outcome: _____

e. Have you ever had a bone density test to check for osteoporosis? No Yes I don't know
If yes, list date and outcome: _____

f. Do you have any balance problems or have had a fall in the last 6 months? No Yes I don't know
If yes, list date and outcome: _____

g. Do you have any difficulty completing your activities of daily living (i.e. showering, dressing, toileting)? No Yes I don't know
If yes, list date and outcome: _____

h. Do you have any concerns about your ability to drive safely or have you had any car accidents in the past 12 months? No Yes I don't know
If yes, list date and outcome: _____

i. Do you have any concerns about your memory? No Yes I don't know
If yes, list date and outcome: _____

j. Do you have any trouble with your hearing? No Yes I don't know
If yes, list date and outcome: _____

k. Have you had your eyes checked for vision problems? No Yes I don't know
If yes, list date and outcome: _____

l. Have you ever had your metabolism or thyroid checked? No Yes I don't know
If yes, list date and outcome: _____

m. Have you ever been told that you have a sexually transmitted disease/infection? No Yes I don't know
If yes, list date and outcome: _____

n. If you smoke, have you ever had an abdominal ultrasound to check for possible aneurysms? No Yes I don't know
If yes, list date and outcome: _____

o. Have you ever received counseling behavioral therapy for any of the following problems?

❑ Weight management or obesity ❑ Nutrition ❑ Smoking or use of other nicotine products ❑ Alcohol use

p. Which of the following screenings have you completed

❑ Colon cancer screen (stool test or colonoscopy ❑ Breast cancer screen (mammogram) ❑ Cervical cancer screen (PAP smear)

❑ HIV/AIDS blood work screen ❑ Hepatitis C blood work screen ❑ Depression or sadness screen

q. Have you had the following vaccines?

❑ Flu ❑ Hepatitis B ❑ Pneumococcal or Pneumonia

Patient Name: _____ DOB: _____

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FIGURE 88.3 (CONTINUED) American College of Lifestyle Medicine long form.

TABLE 88.1
Physical Activity Assessment Tools

	Question(s)	Interpretation
Brief	**Physical Activity Vital Sign (v)**[2,5,6]	Physical Activity Vital Sign
	1. How many days per week do you engage in moderate to strenuous exercise?	Inactive: median <1 min/kw
	2. On average, how many minutes per day do you exercise at this level?	Insufficiently active: 1–149 min/wk
		Sufficiently active: ≥150 min/wk
	Strength and Resistance Exercise[7]	Insufficient: 0–1x/wk
	How many days a week do you engage in strength training or resistance exercises?	Sufficient: ≥2 times/wk
	International Physical Activity Questionnaire Short Form (v):[8] Seven-question survey for the past seven days of physical activity level in adults 15–64 years old.	Low, moderate, or high physical activity
In-depth	**Sedentary Time and Activity Reporting Questionnaire (STAR-Q)** (v)[9,10]	Estimates activity expenditure
	Past month activity and sedentary behavior questionnaire for adults	
	International Physical Activity Questionnaire Long Form (v)[11]	Low/inactive, moderate, or high. Can estimate MET-min/wk of physical activity
	Assesses all types of physical activity in the past seven days.	
Technology	Pedometer	Concrete number of steps or minutes of activity that can be monitored over time
	Smartphones/devices	
	Applications	

v, validated.

88.2.2.3 Laboratory Testing

Basic laboratory evaluation that would be of value in identifying and tracking baseline chronic illness include the following:

Laboratory Test	Reasoning
Complete blood count	Assess for anemia and platelet levels
Comprehensive metabolic panel*	Fasting blood glucose, electrolytes, baseline kidney function, baseline liver function, and albumin level.
Lipid panel*	Assess cholesterol and other lipids.
TSH, Free T4	Thyroid function.
Glycosylated hemoglobin	Blood sugar control over the last three months to monitor for insulin resistance, prediabetes, or diabetes.
hs C-reactive protein	Measure of inflammation associated with CVD.[87]
Vitamin D	Assess for vitamin D deficiency. Deficiency can lead to poor bone development (Rickett's, osteoporosis) and is associated w/some cancers, CVD, DM, autoimmune disease, and depression.[88]
Vitamin B12	Assess for Vit B12 deficiency. Deficiency is associated with hematologic and neurologic symptoms.[89]

*Fasting. IR, insulin resistance; PDM, prediabetes; DM, diabetes mellitus; CVD, cardiovascular disease.

88.2.3 Lifestyle-Focused Assessment and Plan

Once the LM vital signs, physical exam, and appropriate laboratory work have been completed, the next step is to focus on the assessment and plan. It is not possible to discuss all the treatment modalities for lifestyle medicine-related conditions here. We will focus on principles within the encounter to enable patient success in behavior change.

88.2.3.1 Touch Points

The provider should begin the visit by reviewing the patient's chief concern (Figure 88.4). Acutely ill patients or patients with medical emergencies should be rapidly assessed without delay or unnecessary questioning. In this case, only the physical vital signs and pertinent medical history are collected. Once the patient is stable or improving, follow-up visits can be used to address the lifestyle risk factors that may have led to the illness or emergency. It may still be appropriate for the provider to share some pertinent information on lifestyle risk factors during the visit for acute illness. For example, patients with COPD should be made aware during their visit for acute COPD exacerbation that cigarette use is a direct cause and should be discontinued. Chronic care visits and annual physicals are appropriate times to collect physical and LM vital signs.

After a review of the physical and LM vital signs, the highest risk areas should be briefly discussed with the patient to assess for urgency and patient safety. For example, a patient sleeping four hours a night during shift work who reports briefly falling asleep behind the wheel should have an urgent intervention. In-depth LM assessments can be done with further screening after the visit, at a follow-up appointment, or by ancillary staff.

The physical vital signs, blood pressure, heart rate, weight, and so on provide information on whether the unhealthy lifestyle patterns have progressed to the extent of disease formation. Laboratory work and imaging are also helpful as they provide concrete information about the state of one's health or disease. Next, risk calculators as mentioned above, such as the American College of Cardiology

TABLE 88.2
Nutrition Assessment Tools

	Question(s)	Interpretation
Brief	**Rapid 3 Question Assessment**[15] Over the last two weeks, how often have you eaten fast food, sugary drinks (e.g., soda, sports drinks, juice), or packaged foods (e.g., chips, candy, crackers, cookies)? a. Not at all b. Several days c. More than half the days d. Nearly every day On an average day, how many servings of whole fruits and vegetables do you eat (one serving is about a handful and does not include fruit juice)? a. Less than 2 servings b. 2–3 servings c. 4–5 servings d. More than 5 servings How many servings of processed or red meat do you eat in a week?[16] a. Less than 2 servings b. 2–3 servings c. 4–5 servings d. More than 5 servings	The less intake of fast food, sugary drinks (e.g., soda, sports drinks, juice), packaged foods (e.g., chips, candy, crackers, cookies), or processed or red meat, the better it is for one's health. The more whole fruits and vegetables the better for health.
	24 -hour verbal or written dietary recall Include portions, timing, and frequency of foods consumed and any associated symptoms (acid reflux following fatty meal). Asking patients to log an average day of eating, a healthy day, and an unhealthy day can provide a very informative range	As described in Rapid 3 question assessment Associated symptoms should help guide clinical interventions.
	Starting the Conversation (v)[17] An eight-item simplified food frequency instrument designed for use in primary care and health-promotion settings	The final score will be a range from 0 to 16. The lower the score, the healthier the diet.
In-depth	**The SOS-Free (salt/oil/sugar-free) Diet Screener**[18] from T. Colin Campbell Center for Nutrition Studies	Assess for the presence of vegetables and fruits, whole grains, legumes, nuts, and seeds.
	Mediterranean Diet Adherence Screener (MEDAS)(v)[19,20] Rapid assessment of Mediterranean Diet (MD) adherence via 14 questions regarding the main groups of food consumed as part of the MD	The higher the score, the more adherence and positive association with HDL and negative association with BMI, WC, TG, FBG, and TC/HDL ratio.
	Automated Self-Administered 24-hour Dietary Assessment Tool ASA24® (v)[21, 22] Free online tool for completing a 24-hour food recall.	A "Respondent Nutrition Report" is generated after completion, and provides feedback on the reported diet compared to the participant's country-specific dietary guidelines (calories, food groups, and nutrients)
	Dietary Screener Questionnaire (DSQ) (v)[23–25] Nineteen-item questionnaire assessing for the presence of fruits and vegetables, whole grains, added sugars, dairy, fiber, and calcium.	Provides estimates[24] of mean intake of fruits and vegetables (cups/day), added sugars (tsp/day), sugars from sweetened beverages(tsp/day), dairy (cups/day), whole grains (ounces/day), calcium (mg), fiber (gm), red meat (times/day), and processed meat (times/day). Results consistent with 24-hour food recalls.
Technology	Photographs of recent meals[26–28]	Plates of food should resemble ACLM's healthy plate:[29] 50% fruits and vegetables, 25% plant proteins, 25% whole grains, and water to drink.
	Applications	Efficient tracking process that can simultaneously provide nutritional content information (grams of fiber, milligrams of vitamin D).

HDL, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; THG, triglycerides; FBG, fasting glucose; TC/HDL ratio, total cholesterol/HDL ratio;
v, validated.

TABLE 88.3
Stress Assessment Tools

	Question(s)	Interpretation
Brief	**Single Question Stress Scale** How stressful is your life on a scale of one to ten? One means little to no stress and ten means a great deal of stress[33]	Low stress 1–3 Moderate stress 4–7 High stress 8–10 American average 5.4/10 Perceived "healthy" stress 3.7/10
	Perceived Stress Scale-4 (PSS-4) (v)[34] Four-question survey on perceived stress	Scoring is from 0–16. The higher the score, the more perceived stress one is under.
In-depth	**Perceived Stress Scale 10-item (PSS) (v)**[34–36] Ten-question survey on perceived stress	Scoring is from 0–40 with higher scores indicating higher perceived stress. Low stress 0–13 Moderate stress 14–26 High stress 27–40
Technology	Wearable devices Applications	Could allow physiologic tracking of heart rate, blood pressure, and sleep with subjective stress levels. Other applications allow for stress symptom monitoring or journaling alone.

v, validated.

ASCVD Risk Estimator, and guidelines for disease diagnosis, such as those for metabolic syndrome, should be applied to the patient's data. The provider should discuss the patient's unique risk factor profile and any diagnosed medical conditions which may include traditional diagnoses such as diabetes and hypertension, or diagnoses based on lifestyle medicine vital signs such as insufficient sleep, acute or chronic stress, or physical inactivity.

Shared decision-making is essential in a lifestyle medicine visit. Treatment plans should be developed based on the potential detriment of the risk factor and the patient's willingness to change. While obtaining traditional vital signs, the nurse or medical assistant can ask if the patient is ready or willing to make any lifestyle changes. Additionally, if the Lifestyle Medicine Short Form assessment is used, the patient is asked to identify the "Top Three" areas they are most motivated to change. The nurse can potentially provide brief coaching and/or educational information to assist the change before the provider enters the room.

The provider should describe the treatment options: 1) traditional allopathic medicine—treatments are based on evidence-based guidelines, treatment is generally medications or surgical interventions; 2) a combination of traditional allopathic medicine and therapeutic lifestyle change; or 3) intensive therapeutic lifestyle changes. When treatment based on therapeutic lifestyle change alone is chosen, it must be clear that the required intensity must be to the level where lifestyle-related diseases are expected to improve or potentially achieve remission. This concept of required intensity is comparable to antibiotics or seizure medications at which a therapeutic level drug level must be reached for effective therapy.

During treatment discussions, lifestyle medicine providers should be prepared to discuss the following:

- Lifestyle is the foundation of health and often the primary modality of healing while medications are best considered adjuncts
- Compare and contrast lifestyle treatment outcomes to traditional medical care
- Pathophysiology of common lifestyle-related illnesses such as diabetes, high cholesterol, hypertension, and cardiovascular disease
- The emotional, social, and financial cost of therapeutic lifestyle changes such as eating a predominantly whole food, plant-based diet

Once a treatment plan has been decided, the provider should use a coach approach and motivational interviewing to help the patient create action steps toward their treatment goal. Keeping in mind, it may not include any lifestyle change if that is what the patient chooses. Provide engaging educational and motivational materials when warranted.

Motivational materials may also help patients move from contemplation to planning or action. Examples: films like PlantWise™, Eating You Alive™, Forks Over Knives™, or The Game Changers™, or books like The China Study© and Preventing and Reversing Heart Disease©, or programs like Diabetes Undone™[90] or PIVIO™[91] Whenever possible, these resources should not denigrate the medical profession. These may be introduced to the patient as a prescription, flyer, or even a photocopied picture of the cover or web page. The office may prepare preprinted prescription pads for such purpose, or the links may be sent via electronic means to the patient portal.

Establish appropriate follow-up. Refer, if needed, to interdisciplinary team members, specialists, an intensive therapeutic lifestyle change (ITLC) program, or other online or community resources.

The American College of Lifestyle Medicine has created a helpful resource for providers called the "ACLM Reimbursement Roadmap" to appropriately bill for lifestyle medicine visits that is available on their website.[92]

Providers should effectively use their electronic medical records to record and track lifestyle medicine activities,

TABLE 88.4
Well-being Assessment Tools

	Question(s)	Interpretation
Brief	**Patient Health Questionnaire 2 item (PHQ2)** (v)[39,40] Over the last two weeks, how often have you been bothered by the following problems? 0 (Not at all) to 3 (Nearly every day) – Little interest or pleasure in doing things? – Feeling down, depressed, or hopeless?	Total score ≥3 suggests depression. A more in-depth assessment like the PHQ9 or a clinical interview should then be completed.
	Generalized Anxiety Disorder 2 (GAD-2) (v)[41] Over the last two weeks, how often have you been bothered by the following problems? 0 (Not at all) to 3 (Nearly every day) – Feeling nervous, anxious, or on edge? – Not being able to stop or control worrying?	Total score ≥3 suggests anxiety. A more in-depth assessment like the GAD-7 or a clinical interview should then be completed.
	Patient Health Questionnaire 2 item (PHQ4) (v)[42] Combination of the above two screenings PHQ2 and GAD2	Total score is determined by adding together the scores of each of the four items. Scores are rated as normal (0–2), mild (3–5), moderate (6–8), and severe (9–12).
	Abbreviated version of the Satisfaction with Life Scale (SWLS) (v) [43] On a scale of one (lowest) to seven (highest): – In most ways, my life is close to my ideal. – I am satisfied with my life.	Higher scores are associated with higher satisfaction in this area.
In-depth	**Patient Health Questionnaire 9 item (PHQ9)** (v)[40,44,45] A nine-item measure of depression	Scores range from 0–27: 0–4 no or minimal depression 5–9 mild depression 10–14 moderate depression 15–19 moderately severe 20–27 severe depression
	General Anxiety Disorder-7 (GAD-7) (v)[41,46] A seven-item measure of anxiety	Scores range from 0–21: 0–4 no or minimal anxiety 5–9 mild anxiety 10–14 moderate anxiety 15–21 severe anxiety
	Satisfaction with Life Scale (v)[43,47] Five-item questionnaire assessing satisfaction with life: one (strongly disagree) to seven (strongly agree)	30–35 very high score, highly satisfied 25–29 high score 20–24 average 15–19 slightly below average 10–14 dissatisfied 5–9 extremely dissatisfied
Technology	Applications	Allow frequent tracking of subjective well-being, PHQ9 assessment, GAD7 assessment, or depression and anxiety symptoms.

v, validated.

treatment plans, and results. Electronic medical records may also be useful in creating patient registries, tracking routine preventive care and need for screenings, and risk stratification based on data in the system (blood pressure, LM health risk assessment score, or A1c).

Another responsibility of the lifestyle medicine provider is to assess if medications will need deprescribed prior to or during a lifestyle medicine treatment. Generally, the more intense the intervention, the higher the need for medication reduction and monitoring, especially in the case of medications with the potential to lead to acute hypoglycemia or hypotension. If any obstacles to the treatment regimen are present (side effects, complicated administration regimens, daily pill burden, or medication expense), this should be taken into consideration as to which medications should be discontinued first.

Polypharmacy is the prescribing of multiple medications, especially those that are inappropriate, unnecessary, or harmful.[93,94] Deprescribing has been most studied in the elderly, targeting drug classes like anti-psychotics,

TABLE 88.5
Social Relationships Assessment Tools

	Question(s)	Interpretation
Brief	**Loma Linda Social Relationship Questionnaire**[51] Four questions survey, patients rank their answers from one (never) to five (always). 1) I have people who care about what happens to me 2) I have people who accept me at my worst and best 3) I have people I trust at home or work who I can talk to about my problems 4) I get help when I'm sick	Answering "Never" or "Seldom" would be worrisome.
In-Depth	**A Brief Measure of Social Support** also known as **Social Support Questionnaire Short-Form 6 (SSQ6)** (v)[52] Survey inquiring who a patient can count on in six specific areas of life and how satisfied they are with the support.	If "no one" is marked by the patient or if satisfaction is low, this is an area of concern and should be further assessed

v, validated.

TABLE 88.6
Sleep Assessment Tools

	Question(s)	Interpretation
Brief	**Single-Item Sleep Quality Scale** (v)[55] Overall sleep quality in the past seven days is rated on a scale from one (terrible) to ten (excellent).	Sleep quality is a subjective measure. 0 Terrible 1–3 Poor 4–6 Fair 7–9 good 10 Excellent. If a patient answers fair, poor, or terrible, further assessment should be completed
In-depth	**Global Sleep Assessment Questionnaire** (v)[56,57] Eleven questions with four possible responses (never, sometimes, usually, or always) based on the past four weeks. Screens for insomnia, OSA, shift workers disease, RLS, PLMS, parasomnia, and secondary causes.	There is no total score, and any answer besides "never" should be further evaluated.
	STOP-BANG Questionnaire (v)[58, 59] This acronym stands for Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, and Gender, and helps screen for obstructive sleep apnea. Each of the eight items is answered as yes[1] or no[0].	Risk for moderate to severe OSA: 0–2 Low risk 3–4 Further assess 5–8 High risk Sensitivity to detect OSA with a score ≥3 for moderate 93% and severe OSA is 100%.
	Pittsburgh Sleep Quality Index (PSQI) long form (v)[60,61] Assesses seven areas that impact the quality of sleep over the past month via 19 questions with the goal of assessing sleep quality and distinguishing between "good" and "poor" sleepers.	Each of the following areas is scored from 0–3: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The sum of these creates a global score. Global scores ≥5 are consistent with "good" sleepers.
Technology	Wearable devices Applications	Sleep quantity and quality can be monitored through wearable devices and results reviewed on compatible applications.

v, validated.

benzodiazepines, antihypertensives, statins, and non-steroidal anti-inflammatory drugs/COX-2 inhibitors/acetylsalicylic acid.[95–97] Proton pump inhibitors are also frequently targeted for deprescribing.[98–100] Recent lifestyle medicine studies have described their deprescribing protocols during lifestyle interventions.[101]

88.2.3.1.1 Resources for Deprescribing

- Deprescribing.org
- Medstopper.com

If available, consider involving a clinical pharmacist for additional support as they have specific knowledge and training regarding best deprescribing practices.

TABLE 88.7
Substance Use Assessment Tools

	Question(s)	Interpretation
Brief	**NIDA Quick Screen** (v)[62]	If the answer to all the questions above is "Never", screening is complete. Encourage the patient to maintain abstinence.
	Asks about the frequency of use in the past year of alcohol, tobacco products, prescription drugs for non-medical reasons, and illegal drugs (Never, Once or Twice, Monthly, Weekly, Daily, or Almost Daily)	If a patient answers yes to any of the above, further assessment should then be completed.
	Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool. Part One (v)[63]	Any response other than "never" is a positive screen and should be assessed with TAPS-2
	Screens for substance abuse	
	Alcohol Use Disorders Identification Test—Concise AUDIT-C (v)[64,65]	Scored on a scale of 0–12.
		Men score of ≥4 positive
	Three questions, rated 0 (never, low number of occurrences) to 4 (daily, high number of occurrences)	Women score of ≥3 positive
		The higher the score, the higher the likelihood that drinking is affecting the patient's safety.
	(1) How often do you have a drink containing alcohol?	
	(2) How many drinks containing alcohol do you have on a typical day when you are drinking?	Positive scores should be assessed with the ten-team AUDIT.
	(3) How often do you have six or more drinks on one occasion?	
	NIDA Modified Assist (v)[62]	Substance involvement score ranges for risk of illicit or non-medical prescription drug use:
	Appropriate to conduct if Yes to any questions on the NIDA Quick Screen	0–3 Lower risk
		4–26 Moderate risk
		27+ High risk
	Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool. Part Two (v)[63]	Scores have a potential range of 0–3 for tobacco and other drugs, and 0–4 for alcohol.
	Appropriate to conduct if Yes to any questions on TAPS Tool Part One	For tobacco, alcohol, THC:
		≥1 further assess for problem use
		≥2 further assess for substance use disorder
		For all other drugs:
		≥1 further assess for substance use disorder
	AUDIT 10 Item (v)[66, 67]	Score of ≥8 likely harmful or hazardous drinking.
	Appropriate to conduct if AUDIT-C screen is positive	Score of ≥13 for women or ≥15 for men likely alcohol dependence.
Technology	Carbon Monoxide Breath Sensor System (CMBSS)	Monitor the amount of carbon monoxide in one's lungs due to inhaled tobacco use. CMBSS are available over the counter and link with smart devices.[68]
	Smart devices	
	Applications	Applications are available to monitor sobriety for alcohol, narcotics, and some illicit drugs. These are dependent on patient input.

(v) = validated

88.3 LIFESTYLE MEDICINE INTERDISCIPLINARY CLINICAL MODEL

A core competency for the LM clinician is being adept in the development, support, and practice of an interdisciplinary team of healthcare professionals.[1] This "team" may also include appropriate referrals to other independent health professionals to leverage their expertise in enhancing health behavior change interventions.

88.3.1 Chronic Care Model

The Chronic Care Model identifies six fundamental areas that form a system encouraging high-quality chronic disease management which are then applied to a variety of chronic illnesses, healthcare settings, and target populations. This model is valuable when applied in LM as it highlights the components needed for interdisciplinary collaboration as well as a proactive model of healthcare (see Figure 88.5).[102–105]

88.3.1.1 Components of the Chronic Care Model[102, 106]

88.3.1.1.1 Self-Management Support

Patients with chronic illness need support and information to effectively manage their health. This includes information about their disease pathophysiology and behavioral determinants, assistance with self-management skill building, and ongoing support from members of the practice team.

88.3.1.1.2 Delivery System Design

The delivery of care to people with chronic conditions requires not only determining what interventions are needed, but also clarifying team member roles and tasks

TABLE 88.8
Anthropometric Measurement and Body Composition[78]

Test	Measurement	Results
Skinfold thickness testing with calipers	Subcutaneous fat is proportional to the total amount of body fat.	With proper technique, measurements for the percent total body fat can be within 2–3.5% of the gold standard, of hydrostatic weighing. If the evaluator is inexperienced or using poor technique, measurements may only be within 8% (% total body fat)
Bioelectric impedance analysis (BIA)	Measures electrical signals as they pass through fat, lean mass, and water in the body to assess leanness.	Accuracy is based primarily on the machine and the validity of the prediction algorithms.
Dual-energy X-ray absorptiometry (DXA)	Body fat percentage is estimated using the ratio of body mass to body volume.	The most accurate and precise method and can identify regional body fat distribution.

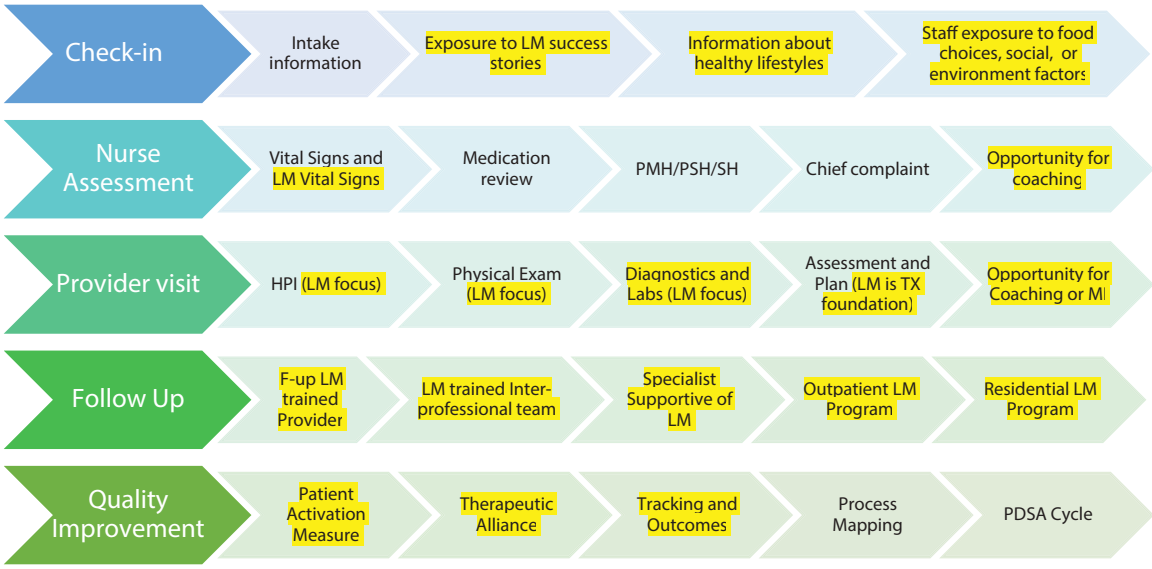
TABLE 88.9
Cardiorespiratory Fitness Testing[79]

Rockport Fitness Walking Test (one mile)[80]	Estimates aerobic power, VO_2 max, after completion of a one-mile walking course as fast as possible using immediate post-exercise heart rate and the one-mile walk time. No heart monitor or equipment is necessary.	Results are then placed into an equation that predicts VO_2 max in $mL \times kg^{-1} \times min^{-1}$. For most individuals, the predicted VO_2 max ranges within 0.335 L/min of the actual VO_2 max.
Six-Minute Walk Test[81,82]	Measures the distance a patient can walk quickly on a hard, flat surface in a period of six minutes. Upon completion distance covered, Borg fatigue and dyspnea levels, SpO_2, and pulse are documented.	Evaluates functional exercise capacity and is particularly useful for measuring response to medical interventions in those with moderate to severe heart or lung disease.
Step Tests[83,84]	Submaximal assessment of VO_2 max that can be implemented in a variety of situations within the general adult population	Heart rate is auscultated or palpated for one minute immediately after the three-minute step test and provides a measure of fitness rating based on calculated norms for age and gender.

TABLE 88.10
Tracking Personal Fitness

Component of Fitness		Starting Date	Follow-up
Cardiorespiratory fitness			
Step test	HR after 3 min stepping and 1 min rest		
Mile test	HR upon completing 1 mile, time		
Muscle strength			
Bench press	Amt of weight, # of reps		
Squat press	Amt of weight, # of reps		
Muscle Endurance			
Push-ups	# in 1 min		
Arm curls	# in 1 min		
Squats	# in 1 min		
Sit-ups	# in 1 min		
Core strength			
Plank test	Time		
Flexibility			
Sit and reach test	Inches or cm reached beyond feet		
Balance			
Standing on single leg	Time		

HR, heart rate.



*Highlight indicates change from a traditional allopathic workflow
**MI= motivational interviewing

FIGURE 88.4 Touch points for lifestyle medicine in a lifestyle medicine clinic.

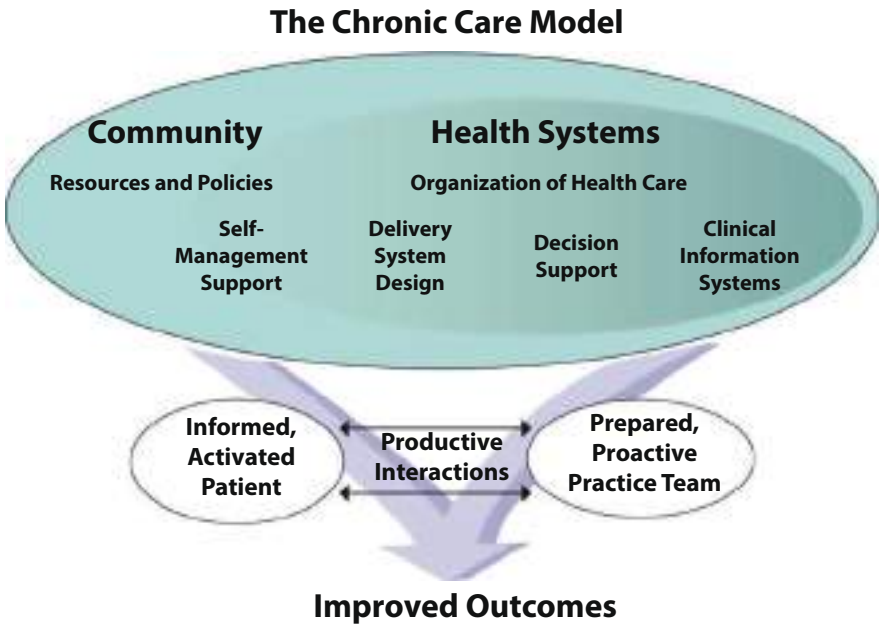


FIGURE 88.5 Chronic Care Model (developed by The MacColl Institute, ©ACP-ASIM Journals and Books, reprinted with permission from ACP-ASIM Journals and Books. Source: Wagner EH. Chronic disease management: What will it take to improve care for chronic illness? *Effective Clinical Practice* 1998;1(1):2–4).

to ensure the patient receives the care they need. This requires making sure that all involved clinicians have centralized, up-to-date information about the patient's status, and implementing follow-up as a standard procedure that is closely tied to the Clinical Information System.

88.3.1.1.3 Decision Support

Where possible, treatment decisions should be based on explicit, proven guidelines. Ideally with integration into the day-to-day clinical practice in an accessible and easy-to-use manner.

88.3.1.1.4 Community Support

Community programs and organizations can support or expand a health system's care for chronically ill patients and can assist in making prevention strategies more actively utilized. Many of the changes required in lifestyle medicine are for a long duration and frequently impact a patient's

social sphere; involving the community can help garner the social support needed to sustain change. Identifying state programs, local agencies, schools, faith organizations, businesses, and clubs that offer programs synergistic with the goals of LM distributes the responsibility and collectively enhances the potential for long-term successful outcomes.

88.3.1.1.5 Health System or a Health Organization

The health system or health organization is composed of leaders, staff, operations, values, and goals. The organization may range from a small primary care clinic to an extensive multisite integrated health system.

88.3.1.1.6 Clinical Information Systems

The purpose of this element is to have a disease-specific database of patients promptly available. This database should alert the healthcare professional about needed healthcare maintenance screenings and tests, and it should provide tracking of the results. In addition, clinical information systems (CIS) should help expedite the exchange of information between different healthcare professionals and patients.

According to the Robert Wood Johnson Foundation:

> Research has long shown that collaboration across healthcare professions improves coordination, communication, and ultimately, the quality and safety of patient care. It utilizes both the individual and collective skills and experience of team members, allowing them to function more effectively and deliver a higher level of services than each would work alone.[107]

Chronic care is part of lifestyle medicine practice. Following a model for chronic care can be an efficient and effective way to implement and maintain an effective LM program.

88.3.1.2 The Interdisciplinary Team

According to the World Health Organization, "Collaborative practice happens when multiple health workers from different professional backgrounds work together with patients, families, careers, and communities to deliver the highest quality of care across settings".[108]

This collaboration also includes the interactions between healthcare professionals to execute quality and safety checks, share information, and help patients comprehend and comply with treatment plans.

The developed interdisciplinary care team is a reinforcing interface that advocates for lifestyle modification in the treatment of chronic disease while supporting high levels of self-efficacy and self-management, both of which are associated with higher levels of treatment compliance.

The steps to building an interdisciplinary team include 1) identifying and/or hiring the right team members, 2) training the team well, 3) setting appropriate expectations, and 4) assessing competency and providing feedback for growth.

Identifying/ hiring	Need to have an authentic interest in lifestyle medicine and be on the health journey, not necessarily being an expert or perfect at it.
Training	Consider enrolling all team members into an intensive therapeutic lifestyle change (ITLC)* program so they can experience the difference in themselves before working with patients. Long-term training may include LM clinical pearls, grand rounds, lifestyle challenges, becoming certified in LM,** and an LM journal club.
Setting expectations	Lifestyle medicine should be looked upon as the foundation of medical treatment. Patient communications should be standardized so patients receive congruent advice on topics such as diet and exercise. Team members should model health behavior with a "do as I do" mindset.
Assessing competency	Patient charts and cases should be reviewed, and meaningful feedback provided to improve patient care and the team's performance.

*Some options for ITLC programs available online include the 21 Day Vegan Kick Start program (free) through the Physicians' Committee for Responsible Medicine PCRM[109] Pivio, formerly the Complete Health Improvement Program (at cost) through the Lifestyle Medicine Institute (LMI);[91] or PlantPure Rx (at cost).[110]

**Several training courses and certifications are now available for staff through the American College of Lifestyle Medicine, Wellness Coaches, and the American College of Preventive Medicine.

A true collaboration from all members of the team requires confidence, commitment, and competency. An interprofessional team includes an internal team and an external team.

The internal team (within the clinic) may include nurses, medical assistants, receptionists, support staff (billing and operations), advanced practice providers, condition management clinicians, health coaches, physical therapists, and fitness experts.

External teams (outside of the clinic) may include other primary care providers, specialists, chiropractors, massage therapists, naturopathic doctors, midwives, hospitals, and payers.

88.3.2 Sample Effective Programs

In a report on the effectiveness of strategies to change the behavior of health professionals and the organization of care to promote weight reduction in those who are overweight or obese, when compared with standard care, educational interventions by general practitioners could reduce

the average weight of patients after one year by 1.2 kg. However, patients may lose more weight (6 kg) after one year if the care is provided by a doctor-dietitian team.[111]

In an Australian general practice, a lifestyle intervention that included a health check with brief lifestyle counseling and referral of high-risk patients to a program consisting of one to two individual visits with an exercise physiologist or dietitian and six group sessions showed that those in the intervention group had increased their physical activity levels and lost more weight if attending the minimum number of group program sessions. Practice nurse involvement was important to sustaining implementation. This integrated model showed that counseling with the physician provided some benefit, but more long-term changes were possible via a group-based approach.[112]

In a study that examined the outcomes and costs of an LHE-delivered translation of the Diabetes Prevention Program (DPP) evidence-based lifestyle intervention for older adults in Arkansas senior centers, participant weight loss averaged 3.7 kg at four months, providing an effective tool for LM system design that occurs in partnership outside the usual clinical settings.[113]

Resources for interdisciplinary collaboration:
www.eatright.org;
www.ideafit.com/find-personal-trainer;
www.medicalfitness.org.

88.4 LIFESTYLE MEDICINE OFFICE SYSTEMS

88.4.1 Information Systems

Information systems are likely present within an existing electronic medical record for tracking HEDIS and other value-based care imperatives and can be used simultaneously with other resources to track lifestyle behaviors, proactively identify high-risk patients, and facilitate LM intervention decision support. Designing an office system that can assimilate this LM data and make it available for routine use by team members is a critical component of a next-generation model for LM care.

88.4.2 Care Settings

88.4.2.1 Group Visits

The value of group visits is that they appropriately allow clinicians to see more patients more frequently for follow-up chronic disease management visits and allow more availability of proactive and coordinated interactions with the clinical team, leading to higher patient and provider satisfaction. Patients receive the benefit of prompt access to care, extra time with the physician and clinical team, and answers to questions they might not have thought to ask (because others in the group ask). In addition, patients may be motivated by the stories and experiences of other patients, gain greater education, and receive more assistance for psychosocial issues.[114]

88.4.2.2 Community and Digital Connection

A referral network to community-based resources is an important element of a comprehensive LM clinical system design, as a number of programs may be offered locally that would provide care that may not be feasible to include within a clinical practice. An example of such is the Diabetes Prevention Program[115] with multiple delivery sites regionally as well as through online delivery systems.

The online community has also expanded access to many LM interventions and can become a readily available resource for patients in helping to provide health education and the social relationships that encourage lifestyle change outside of a clinical setting. In a relevant study, with clear advantages for reach, social media and mHealth technologies offer the ability to scale and engage entire populations at low cost, while developing supportive social networks, connecting patients and providers, encouraging adherence with cancer care, and collecting vast quantities of data for advancing cancer research. Best practices have yet to be developed amid the rapid and numerous development efforts.[116]

88.4.2.3 Lifestyle Medicine and Telehealth

Since the SARS-COV-2 outbreak and the "lockdown", most electronic medical records (EMRs) have incorporated Telehealth systems and these have found broad acceptance by both payers and the public. While telehealth often involves the use of new or sophisticated technology, it is helpful to remember the foundational emphasis of lifestyle medicine on social connection. It is well established that the physician-patient relationship is a therapeutic modality in and of itself[117–119] A lifestyle medicine use of telehealth will seek to utilize it in a way that enhances relationships. It is important to have a shared discussion with patients about how they like to communicate and be communicated with; e-mail/secure message, phone, or video. Clear expectations and setting appropriate boundaries with patients for virtual visits may be important.[120]

88.4.3 Collaboration and Resources

Another core competency from the 2010 JAMA article addresses the measurement of processes and outcomes with the intent of improving the quality of lifestyle interventions in individuals and groups of patients. Data collection and analysis allow the assessment of a patient's current status and movement toward health behavior changes. Following the progress of multiple patients allows for analysis of the system's effectiveness as well as the identification of weak areas. A key element of LM quality improvement is to routinely plan, conduct, and evaluate interventions to improve processes and outcomes. Identifying a team member or committee to collect medical record data and/or perform chart audits facilitates this process, fostering accountability within the system.

88.5 LIFESTYLE MEDICINE QUALITY IMPROVEMENT

88.5.1 Principles of Evidence-Based Medicine

Quality improvement is foundational not only to personal practice, but to population management and health behavior change for patients. While its elements are simple, it is not always intuitive, and expertise only comes with practice. The American Academy of Family Physicians sums up the basic principles of quality improvement as follows: 1) establish a culture of quality in your practice; 2) determine and prioritize potential areas for improvement; 3) collect and analyze data; 4) communicate your results; 5) commit to ongoing evaluation; and 6) spread your successes.[121]

Many of the process and quality improvement principles can be traced back to W. Edwards Deming. His work, most famously adopted by Japanese manufacturing, includes the Plan-Do-Study-Act (PDSA) cycle, and spawned Toyota's LEAN, and Six Sigma.[122] Many of the quality improvement principles from auto manufacturing apply to healthcare, and in today's pay for performance and ACO healthcare environment, strategic use of quality improvement is essential.

The Institute for Healthcare Improvement (IHI) has excellent resources on quality improvement. Much of their "Open School" curriculum has been free for medical students and residents, and it is well worth reviewing. In addition to the basic quality improvement curriculum, they have a curriculum on patient safety/medical mistakes, leadership, and a variety of other topics.[122]

88.5.2 Quality Improvement

88.5.2.1 Process Mapping

Clinical LM practice is unique in that multiple providers may be involved in ongoing care that includes multiple interventions, such as nutrition, fitness, and stress management. Understanding the process flow can offer great value to becoming an efficient system that reduces unnecessary clinical components while providing an effective and efficient LM solution using workflow diagrams (Figure 88.6).[123]

The symbols are important in a process flow map. Ovals show input to start the process or output at the end of the process. Boxes or rectangles show the task or activity performed in the process. Arrows show the process direction flow. Diamonds show points in the process where a yes/no question is asked or a decision is required. Usually, there is only one arrow out of an activity box. If there is more than one arrow, a decision diamond may need to be used. If there are feedback arrows, the feedback loop should be closed, i.e., it should return to the input box.

The process map should have a specific start and end point. Each step should be listed and placed in sequence. Each team member should review it. Analyze the map by asking: What steps are essential and add value? What steps do not add value (and can be removed)? What steps do not add value, but are not avoidable (and might require longer-term solutions)?

The following questions may add even further value: Are the steps done in a standardized way or differently depending on which team member does that step? Consider which way is truly the most effective way. Are steps repeated unnecessarily or out of sequence? Are there process steps where errors occur frequently? Process Mapping fits well with the next step of quality improvement, which identifies and evaluates necessary changes.

88.5.3 Plan-Do-Study-Act

A commonly used construct for quality improvement in healthcare is the PDSA method.[124] This tool enables small-scale improvements over short periods of time. In the Plan

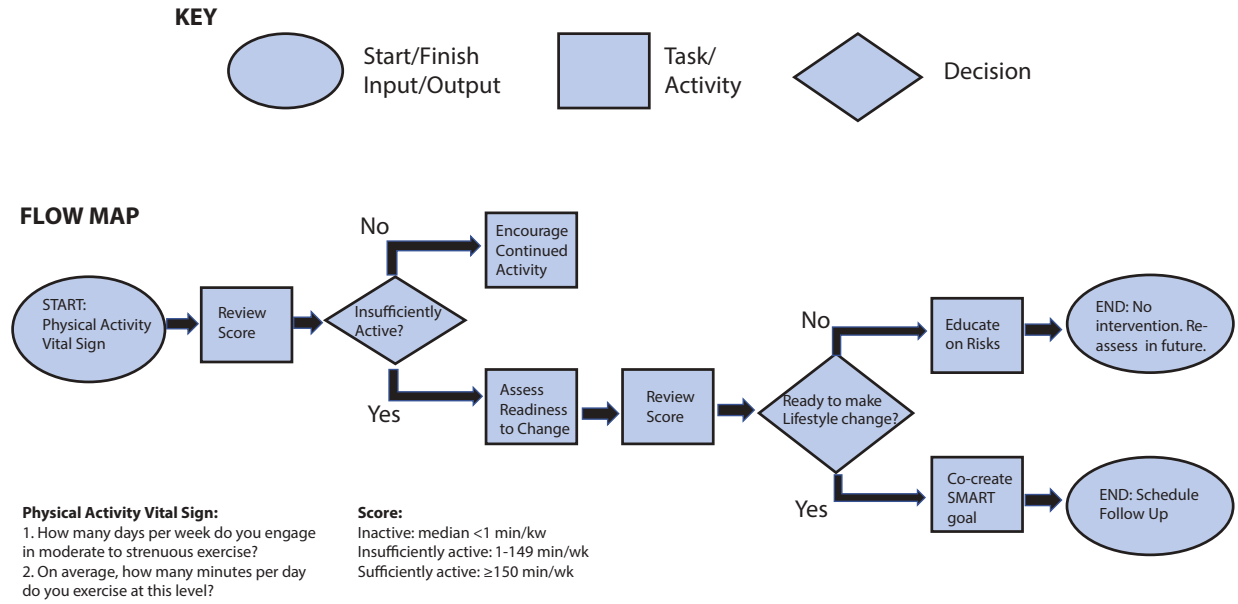


FIGURE 88.6 Process flow map.

phase, the objective is to identify a goal and develop a plan, clearly identifying the who, what, when, and where of the desired "intervention". It is helpful to have a clearly defined cause-effect hypothesis to guide the cycle in making predictions. This allows for refinement of the underlying hypothesis with each cycle of improvement. In the Do phase, the plan is carried out, documented, and the initial data can be analyzed for modifications that may be necessary immediately. In the Study phase, the complete data is analyzed and compared to predictions to create an evaluation and summary of the lessons learned from the process. In the subsequent Act phase, the intervention is either instituted, dropped, or modified based on reflective and constructive evaluation. Resulting refinements may then be added to the selected workflow. (See Figure 88.7.)

The PDSA cycle requires quick planning, small tests of change, and time to evaluate the results for further refinements in an iterative process over several cycles. The optimal end point rarely occurs after one implementation; being nimble and adaptive is at the core of this technique for enhancing the LM clinical process.

88.5.4 Root Cause Analysis

Another tool in quality improvement for understanding the underlying reasons we are producing certain outcomes is through root cause analysis.[125] The fishbone diagram is useful in identifying the causes leading to an effect and can be drawn visually. The participation of the care team is important in gathering comprehensive perspectives as to root causes and to drill down to discover what is occurring. The problem needs to be defined specifically, followed by a quick brainstorm of all possible causes, without the solutions being offered at this stage. Then all these causes are written down or typed into an electronic program. The problem is placed at the head of the "fish". The categories point toward the central line of the fish's "body" as individual branches, representing things such as equipment, process, people, materials, environment, management, communications, policies, and patients.

The team then discusses and analyzes the resulting diagram: Are there repeated causes? Are most causes under one category? A few priority causes are identified to concentrate on, and the possible solutions are reviewed by the team. The chosen solution(s) are then applied using PDSA cycles.

These resources reflect the important conceptualization that LM clinical processes are ongoing and iterative built on the culture of quality improvement. Retaining flexibility in adjusting roles and procedures based on measurement results and openness to innovation is key to shaping next-generation models of care. These processes are key to the successful improvement in lifestyle medicine practices where the variables are so numerous that best practices are virtually impossible to define prospectively.

Resources:

Process mapping (www.draw.io/);

PDSA cycle (www.ihi.org/resources/Pages/Tools/PlanDoStudyActWorksheet.aspx);

Fishbone diagram (Figure 88.8) (www.ihi.org/resources/Pages/Tools/CauseandEffectDiagram.aspx).

88.6 Clinical Process Conclusions

A lifestyle medicine clinical practice is defined by its systematic integration of key lifestyle behavior assessments and counseling into a comprehensive patient-centered process addressing the actual cause of illness. The four key components to consider for LM integration include making

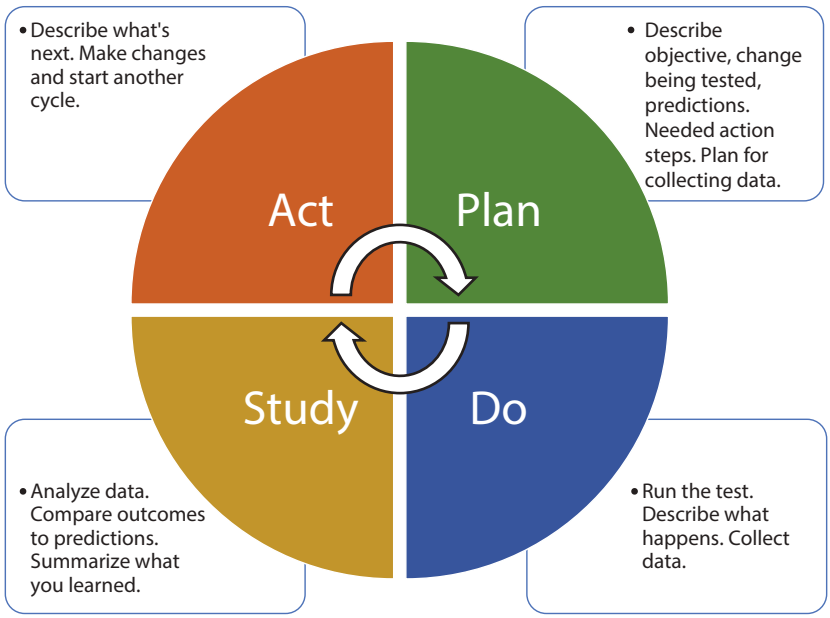


FIGURE 88.7 PDSA cycle.

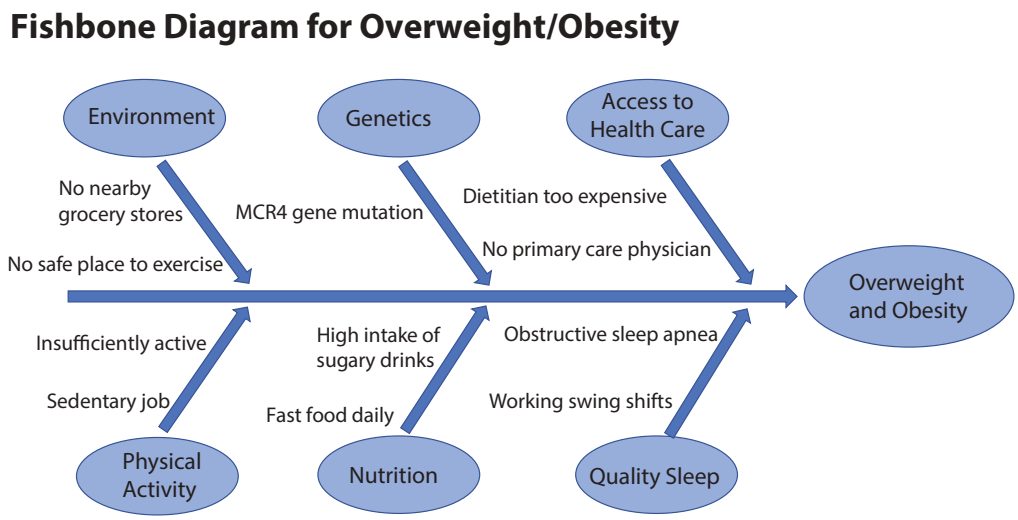


FIGURE 88.8 Fishbone diagram.

lifestyle medicine the foundation of the clinical encounter, using an interdisciplinary clinical care model, creating efficient and effective office systems, and engaging in ongoing quality improvement.

LM treatment addresses reversible unhealthy or risky lifestyle factors and follows evidence-based practice guidelines. Current reactive care models have generally not done well at fostering collaboration between providers or adequately engaging patients in this positive behavior change. An effective proactive system recognizes that tracking LM vital signs, follow-up (possibly through group visits), and a variety of systems for motivating and documenting behavior change are key to the lifestyle practice. This entails fully leveraging partners in the system, such as other health professionals in the office or experts in the community, to provide a consistent message and the required social and educational resources needed to support a lifelong process of making healthful lifestyle choices. At the same time, the LM practice must continually strive for the improvement of office systems, intervention practices, and the ability to motivate patients to change and maintain the healthiest lifestyle choices.

Only a small fraction of an individual's lifetime is spent interacting with a healthcare team. Lifestyle medicine clinical processes need to be designed in such a way as to facilitate real and beneficial change in the habits of a patient's daily life. With intention and design, these encounters can reduce chronic disease and healthcare spending, promote health, and save lives.

CLINICAL APPLICATIONS

- Depending on the time availability of the patient and medical staff, brief or more in-depth assessments of LM risk factors can be incorporated into the clinical visit. Based on the patient's motivation and confidence level for change, evidence-based treatment plans can then be implemented to address unhealthy or risky lifestyle factors.
- The identification of key metrics in clinical practice, such as blood pressure, adiposity, and metabolic syndrome, engenders targeted discussion of lifestyle risk factors and identifies areas for improvement.
- For a successful implementation of an LM intervention and patient lifestyle empowerment, the following should be in place: easily available educational information, a team approach for delivery, and connection with community resources.
- Group visits offer an alternative process in which individual patient concerns are addressed while leveraging the benefits of the dynamics of the group and the potential integration with behavioral health services.
- Telehealth services are now widely available. They may be more convenient and improve access to care for patients.
- Continuous quality improvement is foundational to growing an LM practice. It can be started small, identifying a single process that needs improving. Successful implementation builds the strength of the clinical team and encourages active participation in clinical care and system improvement.

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89 Emotional Health and Stress Management

Neil Nedley, MD and Francisco E Ramirez, MD

KEY POINTS

- Well-being can be optimized by leading individuals away from unhealthy lifestyles and toward healthy coping strategies.
- Simple tools are available for bringing positive changes in thinking patterns and improving mood.
- Lifestyle Interventions, improving thinking skills, and specific behavioral interventions have demonstrated the benefit of stress management.
- Many cases of depression and anxiety may be managed successfully with appropriate lifestyle changes

89.1 BACKGROUND

In physics, the term "stress" was originally used to describe the force on an object that leads to bending or breaking. Relaxation, in contrast, refers to enjoyable, leisure activities indulged during evenings or weekends. According to Lumsden, the first time the term "stress" was used was in the 14th century and referred to a context of affliction, adversity, and hardship.[1] Physiologist Hans Selye first popularized the term stress in his book *The Stress of Life*,[2] which reported on his research. Today, we commonly use the term "stress" to describe our response to the problems and concerns that we encounter in life. Deadlines, economic problems, or problems in relationships can trigger stress. These activating events are called stressors and our reaction to them is referred to as stress.

In 1697, Isaac Newton theorized that in the natural world, for every action there is an equal and opposite reaction.[3] The same principle applies to physiological and psychological stress; the stressor is the action, and stress is the reaction. A wholistic definition of stress might well be an inability to cope with a perceived threat (real or imagined) to one's mental, physical, emotional, and spiritual well-being resulting in physiological responses.[4]

Physiological and psychological stress are major factors in both physical and mental illness and must be addressed for optimal well-being and homeostasis.

We live in a world with increased perceived stress. Seventy-four percent of US adults report symptoms due to stress. The demographic reporting the most is the millennials with 86% reporting the effect.[5]

Stress can have negative health effects and has been linked to all leading causes of death including heart disease, cancer, accidents, cirrhosis, and suicide.[6] This is a significant change since 1955 when the leading causes of death were primarily infectious diseases.[7]

Three categories of stress have been identified: *eustress* (the good type, it can motivating or inspiring such as falling in love or meeting someone famous); *neustress* (a type of stress with no consequential effect such as reading about a faraway news report); and *distress* (considered negative, many times just called stress such as a breakup of a relationship). Distress may be further classified as *acute stress* which may be intense but quickly disappears (such as getting pulled over by police and let go without any a ticket) or *chronic stress*, which appears gradually and lingers for some time, from days to months (such as could be found in someone in an entrapped, unhealthy relationship).

Treating distress with medication has been disappointing. It has become clear that many psychiatric medications (benzodiazepines, SSRIs, antipsychotic medications, stimulants, and others) create neurotransmitter imbalances and a degree of dependence. While medications may be necessary in some cases, there are non-drug lifestyle behavior and mental health tools that show significant (and sometimes greater) effects in bringing improvement to many mental health pathologies. This chapter explores practical lifestyle interventions for optimizing well-being and managing stress, anxiety, and depression. Several tools are introduced to assist the clinician in identifying and measuring responses to interventions. Effective strategies for increasing happiness and well-being are explored followed by evidence-based coping tools for stress management. Positive psychology and cognitive behavior therapy (CBT) are explored as helpful tools for empowering patients to regain healthy control of their own thinking. Various evidence-based lifestyle-focused modalities are discussed for managing stress. An introduction of the *Nedley Hypothesis* provides a novel construct for addressing the modifiable factors in both depression and anxiety. Lifestyle changes, both physiological and psychological (learning to manage thoughts) are likely the most effective long-term strategy for dealing with stress and anxiety as well as several other common mental health disorders.

89.2 WELL-BEING AND MENTAL HEALTH

Mental health may be defined as a state of well-being in which every individual realizes his or her own potential,

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copes with the usual stresses of life, works productively, and makes a positive contribution to their local community and sphere of influence. This positive perspective of mental health is also emphasized in the World Health Organization's definition of health as contained in its constitution: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[8] Astute caregivers may observe an otherwise healthy patient quickly deteriorate physiologically when overwhelmed by psychologic stressors. Stress management then is an essential part of an overall healthy lifestyle. The principles of mental health discussed in this chapter are not only important for a healthy mind but also benefit the whole body.

89.2.1 Adaptive Mechanisms of Mental Health

Coping is a positive and constructive response to stress with the purpose of maintaining emotional well-being. Among the common coping mechanisms are the thoughts, behaviors, and emotions that are used to master, tolerate, reduce, or minimize stressful events.

Two main coping strategy categories are present in individuals dealing with stressful situations. The first is *problem-solving* which focuses on specific actions to deal with the stressor; the second relies on *emotions* to respond to the stressor-triggered emotions. Research suggests that those who use a balance of both are better at handling stress.[9]

Another way of categorizing response to stress is *active* versus *avoidant* coping. Active coping focuses on changing the thoughts about the stressful event or events therefore changing its nature. Avoidant coping seeks to evade dealing with stressful events (underlying cause) and tends toward destructive behaviors (like drug or alcohol addiction) or dysfunctional mental states (like withdrawal). Research shows that avoidance coping has been associated with poorer outcomes.[10]

Various instruments have been developed to identify and quantify individual coping styles such as the *Ways of Coping* measure[11] and the COPE Inventory.[12] Either may be useful in the clinician's clinical practice. The *Ways of Coping* measure identifies various coping mechanisms: confrontative coping, seeking social support, planful problem-solving, self-control, distancing, positive appraisal, accepting responsibility, and escape/avoidance. The COPE is more reliable and has been validated.[13] COPE measures include active coping, planning, seeking instrumental social support, seeking emotional social support, suppression of competing activities, faith, positive reinterpretation and growth, restraint coping, resignation/acceptance, focus on and venting of emotions, denial, mental disengagement, behavioral disengagement, alcohol/drug use, and humor.

89.2.2 Factors Affecting Emotional Well-Being and Mental Health

Multiple Factors affect emotional well-being and mental health. It should be recognized by clinicians and patients that positive change is possible. Individuals can learn to improve their coping skills. A review of the literature on some of these modifiable factors may be instructive for clinicians addressing both beneficial and more pathologic coping methods.

Self-worth is the inherent worth of every human being. There is a basic difference between self-worth and self-esteem. Self-esteem refers to pride in oneself and is primarily a measure of a person's belief in how worthy lovable, or capable they are, in comparison to others. While the two are sometimes confused, they are separate constructs. Studies by Emler, a social psychologist, have shown that people with a high opinion of themselves pose a far greater threat to others than those with low self-esteem.[14] Dr. Backus proposes that, when pride is dominant, it negatively affects self-worth. He identifies that the following behaviors identify pride:[15] trying to be noticed, craving attention, looking for compliments, needing to be important, detesting the idea of being submissive, loathing the idea of admitting to wrongdoing, being strongly opinionated, being argumentative, demanding one's own way, wanting control over others, flaunting of individual rights, refusing advice, being critical yet resenting criticism, being oversensitive, and thinking one has excellences that are, in reality, not present.

On the other hand, confident people who have a positive self-worth are more likely to have a better outlook in life, have a positive attitude and less stress, and lead a more productive life.[16] Feeling loved, trusted, and accepted by family[17] and others is associated with an individual who is more comfortable, safe, and secure. Such a person is better able to communicate and develop positive relationships with others.

Examples of how this construct might be useful might be found in the following:

- The breakup of a dysfunctional family is a commonly painful experience for all those involved, especially children. There is evidence that modeling and encouraging healthy self-worth-based responses improve the future mental health and stress levels of all involved.[18]
- Physical problems such as birth trauma, brain injury, or drug abuse may negatively affect brain chemistry and lead to mental illness. These can adversely affect self-worth and the ability to achieve goals leading to unhappiness and even depression.[19] Taking steps to build self-worth may be helpful in these situations
- It is widely understood that abuse leads to an increased likelihood of mental disorders during childhood and adulthood. Sexual, physical, psychological, and verbal abuse often have negative effects that lead to low self-worth, depression, isolation, and anger: all markers for an unhappy life. Interventions that build self-worth are helpful for these individuals.[20]

89.2.3 Positivity and Happiness

Happiness not only increases positive emotions but also improves physical health. Happy people live longer lives,[21] have more stable marriages,[22] are more creative,[23] and tend to be more generous.[24] There are many ways of improving the outlook and happiness of people. Research demonstrates that positive psychology[25] has a significant impact on increasing positivity and happiness.

Happy and unhappy people experience the same level of emotional pain with traumatic experiences. The difference seems to be that happy people tend to bounce back faster. Both groups experience pain, but the happy group realizes that life can, and most likely will, be better in the future. If the attitude is wrong, a negative mindset will follow. The sooner an individual adjusts the attitude, the faster the development of motivation to positive change.[26]

Dr. Martin Seligman, a pioneer researcher in the field of positive psychology, has focused on finding the keys to happiness. He has used the scientific method to better explore the topic. Data was gathered using extensive questionnaires to identify what made people happy. Three dimensions were identified to cultivate a happy, satisfying life. He uses these descriptive phrases: The Pleasant Life, the Good Life, and the Meaningful Life.[27] He proposes therapy that builds upon each of these principles.

The *Pleasant Life* is about enjoying basic things like friendships, family, our surroundings, and fulfilling the body's needs. He proposes that someone can stay pleasantly in this stage or move on to experience the benefits of the next level: *Good Life*. The Good Life occurs when a person discovers their personal identity and values their unique set of character strengths and virtues,[28] the strengths of which are used to improve the lives of others. Seligman believes that, as personal talents are used to make others happy, personal happiness is strengthened. The last stage, the *Meaningful Life*, adds the identification of a sense of meaning that grows out of the character strengths and virtues, not in a selfish way, but rather for a purpose bigger than self. Dr. Seligman proposes that taking care of oneself and cultivating virtues enables individuals to experience the importance of otherness and motivates outward-focused caretaking. As individuals change their focus and efforts from themselves to others, they sacrifice self-centered wants (not needs) for a greater purpose and develop the highest levels of happiness.

89.3 TOOLS FOR IMPROVING HAPPINESS

We review some practical tools that may assist the clinician in helping patients improve their overall well-being.

89.3.1 Journal Thankfulness

Having a gratitude journal is one of the best ways of improving future thought patterns.[29] The act of physically writing out what an individual is thankful for changes the thought focus, enabling the accentuation of positive things that may not have been otherwise noticed. Identifying just three things per day can make a difference. During times of discouragement, the daily logs can be reread as a reminder of the positive parts of life.

89.3.2 Get the Most Out of a Gratitude Journal

Understanding why one sees the world the way they do, will improve control over emotions. Over time, one can observe how the thoughts are changed from negative to positive. On a daily basis, it is easy to see the negative side of circumstances but the thinking can be adjusted through gratitude journaling. The next step is to add three to five things from each day that were liked. The journaler is then encouraged to relive the situation in the memory and ask questions: Why did the situation take place? What was right about it? Why did it happen? Why did the journaler act in the way he/she did? The next step is to consider something that was not liked. After writing it down, one then seeks to understand why the emotional effect occurred and what thoughts and/or actions helped improve the mood. This exercise will help crystallize the understanding of negative thought patterns. Instead of just repeating negative thoughts over and over in one's mind, one learns how to re-focus the mental energy toward a more positive way of thinking.[30]

89.3.3 Practice to Become an Optimist

Individuals should make an effort to have an outlook of hope and optimism for viewing the future. It is better to avoid focusing on the negative, and rather accentuate positive things, even in disagreeable situations or in conflict with other individuals. If considered carefully, there is almost always a positive perspective that may, at the very least identify, the potential for positive consequences.

89.3.4 Leave the Past in the Past

In addition to gratitude, a second key focus with which to address unhappiness is forgiveness. The Western World, and specifically the United States, is a "ventilationist society that deems it honest, just and even healthy to express our anger"[31] This is problematic because anger is the one emotion that gets worse as it is expressed. It is interesting to note how other cultures commonly deal with similar situations. For example, Asian culture tends to deal quietly with difficult situations, problems, and challenges. Individuals of cultures that use approaches that do not give expression to negative emotions are better at coping with life stressors and are happier.[32]

89.3.5 Dealing with Anger

When angry feelings come, individuals have a choice to either deal with them constructively or destructively. They may choose either a controlled response or be controlled by anger. Suggestions to deal with anger more constructively include the following.

Acknowledge anger: There is no need to deny that the emotion exists. Honesty is best. Accepting the situation and focusing on the wisest way to deal with the situation is the better choice.

When the anger emotion presents itself, it is better to think and not just react. There is wisdom in the saying "when angry count to ten". The key is to take the time to think things through; to identify why the anger arose and what effect this may have on others. The focus should be on finding the best way to respond to the situation.

Anger should not be allowed to take control. Individuals should realize that it is ok to feel anger but is not acceptable to hurt and lash out at others. It is best to be under control in those moments of stress.

Anger should be resolved as soon as possible. In dealing with the cause of the anger, constructive communication with those who triggered the feelings should be included. The focus should be on resolving the problem rather than placing blame. If the problem initially appears unmanageable, a third-person mediator may be helpful.

89.3.6 Deal with the Present

Individuals should break the destructive habits of negative thoughts and actions and build the healthy habit of focusing on enjoying the present. These three steps can increase the experience of daily happiness.

89.4 STRESS AND UNHEALTHY LIFESTYLES

In the 1800s, Sir William Osler described a case of angina pectoris on a businessman and theorized that stress may have been the trigger:

> Living an intense life, absorbed in his work, devoted to his pleasures, passionately devoted to his home, the nervous energy...is taxed to the uttermost, and his system is subjected to that stress and strain which seems to be a basic factor in so many cases of angina pectoris.[33]

Interestingly, in a 12-year study of 3730 petroleum industry workers in China, none of whom had diabetes at baseline, those who experienced increasing job stress were 57% more likely to develop diabetes,[34] which then markedly increases their risk of atherosclerosis.[35] Chronic stress can have many negative effects on the human body[36] and even on the thoughts by impairing the function of the frontal lobe;[37] the pathogenesis can be explained by the way the immune system interacts with the nervous system.[38] While too much stress could have negative effects, the right amount of stress could be beneficial, improving immunity and even helping fight cancer tumors.[39]

Recent studies report that stress levels are increasing, especially in the Western World. A report from the American Psychological Association[40] reported that adults continue to report high levels of stress and many say that their stress has increased over the past year. The report says that 75% of adults experienced moderate to high levels of stress in the past month and nearly half reported that their stress has increased in the past year. This is not a problem confined to adults. The report notes that stress is also a top health concern for US teens between the 9th and 12th grades. The rapidly changing modern world, especially the pandemic, has been an important source of problems. Social media, smartphones, and a permanent internet connection give us constant news 24/7 overloading our minds, sometimes augmenting current problems, such as pandemic and economic issues, and sometimes magnifying small issues.

89.4.1 Assessment

A classic test that has been used in the past to give a numeric value to the stress level is the Social Readjustment Rating Scale (Table 89.1), developed by Holmes and Rahe.[41] A value of 200 points or more in one year indicates an increased risk of disease. It can also be used to assign a numeric value to the stress level an individual is facing. Since not everybody reacts the same way to different levels of stress, the assessed value is a rather rough indicator of stress levels.

89.4.2 The Stress Response

Whether we want to acknowledge it or not, stress and anxiety are part of everyday living for most people. The "stress response" is what determines how stress will ultimately affect us. The human body has carefully orchestrated processes to help us deal with hazardous circumstances. In 1929, Cannon described the process as a "fight or flight" response,[42] which has the purpose of enabling survival in situations of imminent danger. The body's response to a stressful situation is designed to be intense but temporary. In the right setting, the effect of stress hormones is generally beneficial,[43] providing resources needed to deal with such emergencies.

Selye, one of the pioneers in the area, divides the stress response into three phases; Phase 1, alarm reaction; Phase 2, state of resistance; and Phase 3, state of exhaustion. [44] There are similar reactions to all types of stressors. The effect of a new stressor is predictable and progressive.

Stage 1 (alarm reaction) helps focus on what should really have attention. Stage 2 (state of resistance) is when the individual chooses whether to fight or flight in the situation. If the stress is not short-term, the individual is exposed to it for days, weeks, months, or even longer, and it will ultimately progress to stage 3 (state of exhaustion). If the stressor persists in this phase, disease is likely to appear.

The questionnaire by Paramount Wellness Institute[45] (Table 89.2) identifies how current culture has affected individual behaviors. There is no score for the test. Its purpose is to bring awareness and help analyze the ways individuals may be creating or alleviating stress

TABLE 89.1
Readjustment Rating Scale

Life Event	Value
Death of spouse	100
Divorce	73
Marital separation	65
Jail term	63
Death of close family member	63
Personal injury or illness	53
Marriage	50
Fired at work	47
Marital reconciliation	45
Retirement	45
Change in health of family member	44
Pregnancy	40
Sex difficulties	39
Gain of new family member	39
Business readjustment	39
Change in financial state	38
Death of close friend	37
Change to a different line of work	36
Change in number of arguments with spouse	35
Home mortgage over $100,000*	31
Foreclosure or mortgage or loan	30
Change in responsibilities at work	29
Son or daughter leaving home	29
Trouble with in-laws	29
Outstanding personal achievement	28
Spouse begins or stops work	26
Begin or end school	26
Change in living conditions	25
Revision of personal habits	24
Trouble with boss	23
Change in work hours or conditions	20
Change in residence	20
Change in schools	20
Change in recreation	19
Change in church activities	19
Change in social activities	18
Mortgage or loan of less than $100,000*	17
Change in sleeping habits	16
Change in number of family get-togethers	15
Change in eating habits	15
Single person living alone	**
Other, describe	**
Total:	

*Adjusted for inflation.
**Add your own value.

responses. Identifying stressors or triggers can help avoid or minimize causes of stress. The recommendation is to focus on how stressors are affecting life and then identify a solution through healthy cognitive and behavioral coping strategies.[46]

89.4.3 Stress Management

One of the first steps in dealing with stress is to identify the stressors. The most powerful strategies for combating stress often involve targeting specific stressors. When stressors cannot be clearly identified, there are other helpful techniques. Cognitive appraisal refers to the perception, interpretation, and evaluation of the stressor. The process is summarized in Figure 89.1,[47] which summarizes the reaction of stress. The evaluation of the event will determine if an individual appropriately copes with the stress or if it will be augmented, activating endocrine responses that may impair immunity and health.

89.5 TOOLS FOR MANAGING STRESS

Everyone copes with their individual stress. Unfortunately, some of the methods used are not helpful and may even worsen the stress. It seems quite logical that the key to good stress management is to maximize healthy responses while avoiding those that are harmful. Harmful ways of handling stress include addictive behaviors (alcohol, tobacco, marijuana, illegal drugs, food), entertainment television, emotional outbursts, overspending, and others. These should be avoided or removed. Positive ways of dealing with stress include simple things like:

- Laughter decreases the body's stress response and increases endorphins.[48]
- Positive interactions with pets release oxytocin and decrease stress hormones.[49]

Identifying healthy responses facilitate healthy stress management.

89.5.1 Calming the Mind and Body

Learning to calm the mind is an essential element in dealing with stress. The popularity of some commonly used methods does not necessarily make them effective. The authors of the study "Mind the Hype: A Critical Evaluation and Prescriptive Agenda for Research on Mindfulness and Meditation"[50] suggest that one of the biggest challenges with the concept of "mindfulness" is that it is an inconsistently and ill-defined term both in the scientific literature and in popular media. The lack of a standard definition makes effective research and its appropriate prescriptive use very difficult to identify. The authors note that sometimes "mindfulness" denotes being consciously aware. Other times it is a practice in which people take a specific posture and focus on breathing or other "objects". Other times it is defined more as a mental faculty such as retention/memory, discernment, or attention. Another point the authors make is that the lay press describes it more as a cure-all panacea for everything. Finally, they point out that due to its nebulous definition, the research is quite likely measuring unknown factors. For example, those who choose to do

TABLE 89.2
How Current Culture Has Affected Individual Behaviors

Life Event	Value	
1. I keep my smartphone on throughout the day so I won't miss any calls.	YES	No
2. I use my Facebook account more often than my email account.	YES	No
3. I tend to leave the water running while brushing my teeth.	YES	No
4. I eat more than one meal prepared outside the house each day.	YES	No
5. During the day, I constantly check emails and text messages as they come in.	YES	No
6. I drive rather than take mass transit to and from work/college regularly.	YES	No
7. I typically take my laptop, BlackBerry, etc. on vacation with me.	YES	No
8. I have been known to flush unused medications down the toilet.	YES	No
9. I get more of my news from comedy channels than newspapers, TV news, or online news sites.	YES	No
10. I spend less than one hour outside each day in a natural setting.	YES	No
11. I regularly interact (leave comments) on websites I visit.	YES	No
12. I find that I rely more and more on the Internet and electronic devices for information (e.g., Online GPS, Google) and less on memory retention.	YES	No
13. More often than not, I record my favorite TV shows and watch them at my preference or watch episodes of my favorite shows online.	YES	No
14. I recycle all cans, bottles, newspapers, etc.	YES	No
15. I start to feel antsy if I cannot check my email, text messages, or Facebook account each hour or more often.	YES	No
16. I spend more time playing video games or surfing the Internet inside than outside in nature each day.	YES	No
17. I check my emails, tweets, Facebook updates, etc. within 10 minutes of waking up each morning.	YES	No
18. I have one or more tattoos.	YES	No
19. I own more than one smartphone and I use them both at the same time (e.g., phone calls, apps, Google).	YES	No
20. I make more than one purchase online each week.	YES	No
21. I dread answering the onslaught of emails each day.	YES	No
22. I get a bit of a rush or excitement when my smartphone goes off.	YES	No
23. I text message my friends and parents more than I call them by phone.	YES	No
24. I watch movies via the Internet or Netflix.	YES	No
25. I make an effort to buy organic produce each week.	YES	No
26. I have more than 50 websites bookmarked on my computer.	YES	No
27. I have more than 250 friends on Facebook.	YES	No
28. I purchase plastic water bottles rather than use a stainless steel bottle.	YES	No
29. I have more than 25 apps on my iPhone/Android.	YES	No
30. I watch at least one YouTube video per day.	YES	No
31. The majority of my purchases are via credit card or debit card, not cash.	YES	No
32. I post an update to Facebook at least once a day.	YES	No
33. I belong to more than one social networking website.	YES	No
34. I prefer to read books via a Kindle or an iPad than hardcover books.	YES	No
35. I post photos and various items on Pinterest and Instagram each week.	YES	No

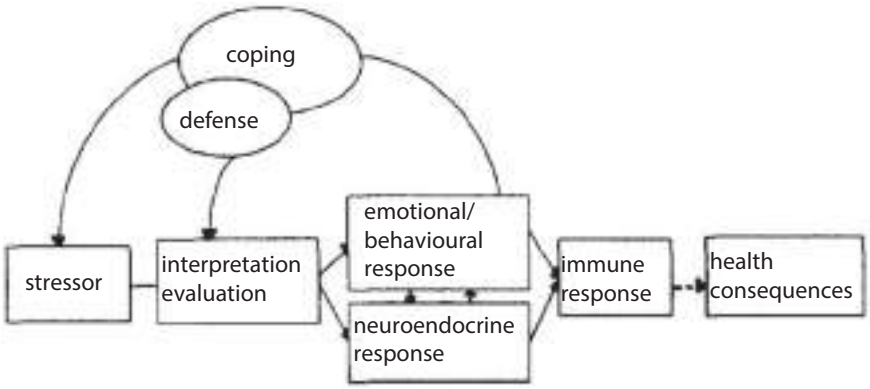


FIGURE 89.1 Cognitive appraisal of stress.

"mindfulness" are more likely to perform more exercise, rest more, eat better, and so on. Therefore, the conclusions may be misleading, especially when done without truly randomly assigned control groups.

Vohs reported that transcendental meditation impairs motivation to complete cognitive and performance tasks and decreases motivation to tackle everyday concerns[51] probably due to a negative effect on the frontal lobes by Eastern meditation.[52] The results were so concerning that he wrote a piece in the *New York Times* titled "Hey Boss, You Don't Want Your Employees to Meditate".[53] Garden reported an increase in depression and suicide among those practicing it.[54] Stress may increase in those who meditate regularly in this way. Schlosser reported that a quarter of those who regularly do Eastern meditation had "particularly unpleasant" psychological experiences related to the practice, including feelings of fear and distorted emotions.[55] Poulin reported that it makes people more selfish and less likely to volunteer.[56] A thorough analysis of the current research was done by Farias and Wikholm who summarized three groups of problems with mindfulness: (1) it is a brand and multimillion-dollar industry with people buying books, apps, and courses; (2) there is an evangelical zeal of mindfulness fans; and (3) the way the scientific studies are reported, in many instances, overstate the benefits and are not reporting or even looking for negative effects, thereby giving a skewed picture. Dr. Farias summarizes, "Currently, with mindfulness, the evidence is not necessarily consistent or conclusive".[57] Their conclusions are not unique, leading psychologists such as Lazarus have documented the negative psychological consequences since the 1970s.[58]

A better alternative may be found in CBT as a time-tested and well-researched mental health management tool that effectively empowers people to handle stress[59] by helping individuals recognize the root causes of stress and dealing with them.[60] CBT operates on the premise that the emotional response is not the result of an activating event but rather emanates from the core belief system. Instead of seeking to avoid activating stressful events, CBT focuses on changing the belief system that makes the emotional consequence worse. Another aspect of CBT focuses on identifying the cognitive distortions that create emotional turmoil. The ten cognitive distortions that Burns delineates are as follows: all-or-nothing thinking, overgeneralization, mental filter, disqualifying the positive, mind reading, fortune teller error, magnification or minimization, emotional reasoning, labeling/mislabeling, and personalization.[61] CBT can also help differentiate needs from wants in order to decrease the physiological stress response. Needs such as air, water, good food, and sufficient warmth are needed for humans to survive. Non-needs such as wanting to be liked by everybody, perfection, or having things our way are nice but optional.[62]

When the mind and body are calm, the levels of perceived stress are diminished. *Relaxation response* is the name given to the physiological effect that is the opposite of stress. Dr. Benson, a professor of psychiatry from Harvard, describes the changes in the body that happen with the relaxation response in this way.[63] On one side, the sympathetic system is activated by stress while the parasympathetic system dominates during the relaxation response. Physiologically speaking, the sympathetic system helps us cope with aggression by activating defense mechanisms and protecting us from imminent danger. On the other hand, the parasympathetic system helps repair, digest, and relax. The relaxation response is the opposite of the stress response in which the heart rate and strength of the contractions increase, blood is shunted to muscles, breathing increases, sweat increases, digestion is slowed, and even glucose increases.

Different techniques have been identified that trigger the relaxation response. Some techniques can help decrease stress such as breaking the day into an achievable to-do list, setting realistic expectations, identifying early signs of stress, making a budget, taking breaks from what is causing stress, or confronting what is stressing you.[64]

We here explore other evidence-based techniques that have been demonstrated to be beneficial and without untoward side effects. Ideally, they are practiced at a set time during the day.

89.5.2 Deep Breathing or Diaphragmatic Breathing

While doing physical exercise, the body requires a higher amount of oxygen to operate. That is why maximal physical

performance necessitates deep breathing.[65] It is known that a low blood oxygen saturation of less than 95% can decrease the ability to perform complex mental tasks. Even people with healthy lungs can decrease oxygen saturation in the body if they have shallow breathing or poor posture. At least one study showed that low oxygen levels can negatively impact mood.[66] Deep breathing can improve and effectively decrease stress.[67] The mechanism by which deep breathing triggers the relaxation response is by bolstering the parasympathetic system's dominance over the sympathetic system.[68]

In a separate study[69] it was found that breathing at a breathing rate of three to six breaths per minute improves oxygen saturation but ideal oxygen levels were reached only during deep breathing at three to six breaths per minute. In a controlled trial of eight weeks, diaphragmatic breathing of four breaths per minute for 15 minutes three times a week decreased stress levels and anxiety while increasing focus and attention.[70]

It is also reasonable to maintain a posture supportive of deep breathing,[71] especially for people who are depressed or are not handling stress well. It is advisable to utilize deep breathing techniques during physical exercise sessions as well as during the day, attempting to breathe deeply at six breaths per minute. It may require a watch at the beginning, but with practice, it is easy to master even without a watch.

89.5.3 Music Therapy

Not all music styles improve mood. Certain music can have the opposite effect. In a recent study, blood pressure measurements were taken and two different types of music were heard. Mozart's Adagio from Divertimento No. 7 had a relaxing effect as shown with a decrease of blood pressure among participants. While a pop-music piece from Queen, Bicycle Race, had the opposite effect, increasing blood pressure.[72]

In a separate music therapy study, participants were encouraged to associate mental images with classical music. Measurements of stress level and mood were taken. The selected pieces were from Respighi, Ravel, Bach, and Brahms, and participants were encouraged to practice introspection. After six sessions over a 12-week period, the 14 volunteers showed improvement on mood tests and reported less depression and fatigue. Also, cortisol, a key hormone in stress, decreased significantly.[73] Measures at 13 weeks showed that mood disturbance, fatigue, and depression were significantly decreased compared with the pre-intervention. Notably, these changes persisted six weeks later, while those in the control group (without music therapy) had no significant changes in cortisol measurements. In this study, participants were not able to select their own music preference, in fact, the age of the participants ranged between 23 and 45 years, a group not commonly exposed to classical music.

McCraty[74] documented the effect of various types of grunge rock in increasing hostility, tension, sadness, and fatigue, while decreasing caring, mental clarity, relaxation, and vigor. Music of the new age genre decreased mental clarity and vigor, and increased fatigue and sadness, while simultaneously improving relaxation, tension, and hostility.

Melodic classical music improved hostility, fatigue, sadness, tension, and relaxation, while decreasing vigor. There was no worsening of any other marks. After 30 minutes of classical music, the stress hormone cortisol dropped by a significant 40%. Interestingly, 30 minutes of techno-music (cyber trip, techno shock, techno magnetic) increased cortisol levels by 40%.[75] A report on the effect of different sounds on anxiety and stress levels identified a six-point improvement with silence as well as a three-point improvement with self-selected music. Heavy metal music worsened it by three points. The most improvement (eight points) in individuals assigned to listen to classical music.[76]

89.5.4 Nature Therapy

Individuals may spend too much time inside buildings. Spending at least 120 minutes a week in nature is associated with better health and well-being.[77] Nature-based interventions have been documented to decrease stress levels, improve depression and anxiety, and improve focus and sleep.[78] A common practice in Japan is called forest bathing, which is simply spending time in nature.[79] Walking for two hours was shown to decrease muscle tension, anxiety, depression, anger, fatigue, and confusion in addition to creating a positive mood.[80]

89.5.5 Bright Light to Improve Mood

Light therapy helps deal with stress by improving emotional control. A double-blind clinical trial in which participants received 30 minutes daily of light therapy for three weeks explored this effect. The light had the same wavelength as daylight. Participants were exposed to pictures of different human faces with various expressions reflecting neutral, angry, or fearful emotions while undergoing an fMRI scan both before and after the light therapy. After three weeks, the brain's ability to control the amygdala (i.e., "fear center") response improved. That is, there was a blunted negative response to faces of fear or anger: the more intense the light, the greater the effect.[81] The researcher commented, "We humans respond naturally to other people's anger and fear. But we observed that the participants responded less to fear in the pictures after the light treatment". The light had an effect on the frontal lobe's ability to control the amygdala, therefore, controlling emotional response. In a randomized study, participants were randomized to pale blue light or red light (with no known benefits to the body) exposure; they were told to use it every morning for one hour over three weeks. Patients who underwent blue light therapy had higher levels of evening melatonin and a drop-off in cortisol, which, at the start of the study, had been elevated.[82]

89.5.6 Sweating Off Stress

Exercise is an integral part of stress management as well. It is understood that general health is improved by a regular and sustainable exercise routine and that excessive exercise can lead to fatigue and injury and decreases the ability to maintain the program in the long term. Exercise is also important for general brain health (stimulating BDNF, etc.) and it is protective against chronic stress effects. Exercise training induces changes at the level of muscle gene expression that can increase kynurenine aminotransferases, enhancing the conversion of kynurenine into kynurenic acid which protects the brain from stress-induced changes associated with depression.[83] Moderate exercise not only decreases current stress but research shows that the effect lasts for extended periods post-workout.[84]

Participation in physical activity is preferred to watching sports as it increases both fitness and well-being. This benefit obviously occurs during exercise, not by simply observing. Research suggests that the emotional ups and downs of watching sports can have a substantial negative effect on the cardiovascular system and level of stress.[85] Under high stress, those who are physically active have less negative cardiovascular risk factor response.[86] There is evidence that only about half of stressed individuals are taking advantage of the stress-relieving effects of exercise.[87] When exercise is performed in nature, the levels of stress decrease even more. Park documented how people who walked in a forest had lower levels of cortisol and blood pressure afterward than those who exercised in a city environment.[88]

89.5.7 Power Rest for Stress

Excessive stress often interferes with sleep and stress often leads people to chronically shorten the nightly rest. A vicious cycle forms. Insufficient sleep increases stress, and the increase in stress worsens sleeplessness. The increased sleeplessness leads to still more physiological and emotional stress.[89] This leads to beginning the day with a sleep deficit and a shortage of the "dream work" process that enables the brain to clean out and organize the emotions of the previous day. A daytime nap may be a tool to assist these individuals with decreasing stress levels. A short nap may allow people to catch up on some desperately needed sleep but has benefits even for those who sleep enough at night. A nap helps keep emotions under control, increases cognition,[90] and improves memory.[91]

The duration of the nap is related to the desired effect. A 15-minute nap is often enough to increase energy levels for the rest of the day.[92] For calming down the nerves and further improving cognition function, a longer nap or exercise[93] may be a better choice than caffeine. Caffeine appears to affect nighttime sleep by interfering with the production of melatonin.[94]

A daily nap habituates the physiology to a certain time to rest during each day. Taking routine daily naps improves the quality of the sleep at night.[95] Ideally, improving nighttime sleep with scheduling, non-drug therapies, relaxing exercises, and good sleep hygiene will also improve stress management capacity

A weekly rest in which participants turn off stressful things in life and enjoy a day with family and friends might be one of the secrets to longevity exercised by those who take a "Sabbath" to put aside the business of life, have a meaningful connection with family and friends, and reassess their purpose in life each weekend.[96] Research of weekly cycles (circaseptum/circaseptan) supports the idea that a weekly rest is necessary to reduce stress. Larsen and Kasimatis provided evidence that the seven-day week is itself a product of an endogenous circaseptan rhythm. Just as the best time for daily rest is at night, Larsen and Kasimatis findings suggest that there may be a certain time during the week that is better for obtaining the weekly rest, as stress hormones were found to be the lowest in their study, summarizing their finding as:

It appears that … there is a strong weekly rhythm in day-to-day mood. This pattern shows a peak around Friday night or Saturday and a trough around Monday or Tuesday. When a sine wave with a 7-day period is superimposed in phase.[97]

89.5.8 Wash Off Your Stress with Hydrotherapy

There is evidence that hydrotherapy (or aqua therapy), the application of water treatments, can help many medical conditions,[98] improve immunity,[99] and could help reduce stress.[100] Toda reported that water bathing reduced salivary cortisol,[101] and Marazziti reported that water treatments increased serotonin, potentially improving mood.[102] Whole body water treatments are beneficial and simple contrast foot baths were documented to reduce the stress response by calming down the sympathetic nervous system.[103] Shevchuk[104] explained the benefits of hydrotherapy in the body by the increase of beta-endorphins (which create a sense of well-being), an increase in blood flow to the brain, activation of the immune system, and increasing neurotrophins, which stress tends to decrease.

89.5.9 Caffeine

Caffeine is a popular stimulant. In the United States, 75% of those under 18 years of age consume caffeine on any given day.[105] It has been observed that caffeine raises stress hormones.[106] The American Psychiatric Association notes that disorders caused by caffeine may be characterized by panic attack symptoms that resemble mental disorders.[107] In light of this, it is ironic that many use caffeine to try to "treat" their stress-related problems. Using caffeine to cover for sleep deprivation does not help mood or cognitive function.[108,109] It is also interesting to note that the alertness associated with caffeine use seems to be limited to the cessation of withdrawal symptoms.[110]

A regular caffeine user who is stopping use should expect withdrawal symptoms such as headache, sleepiness,

laziness, and a decrease in alertness. Usually, days one and two tend to be more severe, however, in the following five days, the symptoms taper off and disappear. DSM-5 named caffeine withdrawal a formal disorder.[111] Historically, the World Health Organization has included caffeine on the list of psychostimulants that produce dependence and withdrawal disorders.[112]

Lifestyle choices can introduce oxidative stress that can have a negative effect. Behaviors such as lack of sleep and excess body fat are widely accepted as some of the sources. Seyedsadjadi[113] documented that caffeinated beverages are also significantly associated with oxidative stress in the body, accelerating aging and increasing the risk of chronic degenerative diseases. It may cause cognitive deficits due to its negative effects on sleep, as it causes sleep deprivation.[114]

89.5.10 Alcohol

Another commonly used "self-treatment" for stress is an alcoholic drink. Similar to the tobacco industry, the alcoholic industry orchestrates public messaging to increase the use of their products and downplay untoward effects. This was well documented in *Alcohol Review* in an article entitled "How alcohol industry organizations mislead the public about alcohol and cancer".[115] Alcohol weakens the ability to cope with stress and anxiety by lowering the level of three key brain hormones (serotonin, GABA, and CRH). This is consistent with animal studies that demonstrate the lowering of brain serotonin and GABA levels in habitual imbibers.[116] These are key neurotransmitters for dealing with anxiety. Alcohol not only interferes with the brain's ability to deal with stress but appears to increase the risk of depressive symptoms.

Interestingly, alcohol stimulates hypothalamic corticotropin-releasing factor neurons. Since alcohol acts directly on the CRF gene, but not on pituitary corticotrophs, alcohol effectively blunts the responses of the hypothalamic–pituitary–adrenal axis to alcohol. Unfortunately, this can be long-lasting, even permanent, negatively affecting how stress is handled in the body.[117] Chronic alcohol use can contribute to long-term anxiety and depression, and in the short term, it also undermines the capability of the body to respond to stress. While some argue for the health benefits of alcohol, at least one meta-analysis showed the absence of any mortality benefit compared with lifetime abstention.[118] Any level of alcohol consumption will decrease brain volume.[119] *Lancet Oncology* reported that alcohol causes 740,000 cancers globally,[120] even light consumption increases the risk of cancer.[121] *The Lancet* reported that there is no benefit in drinking alcohol, especially people under 40 years should not use alcohol.[122] Worryingly, alcohol usage increased during the last COVID-19 pandemic.[123]

89.5.11 Diet and Stress

Many do not realize the connection that exists between diet and mental health. Nutrition is one of several factors interacting together in the pathogenesis of at least some mental illness. For example, many people going through high levels of stress or depression demonstrate a loss of appetite,[124] others respond with midnight polyphagia.[125] Tryptophan, a dietary amino acid, is the dietary precursor of serotonin, a key neurotransmitter in stress and depression. As the body has no significant amino acid stores, tryptophan-rich foods eaten regularly are necessary for optimal function. Large neutral amino acids (LNAA), of which tryptophan is one, compete to enter the brain at the blood–brain barrier through an insulin-dependent carrier.[126] If the diet is moderate in tryptophan and high in LNAA, it may result in low levels of tryptophan in the brain, even with "adequate" tryptophan intake. One example demonstrating this might be seen in comparing the effects of tofu and cow's milk, which is high in tryptophan and very high in LNAA. This soybean curd is high in tryptophan but lower in LNAA and results in significantly greater tryptophan uptake into the brain. The practical application of this was demonstrated in a trial in which individuals were subjected to uncontrolled stress. Those with a diet lower in carbohydrates and higher in protein (tryptophan) had lower brain tryptophan than those consuming the high carbohydrate, lower protein diet. Those who had a diet lower in protein and higher in complex carbohydrates had more depression induced by stress, less energy, and higher levels of cortisol, while the diet higher in carbohydrates prevented those harmful effects.[127] The authors conclude that individuals prone to stress have a higher risk of serotonin deficiency in the brain. As a general rule, animal products are higher in LNAA while plant foods have a lower amount. The solution to the problem is consuming a complex carbohydrate-rich diet (whole plant foods) with adequate tryptophan and lower in LNAAs such as legumes (black eyed peas for example). This is consistent with the recommendation to consume a whole-food plant-based diet in order to help with stress control, reduce anxiety, and improve mood.[128] Tyrosine can help with stress. In a study, those given tyrosine had significantly reduced headache, stress, fatigue, muscle aches, and sleepiness compared with controls.

Improvements were noted in mood and mental states (happiness, mental clarity, hostility, and tension) and cognitive tests (math skills, coding map compass, and pattern recognition) in the tyrosine group.

Feelings of vigor and improvements in blood pressure.[129] Eating in an intermittent fasting pattern, such as eating only twice a day, can bring down stress levels and improve health.[130]

89.6 SPIRITUALITY AIDS STRESS MANAGEMENT

According to research on the longest-living centenaries, one pattern that emerges is the effect of spirituality on stress levels and longevity. Li et al. report that "Frequent attendance at religious services was associated with significantly

lower risk of all-cause, cardiovascular, and cancer mortality among women".[131] People in the Blue zones live in communities with significant religious support. They tend to have a purpose and meaning in life. The Okinawan Japanese call this Ikigai. It is thought to reduce the risk of death[132] and improve mental health.[133] Those who participate in religious activities stress less over finances, health, and daily concerns than non-spiritual types.[134] Participating in prayer and Scripture reading has a positive effect on blood pressure compared with those who do not.[135] Immune function, as measured in IL-6, is better among those who attend religious services on a regular basis.[136] Those with depression recover faster. "Depressed patients with higher intrinsic (inner) religiosity scores had more rapid remissions than patients with lower scores".[137] In another study of 92,000 women, those who attended a religious service at least once a week had a 20% reduction in death even if they were smoking, drinking alcohol, and not doing exercise.[138] Albert Ellis, founder of CBT and rational-emotive therapy, addressed the advantage of spiritual material in mind improvement when he wrote "I think that I can safely say that the Judeo-Christian Bible is a self-help book that has probably enabled more people to make more extensive and intensive personality and behavioral changes than all professional therapists combined".[139] Of interest is an article published in the English newspaper *Metro* entitled, "I'm an atheist who goes to church—here's why you should too". The author shared his experience of fellowshipping with Christian believers and the benefits he experienced.[140] If a strong spiritual element is combined with a healthy lifestyle, it appears to work synergistically in combating stress as loneliness increases stress levels. As Jean-Paul Sartre said, "If you are lonely when you are alone, you are in bad company". Social support confers resilience to stress.[141] Rather than withdrawing when under stress, conscientiously stay connected

89.7 DEPRESSION AND ANXIETY

Depression is a serious and common problem around the world, affecting 400 million people across all ages. It is also the leading cause of disability worldwide.[142] The number of people developing depression has increased since 1915.[143] Major episodes of depression now occur frequently by age 25.[144] Medications for managing anxiety are sometimes used for depression.[145] Anxiety often coexists with depression and may be related to causation.

The common standard for diagnosis of depression and anxiety is that of the DSM-V.[146] The overall risk of depression has increased over time.[147] The incidence of depression for outpatients in a primary care setting is between 15.3% and 22% of all patients seen in consultation.[148] People who commit suicide commonly visit their primary care provider in the month before their suicide.[149] Unfortunately, statistics show that primary care physicians fail to recognize depressive symptoms in 30% to 50% of patients who have depression.[150]

89.7.1 Effective Screening for Depression/Anxiety

Time limitations during consultations may impair proper screening, however, two key screening questions can help identify those that may have depression:

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

When used in primary care for patients who are not using psychiatric medications, these two questions have a sensitivity of 97% and a specificity of 67%.[151]

Another quick and easy-to-apply tool used in DSM-V criteria is the Patients Health Questionnaire (PHQ-9), which not only measures the severity of depression but can be used to follow up the treatment of depression.[152] It can be accessed for free at www.phqscreeners.com.

There are other more detailed tests such as the proprietary Beck Depression Inventory II (BDI-II).[153] The BDI-II lists 21 symptoms that are scaled for severity. Though originally designed to be administered by clinicians, it can be self-administered and takes five to ten minutes to complete.

Anxiety affects approximately 3% of patients in primary care settings, while another 4% suffer from social phobia.[154] Among the tools used to diagnose anxiety is the Hospital Anxiety and Depression scale. Its length makes it somewhat impractical for office-based use.[155] A more useful test is the Generalized Anxiety Disorder Scale (GAD-7), which is designed and validated for primary care usage. There is also a short version of two questions called the GAD-2, which has a good negative predictive value. The two questions are as follows:

- Do you feel nervous, anxious, or on edge?
- Are you unable to stop or control worrying?

Another widely used instrument is the Beck Anxiety Inventory (BAI) which measures anxiety by focusing on somatic symptoms. It is also designed as a self-report tool.

A more extensive test is the Depression and Anxiety Assessment Test (DAAT) which measures depression and anxiety, as well as emotional intelligence, and may identify the underlying cause(s) of mental health problems, many of which can be reversed when found. The tool was found to have sensitivity and specificity higher than the Papanicolaou smear (Pap smear).[156]

89.7.2 Management

With the availability of genetic and metabolic testing, approaches to medical problems are slowly moving toward more individualized care. This is the focus of the personalized medicine movement.[157] A recently developed construct demonstrates this in the approach to those with depression and anxiety. As described in the published paper, the

Nedley Hypothesis derives from 100 plus identified "causes" of depression and anxiety from the medical literature.[115,158] These have been categorized into ten categories. The hypothesis proposes that having four of those ten categories active will trigger a depression and/or anxiety episode. An active category is called a hit. These are listed below

1. Genetic hit: Family history of depression or suicide.[159]
2. Developmental hit: Early puberty in girls (menarche of 11 years or earlier), history of depression in adolescence, not being raised by both biological parents,[160] suffered sexual abuse.[161]
3. Nutrition hit: Low dietary tryptophan,[162] low omega-3 intake,[163] diets high in cholesterol,[164] saturated fat,[165] and sugar,[166] marked anorexia among others.[167]
4. Social hit: Absence of social support,[168] negative, stressful life events,[169] grandparents who raise grandchildren,[170] immediate family member is an alcohol or drug addict.[171]
5. Toxic hit:[172] High lead,[173] mercury,[174] arsenic, bismuth, or other toxins.[175]
6. Circadian rhythm: Regular insomnia,[176] sleeping more than nine hours or less than six hours a day, irregularity in eating and sleeping.[177]
7. Addiction: Use of alcohol, tobacco,[178] heavy caffeine,[179] benzodiazepines,[180] or illicit drugs.[181]
8. Lifestyle: Not on a regular exercise program,[182] not exposed to 30 minutes of bright light,[183] not breathing fresh air.[184]
9. Medical condition: Various medical conditions like hypothyroid,[185] hepatitis,[186] autoimmune disease,[187] uncontrolled diabetes,[188] hyperlipidemias,[189] etc.
10. Frontal lobe: Involved in activities that suppress the frontal lobe,[190] not enough activities that stimulate the frontal lobe.[191]

Therapy based on the *Nedley Hypothesis* is focused on identifying the causes of depression and then individualizing treatment with long-term lifestyle changes to address as many of the modifiable causes as possible, with the recognition that not all causes are modifiable. One way of identifying those causes is by taking the DAAT, which will efficiently identify the caregiver with the various categories of cause. With this knowledge, the caregiver can make prescriptive suggestions to improve depression,[192–194] anxiety,[195] and emotional intelligence[196] in a matter of days.[197] The program shows an 88% response rate among depressed participants[198] and a 97% response rate when applied to hepatitis C positive individuals.[199]

89.8 SUMMARY

Lifestyle interventions have been demonstrated to help deal with stress as effectively as non-drug therapy. Positive psychology has proposed practical steps to not only decrease stress but also improve happiness in life. In order to provide optimal care for those with stress, it is important to address health behaviors such as nutrition, exercise, rest, and so on. Unhealthy patterns of thinking should be recognized and changed as long-term stress management requires healthy thinking. Anxiety often develops with long-term stress.

The ten-hit hypothesis has been documented to help identify the triggers of depression and anxiety and aid in their treatment. DAAT has been developed to assist clinicians in quantifying depression, anxiety, and emotional intelligence as well as identifying the potentially reversible causes, thereby allowing efficient identification of actionable goals for therapeutic lifestyle interventions.

CLINICAL APPLICATIONS

- Individuals can improve their mental and physical health by developing healthy coping strategies with which to address life's stressors.
- Focusing on belief system distortion of truth (CBT), activation of the relaxation response, and a healthy diet, along with avoidance of harmful substances, help develop a healing response to stress.
- The *Nedley Hypothesis* has provided a useful evidence-based construct for efficient risk-factor identification ("hits") and effective lifestyle therapy for both anxiety and depression.

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90 High-Intensity Therapeutic Lifestyle Change

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KEY POINTS

- The strongest and most compelling evidence for the effectiveness of therapeutic lifestyle change comes from studies of intensive therapeutic lifestyle change (ITLC) treatment because it produces the most dramatic treatment effects, just like higher dosing of pharmacological agents. Conversely, few non-intensive lifestyle change programs have been studied directly, and their effectiveness is presumed based on published ITLC studies.
- ITLC can produce dramatic treatment effects in hours or days, such as improved cardiac perfusion and increased insulin sensitivity. Epigenetic studies reveal that gene expression changes within minutes following intensive (dramatic) lifestyle changes.
- ITLC maximizes LM treatment dosing to produce the induction phase needed to transform self-efficacy and enable the patient to sustain lifestyle change. Nothing transforms self-efficacy, and thus lifestyle change goals, more than experiencing a dramatic improvement in one's own health, and no LM treatment can transform health more dramatically than ITLC.
- LM treatment intensity has two components or dimensions—the intensity of contact hours and the degree or extent of lifestyle changes made. Maximally effective ITLC generally maximizes both components.
- Much of the lifestyle change needed by society for good health can be accomplished with relatively mild therapeutic interventions provided with what are known as therapeutic lifestyle changes (TLC). However, for advanced or severe conditions, mild interventions are inadequate and often ineffective. Such cases demand stronger dosing with more dramatic treatment effects. This is where high-intensity therapeutic lifestyle change is required, known as ITLC. This chapter reviews the research and clinical features of ITLC.

The following is a definition of intensive therapeutic lifestyle change (ITLC), which is contrasted and compared with non-intensive therapeutic lifestyle change (TLC).

- ITLC utilizes an intensive, total-immersion approach to change rather than the more gradual, incremental changes commonly recommended by clinicians. This "full court press" includes a comprehensive, multi-factorial lifestyle change approach. If the treatment begins in a residential facility, therapeutic meals are typically prepared and served, exercise is scheduled multiple times a day, educational activities are conducted, and plenty of sleep is included. The patient has four to eight hours of contact with intervention staff most weekdays for a few weeks with decreasing intensity until the patient returns home. Ideally, follow-up contact with supportive interventionists continues by phone, email, text, and/or online for some weeks or months. Follow-up is commonly the weak link in most LM interventions, especially with residential ("inpatient") ITLC treatment. It would be preferable for an ITLC intervention to be followed by TLC treatment with the patient's primary care provider (PCP). Better execution of this aspect depends on more widespread training and experience for clinicians, as well as an appropriate reimbursement system to deliver these medically necessary LM services.
- TLC typically utilizes less intensive interventions with a more incremental, gradual approach to lifestyle change. As such, it provides dosing sufficient to prevent disease but may be inadequate to treat existing disease, especially when the disease is advanced or severe, and requires maximal treatment effect. TLC treatment typically consists of interventions provided as part of a shared medical appointment or educational group program, a series of focused medical visits, or even a clinical encounter during routine medical care. When a patient is fully motivated and ready to make significant changes in personal lifestyle choices, TLC can produce treatment effects as dramatic and extensive as ITLC does. This illustrates the twin dimensions of motivation and intensity—when motivation is high an individual is more likely to invest, time, money, and personal effort in the process, and when the extent of appropriate lifestyle change is maximal, TLC can be as effective as ITLC.

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The more severe and advanced the patient's condition, the more extensive and immediate the need for therapeutic treatment. In pharmacological terms, this is accomplished by using a higher starting *dose*. In LM, this involves changing all (or at least the majority) of unhealthy behaviors to healthy ones. Hence the term *intensive* TLC. Established habits, by definition, have an inertia that must be overcome to have real and lasting change. This is accomplished with what can be referred to as an "induction phase". It is commonly more controlled and "restrictive" than subsequent ongoing treatment needs to be. Once the induction phase has replaced the toxic habits with health-promoting ones, it is easier for the patient to maintain the new habits than it was to learn and adopt them. The induction phase may last anywhere from a few days to several weeks, depending largely on the seriousness of the underlying lifestyle disease pathology and the patient's level of motivation.

Another benefit of an induction phase is the transformational impact it has on the patient's self-efficacy and personal goal-setting. The dramatic improvements produced by an immersive and intensive lifestyle change, as well as the simplicity of the changes, transform the patients' perspective about lifestyle change through the development of hope. Patients typically have no idea it could "work so fast, make so much difference, and be so easy". As a result, their confidence and hope are increased, and they embrace higher goals. The transformation experienced in the induction phase enhances the effectiveness of subsequent LM interventions.

This is particularly evident when using motivational interviewing (MI) techniques. MI seeks to assist subjects in making changes of their own choosing. After a transformational personal demonstration of the effectiveness of intensive lifestyle changes, subjects are commonly no longer content with the goals they had previously chosen—they want to achieve more. This phenomenon can be likened to the pharmaceutical loading dose required to reach the therapeutic range.

When less dramatic lifestyle changes are made and no significant improvement is perceived, an opposite effect also operates in which subjects become demotivated to continue lifestyle changes. "Why do all this work?!" they understandably wonder. Generally, unless the patient sees substantive, even dramatic, benefits within three to four weeks, they will abandon the effort to make change. This effect explains why a personalized, quality, intensive induction phase is so important, and why the lifestyle intervention should include the behaviors that have the largest possible treatment effects.

Major research studies of ITLC treatment are instructive and should be used to plan and provide patient experiences. What follows is a review and discussion of select major trials pertinent to the leading lifestyle-related diseases.

- Lifestyle Heart Trial (Ornish, *Lancet* 1990, Ornish, *JAMA* 1998)
- Pritikin Program (Barnard RJ, *Am J Cardiol* 1997)
- Lyon Diet Heart Study (deLorgeril M, *Circulation* 1999)
- CHIP program (Aldana SJ, *J Occup Environ Med* 2005)
- Esselstyn study (Esselstyn CB Jr, *J Fam Pract* 2014)
- DPP (Knowler, *N Engl J Med* 2002)
- Counterpoint study (Lim EL, *Diabetologia* 2011)
- DiRECT trial (Lean MJ, *Lancet* 2018)
- Beta-cell regeneration via FMD (Cheng W-C, *Cell* 2017; Wei S, *Nutri & Metabol (Lond)* 2018)

The one-year results of the Lifestyle Heart Trial (LHT) were first published in *The Lancet* in 1990[1] and the five-year results were published in *JAMA* in 1998.[2] The LHT used a randomized invitational design to assign 28 subjects with CAD to experimental treatment using ITLC and 20 subjects to usual care. The experimental subjects participated in the Ornish Program without statin medications, while the usual care subjects received written advice to make more modest lifestyle changes (NCEP Step II) and to follow the advice of their physicians. Primary outcomes were CAD blockages and cardiac events. Lipids, medications needed, and program adherence were also tracked. Thirty-five subjects participated in the five-year measures: 20 experimental and 15 controls.

At one year, the experimental subjects had a 37% reduction in LDL, a 91% reduction in angina, and a 5.5% regression of stenoses (40% blockage to 37.8%). In contrast, at one year, the controls had a 6% reduction in LDL, a 165% *increase* in angina, and an 8% *progression* of stenoses (42.7% blockage to 46.1%). At five years, experimental subjects had a 7.9% decrease in stenoses while controls had a 27.7% *increase*. The controls *not taking statins* had a 46.7% *increase* in stenoses (40.7% blockage to 50.7). No experimental subjects took statins.

The difference in blockages at five years with ITLC versus enhanced usual care in controls not using statins was striking, with ~7.9% regression v 46.7% progression. That is a combined difference of 54.6%. In other words, the subjects receiving neither ITLC nor statins had an RR of 1.54 for CAD blockages compared with those receiving ITLC without statins.

It is important to understand that the controls received *enhanced* usual care in that they all received written information about the NCEP Step II dietary and lifestyle recommendations. We do not know how many may have received more careful medical care as a result of being in the study, but it is unlikely that any received deficient care.

Another way of looking at the LHT results is that even enhanced usual care is both ineffective and inadequate. It is thus distinctly *not* best practice, evidence-based LM to simply provide patients written information about lifestyle change and consider it to be LM. That kind of care is more similar to the control treatment which, at best, only *slowed* CAD than it is to the ITLC experimental treatment shown to arrest and *reverse* CAD (see Figure 90.1).

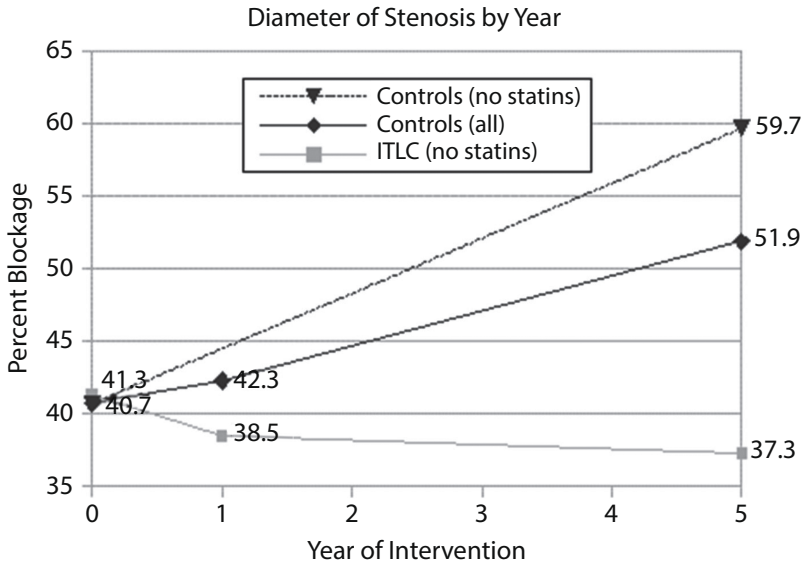


FIGURE 90.1 Change in coronary artery stenosis for experimental and controls.

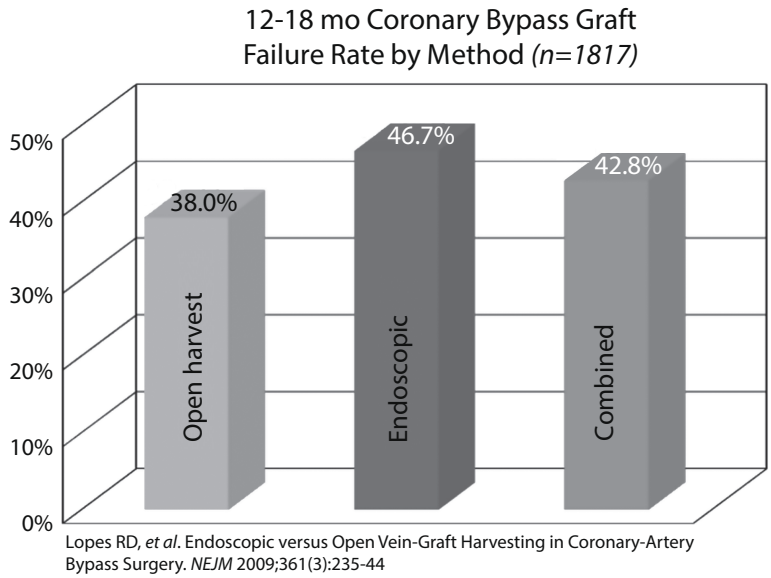


FIGURE 90.2 Bypass graft failure rate by vein harvesting method.

Figure 90.1 shows the changes in the percent blockage of coronary artery stenoses during the five-year Ornish Program. The controls receiving enhanced usual care were dying from CAD while the treatment group was reversing their disease—without medications. (The controls not receiving statins are shown with a dotted red line. All differences were statistically significant.)

These results are in striking contrast to the 12–18-month failure rate for coronary artery bypass grafts reported by Lopes et al. in 2009[3] (see Figure 90.2).

Note that the average failure rate in 12–18 months was ~43%, but the failure rate for the common endoscopic excision technique was ~47%. These patients did not receive any LM care, either ITLC or TLC. Without lifestyle change, the venous grafts occlude faster than the original arteries.

Results from the Pritikin Program were published in 1997[4] The results from this pre- vs post-LM analysis show that an aggressive diet and exercise program, when added to cholesterol-lowering drugs, can result in a dramatic reduction in total cholesterol, as well as in triglycerides. The drugs alone reduced total cholesterol by 20%, whereas the combined drugs plus lifestyle intervention achieved an additional 19% reduction. These results are significantly greater than other published studies combining drug and diet therapy. The conclusion was that diets with 25–30% calories from fat when added to drug therapy have minimal effects on serum cholesterol, whereas the Pritikin 10% fat-calorie diet reduces cholesterol by almost double the amount of the drugs alone. Table 90.1 and Figure 90.3 (adapted from Table 90.1 and Figure 1, Barnard et al.[4])

TABLE 90.1
Effect of Intensive Lifestyle Changes on Serum Lipids in Patients Taking Cholesterol Drugs

Effect of Intensive Diet and Exercise on Serum Lipids in Patients Taking Cholesterol-lowering Drugs

	Before mq/dL	After mq/dL	%Δ
Total group, n=93			
Total cholesterol	220 ± 4	178 ± 4	19%
LDL cholesterol	126 ± 4	101 ± 3	20%
HDL cholesterol	55 ± 1.5	49 ± 1.3	11%
Triglycerides	195 ± 10	139 ± 6	29%
Primary prevention, n=40			
Total cholesterol	234 ± 6	181 ± 5	23%
LDL cholesterol	136 ± 6	104 ± 4	24%
HDL cholesterol	55 ± 2.5	51 ± 2.2	7%
Triglycerides	216 ± 17	131 ± 9	39%
Secondary prevention, n=53			
Total cholesterol	210 ± 5	175 ± 6	17%
LDL cholesterol	119 ± 4	99 ± 5	17%
HDL cholesterol	57 ± 1.9	52 ± 1.8	9%
Triglycerides	179 ± 11	146 ± 9	18%

'After' values significantly less than 'Before' values; p<0.01 HDL & LDL

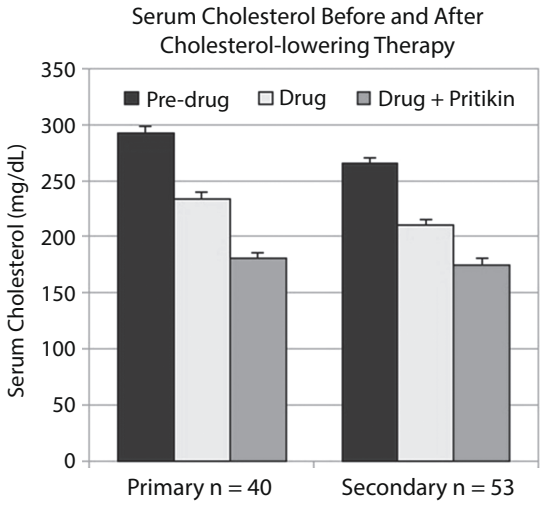


FIGURE 90.3 Effect of intensive lifestyle changes on serum lipids in patients taking cholesterol drugs.

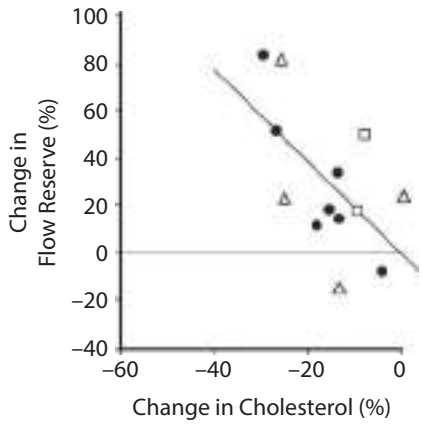


FIGURE 90.5 Change in flow reserve with change in serum cholesterol.

show the changes in serum lipids at baseline, with statins, and with statin plus Pritikin.

Results from 4587 participants in the Pritikin Program from 1977 to 1988 were published in 1991[5] and reviewed in 2005[6] Figure 90.4 shows the lipid-lowering effects significantly exceeded those of the NCEP Step I and Step II dietary interventions (Figure 90.4 adapted from Figure 1, Roberts et al.[6]).

Results from 13 participants in the Pritikin Program who underwent myocardial blood flow and flow reserve studies were published in 1995.[7] The improvements were strongly associated with reductions in serum cholesterol. Figure 90.5 (adapted from Figure 3, Czernin et al.[7]) shows changes in myocardial flow reserve (%) as a function of changes in cholesterol (%). Patients with coronary artery disease are represented by open triangles, patients with hypertension by open squares, and normal participants by closed circles.

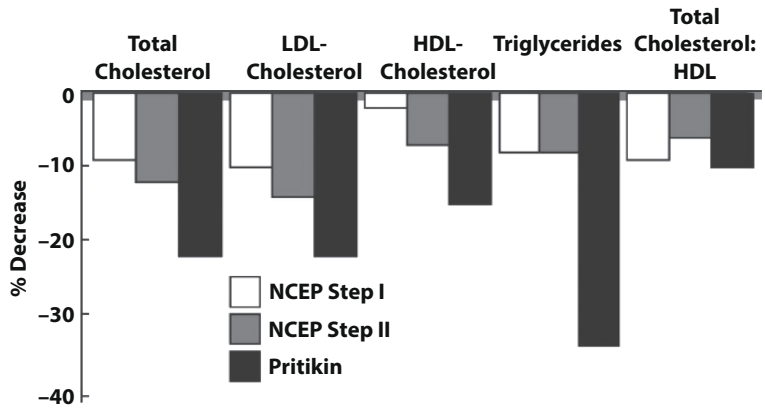


FIGURE 90.4 Changes in cholesterol for NCEP Step 1 and 2 vs Pritikin.

Reductions in cholesterol levels (x axis) were associated with increases in myocardial flow reserve (y = 2.9–1.9x (for x = 0); r = 0.56; SEE, 0.85; P < 0.05).

Results from the first outpatient Pritikin ICR Program (Intensive Cardiac Rehab) were published in 2022 by Racette et al.[8] Outcomes from the Pritikin ICR were compared retrospectively to outcomes from a traditional cardiac rehab program (CR) in 1963 patients treated at a large academic health center. The ICR resulted in improvements (P < 0.001, pre vs post) in all anthropometric measures, dietary patterns, six-minute walk test (6MWT) distance, all short physical performance battery components (SPPB: balance, 4 m walk, chair rise), grip strength, and health-related quality of life. The improvements in anthropometrics and dietary patterns were greater in ICR than in CR. Figure 90.6 (adapted from Figure 1, Racette, et al.) shows changes

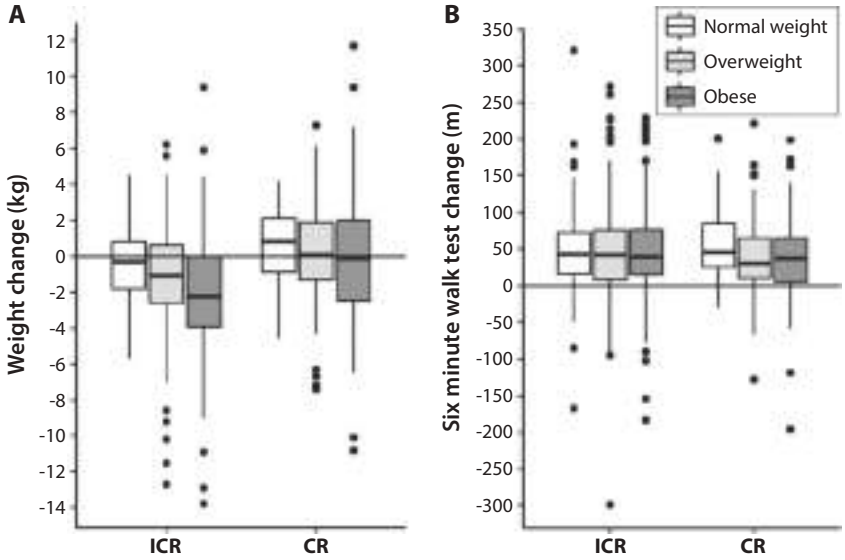


FIGURE 90.6 Change in weight and six-minute walk test by weight category for ICR vs CR.

TABLE 90.2
End Points and Risk Ratios for Controls vs Experimental Group

Endpoints in the 2 Groups and Risk Ratios Calculated with the Cox Proportional-Hazards Model

	Control		Experimental			
	Number	Rate*	Number	Rate	Risk Ratio† (95% CI)	*P*
Major primary end points						
Cardiac deaths	19	1.37	6	0.41	0.35 (0.15-0.83)	0.01
Nonfatal AMI	25	2.70	8	0.83		
Total primary end points (composite outcome 1)	44	4.07	14	1.24	0.28 (0.15-0.53)	0.0001
Noncardiac deaths	5	0.36	8	0.54		
All-cause deaths	24	1.74	14	0.95	0.44 (0.21-0.94)	0.03
Major secondary end points						
Periprocedural infarction	2		0			
Unstable angina	24		6			
Heart failure	11		6			
Stroke	4		0			
Pulmonary embolism	3		0			
Peripheral embolism	2		1			
Total secondary end points	46	4.96	13	1.35		
Total primary + secondary end points (composite outcome 2)	90	9.03	27	2.59	0.33 (0.21-0.52)	0.0001
Minor secondary end points						
Stable angina	29		21			
Elective myocardial revascularization	45		37			
Post-PTCA restenosis	15		9			
Thrombophlebitis	1		2			
Total minor end points	90	9.71	68	7.04		
Total major and minor end points (composite outcome 3)	180	18.74	95	9.63	0.53 (0.38-0.74)	0.0002

in body weight and 6MWT distance among patients in ICR or CR. Box-and-whisker plots depicting median change (middle line in each box), IQR (whiskers), and outliers (circles above and below the whiskers) for weight (A) and 6MWT (B) by body mass index category at baseline.

The final results from the Lyon Diet Heart Study comparing a Mediterranean diet to a prudent Western diet for the secondary prevention of heart disease were published in 1999[9] with a mean follow-up of 46 months. The study had been stopped and unblinded after only 27 months because of the dramatic risk reductions with the Mediterranean diet (adjusted risk ratios ranged from 0.28 to 0.53) but the researchers followed up the subjects for the intended term of the study. Table 90.2 shows the outcomes of the study (Table 90.2 adapted from Table 1, deLorgeril et al.[9]).

This study showed impressive outcomes for the Mediterranean diet compared with the NCEP Step II diet with a tremendous reduction in the risk of cardiac events following a myocardial infarction. However, no quantitative measures of CAD or stenoses were collected as was done in the LHT and Esselstyn's first cohort. Thus, this study did not prove that diet could arrest or reverse CAD, as with the other two studies. As of this date, the author knows of no clinical trials proving arrest or reversal of CAD stenoses using a Mediterranean diet without medications as was shown in the LHT and the first Esselstyn cohort. Nonetheless, this study does show that the Mediterranean diet was much more effective than the Step II (prudent) diet in lowering the risk of cardiac events following myocardial infarction.

Table 90.3 and Figure 90.7 describe the end points for the experimental and control groups with the final values for selected measures. The figure shows the survival curve without non-fatal infarction and without major or minor secondary endpoints (Table 90.3, adapted from Table 2, deLorgeril et al.[9] Figure 90.7, adapted from Figure 3, deLorgeril et al.[9]). The experimental group had significantly fewer events. The conclusion was that the Mediterranean diet is an effective secondary prevention compared with the Step II diet.

Results of the Complete Health Improvement Program (CHIP Program) were first published in 1998.[10] Results from a randomized work site study were published in 2005.[11] Results from a community-based randomized study were published in 2005[12] and 2006[13]

The first randomized study determined the behavioral and clinical impact of a work site chronic disease prevention program. Working adults participated in a randomized trial of an intensive lifestyle intervention. Nutrition

TABLE 90.3

Risk Factors and Biometrics Recorded on Final Visit

Main Risk Factors and Selected Biological Parameters Recorded on the Final Visit

	Control (n=204)	Experimental (n=219)
Body mass index, kg/m^2	26.9 (3.4)	26.3 (3.7)
Systolic blood pressure, mm Hg	128 (16)	128 (17)
Diastolic blood pressure, mm Hg	79 (10)	78 (11)
Total cholesterol, mmol/L	6.18 (1.04)	6.20 (1.06)
Triglycerides, mmol/L	1.75 (0.83)	1.94 (0.85)
HDL-cholesterol, mmol/L	1.28 (0.34)	1.29 (0.34)
LDL-cholesterol, mmol/L	4.23 (0.98)	4.17 (0.93)
Lipoprotein (a), g/L	0.35 (0.49)	0.33 (0.35)
Albumin, g/L	47.10 (2.88)	47.28 (3.07)
Glycated hemoglobin, %	4.61 (1.23)	4.66 (1.52)
Creatinine, µmol/L	116 (20)	115(21)
Uric acid, µmol/L	348 (81)	338 (87)
Leukocyte count, x10^9/L	6.00 (1.69)	5.99 (1.68)
Current smokers, %	17.9	18.3
Medication, %		
Anticoagulant agents	16.1	11.4
Anti platelet agents	69.7	75.8
β-Blocking agents	47.3	47.5
Calcium channel blockers	28.4	25.6
ACE inhibitors	17.4	18.3
Lipid-lowering drugs	34.0	26.5

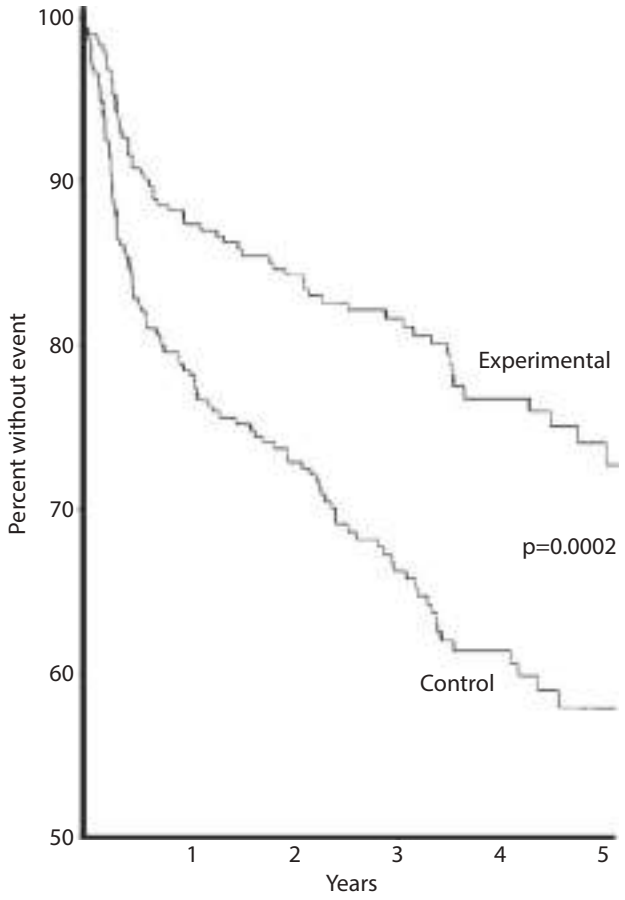


FIGURE 90.7 Changes in the control group vs experimental group.

and physical activity behavior and several chronic disease risk factors were assessed at baseline, six weeks, and six months. Participants significantly improved their cognitive understanding of good nutrition and physical activity and had significantly better nutrition and physical activity behavior at both six weeks and six months. Participants also had significantly lower body fat, blood pressure, and cholesterol. The study concluded that this work site chronic disease prevention program could significantly increase health knowledge, improve nutrition and physical activity behaviors, and reduce many employee health risks.

The second randomized study assessed the clinical impact of lifestyle change education on chronic disease risk factors within a community. Participants included 337 volunteers aged 43 to 81 years from the Rockford, IL, metropolitan area. The intervention group attended a 40-hour educational course delivered over four weeks. Participants learned the importance of making healthful lifestyle choices and how to make improvements in nutrition and physical activity. Changes in health knowledge, nutrition and physical activity behavior, and several chronic disease risk factors were assessed at baseline, six weeks, and six months. Beneficial changes in scores tended to be significant for the intervention group but not for the control group. Variables with improved scores included health knowledge, percent body fat, total steps per week, and most nutrition variables. Clinical improvements were seen in resting heart rate, total cholesterol, low-density lipoprotein cholesterol, and systolic and diastolic blood pressure. The control group experienced comparatively small but significant improvements in health knowledge, systolic and diastolic blood pressure, glucose, and some nutrition variables. For almost all variables, the intervention group showed significantly greater improvements. The study concluded that the lifestyle modification program was an efficacious nutrition and physical activity intervention in the short term with the potential to dramatically reduce the risks associated with common chronic diseases in the long term.

Table 90.4 is drawn from the two RCTs described above, the work site trial with 145 participants[15] and the community-based trial with 348 participants[16,17] These results were actually better than those for the Ornish Program in the Lifestyle Modification Program Demonstration study (LMPD) conducted by Brandeis University, published in 2009[14] and 2014[15]

The five-year results of 22 subjects on the Esselstyn Program were reported in 1995[16] and the 12-year results were reported in 1999[17] These outcomes were described in detail in Dr. Esselstyn's book published in 2007.[18] Results from a second cohort (198 subjects) with an average of 3.7 years on the Esselstyn Program were published in 2014[19] The study relied on a pre- versus post-intervention analysis of self-selected subjects. The first cohort consisted of patients with severe disease and no further conventional

TABLE 90.4

Risk Factor Reductions in CHIP Randomized Clinical Trials

Cardiac Risk Factor Reductions in CHIP Randomized Clinical Trials (RCT)

	CHIP Program RCT[2] (n 145)				CHIP Program RCT (n 348)			
Risk Factor	**6 wk.**	**sig.**	**6 mo.**	**sig.**	**6 wk.[3]**	**sig.**	**6 mo.[4]**	**sig.**
Body weight (lbs)	–5.5	0.0001	–7.5	0 0001	–7.3	0.0001	–8.6	0.0001
BMI (kg/m^2)	–0 9	0 0001	–1.6	0 0001			–1.3	0.0001
SBP (mm Hg)	–1.8	NS	–2.0	NS	–2.7	NS	–1.0	NS
DBP (mmHg)	–2.3	NS	–2.7	0.0506	–2.7	0 01	–1.7	0.04
Total Chol. (mg/dl)	–26.4	0 0001	–12.9	0.0153	–23.3	0.0001	–5.0	NS
HDL (mg/dl)	–7.3	0.0001	4.1	0.0006	–6.2	0.0001	–0 4	0 045
LDL (mg/dl)	–19.5	0.0001	–7.1	NS	–17.3	0.0001	4.0	NS
Triglycerides (mg/dl)	1.5	NS	–8.4	NS	–001	NS	–7.0	NS
Cardiac Functional Capacity (METs)								
Resting HR	-4.5	0.0111	–2.9	NS	–3 0	NS	–2.2	0.03
FBS (mg/dl) for baselines ≥126					–39.6	0.0001	–6 9	0.01

Notes:

[2] From Table 3 in Aldana SG. et al. J Occup Environ Med. 2005:47:558-564. All values shown are for intervention minus controls.

[3] From Table 4 in Aldana SG, et at. J Am Diet Assoc. 2005:105:371-381. except for FBS which is calculated from Tables 1 and 2. All values shown are for intervention minus controls, (change for intervention group minus change for control group)

[4] From Table 5 in Aldana SG. et at. Prev Chronic Dis. 2006 Jan. Available from: http://www.cdc.gov/pcd/issues/2006/jan/'5_0088.htm, except FBS which is calculated from Tables 6 and 7. All values shown are for intervention minus controls.

treatment options. Main outcome measures included lipids, medications, and angiographic studies of coronary blockages. The Esselstyn Program uses a non-residential ITLC intervention that includes a five-hour intensive educational session that teaches a strict plant-based diet emphasizing leafy greens with 10%E from fat and no added oils or nuts. In the first cohort, adherence and lipids were monitored biweekly for five years. Adherence was high (77% in first cohort, 89% in second) with consistent improvement or reversal in adherent subjects.

In the first cohort, 17 of 22 subjects were adherent with the 12-year intervention (77%) and showed uniform improvement, with somewhat more improvement at five years than at 12 years. Mean total cholesterol was 137 mg/dL at 5y and 143 mg/dl at 12y. Mean LDL cholesterol was 76 mg/dL at five years and 82 mg/dl at 12 years. Mean triglycerides were 143 mg/dL at five years and 143 mg/dl at 12 years. Eleven of the 17 underwent angiographic analysis at five years and none showed progression, while 8 of 11 (73%) showed regression. There were no adverse events (no angina, no PCI, etc.) during the 12 years although the same 17 subjects experienced 49 coronary events in the eight years prior to starting the treatment. Notice the imaging showing improvement in perfusion and reversal of CAD in Figure 90.8 (adapted from Figures 1 and 2, Esselstyn et al.[19]).

In the second cohort of 198 patients (Table 90.5), 144 of 177 adherent subjects showed improvement (81%) with 39 of them showing reversal (22%), while 15 remained stable (8%) and 18 worsened (10%). This compared with none of the 21 non-adherent subjects showing improvement, eight remaining stable (38%), and 13 with worsening disease (62%).

Results from the Diabetes Prevention Program were first published in 2002[20] The study randomly assigned 3234 non-diabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of ≥7% weight loss and at least 150 minutes of physical activity per week. The participants averaged 51 years with a BMI of 34, 68% were females and 45% were of minority ethnicity.

The average follow-up was 2.8 years. The study ended early because the interventions were dramatically more effective than placebo. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58% (95% confidence interval [CI], 48–66%) and metformin by 31% (95% CI, 17–43%), as compared with placebo; the lifestyle intervention was significantly more effective than metformin. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle intervention program, and 13.9 would have to receive metformin.

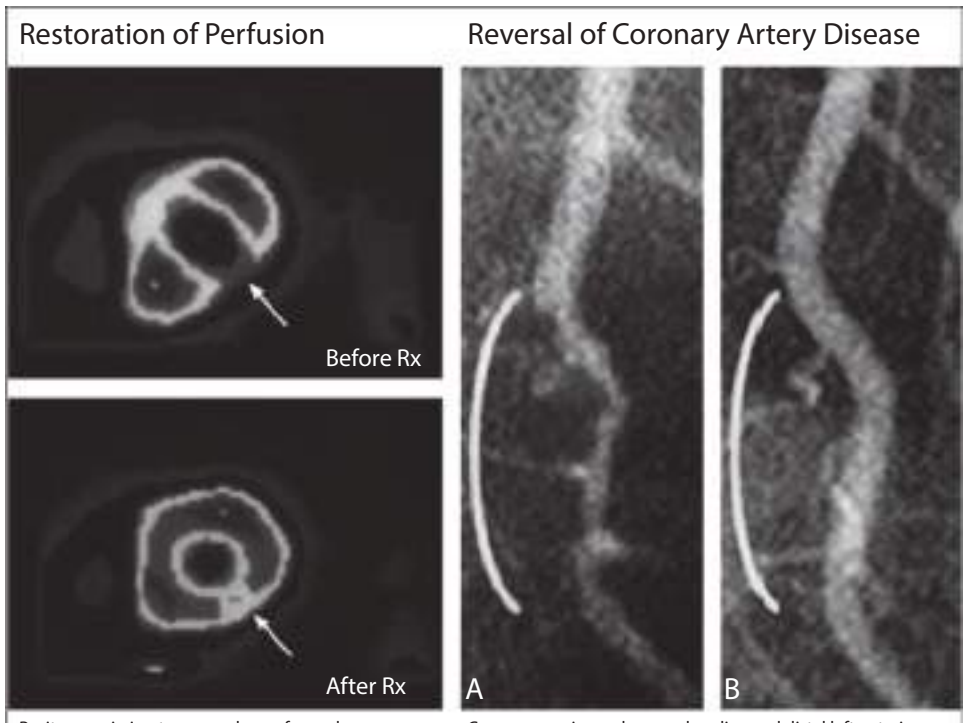


FIGURE 90.8 Cardiac perfusion after three weeks on plant diet and regression of LAD stenosis in 32 months.

TABLE 90.5

Outcomes in Adherent Patients vs Non-Adherent Patients in a Cohort of 198 Patients

Outcomes of adherent versus nonadherent patients in cohort of 198 patients

Characteristics	Adherent patients	Nonadherent patients
Total, N (%)	177 (39)	21 (11)
Men, N (%)	164 (93)	16 (76)
Age (mean ± SD)*	63 ± 10.1	62.3 ± 9
Outcomes, N (%)		
Improved	144 (31)	0
Symptom reduction	105 (94)†	0
Reversal‡	39 (22]	0
Stable	15 (8)	8 (38)
Worse§	18 (10)	13 (62)
Adverse outcomes unrelated to nutritional intervention	9 (50)	0
Disease progression	4 (22)	13 (62)
Death	5 (28)	2 (15)
Non-cardiac**	5 (100]	0
Cardiac	0	2(100)

NOTES: SD, standard deviation; CABG, coronary artery bypass graft.

• Data missing for 5 adherent patients and **1** nonadherent patient.

† Percentage of 112 patients who complained of angina at start of intervention.

‡ One patient with A-fib had documented angiographic reversal after 5 years in the study, then refused warfarin 2 years after last angiogram and suffered a nonfatal stroke.

§ P<. 001 for fewer worse outcomes in adherent patients (Fisher's exact test).

¶ One patient enrolled with malpositioned dissecting stents that required CABG.

Before enrolling the patient had 3 stents placed; one occluded at 3 years into the study and was restented.

** Includes 3 cancer-related deaths, 1 fatal pulmonary embolism, and 1 case of pneumonia.

The study concluded that lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk, but the lifestyle intervention was almost twice as effective as metformin. Figure 90.9 shows the cumulative incidence in percent for each of the three groups during the period of the study (Figure 90.9, adapted from Figure 2, Knowler et al.[20]). The diagnosis of diabetes was based on the criteria of the American Diabetes Association at the time of the study.[21] The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison).

Considering the various LM treatment programs with published results described above, they fall into two broad categories—those that have been shown to arrest and reverse existing disease, and those proven to slow the progression or delay the onset of disease. The studies reveal that the standard lifestyle and dietary recommendations are inadequate to arrest or reverse disease, but they can slow progression. For example, the NCEP Step I and Step II dietary recommendations do not prevent the onset or progression of CAD, HTN, or diabetes. And, neither do the ADA dietary recommendations prevent the onset or progression of diabetes. The DPP, for example, delayed the onset of DM2 but did not arrest or lead to diabetes remission. Serum glucose and glycosylated hemoglobin continued to rise in all three groups.[20] In fact, it was only intended to delay the onset of type 2 diabetes, and it has been shown to do that more

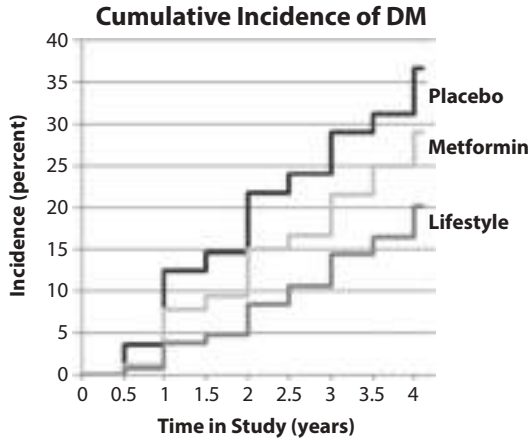


FIGURE 90.9 Cumulative incidence of diabetes in four years for three study groups.

effectively than metformin plus advice to lose weight and eat healthy. Similarly, the DASH diet controlled stage 1 HTN, but has not been shown to normalize blood pressure. The Mediterranean diet demonstrated a reduction in cardiac risk and delayed onset of CVD, but it does not reverse established disease.

The primary reason that some of these LM treatment programs do not reverse chronic disease is that they are not sufficiently intense to achieve this therapeutic effect. As the

descriptions above reveal, the LM treatment programs that demonstrate reversal of disease use intensive interventions that include intensive patient contact and the adoption of dramatic lifestyle changes. They typically use a low-fat, high-fiber plant diet with moderate physical activity.

The treatment of type 2 diabetes and insulin resistance provides an excellent example of the need for and importance of using sufficiently intense lifestyle interventions in order to maximize treatment effect and arrest or reverse disease. The DPP, described above, delays the onset of type 2 diabetes. Nonetheless, it did not demonstrate the arrest or reverse of impaired glucose tolerance (pre-diabetes) or type 2 diabetes, although it did improve diabetes management and reduce the amount of medication needed.

In contrast to the DPP lifestyle intervention, a more intensive lifestyle change, which includes a very low-calorie diet (VLCD), has been shown to arrest and reverse type 2 diabetes in multiple settings. After publishing in 2011 the results of the Counterpoint study using a VLCD to reverse pancreatic and liver triacylglycerol and restore beta-cell function, including early phase insulin secretion[22] the researchers collected data on 77 individuals who initiated the VLCD on their own to reverse their type 2 diabetes. Those results, published in 2013[23] showed that both short-term (<4y) and long-term (>8y) diabetes could be reversed with VLCD by motivated individuals.

The 77 subjects (66 men, 11 women, 56.4 ± 9.7 years) had a median diabetes duration of 5.5 years (3 months to 28 years). Duration was further categorized as short (<4 years) n = 30; medium (4–8 years) n = 25; long duration (>8 years) n = 14. Prior to undertaking energy restriction, diabetes treatments were as follows: metformin (n = 36); sulphonylurea (13); diet alone (10); insulin (6); glucagonlike peptide-1 agonist (3); thiazolidinedione (3); and dipeptidyl peptidase-4 inhibitor (2). Proprietary liquid meal replacements were used by 38 individuals and energy intake was restricted without the use of special products in 34 individuals. Support from a healthcare practitioner during the diet was reported by 27 people and 25 felt that they had a negative response to request for support. The median diet duration was eight weeks (range 1–104 weeks).

Self-reported weight fell from 96.7 ± 17.5 kg at baseline to 81.9 ± 14.8 kg after weight loss ($P < 0.001$). Self-reported fasting blood glucose levels fell from 8.3 mmol/l (5.9–33.0) to 5.5 mmol/l (4.0–10.0) after the weight-loss period ($P < 0.001$). Pre- and post-diet HbA1c was available in 20 subjects and fell from 58 mmol/mol (40–115) (7.5% [5.8–12.7]) to 45 mmol/mol (26–57) (6.3% [4.5–7.4]) ($P < 0.001$). Diabetes reversal was considered to have occurred in 61% of the population. In the non-reversal group, improvements sufficient to allow the discontinuation of antidiabetic medications occurred in five individuals. Reversal of diabetes was observed in 80% of those with > 20 kg weight loss, 63% of those with weight loss 10–20 kg, and 53% of those with < 10 kg weight loss. The mean weight loss in individuals who reported diabetes reversal was 16.0 ± 6.9 kg and was 12.8 ± 4.9 kg in those who did not achieve reversal of diabetes. There was a significant correlation between the degree of weight loss (%) and reported fasting glucose levels (Rs –0.38, $P = 0.006$). Of those achieving loss of > 20% of body weight, only three people did not achieve reversal of diabetes. The reversal rates in the short-, medium-, and long-duration groups were 73, 56, and 43%, respectively, and in those losing > 15 kg in weight, the reversal rates were 82, 64, and 75%, respectively.

This is a striking contrast to the small diabetes remission rate found in the LookAHEAD Trial using what was called "Intensive lifestyle intervention" and standard "Diabetes support and education", published in 2012.[24] Figure 90.10 shows the prevalence of any remission and the estimated duration of remission in the study (adapted from Figures 2 and 3, Greg et al.[24]).

Notice that the prevalence of any remission was ~2% for standard diabetes support and education, and the maximum

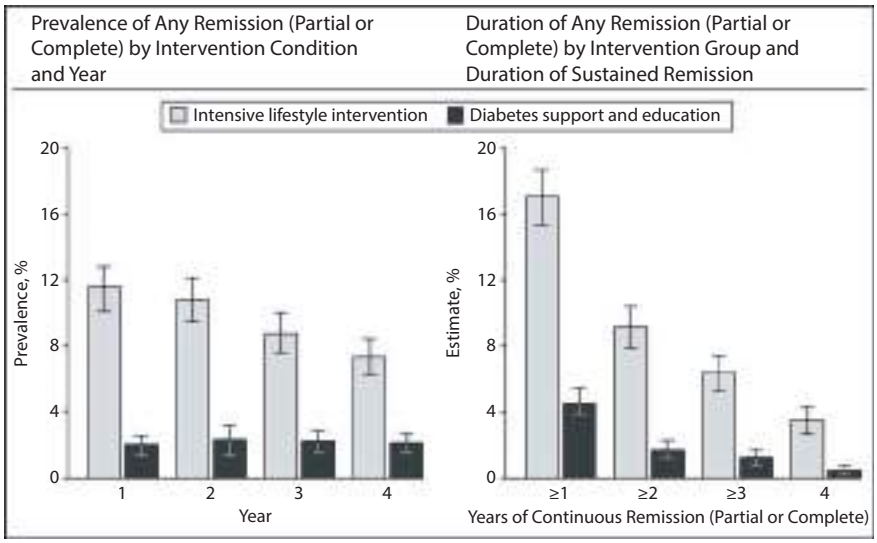


FIGURE 90.10 Prevalence and duration of remission by intervention type over four years.

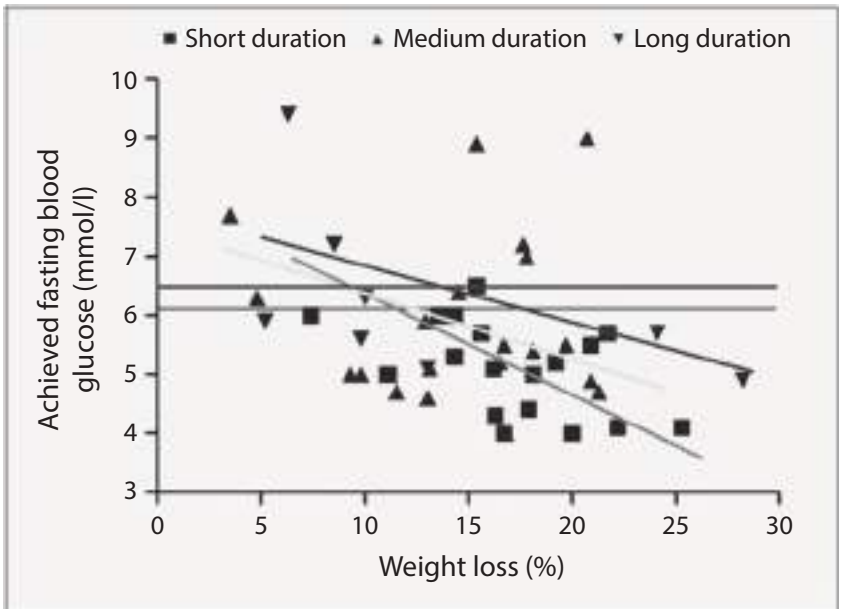
was <12% for the intensive lifestyle intervention. The "so-called2 intensive lifestyle intervention was significantly more effective than the standard diabetes support and education, but much less effective than the very-low-calorie diet in the Counterpoint study.

Longer-term data from eight of the 77 individuals in the Stevens study mentioned above indicate a sustained benefit on blood glucose levels following cessation of tight energy restriction. These individuals, all male, undertook an eight-week period of energy restriction, with four individuals using a meal replacement product. Sustained reversal of diabetes was confirmed by HbA1c in six individuals and by oral glucose tolerance test in two individuals. Details on glycemic control and weight change for these individuals are shown in Table 90.6 (adapted from Steven et al.[23]).

Figure 90.11 shows the self-reported fasting blood glucose levels at the end of the diet period in relation to the degree of achieved weight loss (Figure 10.11 adapted from Figure 1, Steven et al.[23]). The solid line at 6.1 mmol/l represents the diagnostic cut-off for diabetes reversal used in the study, while the solid line at 6.5 mmol/l represents the then accepted cut-off for partial remission, as defined by Buse et al. in 2009.[25] (It should be noted that the Buse et al. consensus has been updated by Riddle et al.[26]) A positive

TABLE 90.6
Time since Intervention, Glycemia, Diabetes Duration, and Weight Changes for Eight Study Subjects

				Weight Δ (kg)	
Subject	Time since diet period	Reported glycaemic control at this time	Diabetes duration	during diet	following diet
1	8 months	HbA_{1c} 40 mmol/mol (5.8%)	4 months	–7.3	+3
2	7 months	HbA_{1c} 36 mmol/mol (5.4%)	3 years	–30.4	–12.4
3	5 months	HbA_{1c} 35 mmol/mol (5.4%)	1 year	–18	+5
4	5 months	HbA_{1c} 39 mmol/mol (5.7%)	3 years	–20.4	+2.2
5	5 months	HbA_{1c} 33 mmol/mol (5.2%)	6 months	–17	+7.5
6	5 months	HbA_{1c} 38 mmol/mol (5.6%)	8 months	–25.4	+5.4
7	3 months	Oral glucose tolerance test Fasting plasma glucose 6.1 mmol/1 2-h plasma glucose 6.3 mmol/1	4 years	–17.5	+2.5
8	3 months	Oral glucose tolerance test Fasting plasma glucose 5.1 mmol/1 2-h plasma glucose 6.0 mmol/1	6 months	–18	–3



Self-reported fasting blood glucose levels at the end of the diet period in relation to the degree of achieved weight loss. The solid line at 6.1 mmol/l represents the diagnostic cut-off for diabetes reversal.

FIGURE 90.11 Fasting blood glucose and weight loss for short-, medium-, and long-duration diabetes.

association is evident between weight loss and achieved fasting glucose, and the shorter the duration of diabetes, the stronger the relationship. Notice the line representing the correlation for short-duration subjects has a greater slope than the line representing the medium-duration subjects, which has a greater slope than the line representing the long-duration subjects.

Building on the success of these two studies, the researchers conducted and published in 2016 results on 30 subjects with type 2 diabetes who consumed a VLCD for six months.[27] The subjects were categorized as responders if they achieved a fasting serum glucose of <7 mmol/L after the VLCD intervention. The non-responders did not recover a first-phase insulin response, nor did their glucose levels normalize, though their weight dropped just like the responders. Evidently, there is a metabolic difference between the responders and the non-responders, perhaps of genetic origin. Figure 90.12 shows the changes in fasting plasma glucose, glycosylated hemoglobin (HbA1c), and weight for responders (●) and non-responders (Δ). (Figure 90.12, adapted from Figure 1, Steven et al.[27] The gray band represents the stepped transition from VLCD to isocaloric eating of solid foods. Data are mean ± SEM.)

The results of another study by the same researchers were published in 2015 showing that a VLCD properly administered and supported would normalize glucose metabolism in about half of diabetics with duration >8 years.[28] Duration of diabetes and achieved fasting glucose were positively correlated such that glucose normalization was more frequent and robust for subjects with shorter-duration diabetes.

The researchers concluded:

> In people with Type 2 diabetes of > 8 years' duration, a therapeutic trial of a very-low-calorie diet may be undertaken with a 50% chance of achieving non-diabetic fasting plasma glucose levels, without any other antidiabetic therapies. For those who do not achieve non-diabetic plasma glucose levels, general health, blood pressure and lipids will be considerably improved. These insights highlight the potential for use of a very-low-calorie diet in long-duration Type 2 diabetes and carry implications for everyday clinical practice.

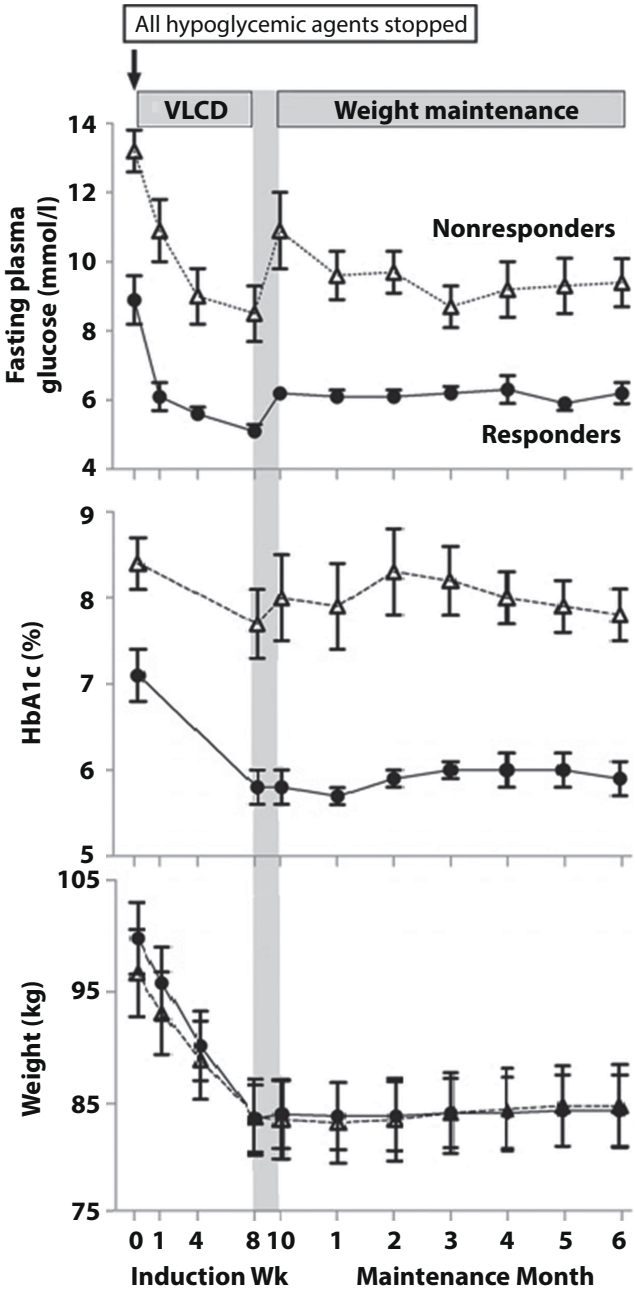


FIGURE 90.12 Changes in fasting serum glucose, HbA1c, and weight in responders and non-responders.

Continued follow-up of subjects from their previously cited studies reveals that responders can maintain normoglycemia for >3 years, even in the presence of modest weight gain (4 kg).[23]

First-year results from the DiRECT Trial by Lean et al. were published in *The Lancet* in 2018[29] and the two-year results in 2019.[30] It was an open-label, cluster-randomized trial with 49 primary care practices in Scotland and England randomized to provide either a weight management program (intervention) or best-practice care by guidelines (control). Subjects were 20–65 years of age who had been diagnosed with T2D within the last six years, with a BMI of 27–45 kg/m^2, and not on insulin. The intervention consisted of withdrawal of antidiabetic and antihypertensive medications, total diet replacement (825–853 kcal/day formula diet for three to five months), stepped food reintroduction (two to eight weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes included weight loss of 15 kg or more (~33 lbs) and remission of diabetes, defined as HbA1c <6.5% (<48 mmol/mol) after ≥2 months off all antidiabetic medications, from baseline to one year. Findings showed that at one year almost half (46%) of participants achieved remission to non-diabetic state off all antidiabetic medications. They concluded that remission of T2D is a practical target for primary care. One-year results are shown in Figure 90.13 (adapted from Figure 2 in Lean et al.[29]). Note the dose-response relationship between weight loss and T2D remission.

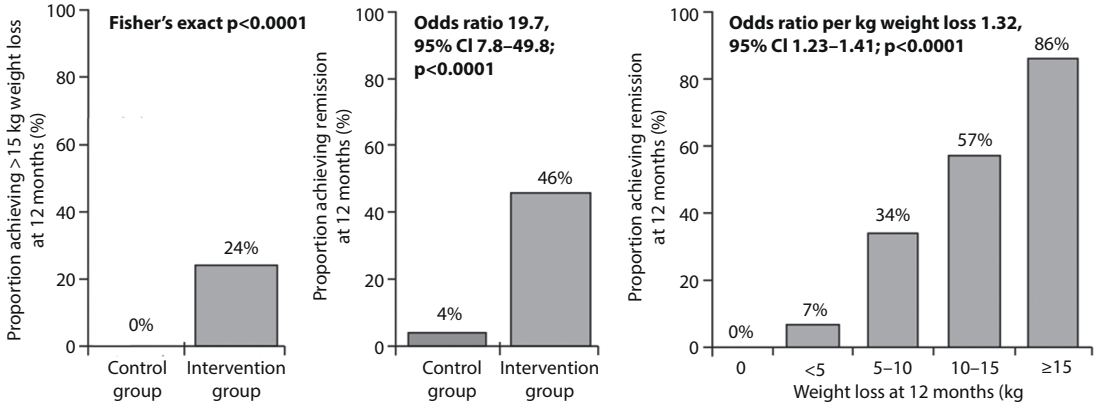


FIGURE 90.13 Weight loss and remission rates in controls vs intervention group in the first year.

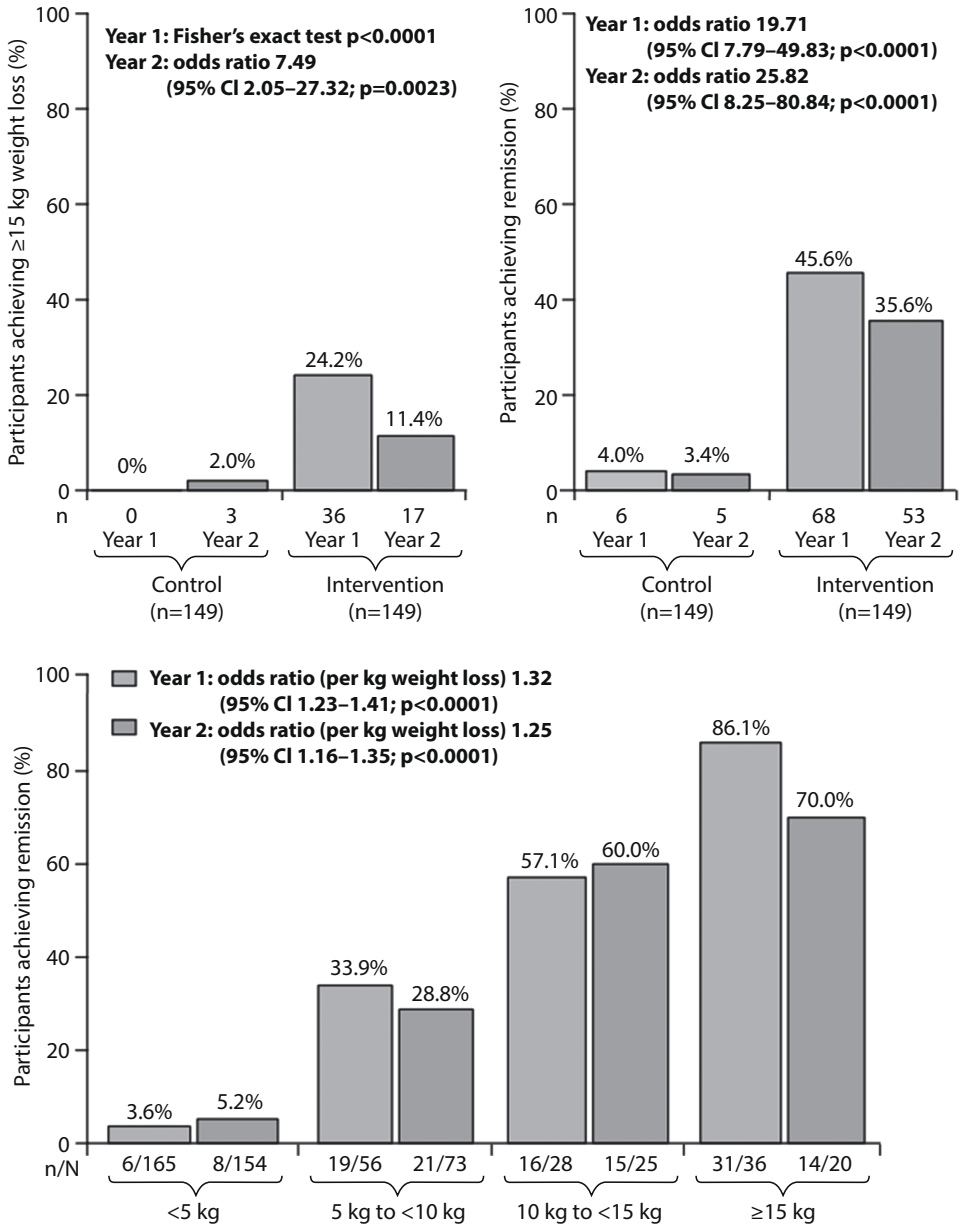


FIGURE 90.14 Weight loss and remission rates in controls vs intervention group in the first two years.

Two-year results revealed decreases in weight loss and T2D remission. Overall remission dropped from 45.6% to 35.6%. The percentage with ≥15 kg weight loss (~33 lbs) dropped from 24.2% to 11.4%, with their remission rate dropping from 86.1% to 70.0%. Figure 90.14 shows the results at two years (adapted from Figure 2 in Lean et al.[30]).

The results of a fasting-mimicking diet (FMD) in diabetic mice were published in 2017 and replicated in 2018.[31,32] This research found that FMD was effective in reversing both type 1 and type 2 diabetes in mice. This was the result of the epigenetic effects of FMD on pancreatic cells that induced beta-cell neogenesis. Figure 90.15 shows the findings of the study.

Similar findings were published in 2018 by another research group, confirming the validity and reproducibility of the treatment effects of an FMD on beta-cells and glycemia (see Figure 90.16; adapted from Figure 1, Wei et al.[32]).

This intensive FMD intervention is also being studied in humans and has produced promising metabolic effects and improvements in the common risk factors for chronic disease.[33] Figure 90.17 shows the findings of the study.

As these results in type 2 diabetes show, lifestyle change has a "therapeutic window" for dosing that largely determines its effectiveness. As with pharmaceuticals and most modalities, an inadequate dosing results in minimal to no significant therapeutic effect. Conversely, when the dosing is too high, toxicity can develop (e.g., too little change in diet and nothing happens, as with the standard diabetes support and education intervention, whereas harm may be caused by a severely prolonged fast). Much of ITLC and TLC is being "under-dosed" and thus is being declared ineffective. More recent research is demonstrating that properly dosed ITLC is highly effective in reversing underlying pathophysiology, even inducing pancreatic β-cell neogenesis in some cases. This was thoroughly reviewed in an analytic review with an ACLM position statement on T2D remission.[34]

Some of the key treatment modalities or components common to the majority of these proven ITLC intervention programs include the following:

- Minimally processed whole plant food diet with little if any cholesterol-containing foods (animal products)
- Fasting with reduced consumption, from portion control to water-fasting and intermittent fasting (IF)
- Abundant regular, moderate exercise, with a gradual increase from inactivity
- Adequate restful sleep, with bedtime well before midnight and early rising
- Generous hydration with water (avoiding sweetened beverages or juices)
- Stress management education including cognitive behavior therapy methods
- Peer group dynamics, with patients supporting one another in lifestyle change (social)
- Spiritual emphases on purposeful living (mental and spiritual)

Therapeutic lifestyle changes are considered "intensive" when large changes are made that dramatically improve biometric measures of health and disease. Therapeutic lifestyle change interventions are considered "intensive" when frequent patient encounters of longer duration are used to help patients make large changes rapidly that dramatically improve biometric measures of health and disease. This type of LM treatment requires close supervision and oversight by an LM clinician trained in LM and licensed to

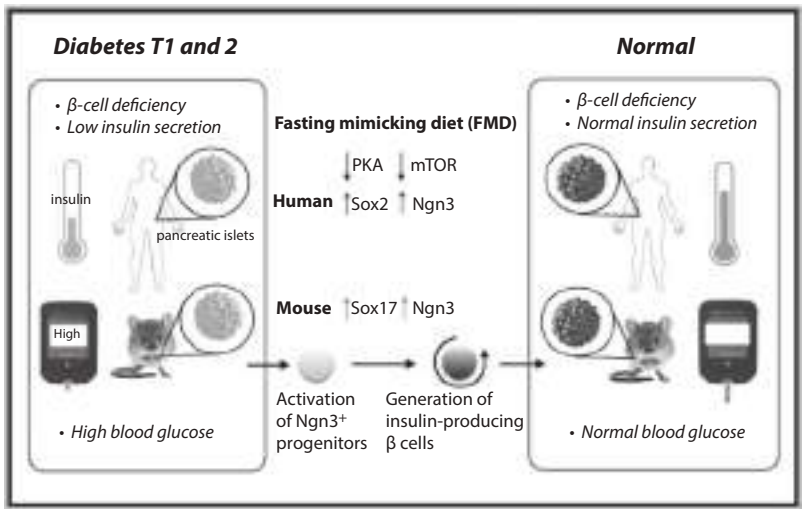
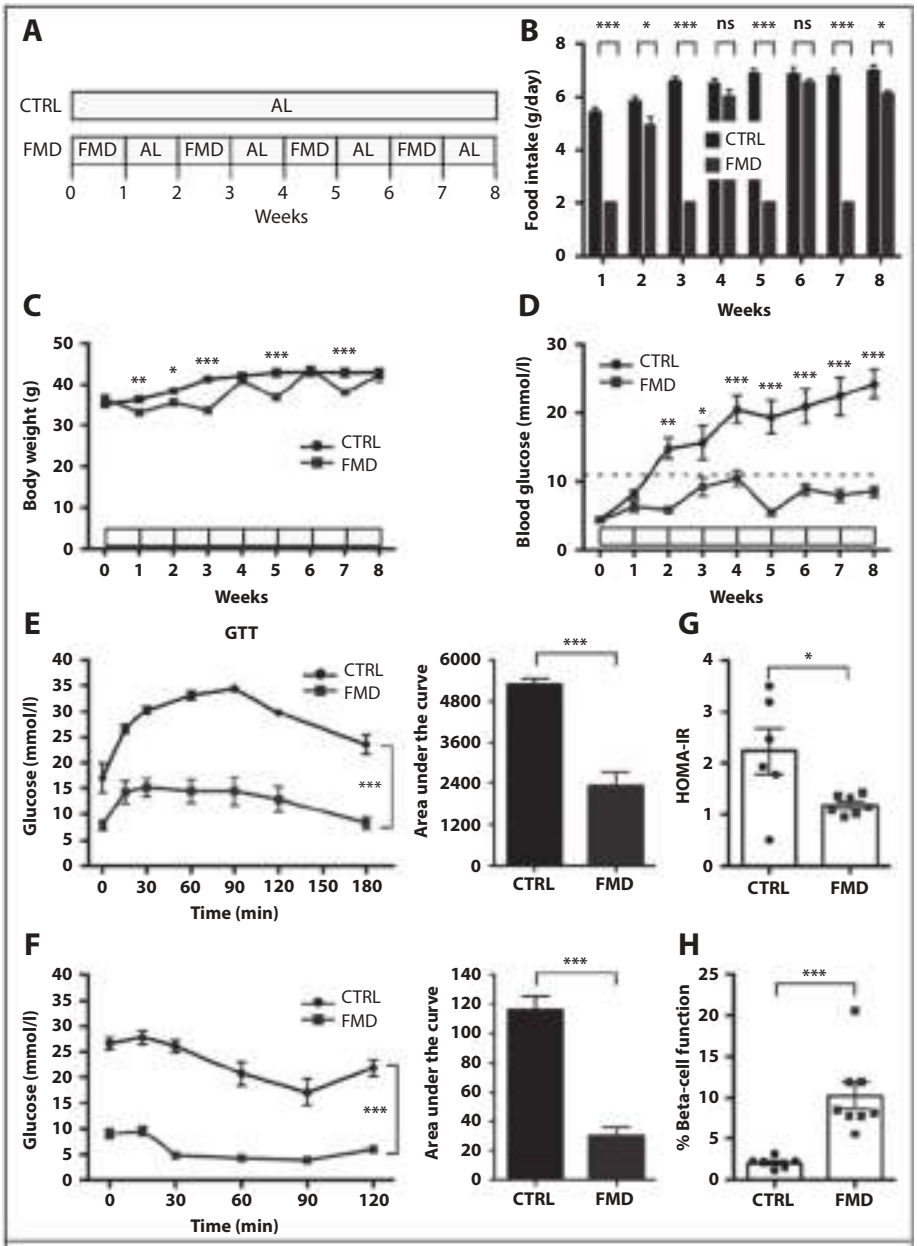


FIGURE 90.15 Graphic abstract of effects of fasting-mimicking diet in human tissue and mouse.



Intermittent FMD intervenes in type 2 diabetes in db/db mice. A Experimental scheme to determine effects of the FMD in T2D in leptin receptor-deficient db/db mice. Six-week-old male db/db mice were assigned to two groups: control and FMD (n = 8 for each group). Each FMD cycle entails 7 days of FMD and 7 days of ad libitum feeding (AL). During free feeding, mice received a regular chow identical to that given prior to the FMD and that given to the ad libitum (AL) controls. B Food intake. C Body weight. D Blood glucose levels. Blood samples were collected on the last day of each cycle. Mice were fasted for 6 h (morning fasting) for blood glucose measurements (n = 8 for each group). A fasting blood glucose level of > 11.1 mmol/L was defined as diabetic (dotted line). E & F Glucose tolerance test and insulin tolerance test at week 9.The area under the curve is shown on the right. G Homeostatic model assessment (HOMA) of insulin resistance (IR) and H steady-state β cell function (%B) at week 9. Data are expressed as the mean ± SEM, n = 8 per group. $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, ns for nonsignificant.

FIGURE 90.16 Fasting-mimicking diet intervention changes in type 2 diabetic mice (db/db).

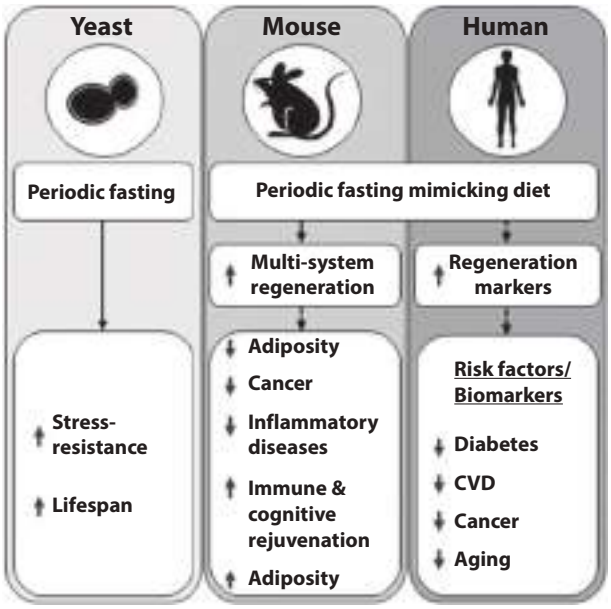


FIGURE 90.17 Graphical abstract of effects of fasting in yeast and fasting-mimicking diet in mice and humans.

deprescribe medications. Intensive cardiac rehab (ICR) LM programs, for example, are "intensive" therapeutic lifestyle change interventions. They produce dramatic improvement in multiple biometric measures of health and disease status and require supervision and oversight by a qualified physician.

ITLC is the form of LM treatment demonstrated by abundant randomized and non-randomized studies to reverse disease. It is not readily provided in the typical medical office setting and it is significantly underutilized. It needs to be followed by appropriate TLC support by PCPs to enable patients to maintain the health-promoting lifestyle choices learned and embraced during ITLC treatment. Often, ITLC is the "missing link" in the practice of LM that could potentiate subsequent LM treatment and make it more effective and sustainable. (In pharmacological terms, it increases dosing and prolongs half-life.) It has been found to be more powerful than many conventional treatments now in use, with many beneficial and no significant harmful side effects.

Sidebar table: Illustrative ITLC Programs

Name and Location	Type/Setting	Strengths	Weaknesses
Ornish Program Franklin, TN	Outpatient, hospital, or clinic	Approved for ICR reimbursement; well-proven effectiveness	Limited availability, cost
Pritikin Program Miami, FL	Live-in residential and outpatient	Approved for ICR reimbursement; well-proven effectiveness; one of the first programs (1970)	Limited availability (outpatient option will help), cost
McDougall Program Santa Rosa, CA	Live-in residential and telemedicine	Among the oldest programs (1970s) affordable; good web support	Limited availability (single location or online)
NEWSTART Program Weimar, CA	Live-in residential	Among the oldest programs (1978)	Limited availability (single location)
Pivio/CHIP Program Loma Linda, CA	Outpatient, hospital, community, corporate, and web	Scalable (video-based); effective (two RCTs); affordable	Australian style recipes; HRA weak
Canyon Ranch Tucson, AZ	Live-in residential	Well-established program	Limited availability (multiple locations); cost
Mastering Diabetes CA	Web-based, focused on type 1 diabetes	Affordable; convenient, and helpful for all forms of diabetes	Limited studies[35]
Other similar programs exist in the United States and the world	Live-in, community, corporate, and web	Varies by program	Varies by program

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91 Physician Health Practices and Lifestyle Medicine

Erica Frank, MD, MPH, FACPM and Debora Holmes, MES

KEY POINTS

- Physicians and medical students with healthy personal habits more consistently report counseling their own patients about these habits.
- Given these data, it is increasingly important for medical schools to proactively produce healthy doctors; however, only one study has documented this type of intervention.
- The "Healthy Doctor = Healthy Patient" relationship itself should encourage prevention-oriented healthcare systems to better support and evaluate these positive effects on patients.

91.1 INTRODUCTION

Past studies have found that physicians and medical students who report healthy personal habits more consistently report counseling their own patients about related habits.[1–6]

Most recently, however—instead of merely relying on physicians' self-reported counseling and preventive practices—the relationship between healthy doctor and healthy patient has been assessed through objectively measured clinical experiences. In so doing, researchers have documented a consistent, positive relationship between physicians' and patients' preventive health practices.[7–9]

In addition, this chapter emphasizes the importance of "growing" proactive medical doctors in the good soil of responsive medical schools and universities—although, to date, it appears that only one large-scale study[8, 9] has documented this type of intervention.

The objective establishment of the "Healthy Doctor = Healthy Patient" relationship (a term first used in Frank, Smith, and Fitzmaurice[8]) should, in and of itself, encourage prevention-oriented healthcare systems in order to better support and evaluate these positive effects on patients. This chapter details past studies and methods and provides suggestions and strategies for future and ongoing success in counseling and treatment.

91.2 CONTEMPORARY PHYSICIAN MORTALITY RATES AND WHY THEY ARE LOWER THAN OTHER GROUPS

91.2.1 Summary of Physicians' Health (Men) in the United States

The data shown in Table 91.1 derive from US deaths occurring in 28 states between 1984 and 1995. Among both White and Black men, physicians were, on average, older when they died (73.0 years for White and 68.7 for Black) than lawyers (72.3 and 62.0), other professionals (70.9 and 65.3), and all men (70.3 and 63.6). The top ten causes of death for White male physicians were essentially the same as for those of the general population, although the physicians were more likely to die from cerebrovascular disease, accidents, and suicide; they were less likely to die from chronic obstructive pulmonary disease, pneumonia/influenza, or liver disease than other professional white men.

In this particular collection of data, mortality outcomes suggest that—at least for men—physicians make healthy personal choices.[10] These and other findings[6,11–14] began to seriously dispel the "myth of the unhealthy doctor" several years ago.

91.2.2 Summary of Physicians' Health (Women) in the United States

Other studies had already expressly shed light on reasons for decreased physician mortality as compared with other groups.[12,15] Table 91.2 illustrates certain characteristics of women physicians versus those with different socioeconomic statuses. Women physicians were more unlikely than other women of high socioeconomic status to smoke (and even more unlikely than women who were not of high socioeconomic status). The few physicians (3.7%) who did smoke reported consuming fewer cigarettes per day than other women, and the physicians who had ceased to smoke reported quitting at a younger age than women in the

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TABLE 91.1
Occupation and Average Age of Death for US Men over Age 25, Years 1984–1995

Race/ Sex	Occupation	Number of Deaths	Average Age at Death
White men	Physicians	13,790	73.0
	Lawyers	14,389	72.3
	All professionals	214,744	70.9
	All deaths	3,386,475	70.3
Black men	Physicians	372	68.7
	Lawyers	258	62.0
	All professionals	14,059	65.3
	All deaths	443,585	63.6

Source: Data from the National Occupational Mortality Surveillance database.

general population. Women physicians were less likely to report abstaining from alcohol; however, those who drank reported consuming less alcohol per episode than other women and were less likely to experience alcohol binges than women in the general population.[12]

Unlike women in the general population and even unlike other women of high socioeconomic status, women physicians reported healthy behaviors exceeded national goals for the year 2000 in all examined behaviors and screening habits. Women physicians described generally good health habits even when compared with other socioeconomically advantaged women; these physicians self-reported that they had exceeded all examined national goals for personal screening practices and other personal health behaviors.[3,16,17]

91.2.3 Summary of Canadian Physicians' Health

Studies have shown that 90% of Canadian physicians are in good health, and 66% are in very good health (compare this with 70% of 20-to-34-year-old Canadians in the general population who are in very good health). Eight percent of

TABLE 91.2
Health-Related Behaviors of Women Physicians Compared with Those of Other Women (30–70 years of age) of High and Not High Socioeconomic Status

Characteristic	Not high SES BRFSS	High SES BRFSS	Women Physicians
Cigarette smoking			
Smoking (%)			
Never	52.9(0.4)**	64.0(1.9)**	77.7(0.7)
Current	25.0(0.4)**	8.0(1.0)**	3.7(04)
Average cigarettes/day	17.6(0.2)**	16.0(0.2)	12.0(1.1)
1 cigarette-abstinent day in last year (%)	50.5(0.9)**	47.0(6.1)**	75.3(4.0)
Number of years quit (%)			
<1 year	11.9(0.5)**	6.7(2.1)	3.5(0.8)
1 - <5 yrs.	20.8(0.7)	14.0(2.3)	16.2(1.7)
>5 yrs.	67.3(0.8)**	79.3(2.9)	80.3(1.9)
Alcohol drinking			
No drinking in past month	43.9(0.4)**	63.3(1.9)**	72.4(0.9)
Average days/month drinking	6.1(0.1)**	7.2(0.3)**	8.5(0.2)
Average drink/episode	2.0(0.0)**	1.6(0.0)**	1.4(0.0)
Average episodes/month of >4 drinks	0.4(0.0)**	0.l(0.0)	0.l(0.0)
Other			
Average fruit & vegetable score	3.3(0.1)**	3.8(0.1)**	3.5(0.0)
Average Block dietary fat score	27.3(0.3)**	21.6(0.9)	24.1(0.3)
Seatbelt wealing (%)			
Always/Nearly always	85.5(0.3)**	95.1(0.8)	96.3(0.4)
Sometimes/Seldom	11.3(0.3)**	4.5(0.8)**	3.3(04)
Never	3.2(0.2)**	0.4(02)	0.4(0.1)

*p ≤ 0.01 for the difference between this BRFSS category and WPHS
**p ≤ 0.0001 for the difference between this BRFSS category and WPHS
Notes: SES, socioeconomic status; BRFSS, Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention (Atlanta GA); WPHS, Women Physicians' Health Study.

Canadian physicians are obese (compared with 23% in the general population); 25% of female doctors are overweight and 55% of male doctors (versus 53% and 65%, respectively, in the general population); and 3% smoke cigarettes (versus 18% of women and 15% of men in the general population).[18]

Frank and Segura found in their 2009 study that women physicians ate fruits and vegetables 5.3 times/day and men 4.5 times/day (versus 48% of Canadian females and 34% of males eating fruits and vegetables 5 times/day); 0.8% of women physicians (versus 9% of other women) and 1.3% of men physicians (versus 23% of other Canadian men) binged. Overall, physicians averaged 4.7 hours of exercise each week.[18]

91.3 PHYSICIANS' PERSONAL HABITS AND PATIENT HEALTH

Do physicians' healthier personal habits make a difference clinically? In other words, why should we care so much about physician health?

One of the strongest predictors of health promotion counseling is whether the physician practices healthy behavior. Conversely, many physicians report difficulties in counseling patients about behaviors they themselves do not practice.[19,20]

Physicians are key health role models and advisors who often meet with patients during potentially impressionable times, and their personal health behaviors affect their credibility and ability to engage their patients in similar healthy behaviors.[21] Importantly for the busy doctor, it seems that simply talking to patients about one's personal health practices improves the efficiency of one's health promotion practices. Providers who disclose their personal health practices are perceived as more credible and motivating.[5,21] In fact, the majority of people cite their physician as their primary source of information regarding healthy lifestyle decisions and are more likely to adopt a healthy behavior when their physician recommends it.[14]

Not only is practicing healthy behavior oneself strongly correlated with a physician's counseling of patients on said behavior,[19] this may actually hold true regardless of the physician's actual health status; physicians attempting to improve their own poor habits have been found to counsel patients significantly more often than physicians who were not trying to change their behaviors.[22]

We know that counseling patients makes a difference in their habits and their health and that North Americans' poor behavioral choices regarding diet, exercise, alcohol, and tobacco account for substantial mortality rates—approximately 40% of US mortality[23]—but, even so, physicians do not perform prevention counseling at very high rates.[24–28]

91.4 PHYSICIAN EXERCISE AND HEALTHY PATIENTS

As previously established, those physicians with the healthiest habits are most likely to advise their patients about related preventive habits. This is particularly true for exercise.[29]

North American physicians (and medical students) generally report significantly better exercise habits when compared with their same-age peer groups, which in turn highly correlates with positive mental and physical health outcomes not only for the physicians but also for their patients. As with other healthy habits, findings on exercise highlight the importance of medical school and physician "health interventions" in order to increase present and future rates of physician-delivered exercise prescriptions.[11,14,17,24,27,28,30–46]

91.5 WHICH DETERMINANTS MATTER MOST WHEN IT COMES TO PHYSICIANS COUNSELING PATIENTS?

Determinants surrounding physicians' personal habits—exercise represents but one example—are worth knowing because intervention on malleable variables can then occur, producing physicians with stronger prevention-related skills.

To explore the effect of potential counseling- and screening-related variables in 4501 respondents to the *Women Physicians' Health Study*, a questionnaire-based study of a representative sample of US women doctors was performed.[3] Table 91.3 delineates the study's central findings.

Being a primary care practitioner and having related healthy habits were the most significant correlates of US women physicians' self-reported prevention-related counseling and screening practices. Table 91.4 exhibits these specifics.

91.6 INDIVIDUAL CASE STUDY 1: FOR ONE PHYSICIAN, HEALTHY MEETS MULTITASKING

Before laptop computers emerged on the scene, I (Dr. Erica Frank, chapter co-author) read journals and books that were not too heavy to hold while I pedaled an exercise bike. But once I had ridden a few miles with a laptop secured to the front of my bike, I knew I had found my preferred regular exercise modality. Here was a health-promotion activity that satisfied so many criteria simultaneously! I no longer experienced remorse over wasting time getting a special outfit for exercise, getting to and from my place of exercise, or even performing the exercise itself (no longer feeling that my brain, hands, and quadriceps should all have higher purposes). Additionally, I no longer stewed in boredom while exercising, a serious impediment to any previously regular exercise.

In the thousands of miles ridden since that day, I have not only learned to bike and simultaneously read and write, but even to chair conference calls—although the latter usually with the video function turned off.

And now when I leave home, I also strive for fun, multitasking exercise. As an assistant professor, I would usually commute to and from work on my bicycle, about 20 minutes

TABLE 91.3

US Women Physicians' Personal Health Practices versus Their Counseling or Screening Patients at Least Once per Year

Physician's fat consumption	% counseling on cholesterol at least lx/year**
Below median fat score	30.2%
Median fat score	22.6%
Physicians' exercise complies with	% counseling on exercise at least lx/year**
CDC/ACSM rec.	46.1%
Doesn't comply with CDC/ACSM rec.	39.6%
Physicians' alcohol consumption	% counseling on alcohol at least lx/year**
≤2drinks per week	41.7%
>2 drinks per week	31.9%
Physicians' cigarette smoking	% counseling on tobacco at least lx/year
Non-smoker	63.4%
Current smoker	47.8%
Physicians' receiving flu shot in last yr.	% recommending flu shot lx/year***
Yes	51.2%
No	32.9%
Physicians' performed breast self exam	% performing breast exam lx/year
≥12x/year	61.6%
<12x/year	51.0%
Physicians' sunscreen use	% doing skin cancer counseling lx/year***
Always/almost always	30.6%
Seldom/rarely/never	19.3%
Post-menopausal physicians' HRT use	% counseling about HRT 1 x/year***
Yes	45.5%
No	28.8%
Physicians' cholesterol tested	% screening/counseling patients on cholesterol at least lx/year***
Yes	33.8%
No	21.9%
Physicians' blood stool tested	% screening/counseling patients re: colorectal Ca at least lx/year
Yes	35.9%
No	31.6%
Physicians' skin examined	% doing cancer/sunscreen screening/counseling at least lx/year
Yes	36.2%
No	22.3%

**p≤0.01; ***p≤0.001.

TABLE 91.4

Models for Significant Correlates of Women Physicians' Counseling on Prevention at Least Once a Year, by Prevention Type

	Cholesterol	BP	Colorectal cancer	Skin Ca/ sunscreen use	HIV risks/testing	Flu vaccine	Diet
Practices related personal habit	***	--	--	****	--	****	--
Has screened self in past year	****			****	--	--	--
Personal history of related disease						--	--
Changing related habits	*	--	*	--	--	--	--
Ethnicity	****						***
Primary Care/Ob/Gyn	****	****	****	****	****	****	****
Region of country	--						*
Practice site	****					*	
More work control							
More career satisfaction							
Performs more CME						**	

TABLE 91.4 Continued
Models for Significant Correlates of Women Physicians' Counseling on Prevention at Least Once a Year, by Prevention Type

Weight	Exercise	Smoking Cessation	Alcohol	Breast Exam	Mammogram	Hormone therapy
--	*	**	****	**	--	***
--	--	--	--	--	**	
	--	--	--			
	**	*	--	--	--	
***						
****	****	****	****	****	****	****
			*			*
						*
						**
**	*		**			

*p≤0.05; **p≤0.01; ***p≤0.001; ****p≤0.0001

to Emory University or to Grady Memorial Hospital each way; this was a wonderful way to begin and end each day. Likewise, I have found it is often an educational and cardiovascular treat to walk around a new urban or biologically rich environment en route to a task. Walking while talking with friends can be fruitful too, whether with a buddy in person or on the phone, a child in a stroller, or as a stroll with a significant other that pays attention to the light, weather, and one's shared ecosystem.

And how do I judge the efficacy of my activities? At age 55 I retain a normal BMI, blood pressure, and lipids without medication, can accomplish without pain any physical feats needed or desired, and sporadically participate in triathlons without special preparation before or any pain after, although always (and contentedly) at the very back of the pack.

INDIVIDUAL CASE STUDY 2: EXERCISE VANQUISHES STRESS

When she had completed the first half of her medical internship in the oncology department of a large community hospital, Verena R. had a very hard time leaving behind the suffering and strokes of fate that her patients endured when she stepped through the hospital's exit door each night. In addition, she lived in staff housing in very close proximity to the hospital—her living room faced the windows of the ward in which she worked. She just could not seem to get away.

That is when Verena took up running. Every day after work, she exchanged her scrubs for running tights and a t-shirt and took off into the nearby forest. Sometimes she listened to music, podcasts, or audiobooks; sometimes her brain needed peace and quiet, and she would simply run and become one with the beautiful natural settings surrounding her.

After an hour or so, Verena would return home drenched in sweat but with a peaceful mind. She was able to create the much-needed distance and larger perspective that allowed her to continue working in the medical profession without sacrificing her own well-being. Six years later, she still runs, having completed several half-marathons, a marathon, and a half-ironman distance triathlon. The sport has given her joy, a healthy body, and best of all, her most important outlet for stress. Thanks to running, she falls asleep happy and content every night.

91.7 A NEW, OBJECTIVE VIEW FROM ISRAEL'S LARGEST HMO

Instead of merely relying on physicians' self-reported counseling and preventive practices, the Healthy Doctor = Healthy Patient[8] relationship was recently assessed through objectively measured clinical experiences.

Frank et al.[7] accessed complete vaccination and screening records from Clalit Health Services (CHS), Israel's largest health maintenance organization, the electronic medical records of (a) primary care physicians who worked in and were also patients in CHS (n = 1488), and (b) these CHS physicians' adult patients (n = 1,886,791),

Eight prevention-related (screening and immunization practices) quality health indicators were chosen:

1. Mammography in women 50–74 years of age
2. Colorectal cancer screening in patients 50–74 years of age
3. Low-density lipoprotein (LDL) measurement every five years for patients aged 35–54 and yearly among patients aged 55–74 years
4. Blood pressure measurement every five years for patients aged <40 years
5. Blood pressure measurement every two years for patients 41–54 years
6. Blood pressure measurement annually for patients ≥55 years

7. Pneumococcal vaccination among patients with a chronic illness and those ≥65 years
8. Annual influenza vaccine among patients with chronic illness and those ≥65 years

For all eight indicators, patients whose physicians were compliant with the preventive practices were more likely ($p < 0.05$) to also have undergone these preventive measures than patients with noncompliant physicians. The investigators also found that more closely related preventive practices showed an even more robust relationship.[7]

91.8 HEALTHIER PHYSICIAN HABITS: PATIENTS RESPOND

As touched upon earlier, providers who disclose their healthy personal health practices are perceived as more credible and motivating; rates of prevention counseling increase and patients become more receptive to health promotion counseling from physicians who demonstrate healthy behaviors themselves.[21,47] Frank, Breyan, and Elon[21] conducted a small study (n = 130) in an Emory University general medical clinic waiting room. They randomized individuals to watch either a standard two-minute video from me (co-author Frank) on healthy diet and exercise habits, or the standard video plus an extra 30 seconds divulging my personal health habits regarding diet and exercise. Patients found me in the "physician-disclosure" video to be significantly healthier ($p = 0.004$), also finding me more believable and more motivating overall. Specifically, regarding both diet and exercise, patients found the extra 30 seconds made me more believable about diet and exercise ($p = 0.006$ and $p = 0.002$, respectively) and also more motivating on diet and exercise ($p = 0.006$ and $p = 0.004$, respectively).[21] Figures 91.1 and 91.2 exhibit these results in graph form.

91.9 DOES COUNSELING ACTUALLY MAKE A DIFFERENCE IN PATIENT OUTCOMES?

Is counseling worth the time? Yes, since tobacco, diet, exercise, and alcohol account for about 40% of US mortality, and counseling from one's physician on these topics increases the likelihood that patients will act healthily.[23]

Surely, then, physicians must be counseling their patients increasingly… and, if not, why not, and what can we do about it?

91.10 THE HEALTHY DOCTOR = HEALTHY PATIENT PROJECT

The Healthy Doctor = Healthy Patient project was a five-year-long action research intervention, performed at Emory University School of Medicine and led by co-author Frank, to improve medical student health, with the hypothesis that this could improve patient health. The scientific foundation of the Healthy Doctor = Healthy Patient principle is as follows:

- North American physicians tend to live longer than their peers.
- Physicians live longer because they have healthier habits (including as medical students) than their contemporaries.
- Four behavioral choices (exercise, diet, alcohol, and tobacco) account for about 40% of US mortality.[23]
- Physicians and medical students with the healthiest habits are more likely to advise their patients about related preventive habits.
- Appropriate physician revelation about healthy personal habits can make physicians more believable and motivating to patients.

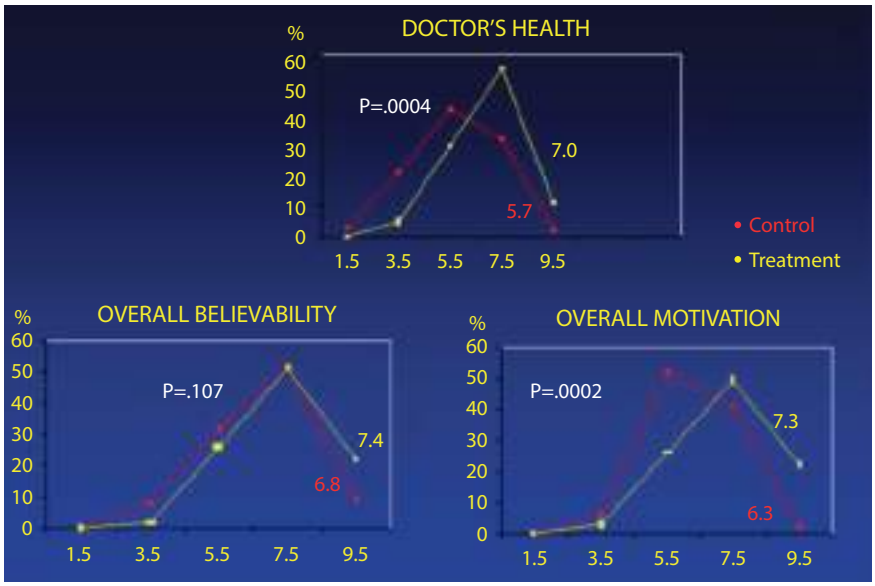


FIGURE 91.1 Emory University waiting room study: doctor's health, overall believability, and overall motivation.

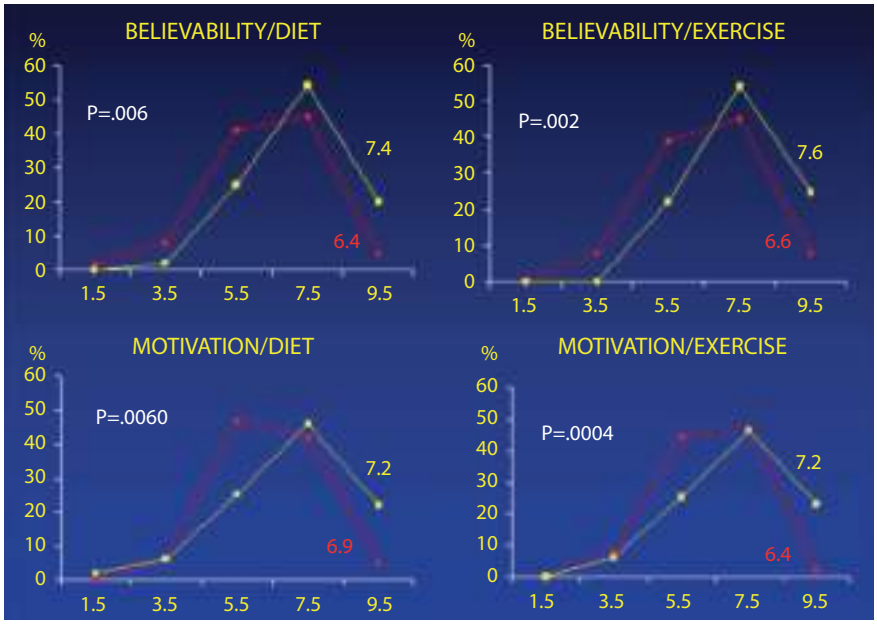


FIGURE 91.2 Emory University waiting room study: doctor's believability with respect to diet and exercise, and doctor's motivation with respect to diet and exercise.

- When medical schools encourage students to be healthy, it positively and significantly influences the students' patient counseling frequency ($p = 0.002$) and their perceived relevance ($p = 0.0007$) of such counseling.
- Counseling patients makes a difference in patients' habits and their health.
- Despite all this, many physicians have areas of potential personal health improvement and do not perform prevention counseling at very high rates.

To determine basic health practices and status, a survey was conducted of medical students (n = 2316 individuals responding to ≥1 survey) in the Class of 2003 at freshman orientation, entrance to wards, and senior year in a nationally representative sample of 16 medical schools (response rate = 80.3%). Most medical students (84%) reported never having smoked cigarettes, and both genders typically drank two drinks per drinking episode (with bingeing more common among men). Students exercised a median of at least four hours per week, and preferred strenuous exercise. Medical students across all years and both genders reported a median of seven hours of sleep per night. Nearly all (97%) reported their health to be at least good, typically with one or fewer days of poor physical or mental health in the past month. Both genders (particularly women) were unlikely to be overweight or obese. Reported rates of any chronic condition were ≤2% except for hypertension among men, and obesity, dyslipidemia, and depression in both genders. Unlike their other relatively positive behaviors compared with their peers, medical students had variable rates of preventive screening.[8,48]

Overall, medical students in the United States were healthy and reported many good health behaviors when compared with other young US adults. However, for some, there was room for improvement, as health behaviors and personal health practices either did not meet national goals or placed students at risk.[48] For example:

- Average daily fruit/vegetable consumption (2.5 servings) was as poor as that of their peers.
- Binge drinking rates (25% females and 43% males) for the previous month were also poor, with no change over medical school ($p = 0.5$).
- Unlike their other relatively positive behaviors as compared with their peers, medical students had low rates of preventive screening.

91.11 MORE ON MEDICAL STUDENTS AND PERSONAL–CLINICAL RELATIONSHIPS

The Healthy Doctor = Healthy Patient relationship ideally begins with freshman medical student interventions: medical schools must concentrate on maximizing the growth of these ideals—and individuals—early on. For example, to determine personal and clinical exercise-related attitudes and behaviors of freshmen US medical students, Frank et al.[49] looked at the 1906 entering freshman medical students (response rate = 87%; average age = 24 years) in the 17 US medical schools surveyed. Students reported a median of 45 minutes per day of exercise, 80 minutes per week each of mild and moderate exercise, and 100 minutes per week of strenuous exercise. Nearly all freshman medical students (97.6%) engaged in some moderate or vigorous exercise in a typical week, with 64% complying with US

Department of Health and Human Services exercise recommendations. Most (79% of) freshmen believed it would be highly relevant to their future practices to counsel patients about exercise; professional predictors included the intention to be a primary care provider, and personal predictors included excellent general health, a prevention emphasis by their personal physicians, and performing more strenuous exercise.[49]

The follow-up study by Frank et al.[2] reported predictors of multiple prevention counseling practices among US medical students. These results are summarized in Table 91.5 and Figure 91.3.

91.12 STUDY: COLOMBIAN MEDICAL STUDENTS' HEALTHY PERSONAL HABITS AND ATTITUDES TOWARD PREVENTIVE COUNSELING

Physician-delivered preventive counseling is important for the prevention and management of chronic diseases. Data from the United States indicate that medical students with healthy personal habits have better attitudes toward preventive counseling.

The following study, the first relating to this association in medical students in developing regions, examined the

TABLE 91.5
Medical Students: Personal Health Behaviors versus Counseling Frequency and Perceived Relevance

	N	Relevance (% highly)	p-value	N	Frequency (% usly/alwys)	p-value
Alcohol Consumption			0.003			0.2
Heavy/Binge Drinker	1561	46		493	24	
Light to moderate	2008	55		589	30	
None	1015	62		291	32	
Tobacco use in past month			0.009			0.001
None	3663	69		1116	58	
Light/infrequent	808	63		213	50	
>10 cig/smk day or >19 days any tub.	156	58		57	47	
Priority of practicing safe sex when sexually involved			0.0006			0.0040
Sexually active singles						
< High	512	46		190	10	
High	1552	59		369	21	
Fruit & Vegetable Consumption servings/day			0.0006			0.03
>= 0 to <= 1.9	1075	49		381	13	
> 1.9 to <= 2.7	1062	61		307	15	
> 2.7 to <= 4	1098	62		285	20	
>4	1055	70		266	24	
Exercise Score Based Upon Godin score Quartiles			0.3			0.08
>= 0 to <= 26	1104	66		329	26	
>26 to <= 41	1085	69		294	33	
>41 to <= 57	1114	70		327	29	
>57	1053	71		323	36	

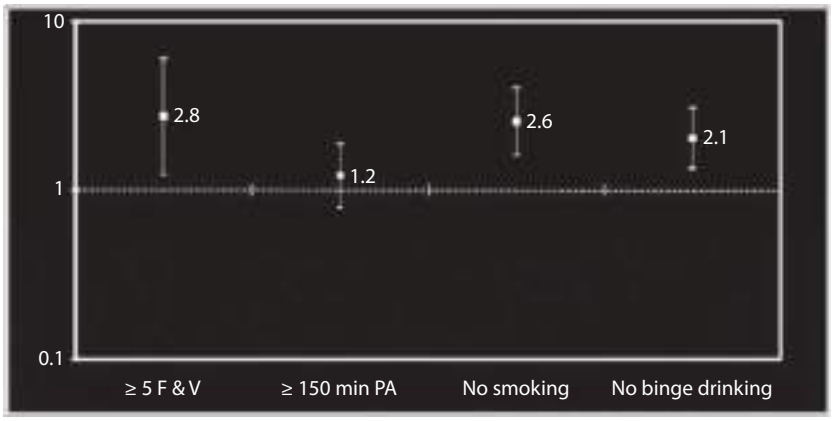


FIGURE 91.3 Medical students' health habits (fruit/vegetable intake, physical activity, cigarette smoking, and drinking) and related counseling attitudes.

TABLE 91.6
Personal Health and Perceived Counseling Relevance, Senior Medical Students (n = 254), Bogotá, Colombia, 2007

Topic	OR	P-value
≥ 5 fruits/vegetables per day	4.7	0.006
≥150 min/week of moderate-to- vigorous physical activity	1.7	0.3
Non-smokers	2.6	
Alcohol abstainers	2.6	

association between personal health practices and attitudes toward preventive counseling among first- and fifth-year students from eight medical schools in Bogotá, Colombia.[1,33]

During 2006, a total of 661 first- and fifth-year medical students completed a culturally adapted Spanish version of the Healthy Doctor = Healthy Patient survey (response rate = 78%). Logistic regression analyses were used to assess the association between overall personal practices on physical activity, nutrition, weight control, smoking, alcohol use (main exposure variable), and student attitudes toward preventive counseling on these issues (main outcome variable), stratified by year of training and adjusting by gender and medical training-related factors (basic knowledge, perceived adequacy of training, and perception of the school's promotion on each healthy habit).

The median age and percentage of females for the first- and fifth-year students were 21 years and 59.5% and 25 years and 65%, respectively. After controlling for gender and medical training-related factors, the investigators found that the consumption of five or more daily servings of fruits and/or vegetables, and not being a smoker or binge drinker, were associated with a positive attitude toward counseling on nutrition (OR = 4.71; CI = 1.6–14.1; p = 0.006) smoking (OR = 2.62; CI = 1.1–5.9; p = 0.022), and counseling on alcohol (OR = 2.61; CI = 1.3–5.4; p = 0.009). Data for senior medical students (independent of gender and medical-related training factors) are seen in Table 91.6.[1]

As with the US physician and medical students, a positive association was found between the personal health habits of Colombian medical students and their corresponding attitudes toward preventive counseling, independent of gender and medical training-related factors.

Importantly, these findings also suggest that within the medical school context, interventions focused on promoting healthy student lifestyles can potentially improve these future physicians' attitudes toward preventive counseling.

91.13 INTERVENTION FOR MEDICAL STUDENTS: A LARGE-SCALE CASE STUDY

Our analysis and quantitative assessment of our four-year-long intervention did, in fact, indicate that the intervention had promoted healthy physical habits among medical students.[8,9] The class of 2003 (using the class of 2002 as a control) at Emory University School of Medicine was extensively studied after various interventions were performed throughout their schooling; several specifics are provided in this section to provide potentially useful ideas for other institutions.

Curricular and extracurricular interventions for first-year medical students included the following:[8]

- Orientation lecture on Healthy Doctor = Healthy Patient principles
- Anatomy manual on muscles and related exercises
- Use of students' data in biostatistics class and for homework
- Student presentations on physician health in small group sessions
- Lunchtime panels (with free, healthy lunch) on well-balanced, integrated lifestyles
- A "healthy quick cooking" class
- Personal health prescriptions provided to students subsequent to lifestyle review
- Hike and healthy dinner at an energy-independent mountain lodge

Curricular and extracurricular activities for second-year medical students included the following:[8]

- Working with Problem-Based Learning mentors on the Healthy Doctor = Healthy Patient concept
- Pathophysiology of hepatic disease, lecture on personal practices
- Behavioral science, one-hour talk on medical student alcohol/tobacco use
- Behavioral science, physician panel of former substance users
- Nutrition course, plant-based diet lecture
- Exercise elective and seminar
- Monthly walks/runs
- Sponsored entrance fees for races
- Wine-tasting seminars to teach about more appropriate use surrounding alcohol
- "Health Heads Up", a monthly emailed summary of a half-dozen prevention-related studies written by classmates
- Weekly yoga classes
- Healthy breakfasts before exams
- Healthy Asian cooking class
- Massage with free lunch (talk and demo), with data on the physiological effects of massage
- Principal investigator presented Healthy Doctor = Healthy Patient at the Student National Medical Association meeting in Atlanta
- Lunchtime yoga/meditation seminar by visiting doctor on the health and psychological effects of yoga and meditation (free healthy lunch provided)

- Personal health prescriptions provided to students subsequent to lifestyle review
- Lunchtime talk (free healthy lunch provided) on pathophysiology of stress and what can be done about it

Curricular interventions offered for third- and fourth-year medical students included:[8]

- *All clerkships*: Dr. Frank (principal investigator) met with clerkship directors, encouraging healthy food on occasions (e.g., morning Grand Rounds, lunchtime didactics) where food would typically be offered to the students, and at least one additional clerkship-based personal health promotion activity for the medical students.
- *Dermatology*: letter on the importance of skin cancer prevention for themselves and their patients, a review article on skin cancer-prevention strategies, and a container of sunscreen for their own use.
- *Ethics/medicine*: completed advanced directives and living wills.
- *Ethics/psychiatry*: completed a Beck Depression Inventory and an alcohol (CAGE) screening questionnaire.
- *Family/internal medicine*: tobacco lecture, instruction, and practice with health-risk appraisals (HRAs), and model counseling.
- *Family medicine*: students (and occasional preceptors) kept one-week logs of daily number of fruits/vegetables and exercise amount/type; students wrote descriptions of their ideal lifestyle a decade hence.
- *Gynecology/obstetrics*: articles assigned on women physicians' characteristics during pregnancy, sexual abuse/domestic violence rates, and depression/suicide rates; students given American Cancer Society breast self-exam shower card; students given condoms and emergency contraception offered (as requested).
- *Pediatrics*: presentation on personal health practices on rotation and in life.
- *Psychiatry*: suicide and depression article.
- *Surgery*: presentation on personal health practices of a director.
- *Validation project:* validation study for food-frequency screener, including five in-person, 24-hour recalls; two food-frequency questionnaires; personal analysis of fat and fruit/vegetable intake

In this four-year controlled trial addressing lifestyle behaviors over the course of medical school, the final analysis found that medical student had made improvements in their personal health practices. For instance, control group males increased their use of tobacco products between ward orientation and their senior year, while intervention group males decreased their use—the control males reported twice the tobacco use reported by males in the intervention (43% versus 22%, p = 0.02), although the two groups had previously reported very similar levels (31% versus 29%, p = 0.8).[5,9] Importantly, students' diet counseling and exercise counseling (as reported by standardized patients) were also strongly positively related to the intervention.[9]

Observational Healthy Doctor = Healthy Patient study hypotheses were confirmed:

- Medical students were healthy and reported many good health habits when compared with other young US adults.
- Medical schools' encouragement of students to be healthy significantly influences students' patient counseling frequency (p = 0.002) and perceived relevance (p = 0.0007) of such counseling.[8]
- Medical students' personal health practices are correlated with their counseling frequency (p <0.0001) and perceived relevance (p = 0.008).[2]

A medical student-focused health promotion intervention can improve students' self-reported personal health behaviors, their perceptions of the healthfulness of their medical school environment, and their (objectively measured) standardized patient prevention counseling practices.[9] Likewise, the comprehensive study by Frank et al.[2] found that students reporting a healthier medical school environment also reported highly significantly better patient counseling practices. The remarkable effect of student interventions on the frequency of their patient counseling is exhibited in Table 91.7.

These findings suggest that further refinements and broader implementation of interventions such as those discussed in this chapter could be efficient and valuable methods to improve the health of healthcare professionals and the vast populations of patients they serve.

TABLE 91.7

Effect of Student Interventions on the Frequency of Counseling Patients during Their Examinations

Topic	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P Value from Adjusted Odds Ratio
Diet	1.49 (1.04–2.12)	1.49 (1.01–2.19)	0.04
Exercise	1.65 (1.16–2.35)	1.56 (1.04–2.34)	0.03

Extensive versus minimal/no counseling (adjusted for gender, intended specialty, and agreement, at baseline, with the statement "Physicians have a responsibility to promote prevention").

91.14 INTERVENTION FOR PHYSICIANS

Although physicians' and medical students' personal health practices are better than those of the general population (at least in Canada and the United States), multiple studies suggest the need to further foster physicians' personal preventive practices, both to promote the personal health of physicians themselves and to improve outcomes for their patients.

In addition, such programs need to be studied in order to determine how best to actively encourage physician health and, correspondingly, the Healthy Doctor = Healthy Patient association.[7,8] To date, this chapter's authors know of no such published studies, although we are now collaborating with Bar-Ilan University's (in Safed, Israel) medical school and with www.NextGenU.org's (in >200 countries) free, accredited lifestyle medicine course on such a study. We look forward to encouraging and enabling other such interventions—particularly with readers of this chapter interested in such (Erica.Frank@ubc.ca, efrank3g@gmail.com, and EFrank@NextGenU.org being enduring emails for such purposes).

91.15 BOTTOM LINE

The health of North American (and most other studied physician populations) is, according to multiple studies, very good, although there is room for improvement in our physical (and particularly for our) mental health among both physicians and medical students. Especially when looking through the lens that shows a healthy doctor is more likely to produce a healthy patient, physicians' health status takes on paramount importance.

The medical and healthcare communities, along with North American universities, must implement new approaches to achieve these goals. As physicians, we must (a) discuss ways to simultaneously improve our health and that of our patients, and (b) consider the most important new questions to ask regarding physician health. We must take care of ourselves as well as our patients: when we do, we will witness more positive personal health outcomes for all concerned.

Physician health is rarely systematically promoted anywhere in the world, suggesting that policymakers believe that physicians are already adequately supported. In the few places where support programs for physicians exist, they concentrate heavily on suitability and competence to practice, mental health and illness (especially around substance abuse), and practice-related psychological motivation and physical stamina. The medical profession needs to do more than this, however—a failure to miss these opportunities is also a failure to efficiently improve the health of everyone in the system.[7]

CLINICAL APPLICATIONS

These findings should encourage leaders to test various ways to address and promote the following:

- Physician health, including and especially as a way to encourage patient health.
- Recognition that physicians' patient counseling is strongly related to the physician's own health practices.
- Medical student health through efforts to ensure medical schools produce healthy doctors and avid preventionists.[50]
- Healthcare systems that promote and support physician health around the globe.
- Recognition that physicians can positively influence patient health by counseling patients on prevention and health-promoting behaviors.
- The health of entire patient populations, which profit from more efficient and effective health promotion counseling.[5]
- Further exploration of the correlations between physicians' healthy personal habits and prevention-related counseling and screening, which should encourage new directions for physician training.

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92 Physician Burnout

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KEY POINTS

- Lifestyle medicine principles play a vital role in helping to minimize the individual symptoms and risk factors before, during, and after the appearance of burnout syndrome.
- Burnout is a result of stress, improper diet, lifestyle factors, and inadequate support from the workplace environment.
- Implementing mindfulness, primordial, primary, secondary, and tertiary prevention techniques can slow or prevent the progression of burnout.
- Mentoring future generations of medical professionals in lifestyle medicine can minimize the risk of burnout while promoting professional well-being.

92.1 INTRODUCTION

Burnout has been defined in the academic literature within multiple disciplines in medicine as related to chronic, unmanaged work-related stress. We will limit this chapter to physician burnout, although the literature for nurses, physician assistants, and other allied health providers is robust as well. Freudenberger first formally defined burnout in 1974. It is now seen as a multidimensional work-related syndrome consisting of emotional exhaustion, depersonalization, and a low sense of accomplishment from work.[1,2] Prior to the COVID-19 pandemic, physicians were already reporting stressful circumstances at work with over 50% reporting burnout. Physician well-being and self-care are essential for our healthcare system. Self-care has been defined by the WHO as the "ability of individuals, families, and communities to promote health, prevent disease, and maintain health and to cope with illness and disability with or without the support of a health-care provider".[3] This chapter focuses on the current literature on a complex construct of physician burnout while fully acknowledging that organizational interventions will be needed to truly address this burnout pandemic. Lifestyle medicine principles play a vital role in helping to minimize the individual symptoms and risk factors before, during, and after the appearance of burnout syndrome.

92.1.1 Nosology of Burnout Remains Controversial

Burnout is complicated to study since many countries describe it differently. According to the ICD-11's classification in January 2022, burnout is an occupational syndrome correlated with employment rather than individual mental health diagnoses and is regarded independently from mood disorders, adjustment disorders, anxiety disorders, or disorders specifically associated with stress.[4] In North America, burnout is noted to be related to work and not a diagnosable medical condition. The current version of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5-TR, does not include burnout as a diagnostic category.

Two countries are leaders in the burnout space, Sweden and The Netherlands. Since 1997, with the ICD-10 addition of burnout as a syndrome, Sweden has recognized burnout as a disease.[5] Sweden later modified their country's burnout diagnosis in 2005 through the inclusion of an additional diagnostic criterion, difficulty in life management, called *vital exhaustion*. Vital exhaustion encompasses a presentation with remarkable similarity to symptoms of clinical depression, including irritability, two weeks of low energy, emotional lability, difficulty concentrating, sleep difficulties, and dizziness. To uphold qualification as *vital exhaustion*, these symptoms must have a direct impact on the execution of work responsibilities. It is important to note that Sweden citizen's access to care and services, including treatment, sick days, and disability, is contingent on this vital exhaustion diagnosis. The Netherlands similarly considers burnout a diagnosis and uses the term *overstrain* for this diagnosis with a prevalence of 3–7% that spans numerous professions.[6]

92.2 WHAT IS THE EXTENT OF THE PROBLEM?

Recent studies in the United States have shown that 40–54% of physicians report at least one symptom of burnout as assessed by the Maslach Burnout Inventory (MBI) with significant variation between physician practice specialty and setting.[7–10] Academic physicians have noted a 30% lower risk for burnout than private practice physicians.[8–11] Moreover, only 40.9% of private practice physicians contend that they have enough time outside of work for personal/family life, with 14.6% neutral and 44.5% in disagreement with this statement. The physician specialty with the highest burnout includes physicians on the frontline, e.g., primary care and emergency medicine. Notably, women and early career physicians have also been found to be at increased risk for burnout after considering adjustments for professional and personal factors.[12–14]

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Several studies have reported that 45–56% of medical students and more than 60% of resident physicians have at least one symptom of burnout even though they enter medical school with higher psychological well-being than their peers.[15–18] Additionally, there is limited data available regarding the risk of burnout for self-identified lesbian, gay, bisexual, and transgender students and physicians, as well as the implications of race in burnout likelihood.

It can be seen that physician burnout may result in a multitude of consequences, including mental health issues for physicians, quality of care, litigation risk, job performance, physicians abandoning the field of medicine, patient satisfaction, and adherence of patients to prescribed treatments, along with countless other repercussions. To further complicate the issue, an unhealthy work environment can generate extensive human and financial costs. As an illustration, studies from 2018 determined that reduced clinical hours and physician turnover have a direct association with an estimated US$4.6 billion in annual costs.[10]

92.3 SYSTEMIC ETIOLOGICAL ISSUES

Multiple systemic etiological issues for developing burnout in the workplace have been identified, including overwhelming stressors in the work environment. Many authors, such as Maslach and Leiter in 1997, have implied that organizations *cause* physicians personal stress and a decreased sense of intrinsic worth with work becoming an obligation, with redistribution of power and questionable citizenship practices of institutions.[19]

As medical educational institutions have altruism as a required quality for future students, the mismatch continues to widen between the nature of the job and the nature of the person attracted to the profession. This mismatch leaves physicians often reporting a lack of control in the workplace with productivity goals misaligned with their internal drives. Physicians may feel overworked with conflicts with management, and experience an overall breakdown in community. Electronic health records, insurance mandates, and the corporatization of healthcare all contribute to stress, as they increase administrative and clerical burdens and decrease autonomy and flexibility, respectively. Unpaid work time including the often cited "pajama charting" time at home in the evenings increases stress and overwork, often contributing to the erosion of the professional versus personal boundaries for physicians.[20]

Race and the systemic and systematic issues in healthcare are emerging topics that also may contribute to the unfair training and work environment for many racial minorities that make up the underrepresented minorities and first generation in healthcare.[21]

92.4 WHAT ARE THE CONTRIBUTING FACTORS TO PHYSICIAN BURNOUT?

In 1977, Maslach and Leiter identified six factors in the workplace contributing to burnout. These six facts include a lack of control over work and responsibilities, an unrealistic workload, a disconnect between the reward and effort required in medical practice, an erosion of trust within the system, a lack of community in the workplace, and a misalignment of values and incentives.[19]

The current literature continues to support the argument that burnout is primarily a systemic issue with clear antecedents as first described in 1977. The authors agree that systemic issues are the primary etiology of burnout; this section addresses personal vulnerabilities that can make physicians especially susceptible to the development of burnout. Historically, society has perpetuated the cultural expectation that physicians must first and foremost care for those in medical need and serve the greater good under all circumstances. Physicians' health and personal desires typically assume secondary status to the required altruist mandate of medicine; however, this expectation is often upheld by providers at the cost of their own health. Is this a strong foundational structure for physicians to have as they counsel patients to take care of themselves? Are we creating a system of double standards?

US medical students are groomed to succeed from an early age to enter the competitive selection process. Medical students typically have a history of academic achievement that comes from years of striving for perfectionism with limited experience with failure. They are often seen as the smartest students in the classroom and serve as mentors and tutors from middle school and beyond. At first, these traits would be seen as admirable. The question is: How are these standards of personal performance potentially affecting the physician in their personal and professional life during their lifespan?

The field of lifestyle medicine has an opportunity to support the health of physicians along with informing physicians on the management of the health of their patients. Systemic organizational issues abound in the healthcare system leading to physicians often expressing a lack of support. How can a physician be expected to help others when they are feeling that they are not receiving adequate psychological support? In addition, the negative treatment of medical students and trainees is commonly described in the literature within our performance-driven medical culture.[22] As students who are unaccustomed to criticism continue through their medical training, one has to wonder how their sense of self holds up to the multiple mistakes that they must make throughout the learning process. Maybe we need to include areas in medical education that allow for failures to be encouraged and supported as part of the curriculum.

Medical students have often excelled in tasks and are inexperienced with the psychological mechanisms to cope with being told that they are inadequate. Overwhelmed with studies and patient care, trainees may psychologically compartmentalize their disappointments within themselves, awaiting time to process the feelings and grieve and mourn the sickness and death that they witness. Trainees experience erosion of their self-care with their laudable personal and professional goals as the time to process often never comes as the workload only increases with every year of

practice. Medical professionals are known to be hardest on themselves and this harshness is mirrored in the healthcare system on multiple levels. This is compounded by the lack of time to grieve and process the emotions associated with the burden of learning to become a physician. These same students and residents who are at times systematically belittled during their own training may adopt the same negative strategies on the next generation of trainees, thereby perpetuating this toxic culture.

92.5 BURNOUT AND MENTAL AND PHYSICAL HEALTH

Considering the stressors in the healthcare environment, physicians react either positively or negatively, resulting in consequences on their health and well-being. With stressors that are persistent and displeasing, physicians may react in ways that worsen their health. This relentless feeling of hopelessness felt by the physicians puts them at a greater risk for burnout.

Stress may also result in physiological changes such as blood-sugar imbalances, hypertension, structural changes in bone density and the brain, muscle tissue loss, and lowered immune responses.[23] The structural changes in the brain are a result of decreased grey matter volume in the hippocampus, as chronic stress impacts the hypothalamic-pituitary-adrenal (HPA) axis.[24] Stress response can be improved by the physician's mental control over the stressor and can be mediated by the prefrontal cortex inhibition of the brain and limbic system structures.[25] Similar to lifestyle medicine, resilience research shows that addressing the stressors proactively and having active coping mechanisms are the most effective ways of combatting stress in the work environment and ultimately lessening the risk for burnout.[26]

Implementing active and healthy responses to stressors has been shown to help the body return to its original state. Such healthy responses align with lifestyle medicine interventions that focus on exercise, diet, and sleep to address the inflammatory response of stress. Research shows that the complex neural processes underlying stress and stress resilience involve genetic, epigenetic, neurobiological, and environmental factors.[27] Addressing these factors with lifestyle medicine interventions will slow or prevent the growth of stress-related burnout.

92.6 SYMPTOMS OF BURNOUT

The five categories of symptoms associated with burnout are discussed further. These include physical, affective, cognitive, behavioral, and motivational symptoms.[28]

92.6.1 Physical Symptoms

Physical symptoms often seen with burnout have been linked to a sympathetic nervous system activated stress response, hypercholesterolemia, type 2 diabetes, metabolic syndrome, musculoskeletal pain, dysregulation of the HPA axis, weakened immune function, systemic inflammation, and cardiovascular disease.[29] The sympathetic nervous system activated stress response from burnout is associated with anxiety symptoms such as increased heart rate and blood pressure, nausea, headache, and restlessness.[30]

92.6.2 Affective Symptoms

Many affective symptoms of depression and anxiety are associated with burnout. These include changes in mood, increased tension, anxious and heightened feelings, and irritability. Evidence supports that burnout along with depression and anxiety are associated with fibrinogen, which is gender-dependent, and the inflammatory marker C-reactive protein (hs-CRP).[31]

92.6.3 Cognitive Symptoms

Cognitive symptoms include helplessness, a cynical perception of others, and pessimism. Additional cognitive impairments, such as subjective memory, executive functions, and less attention, are associated with long-term burnout.[32]

92.6.4 Behavioral Symptoms

Emotional outbursts, medical errors, declined productivity, and increased job turnover are all behavioral symptoms associated with physician burnout. When physicians experience burnout, they are more likely to retire earlier or change their specialty because of the detrimental impact on well-being.[33]

92.6.5 Motivational Symptoms

When physicians experience burnout, they often question their role in the workplace and their decision to become a medical professional. These questions are generally supplemented by decreased motivation and loss of interest.

92.6.6 Overlapping Symptoms

As the symptoms of burnout heavily overlap with psychiatric conditions, such as adjustment disorder and major depressive disorder, the conditions are often difficult to understand within a patient. Early assessment and treatment of psychiatric disorders can occur with a psychiatrist's proficient psychological knowledge and clinical diagnostic experience to reduce the impacts of the illness.[34] Although chronic fatigue, exhaustion, and burnout share some common symptoms, chronic fatigue is not situation-dependent. Also, the lowered energy associated with burnout tends to be prolonged compared with exhaustion.

There are a few biomarkers that have been isolated to help differentiate burnout from other mental health disorders.[35] Decreased DNA methylation at the NR3C1 glucocorticoid receptor gene and the SLC6A4 serotonin transporter gene have been noted in burnout.[36] This pattern

of methylation appears different from that seen in patients who are depressed or in the stress response. There is also increasing interest in the differences in methylation in the BDNF gene in depression, stress, and burnout.[37]

92.7 BURNOUT ASSESSMENT

Table 92.1 summarizes burnout assessment tools.

92.8 A PREVENTION MODEL FOR RISK FACTOR REDUCTION

Since physician burnout is a systemic problem, changing the systems of healthcare and addressing the roots of the problem will require an effort by multiple parties in the system. The National Academy of Medicine is leading the national-level movement to improve the structure, organization, and culture of healthcare.[1] In Merlo and Rippe, specific interventions for burnout to be conceptualized as risk factor reduction using an occupational health prevention model have been proposed.[38] Physicians who practice healthy lifestyles not only affect their quality of life but also result in improved patient care. Prevention can be inordinately helpful in health promotion prior to disease onset. Of note, in occupational health, the standard approach to describe the process of risk reduction includes three levels: primary, secondary, and tertiary levels. While this approach is relevant to the discussion of burnout risk reduction, the Merlo and Rippe Model adds a fourth category—primordial prevention—which can increase the efficacy of the model. Figure 92.1 describes the intervention stages for the effective prevention of burnout using lifestyle medicine.

92.8.1 Primordial Prevention

Primordial prevention is a mechanism that avoids risk factors for burnout before they can affect the individual. This

TABLE 92.1
Burnout Assessment Tools

Assessment Tools	Abbreviation	Number of Items	Cost	Description
Maslach Burnout Inventory-Human Services Survey for Medical Personnel	MBI-HSS	22	Modest	Covers emotional exhaustion, depersonalization, and low sense of personal accomplishment
Oldenburg Burnout Inventory		16	None	Positively and negatively framed items. Covers exhaustion and disengagement from work
Copenhagen Burnout Inventory		19	None	Positively and negatively framed items. Covers personal, work, and client-related burnout
Stanford Professional Fulfillment Index	PFI	16	None for non-profit use with permission	Covers work exhaustion and interpersonal disengagement from burnout and professional fulfillment
Well-Being Index		7 or 9	Free for non-profit and research use with permission	Identify distress in several dimensions with yes/no responses

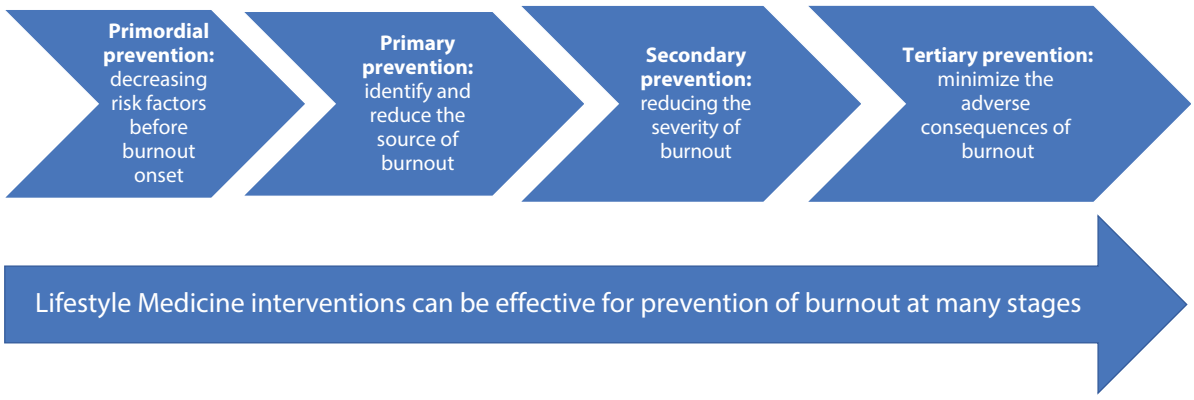


FIGURE 92.1 Individual-focused burnout risk reduction strategies can target primordial, primary, secondary, and tertiary prevention (figure from Merlo G, Rippe J. "Physician burnout: a lifestyle medicine perspective". ***American Journal of Lifestyle Medicine*** 2021, 15(2):148–157.Used with permission of the Editor, Dr. James Rippe).

concept was highlighted by the American Heart Association (AHA) in 2010 as a technique to reduce the impact of heart disease by avoiding risk factors.

Lifestyle medicine welcomes healthy living to decrease risk factors for burnout by intervening in all six pillars of lifestyle medicine. These interventions improve physical and mental health, thus serving as a preventative buffer to burnout. Focusing on forming and maintaining healthy relationships can weaken feelings of loneliness and social isolation.[39] Building these supportive networks in the workplace along with seeking to reduce stigma about burnout, increasing or maintaining job control, maintaining physical well-being through exercise, adequate sleep, and avoiding tobacco and other risky substances are all ways to prevent and reduce the risk factors of burnout before it begins.[40] Strategies that are personalized include self-care, healthy eating, wellness, mindfulness, and social connectedness.

92.8.2 Primary Prevention: Primary Prevention Strategies Can Be Systems-Based and Individual-Focused

92.8.2.1 Systems-Based Primary Prevention

Primary prevention interventions are typically systems-based and seek to identify and minimize the source of burnout by promoting change within the organization. This mechanism emphasizes human care, empathy, compassion, and overall workplace culture that may allow physicians to find purpose in their work. Systems-based primary prevention has six major goals, as outlined by the National Academy of Medicine Clinician Burnout committee:[11]

- Create positive work environments: Reform healthcare work systems by creating work environments that minimize burnout and reinforce quality healthcare. To promote joy in the workplace, organizations should implement programs that support the well-being of healthcare workers and improve patient satisfaction.[41] These designs should be human-centered and followed along with the co-creation of a healthy work culture and organization with physicians.
- Create positive learning environments: Promote learning within the workplace by modifying the education and training of health professionals. The consistent opportunities for growth and learning slow and prevent the progression of burnout and foster professional well-being.
- Reduce administrative burden: Strengthen clinicians' professional well-being by minimizing the pressure and stress from regulations and standards brought by standards-setting entities such as government agencies from all levels, professional organizations, and accreditors.
- Enable technology solutions: Increase the use of technology within healthcare settings to optimize patient care and support the clinician.
- Provide support to clinicians and learners: Encourage seeking support and reducing the stigma surrounding burnout. Supporting the services that prevent and improve burnout will promote professional well-being within the work environment.
- Invest in research: Increase the research on clinician professional well-being by allocating funds and resources.

92.8.2.2 Individual-Focused Primary Prevention

Systems-based primary prevention strategies may also be implemented as individual-focused lifestyle medicine interventions, as described in the primordial prevention section. Despite the similarities, primary prevention addresses the symptoms of burnout after they are experienced by a physician, whereas individual-focused primary prevention will mostly be in the workplace. Primary prevention measures also address the unmet psychological and professional needs of physicians, including workload, community, emotional support, decreasing isolation, and personal issues. One recent study investigated a nine-month facilitated peer group support based on the Balint approach for physicians meeting twice a month and was found to reduce burnout symptoms.[40] Mindfulness has been shown to reduce burnout, reduce medical errors, and increase professionalism.[42] Professional coaching interventions may also be helpful.[43] Enhancing professional self-efficacy represents one of the ways to decrease stress and potentially prevent burnout. Bandura discusses ways to improve self-efficacy through experiences that help in performance mastery either directly or vicariously (watching a colleague affect change). Some suggest that healthcare organizations should adopt a distributive leadership model, and have physicians actively design and lead.[25]

92.8.3 Secondary Prevention Interventions

Secondary and tertiary prevention interventions address the symptoms rather than the root of burnout. Secondary prevention interventions seek to minimize the consequences and severity of burnout after they are noted through early detection and aim to treat the burnout symptoms before their negative impact on the individual and the community. Developing an ongoing screening program using validated approaches standardizes the secondary prevention process. In addition, providing resources for the detected physicians will foster an open community and lessen the stigma surrounding burnout, while promoting a healthy culture of professional well-being. Other examples of secondary prevention techniques that follow lifestyle medicine include stress management programs and mindfulness techniques. Practicing mindfulness effectively guides the physician's

mind toward reducing distress about factors out of their control.

92.8.4 Tertiary Prevention

Since physicians may fail to be noticed by primordial, primary, and secondary prevention, tertiary prevention aims to mitigate the consequences of the ongoing condition. Tertiary prevention utilizes employee assistance programs and referrals to ensure that the individual has the resources to support their health and prevent further deterioration of their well-being. Clinical depressive disorders and anxiety disorders, among other psychiatric disorders, may result from burnout.

92.8.4.1 Nutrition in Depression and Anxiety

Studies show that a healthy diet is associated with a lowered risk of depression.[44] Additionally, one meta-analysis concluded that following a plant-based Mediterranean diet led to a 27–32% risk reduction of depression.[45] Some studies have reported that the link between the gut microbiome and depression and anxiety is improved with probiotics and is influenced by lifestyle factors, including stress, diet, and dietary inflammatory index.[46,47]

92.8.4.2 Exercise in Depression and Anxiety

Many studies show the beneficial impact that exercise has on mood, stress, anxiety, and sadness to treat depression and anxiety.[48–50] Several neurological pathways are involved with these effects, including increased grey and white matter volume, neurogenesis changes in the hippocampus, heightened production of vascular endothelial growth factor, and the formation of new synapses between neurons.[51–53]

92.8.4.3 Tobacco Use and Psychiatric Disorders

Tobacco use is associated with increased risk for psychiatric disorders, namely depression and anxiety.[54,55] Supporting this association, a recently published meta-analysis showed that smoking tobacco significantly increased the risk of depression.[56]

92.9 CONCLUSION

Lifestyle medicine can be influential toward the treatment and prevention of burnout by informing healthcare professionals about intervention measures. Significant literature validates that healthy lifestyles effectively improve health and lower the risk for chronic disease; thus, they should be optimized when addressing burnout. Lifestyle medicine encourages physicians to find a sense of purpose and joy in their work. Working without satisfaction and meaning may misalign providers' values and the healthcare system. Helping patients improve their lifestyles to be healthier and decrease the symptoms of chronic disease within their everyday lives will professionally gratify the physician. Applying lifestyle medicine practices can help reduce the ever-present and significant challenge of physician burnout.

CLINICAL APPLICATIONS

- Applying lifestyle medicine interventions is crucial for minimizing the risk of burnout and promoting healthy lifestyles in lifestyle medicine practitioners.
- Lifestyle medicine clinicians ought to take an active role in medical education to help future generations of medical professionals be more prepared to address self-care and wellness through prevention.
- Physicians can attend to their own self-care by embracing the six pillars of lifestyle medicine, thereby modeling healthy behaviors for others in the healthcare system.

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93 Lifestyle Medicine Research

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KEY POINTS

- Lifestyle-based medical treatment is founded on well-established areas of research on health behaviors, including diet, physical activity, sleep, stress management, social connection, and avoidance of risky substances such as drugs and alcohol.
- Original research on how to operationalize lifestyle medicine (LM) in practice is growing, but many gaps remain.
- Guideline development is the ultimate goal of translating evidence into practice.
- More research is needed at all levels in the hierarchy of evidence to advance the field of LM and create an adequate research base for guideline development.
- Clinicians can maximize their contributions by collaborating with academic researchers on larger-scale/more rigorous projects.
- Clinicians whose capacity for research is limited to what can be embedded in existing clinical care may wish to publish case reports, retrospective chart reviews, or results from existing structured programs.

93.1 CURRENT STATE OF LIFESTYLE MEDICINE RESEARCH

The importance of health behaviors in the areas of nutrition, physical activity, sleep, stress management, social connection, and avoidance of risky substances such as drugs and alcohol are well established, with an evidence base comprised of thousands of original works of research. All of these individual domains of health behavior have a multitude of prospective cohort studies and randomized controlled trials demonstrating the positive benefits of eating whole, plant foods, engaging in regular physical activity, maintaining good quality sleep, minimizing chronic stress, nurturing social relationships, and avoiding drugs and alcohol. The top risk factors for chronic disease have been identified as modifiable factors (smoking, high BMI, high blood glucose) influenced by lifestyle choices, such as found in the Global Burden of Disease Study,[1] as well as in large prospective cohort studies such as the Harvard Nurses' Health Study and Health Professionals Follow-up Study.[2] It is known that when individuals, on their own, practice healthier lifestyles, they have better health outcomes.

Due to this extensive foundation of evidence, existing clinical practice guidelines, such as those from the American Diabetes Association, American Heart Association, and American Cancer Society,[3–5] recommend lifestyle approaches as a foundational part of primary care and management of chronic conditions. However, even given this consistent theme in guidelines, the health improvements that are possible following lifestyle modification as medical treatment and the implementation of lifestyle medicine (LM) into standards of care are not yet well-explored. Much more peer-reviewed data is needed on lifestyle treatment as a form of medical care with the ability to treat and/or reverse disease. Subsequently, data is also needed on the factors that facilitate adherence to the prescribed lifestyle treatments in the short- and long-term, and on the capacity of lifestyle-based treatment to work well in the current fee-for-service model and emerging value-based models of healthcare reimbursement.

At the same time, research focused on LM has dramatically increased in peer-reviewed publications in recent years. A Medline/PubMed search for these keywords yields 878 results in total at the end of November 2022, with only 161 of these being reviews. When restricted to the title/abstract (narrowing to articles more centrally focused on lifestyle medicine), a total of 549 results remain, with only 124 being reviews. Additionally, there are also substantial numbers of publications on some of the specific aspects of LM practice that do not necessarily use the keywords "lifestyle medicine", such as physician activity prescriptions and shared medical appointments. Thus, the body of original work is growing and will continue to grow in the future as more professionals become aware of the remarkable results possible with lifestyle interventions, and as academic researchers see the potential of partnering with LM clinicians.

The purpose of this chapter is to provide LM clinicians with an orientation on research methods and strategies to encourage active participation in research.

93.2 WHY DO WE NEED RESEARCH? EVIDENCE LEADING TO IMPROVEMENTS IN CARE

Evidence-based medicine (EBM)[6] has refined our understanding of how to make medical decisions and has emphasized the need for trustworthy clinical practice guidelines based on current, best research evidence to improve the

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quality of care. Guideline development is the ultimate goal in translating evidence into practice, and guideline development in the field of LM is just beginning. Developing multidisciplinary guidelines offers the most meaningful opportunity to influence practice decisions, and while most existing guidelines for managing chronic disease mention lifestyle, very few, if any, provide clear and actionable recommendations to help clinicians operationalize a broad injunction to incorporate lifestyle into treatment. Guideline recommendations are optimally based on high-level evidence, such as randomized controlled trials (RCTs) or systematic reviews of such trials, but for many LM interventions for chronic disease, the evidence base is less robust. The field of LM needs more research to be conducted to demonstrate the effectiveness of lifestyle interventions for chronic disease, characterize best practices in LM treatment, and augment the evidence base for developing clinical practice guidelines,

To build a body of evidence, construct a theory, and demonstrate a causal relationship (e.g., showing that lifestyle treatment prompted improvements in health outcomes), a body of consistent evidence from a variety of practice settings is needed. To eventually justify resources being spent on large-scale, rigorous clinical trials, it is often necessary to first produce pilot data, mechanistic data, or survey research to demonstrate proof of concept. Contributing to this pool of observational data creates an opportunity for every LM clinician to get involved, which absolutely relies on the efforts of many to create forward motion and momentum in the research space.

Medical and epidemiological research is often evaluated using the hierarchy of evidence (Figure 93.1), a foundational framework in epidemiology that places lower-cost, easier, and less rigorous research at the bottom and moves up to higher-cost, more complex, and more rigorous research at the top. Evidence making the strongest case for causality is placed at the top. Different variations, including similar diagrams, of the hierarchy of evidence exist and are available online. In a similar vein, a variety of organizations have defined their own "levels" of evidence,[7] such as the Centre for Evidence-Based Medicine[8] or the GRADE Working Group.[9] These evaluations are used in conducting systematic reviews and then sometimes in using the evidence in an evidence to decision-making process to write guidelines.[10] However, all place weaker study designs that are primarily hypothesis-generating at the bottom and strongest designs supporting causality at the top.

Typically, systematic reviews and meta-analyses, which combine and synthesize the results of multiple studies on the same exposures and outcomes, are considered the strongest form of evidence because they provide support for the consistency and repeatability of results (discussed below). It is possible to conduct a systematic review on any type of study, but those that synthesize the results of randomized controlled trials are considered the strongest evidence, followed by those on prospective cohort studies.

While there are several challenges specifically associated with implementing a randomized controlled trial design in lifestyle and behavioral research, with the top challenge being that is difficult if not impossible to randomize individuals to a health behavior and expect them to remain adherent for years following that randomization,[11] that does not mean the goal of RCTs should be abandoned. Many intermediate and short-term outcomes can be examined in an RCT context, and blinding of subjects to their group, though typical in pharmaceutical research, is not necessary. While prospective cohort studies are well-suited to capturing hard endpoints (mortality rates) and outcomes over the lifespan, lifestyle interventions can perform well in an RCT context, and it is important to utilize this highly important form of study design.

In regard to advancing the field of lifestyle medicine research, *conducting research at any level* (depicted in Figure 93.1) *has the potential to make a valuable*

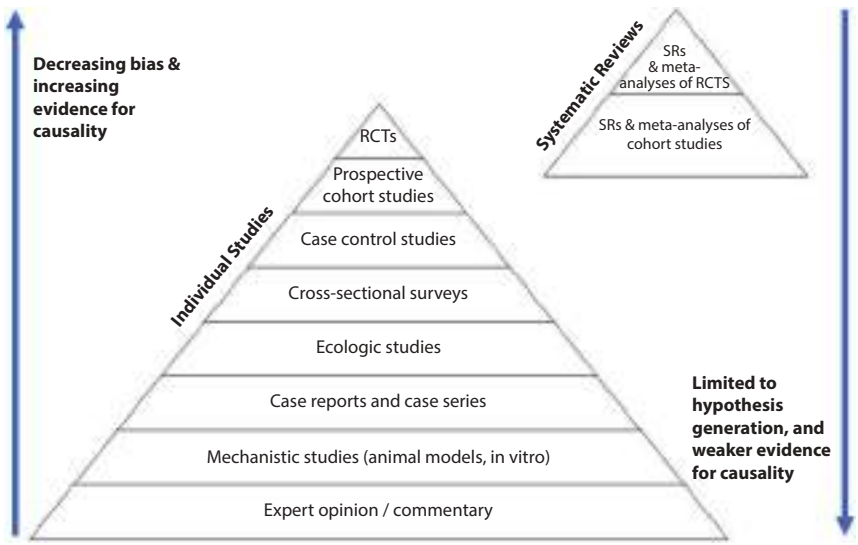


FIGURE 93.1 The hierarchy of evidence. RCT, randomized controlled trial; SR, systematic review.

contribution. Biochemical researchers engaged in mechanistic studies using animal models may wish to consider asking questions relevant to lifestyle medicine practice. Epidemiologists can consider administering cross-sectional surveys to LM practitioners and patients. Clinicians who observe improvements in patients following lifestyle treatment may wish to publish case reports on their results. All stages of research can contribute to the eventual justification of a randomized controlled trial (RCT) on a specific question. The cost of an RCT is high due to the logistics, number of team members needed, data collection and biometric assessments, and follow-up required to run a successful trial. However, the more lower-level evidence that exists, the stronger the justification for funding a larger, rigorous study such as an RCT.

The reason for categorizing evidence in this way is to describe the *relative contributions* made by different types of evidence toward building a case for a causal relationship between the exposure or intervention of interest and the outcome of interest. In public health and epidemiology, the case for a causal relationship is evaluated by considering the breadth of the evidence, and one common conceptual model used is the Bradford Hill Criteria. This set of criteria was first introduced by Sir August Bradford Hill in 1965[12] to create a basis for decision-making in occupational medicine when identifying causes of disease. Though various updates have been proposed[13, 14] for better application to modern epidemiology and medical science, overall, this framework continues to serve as a useful organizational principle for building a theory and identifying gaps in the literature. The original nine criteria are presented in Table 93.1.

To address all of the points in Bradford Hill's list takes more than one or even several studies; thus, growing the body of evidence with a variety of study designs is critical. Table 93.2 presents a summary of study designs, strengths, and limitations. Clinicians interested in participating in LM research can consider which of these are possible, given resources, organizational support, time/bandwidth, and funding.

The selection of a particular design depends on the research question and gaps being filled, the previous evidence in existence, and the resources available to execute a study. In addition to the characteristics of the study design itself, other aspects of the study design affect rigor and feasibility. For example, a prospective study, in which data collection is conducted before the outcome is observed, provides stronger evidence of causality than a retrospective study, in which data collection happens after the outcome has been identified. Cohort studies, case-control studies, and case series may be either prospective or retrospective. Often, a retrospective patient chart review might be less expensive and easier to execute than a prospective case-control or cohort study.

Finally, an experimental design will produce stronger evidence for causality than an observational design because without manipulating the exposures or intervention(s) of interest, it is more likely outside factors (confounders) could influence the outcomes in ways the analysis does not account for.

TABLE 93.1
Bradford Hill Criteria for Causality and Application in Lifestyle Medicine Research

Criterion	Example Applications in Lifestyle Medicine
Strength of the association (the effect size)	Is the effect observed statistically and clinically significant? Does HbA1c drop by a large margin or by a tiny amount with a particular diet or exercise program? With a particular medication?
Consistency (repeatability)	Is the effect repeated across different settings and by different researchers? Are different clinicians and researchers able to reproduce the same drop in HbA1c? A result that is found in one instance and never repeated provides limited evidence that the effect seen is real and not due to chance.
Specificity (result is limited to a particular population or setting)	Is the effect observed broadly or only under certain circumstances? Are all individuals with type 2 diabetes able to reduce their need for medications or is that limited to those who make specific lifestyle changes or undergo specific interventions?
Temporality (cause has to proceed the effect)	Does exposure or intervention lead to the outcome? This is the most important of all the criteria. If any evidence is produced demonstrating the opposite, it does not matter how much convincing data there is of other kinds. Does weight loss happen before dietary habits are changed? If not, then the dietary changes did not cause the weight loss.
Biological gradient (dose-response relationship)	When the dosing of LM treatment goes up, does the effect size also increase? Do patients with type 2 diabetes make greater gains in blood glucose control with larger changes in diet as opposed to more modest changes?
Plausibility (biological mechanism)	Though outcomes in humans may be visible, is there an understanding of why they are happening? What is the biological mechanism that leads to insulin resistance, or reversal of insulin resistance?
Coherence (alignment with existing evidence)	Are the effects observed consistent with other relevant evidence in the field? Is a dietary intervention used to treat type 2 diabetes similar to the kind of diet eaten by populations with very low rates of type 2 diabetes?
Experiment (reducing the exposure reduces the effect)	Can an experiment be conducted to demonstrate a change in the outcome after changing the exposure? When the dosing of LM treatment is reduced, do the same strong effects remain?
Analogy (similarity with other cause-and-effect relationships)	Is there another exposure/intervention that is similar and might produce a similar outcome? Is the blood-cholesterol-lowering effect of eating legumes more similar to the effect of eating vegetables than red meat?

TABLE 93.2
Research Designs Used in Public Health and Medical Research

Design and Definition	Strengths and Best Uses	Limitations
Systematic review Summary of current literature on a particular research question or topic, using predefined inclusion criteria but also following a specific protocol accepted for systematic reviews that involves multiple reviews and a strict inclusion process.	Best used to summarize the weight of the evidence on a particular topic. Most guideline development methods begin with a systematic literature search and screening process that follows systematic review (SR) methodology. All meta-analyses begin with a SR. Because the research question and inclusion/exclusion criteria are defined *a priori*, the risk of bias is minimized. SRs are distinct from narrative reviews, which may introduce the bias of the author around the topic.	Systematic reviews ideally require a team leader with experience in methodology, the participation of a research librarian to assist in searching multiple databases, and multiple team members to properly screen literature, extract data, and help synthesize results. Best practice is to use a team approach.
Meta-analysis Researchers gather data from multiple studies that meet predefined inclusion criteria and analyze data as one dataset	A quantitative synthesis of multiple studies in the field that examined the same exposure and outcome, among similar sample populations. Data from individual studies are pooled and analyzed as one. All meta-analyses begin with a systematic review.	The validity of the results of a meta-analysis depends on how similar the sample populations were to one another, as well as how similarly the exposure and outcome variables were measured. Best practice is to use a team approach.
Randomized controlled trial (RCT) Intervention study with two or more groups, in which individuals or subgroups are randomized to receive either an intervention or a control treatment.	RCTs are typically considered the "gold standard" of research and provide the strongest evidence of causality. Parallel designs are a good choice when there is adequate funding to recruit enough subjects to achieve the desired statistical power. Crossover designs allow investigators to use a smaller number of subjects and test whether the results hold up after exposure to a different experience. Addresses the question of temporality (causes precedes effect), a requirement for causality.	Can be expensive; difficult to randomize lifestyle behaviors over the long term, and results may not apply to long-term outcomes or may have limited external validity. Best practice is to use a team approach.
Intervention trial (single arm) Intervention study with only one group—all subjects receive the intervention.	Can be more affordable and feasible to execute. In clinical settings, a small cohort of patients going through an LM program presents a good opportunity to analyze their results as a single-arm trial and might be something that can be worked into existing workflows with less disruption as compared with planning an RCT.	Because it lacks a control or comparison group, there is less support for specificity, and the case for causality is weaker. Most likely requires a team.
Cohort Compares disease outcomes in more than one group of subjects with different exposures.	Comparing groups of subjects is ideal for being able to generalize results; observational cohort studies allow the study of long-term outcomes. Large sample sizes provide greater statistical power. Cohort studies are a more affordable way to study large groups of people over the long term than RCTs.	Can be expensive to recruit; loss to follow-up may attenuate results. External confounding may be present.
Case-control Compares exposure outcomes between cases (those who have the disease) and controls (non-diseased who were selected to be matched to cases).	Less expensive than cohort studies, no loss to follow-up. Odds ratios can be calculated from case-control studies. Correct application is when the outcome is rare—in these instances, the calculated odds ratio will approximate the risk ratio.	Not typically used when the disease is not rare—in these instances, the odds ratio will overestimate the risk ratio.
Cross-sectional survey A survey that measures a snapshot in time—could be prevalence of disease, death rates, or exposure proportions	Inexpensive compared to RCTs or cohort studies, excellent for generating hypotheses and getting confirming data. Online survey methodology is now a developed field, making it possible to reach disparate geographic or demographic groups in a single study.	Cannot address the question of temporality (cause precedes effect), a requirement for causality.
Ecologic study Assesses correlations between conditions and outcomes in a geographic area—for instance, the correlations between death rates for heart disease by country and average consumption of total dietary fat by country.	Useful for exploratory research to generate hypotheses about possible causal factors for disease, may lead to observational cohort studies and RCTs. It is possible to examine a broad hypothesis and compare patterns across countries, often with publicly available datasets, such as disease burden or consumption patterns.	Ecologic fallacy is attributing the disease outcomes (death from CHD) to the individuals who have the highest rates of fat consumption, when these may, in fact, not be the same individuals
Case reports/series A descriptive study illustrating novel or unusual features of a patient or medical practice.	Case series focus on a number of patients or conditions and how they are related, often describing a similar trajectory through disease and/or treatment. Case reports and series, while lower in the hierarchy of scientific evidence, are valuable as an important mode of communication to make others in the field aware of unusual presentations, complications, or treatments	Case reports and case series are hypothesis-generating and may contribute to the overall coherence of evidence on a topic but, by themselves, do not present strong evidence for causality.
Mechanistic studies Examines precise biological mechanisms in a given cause-and-effect relationship.	Includes in vitro studies and animal models. In vitro studies allow the study of specific mechanisms, are less expensive than studying humans or animals, and pose fewer ethical concerns. Animal experiments allow for the investigation of processes that are common to all or many organisms. Allows measurement and experimentation over the entire life cycle; can ask questions that will not be asked in a human population	Results of in vitro and animal studies may not be generalizable to humans. Further, animal studies may raise ethical issues.

93.3 CONTRIBUTING TO LIFESTYLE MEDICINE RESEARCH FOR CLINICIANS

LM clinicians are uniquely poised to conduct certain levels of scientific research independently, as well as partner with academic/university researchers. There are many advantages to partnering with academic researchers, with some top benefits including the expertise in study planning, data collection, statistical analysis, and scientific writing that most rigorous studies require. Additionally, the work of conducting a study, especially a larger or more rigorous one such as an RCT, will require *substantial bandwidth for extra work beyond what is already required as part of clinical care*. Study recruitment, administration, tracking, data collection, and follow-up with subjects all take time and resources. Finally, there are certain universal requirements for engaging in human subject research that an experienced partner with access to institutional resources can provide, or facilitate access on behalf of the project, such as CITI training and institutional review board (IRB) review of the study protocol, discussed below. Although larger clinical institutions may have access to an IRB, the process would still require significant time on the part of the investigator to prepare materials for IRB submission.

If funding, through either an academic or clinical appointment, supports the effort to conduct research, then it is likely that research is already part of the job/role expectations. If a clinician's role is entirely clinical, the opportunity to engage in research independently is more limited, and the potential for impact can best be maximized by collaborating with an outside group. For many clinicians, the best way to contribute to this effort is to collaborate with academic researchers who have greater capacities in terms of their team members, library support system, facilities, and expertise in scientific methods and writing. For others, who may have more bandwidth, experience, or team resources, there are several ways to get involved directly.

Academic or university researchers have several challenges that would make it appealing to partner with LM clinicians. They often may not have access to a clinical setting in which to deliver medical interventions. Recruitment of subjects is often challenging. Research scientists, while aware of specific requests for funding proposals, may lack an appropriate clinical match to respond to the announcement. They may not be qualified to conduct biometric testing on human subjects or have access to medical facilities to do so. Also of note is the fact that many funding sources are focusing on supporting interdisciplinary, collaborative research; thus, partnering may be appealing.

Clinicians may wish to browse the faculty pages of public health, nutrition, medicine, exercise physiology, and other relevant programs within local universities to find researchers whose interests and experience may be a good fit for LM. A simple email introduction and request to meet may be enough to spark a future collaboration—though it may require multiple conversations and potentially some waiting for the right funding source for an opportunity to take off.

What follows is a discussion of key elements of research involvement, which should provide orientation for some of the nuts and bolts required in conducting research, whether an individual is in a leadership role or simply writing a case report on one patient.

93.4 LITERATURE SEARCH AND REVIEW

No matter how novel or interesting a research question may seem, that novelty needs to be communicated to the larger scientific and medical community. The following questions should be answered when planning a study to justify the project and provide context:

1. What is known and not known about the relevant disease and/or lifestyle intervention—what are the gaps in the knowledge base?
2. What are some proposed mechanisms for the clinical outcomes observed?
3. Why is the study important, and what can other scientists and clinicians learn from this work?

The goal of a literature search is to identify work in the field that is relevant to the research question. In any publication, the discussion of topics such as what is known/not known and proposed mechanisms should be supported by published references, and a literature review is a key tool for identifying appropriate references.

A systematic literature search is conducted using databases such as PubMed and Medline, which are commonly used for health and medicine topics. However, many other databases exist, such as Embase, Cochrane Library, CINAHL, and PsycINFO, and may be appropriate to include depending on the topic. While a comprehensive tutorial on literature searches is out of the scope of this chapter, a brief overview is provided in Figure 93.2. There are many published resources available[15] as well as training materials[16] on how to effectively conduct a literature search.

The nature of novel topics is such that there may not be a good deal of relevant information *directly* related to the



FIGURE 93.2 Workflow of a literature search.

research question, but the literature search finds what is relevant and what provides appropriate background to define gaps in knowledge. For example, if the intended publication is a case report on the use of a whole food, plant-based (WFPB) diet to reverse symptoms of rheumatoid arthritis (RA) in a patient, there may not be literature directly on WFPB diets and reversal of RA. What may exist is literature on diet and autoimmune disease, or on plant-based diets reducing inflammatory biomarkers. Such literature may help to generate a hypothesis about a potential mechanism by which a WFPB could improve symptoms of RA, thus framing the case report presented.

93.5 WORKING WITH AN IRB

The goal of an IRB is to minimize risks for research study participants. IRBs are tasked with ensuring that any risks to human study subjects are appropriate. IRB review applies to research on human subjects. Per the 2018 common rule,[17] *research* is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge", and *human subject* is defined as

> a living individual about whom an investigator (whether professional or student) conducting research: (1) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (2) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Risks to human subjects can include physical risks, psychological risks, social/economic risks, legal risks, and loss of confidentiality with respect to data and identifiable information collected in research. The 1979 Belmont Report[18] released by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research outlines ethical principles and guidelines for the protection of human subjects in research. IRB review committees are guided by these principles in their role of protecting the rights and welfare of research subjects.

While human subjects research that is supported, conducted, or regulated by US federal departments *requires* IRB review, most organizations extend requirements to require IRB review for all human subjects research. In addition, it is important to note that even if an investigator is not affiliated with an organization that requires IRB review, most peer-reviewed journals will require IRB review in order for work to eventually be published.

Many health or hospital systems have their own internal IRBs, making it possible for employees to utilize their services directly. For clinicians in private practice, or in systems without such resources, partnering with an academic researcher or other collaborator with access to an IRB will eliminate this problem. An additional solution is to use a commercially available IRB, or "IRB for hire". One consideration with respect to IRBs for hire is that they are typically fee-based per service request and will charge for each change or amendment submitted, as well as any requested re-review of a protocol. Such costs should be factored into a study budget.

The first step when considering any research involving human subjects is identifying which IRB will receive the submission of the study protocol. Most IRBs have guidance and forms electronically available, so it is recommended to access the IRB's resources to determine what type of review the study will be eligible for and determine what components are needed for the submission. IRB staff are generally highly knowledgeable and available to answer questions. While it is recommended to first read forms and guidance published on the website, investigators may contact the IRB for questions and/or clarifications.

Allow adequate time for IRB review. It is not uncommon for a study undergoing a full review to take weeks or months depending on resources and personnel. It is suggested that one reach out to your IRB to inquire about timelines, particularly if the request for review is time-sensitive. In addition, it is not uncommon for IRB reviewers to ask for additional information and/or revisions to a submitted protocol. This process can add additional time, and all queries/comments from the IRB need to be addressed before a review can be finalized.

Finally, the research team should be involved in any IRB submissions. While the principal investigator will likely lead the development of the protocol, other team members such as project managers/coordinators, research assistants, and statisticians can assist with tasks such as completing forms and developing material which may include data collection tools and recruitment strategies and materials, all of which must be submitted for the IRB to review.

It is important to note that some journals do not require IRB approval to publish case reports, as long as the case has provided consent to have his or her data published.

93.6 SELECTING ASSESSMENT TOOLS AND MEASURES

In writing a research protocol, one key component will be the selection of assessments.

The selection of surveys, biometric assays, anthropometric assessments, or other measures will be influenced by the research question, previous work in the field, and feasibility. The goal is to minimize bias (error) while enabling the data collection necessary to answer the research questions.

Objective measures, such as biomarkers, health metrics, and anthropometric measurements performed by a researcher provide data subject to minimal bias. What inaccuracy may exist can be due to data collection errors or instrument variability.

Subjective and self-reported measures, such as survey data or self-reported height and weight, are also important and often more feasible to collect but may be at risk of greater reporting bias. For example, it has commonly been observed that individuals over-report height and

under-report weight.[19] When the research goal is to understand patient experience, survey data or in-depth interviews will be the best assessment to use. BMI calculated from self-reported height and weight on a survey is a common data point used in epidemiological research, even though it is known to be subject to reporting bias.

In nutrition research, for instance, the use of biomarker data paired with survey data can greatly enhance what can be gathered from surveys alone.[20] For example, a dietary assessment survey might be verified with specific biomarkers relevant to the dietary intake of interest, such as using urinalysis to measure urinary amino acid excretion as a measure of protein consumption and comparing that to what was reported on a 24-hour diet recall or food diary.[21]

In the field of LM, biometric data characterizing disease status and risk for disease is of primary importance, such as blood pressure, blood lipids, blood glucose, and BMI. The American College of Lifestyle Medicine has established a recommended set of performance measures (both biometric and surveys) to assess the effectiveness of LM treatment of chronic disease (for more information, visit http://lifestylemedicine.org/measures). Broad and consistent use of these measures will elevate the quality of reporting on LM treatment.

The validity of the selected assessment is an important consideration. *Validity* in research refers more broadly to whether the results of a research study represent the truth in the reference population. *Internal validity* means the extent to which results represent the truth in the study sample, and *external validity* means the extent to which results represent truth in the larger, real-world population.[22] Similarly, the validity of assessment tools refers to the accuracy of the tool in a given set of conditions—Does it measure what it is intended to measure? How well does it capture a true measure of behavior?[23] Repeatability refers to whether the results will be found consistently, from administration to administration, and is a component of validity. Specific types of validity of assessments are presented in Table 93.3.

93.7 CITI TRAINING

In 2000, NIH required human subjects training for personnel involved in NIH grants or contracts involving human subjects research, and the Collaborative IRB Training Initiative (CITI) was born. CITI provides web-based training in human subject research, with over 2500 organizations subscribing, including academic institutions as well as clinical health networks.[24] Learners who are not members of a subscribing institution are able to purchase CITI training for a fee.

The program began with training focused on biomedical research but has since expanded to include a variety of courses including research training for social, behavioral, and education researchers, training on good clinical practice, and training on animal care and biosafety and biosecurity. The trainings contain varying numbers of modules with short quizzes at the end.

In order to submit a protocol to an IRB, all members of the research team will need to have completed the CITI training required by the associated institution. Please visit https://about.citiprogram.org/ to learn more. CITI training does expire, as defined by the institution, typically every three to four years. Individuals are required to complete "refresher" courses to keep training up-to-date.

93.8 EXECUTION OF THE STUDY

Running a research study may require a study coordinator (highlighting the importance of having enough team members) to handle logistics, communications with subjects, and data collection. As the project progresses, it is very important to carefully follow the protocol approved by the IRB and to notify them if any changes are proposed, *before* those changes are made. When changes to a protocol are necessary, typically an amendment will be submitted to the IRB that presents the change to the protocol in detail. The IRB has the opportunity to review this and either accept or reject the proposed amendment.

93.9 PUBLICATION OF RESULTS

There are many resources online for best practices in scientific writing. General principles to keep in mind are to make statements that are direct and concise and avoid unnecessary verbiage. When writing up results and preparing a

TABLE 93.3
Major Types of Validity in Health Research Assessments

Content validity	The extent to which an assessment comprehensively measures what it is designed to measure, while also avoiding measuring things ancillary to the goals of assessment.
Face validity	The extent to which an assessment appears, "at face value" to measure what it is designed to measure. While this is the weakest form of validity because it relies on human intuition, which can be wrong, it is consistent with simply asking direct questions to address research questions. That application is best suited for survey questions on the subjective or perceived experiences of respondents.
Construct validity	The extent to which an assessment measures an identified set of behaviors or variables associated in a meaningful way to create a construct or idea, such as depression, well-being, burnout, or the consumption of a specific dietary pattern.
Criterion validity	The extent to which an assessment, often a survey, correlates with a known gold standard measure.

manuscript, reference managers are essential and allow writers to store and organize references, automatically insert and format citations in appropriate styles for a particular journal, and avoid formatting errors. Common reference managers include Endnote, RefWorks, Zotero (free), and Mendeley (free).

Different journals have very different scopes and submission guidelines. Be sure to carefully check author instructions for the journal to which the submission is planned. Often, submissions that do not follow journal instructions will be quickly returned without review. In selecting a target journal, it is important to read about the journal's scope, as well as review similar published research in that journal, to determine whether the topic is a good fit. This can be particularly relevant to lifestyle medicine. While it is valuable to share lifestyle medicine research with the broader medical community, do not be discouraged if your first, second, or even third submission to a journal is not accepted—keep trying! Journals often reject articles, not because of poor quality but because the topic does not fit within their desired scope.

Either at the time of submission or upon acceptance, an author may be asked to decide whether to publish the paper with *open access*. Open access means that anyone who comes across the paper (in an online search, for example) will have the ability to access the full text, regardless of whether they subscribe to the journal. If the article is not open access, non-subscribers to the journal will need to pay a fee to the journal to purchase the article. Open access fees can be several thousand dollars, but if a viable option, can help broaden the readership of a paper. While many large academic and/or clinical institutions provide library access with subscriptions to journals, individuals without institutional access may be limited in their ability to read papers that are not open access.

93.10 RESEARCH EMBEDDED IN CLINICAL CARE

The opportunity to participate in larger-scale research projects, with the benefit of a team or significant time to devote to a project is not possible for all clinicians. For those who wish to contribute research to the field of LM but face logistical constraints, several options exist that may make it possible to publish outcomes with limited additional resources.

Conducting a retrospective chart review of patient records may be a viable option for describing results from an LM practice or program. Such results could be organized as a retrospective, case-control study, for example, selecting cases of type 2 diabetes remission and matched controls to compare their behaviors prior to the outcome of remission. It could also be organized as a case series, simply describing themes and repeating characteristics of patients with similar outcomes.

If a practice or health system offers structured LM programs, with a clear date of entry, curriculum or repeating sequence of education and content, and a regular/pre-post assessment schedule, it may be possible to frame one or more cohorts in this program as a single-arm clinical trial and conduct a pre-post analysis of outcomes.

Both retrospective chart reviews of many (>3) patients and single-arm intervention trials overlayed on existing programming would be considered human subjects research, and therefore would require IRB approval and likely involvement from other team members besides the primary clinician, even if they are able to be merged into existing clinical care.

Publishing case reports or case series, discussed below, is one of the most feasible points of entry into research for clinicians. As mentioned previously, single case reports, and often case series of only a few patients are usually not required to have IRB approval by peer-reviewed journals as long as patient permission was obtained prior to submission to the journal. Some journals provide their own template consent forms, or, if not supplied by the journal, clinicians may use their own. These consent forms are typically not submitted to the journal but are required to be stored in a secure location with the patient's records.

93.10.1 Case Reports/Case Series

A case report is a descriptive study illustrating novel or unusual features of a patient or medical practice. *Case reports* are narratives describing a patient's trajectory through a disease diagnosis and/or treatment. *Case series* focus on a number of patients or conditions and how they are related, often describing a similar trajectory through disease and/or treatment.[25] Case reports and series, while lower in the hierarchy of scientific evidence, are valuable as an important mode of communication to make others in the field aware of unusual presentations, complications, or treatments.[26] Remember, while RCTs are the "gold standard" of scientific evidence, research questions often do not begin at RCTs. Instead, research often begins with the observation of something novel or interesting on a small scale that could be documented in a case report, allowing for the generation of research questions and future exploratory research.

Importantly, publishing case reports or case series is a very accessible pathway for clinicians who wish to contribute to the body of original research on lifestyle medicine, as they can be conducted without the support structure of a research team, grant funding, or a research institution. As stated, the field of LM needs more evidence at all levels in the hierarchy of evidence.

Since the goal of a case report/series is to inform the scientific community about something novel that has not yet been well documented in the literature, lifestyle medicine cases, which are often outliers in conventional medicine, make excellent case reports! Some examples of outliers include cases that (1) exhibit a previously unknown disease; (2) suggest a previously underreported association of two distinct diseases; (3) exhibit features of disease that widely differ from what is usually observed; (4) show success using

a previously unrecognized treatment or intervention, such as a lifestyle medicine approach.

93.10.2 Case Report Manuscript Guidelines

Not all journals accept case reports! Be sure to check before tailoring a manuscript to a specific journal.

The target journal chosen will have specific guidelines for formatting and manuscript structure, so remember to check the requirements. As previously discussed, most journals will require patient consent for case reports/series. Some journals will provide authors with a specific consent form to use for that journal. Before putting significant time into a case report, it is important to inform the patient of the desire to write a case report, obtain their consent to be included, and answer any questions. It should be made clear that no identifying information will be included in a published report. If including photos to highlight the case presentation, it should be discussed with the patient and appropriate consent obtained.

An additional resource is CARE (CAse REports), a set of guidelines that provides a checklist for complete reporting of case reports.[27] Certain journals require submission of the CARE guidelines to them when submitting a case report, showing that all items on the CARE checklist have been addressed. CARE is a useful resource to help guide the process of collecting data and writing a case report (http://www.care-statement.org/).

Table 93.4 presents the key components of a successfully written case report.

93.10.3 Research Abstracts

Another way to share information with both the scientific and clinical communities is by submitting a research abstract to a professional conference. If accepted, there is typically an invitation to present a research poster or, in limited cases, an oral presentation at the conference. Presenting at conferences is an effective way to not only share work but also engage with other conference attendees, ranging from those who may share similar experiences to those who may be learning about the work for the first time. Abstracts can come in the form of presenting case reports or case series; however, another option is if one is a member

TABLE 93.4
Components of a Case Report or Case Series Manuscript

Title	• Descriptive and clear, should end with "… a case report" or "… a case series"
Abstract	• Concise summary of the case report, usually about 250–350 words or half page • Contains key information such as a few brief sentences on background and significance, summary of the case presentation, and conclusions (what is the take-home message) • *A reader's first look into the paper—the more exciting findings and the relative impact are highlighted, the more likely someone is to read the work!* • *Not* simply an excerpt from the manuscript • Draft abstract last—it is easier to summarize the case report and highlight important findings in the abstract after the report is written!
Background	• Should address why the case is notable and why it is being reported • May also include a brief background on the disease or treatment • Put the case into the larger context of what is already known and/or published (refer to the previous section "Literature Search and Review") • Typically ends with one to two lines summarizing the objective or aim of the case report/series
Case presentation—tell the story!	• This is where the details of the case are documented—keep them relevant! • Document chronologically and include specific dates whenever possible. Remember, you are telling a detailed story. • Interview the patient(s) to fill in gaps in the story and include their perspective • Consider all the following and include as relevant: disease presentation or diagnosis; intervention or treatment; lifestyle and behaviors (sleep, diet, physical activity, substance use, stress, social connectedness); medication use; recovery, including clinical symptoms and patient experience before and after lifestyle intervention; relevant medical history of patient; pre- and post- intervention laboratory results; practitioner decision-making • If documenting a lifestyle intervention or change, provide details such that someone reading the case report could replicate the intervention/change • Multiple pieces of information add richness to a case report

Discussion/ Conclusion	• Place the case into a larger content
	  • What was learned?
	  • Clinical impact?
	  • Future implications?
	  • Potential mechanisms by which lifestyle change produced the observed outcomes
	• Can include strengths/weaknesses of the report
	• Discussion of implications can include public health, clinical, scientific, and/or economic implications, to name a few

of a research team with access to a variety of data, a single component of a project or dataset can be identified as the focus for the research abstract.

The American College of Lifestyle Medicine welcomes abstract submissions to their annual conference (https://lmconference.org/), and accepted abstracts are additionally published in a special issue of the *American Journal of Lifestyle Medicine* following the conference. ACLM abstract submission topics are broad in scope and include topics such as "Science of Lifestyle Medicine", "How of Lifestyle Medicine", and "Business of Lifestyle Medicine". Other professional and academic societies similarly host conferences and sometimes publish accepted abstracts. While these conferences may not be LM-focused, they provide a unique opportunity to introduce LM concepts into more mainstream medical practice. Before embarking on a project that will result in a research abstract, it is recommended to check with the approving IRB to determine whether a review is needed. Finally, care should be taken to meet the commonly early abstract submission deadlines, as they are typically at least three to six months before the actual conference will take place.

93.11 CONCLUSIONS

Lifestyle medicine research is growing, but substantial gaps exist related to the application of what is known about health behaviors in the context of medical practice. Lifestyle medicine clinicians are poised to make meaningful contributions to the field of research, supporting the development of a sufficient evidence base from which to write clinical practice guidelines. Clinicians should feel encouraged to engage with the research process to any extent possible, which may mean participating in large projects and collaborating with academic researchers or publishing results from clinical practice on a more limited basis, such as with patient chart reviews or case reports.

CLINICAL APPLICATIONS

- Guideline development is the ultimate goal of translating evidence into practice.
- Standards and quality in clinical care are most influenced by guidelines.
- Guideline development requires sufficient evidence on a given topic.
- It is critical for as many LM clinicians as possible to participate in the collective work of generating evidence on LM practice.

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94 Lifestyle Medicine around the World
The WHO Initiative to Combat Non-Communicable Diseases (NCDs)

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KEY POINTS

- The WHO has listed non-communicable diseases (NCDs) as the leading global cause of death resulting in over 71% of all deaths worldwide.
- Risk factors focused on by the WHO include tobacco, insufficient physical activity, harmful use of alcohol, and an unhealthy diet.
- Additional factors include hypertension, overweight and obesity, and dyslipidemia.
- The adverse health implications and economic burden of NCDs are enormous.
- Lifestyle medicine modalities such as increased physical activity, proper nutrition, smoking cessation, healthy sleep, and weight management offer valuable, cost-effective tools to help lower the risk of NCDs around the world.

94.1 INTRODUCTION

There is no longer any serious question that daily habits and actions profoundly impact the likelihood of developing chronic disease. This issue is prominent around the world both in high-income countries (HICs) and low- and middle-income countries (LMICs). The understanding that lifestyle habits impact health has led to a major focus from the World Health Organization (WHO) on lowering the risk of and combating non-communicable diseases (NCDs).[1]

There is a significant role for lifestyle medicine concepts and practices in collaboration with the WHO initiative to combat NCDs around the world. The modalities utilized in lifestyle medicine such as increased physical activity, proper nutrition, weight management, avoiding cigarettes, and decreasing anxiety and stress are all profoundly important to countries around the world.[2–4]

The impact of these concepts has been seen around the world with an increasing number of lifestyle medicine organizations being formed and joining the Lifestyle Medicine Global Alliance. Lifestyle medicine modalities carry virtually no adverse consequences and are highly cost-effective. This makes these modalities highly attractive to countries, irrespective of economic situations within the country.

94.2 EPIDEMIOLOGIC TRANSITIONS

It has been argued that public health transitions through various epidemiologic phases.[5,6] This theory holds that previous epidemiologic transitions have included four basic stages:

- Pestilence and famine
- Receding pandemics
- Degenerative and man-made diseases
- Delayed degenerative diseases

During the stage of "pestilence and famine", infectious disease epidemics and hunger were the most common causes of death in virtually every part of the world. The majority of deaths were caused by such infectious diseases as tuberculosis or plague, various forms of pneumonia, and diarrheal diseases. In addition, high incident child mortality rates resulted in a mean life expectancy of approximately 30 years.

During the next epidemiologic period, the "receding of pandemics" was stimulated by public health advances such as improved food production and distribution as well as sanitary conditions such as cleaner water supplies that reduced deaths both from infectious disease and malnutrition. Heart disease became more prominent as a cause of death, with 10–35% of deaths.

The third epidemiologic stage, called "degenerative and man-made diseases", resulted from continued improvements in economic circumstances as well as changes in diet, activity levels, and behaviors such as smoking. Deaths from infectious diseases decreased dramatically and life expectancy increased to almost 70 years. On the other hand, atherosclerosis resulting from increased consumption of fiber-free calories and decreased physical activity became more prominent in this stage, with coronary heart disease (CHD) and stroke accounting for between 35% and 65% of all deaths.

The fourth epidemiologic stage is called "delayed degenerative diseases"[7,8] In this stage, cardiovascular disease (CVD) and cancer became the major causes of morbidity and mortality. The increases in these diseases have been somewhat mitigated by prevention measures, particularly

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in the area of CVD. Also, treatment modalities such as coronary care units and increased use of various technologies, including diagnostic and therapeutic technologies, have become increasingly utilized in lowering the risk of CVD mortality. In addition, various pharmacologic treatments for hypertension and dyslipidemia (e.g., statins) have also contributed to reducing CVD deaths. Moreover, public health campaigns have highlighted that certain behaviors increase the risk of CVD, and lifestyle modalities can reduce these risks. For example, cigarette smoking cessation represents a prominent model of success. In 1955, 57% of men smoked cigarettes, but by 2012, only 20% of men smoked and the prevalence of cigarette smoking among US women fell from 34% to 15.8%. Moreover, campaigns to reduce the prevalence of hypertension and elevated cholesterol also showed some success.

Unfortunately, it appears that we may now be entering a fifth epidemiologic stage, which has been characterized as the "age of inactivity and obesity".[9] Obesity has risen remarkably and rapidly around the world, and other NCDs associated with these such as type 2 diabetes (T2DM) and atherosclerosis have continued to be a problem with dramatic increases, particularly in the area of T2DM. It is in this fifth phase of epidemiologic transition that lifestyle modalities are destined to play critically important roles.

It should be noted that different countries and areas around the world may be in slightly different phases of these epidemiologic transitions, which is largely dependent on the economic situation in each country. Nonetheless, NCDs remain a problem, irrespective of the overall economics established for a given country. For example, between 1990 and 2013 deaths from CVD increased from 26% to 32% of all deaths globally with a particularly rapid increase in CVD deaths in LMICs.[10] The overall increase in CVD deaths reflects a dramatic increase in LMICs, while they are in a slight decline in HICs.

94.3 THE SCOPE OF THE PROBLEM OF NON-COMMUNICABLE DISEASES

Non-communicable diseases (NCDs) are the leading global cause of death, resulting in more deaths worldwide than all other causes combined.[11] These diseases are highly prevalent in every country around the world, irrespective of economic conditions. If these diseases could be somewhat ameliorated, millions of lives could be saved. This is the underlying rationale for why the World Health Organization has launched a major campaign to ameliorate NCDs. This started with the first Global Status Report on Non-Communicable Diseases in 2008, followed by the second report in 2013.[11] These reports intended to provide a baseline for countries around the globe to start to ameliorate NCDs and their risk factors.

Of the over 60 million global deaths that occurred in 2019, over 71%, according to the WHO, were due to NCDs.[1] These were principally from cardiovascular disease (CVD), T2DM, cancers, and chronic respiratory diseases. Nearly 80% of the NCD deaths occurred in LMICs. Over 80% of CVD and T2DM deaths occurred in LMICs as well as almost 90% of deaths from chronic obstructive pulmonary disease (COPD). Unfortunately, NCDs also kill at a younger age in LMICs, where 20% of NCDs occur in people under the age of 60, compared with 13% in HICs.

A large percentage of NCDs are preventable, according to the WHO, with the reduction of four main behavioral risk factors:

- Tobacco use
- Physical inactivity
- Harmful use of alcohol
- Unhealthy diet

These are the main focus of the WHO NCD initiative. Of course, these risk factors are also central to the field of lifestyle medicine. Many of the modalities of lifestyle medicine are highly appropriate and cost-effective in helping to combat these risk factors.

94.4 THE ROLE OF LIFESTYLE MEDICINE IN COMBATING NON-COMMUNICABLE DISEASES

As already indicated, the modalities of lifestyle medicine are critically important to lowering the identified risk factors for NCDs. With this in mind, numerous organizations specifically in lifestyle medicines have arisen around the world. They have joined forces in an organization called the Lifestyle Medicine Global Alliance (LMGA).[12] This organization emphasizes proper nutrition (plant-dominated diet), regular physical activity, restorative sleep, stress management, the avoidance of risky substances (e.g., cigarettes and alcohol), and positive social connections. While the issues of sleep and positive social connections are very important and constitute two of the pillars of lifestyle medicine, they are not the behavioral risk factors focused on by the WHO. Nonetheless, the LMGA has joined forces with the WHO in a combined effort to lower risk factors for NCDs.

Numerous medical organizations around the world have now focused more attention on the area of lifestyle medicine. For example, the American Heart Association changed the name of one of its professional councils from the "Council on Nutrition, Physical Activity and Metabolism" to the "Council on Lifestyle and Cardiometabolic Health".[13] Among the lifestyle medicine organizations, the most prominent is the American College of Lifestyle Medicine (ACLM) which has, of this writing, over 9000 members and has grown an astonishing 1200% in the last five years, making it the fastest-growing healthcare organization in the United States![14] Other prominent lifestyle medicine organizations include those in Australia and New Zealand (Australasian Society of Lifestyle Medicine)[15] and also in the UK with the British Society of Lifestyle Medicine[16].

Medical facilities are also increasingly embracing the role of lifestyle medicine. For example, the Fuwai Hospital in China, which is one of the largest cardiovascular diagnostic and treatment centers in China, has recently established the "China Lifestyle Medicine Alliance" and sponsored annual conferences on healthy lifestyle medicine. The initial conference attracted over 600,000 participants, indicating how widespread and deep the interest in lifestyle medicine is in China and around the world.[17]

94.5 MAIN BEHAVIORAL RISK FACTORS FOR NON-COMMUNICABLE DISEASES

As already indicated, the WHO has focused attention on four risk factors that play a particularly prominent role in the underlying metabolic and physiologic causes of the global NCD epidemic. These include tobacco, insufficient physical activity, harmful use of alcohol, and an unhealthy diet. In addition, the WHO has identified multiple other underlying risk factors for the epidemic of NCDs.

- Tobacco: Over six million people die from tobacco use each year. This includes both direct tobacco use and secondhand smoke.[18] It is anticipated that this will increase to over eight million people by 2030. Tobacco use accounts for 10% of all annual deaths including 71% of lung cancer, 42% of chronic obstructive pulmonary disease, and nearly 10% of cardiovascular disease. China has the largest number of smokers, and it has been estimated 301 million smokers in China in 2010. There is a greater than 50% prevalence in men, while Chinese women are much less likely to smoke (only about 2% of women smoke cigarettes). Secondhand smoke also contributes significantly to the risk of coronary heart disease. Since 2011, approximately 600,000 smokers died every year as a result of exposure to secondhand smoke. Smoking bans have had both immediate and long-term effects in reducing the likelihood of hospital admissions for various tobacco-related issues.
- Insufficient activity: The WHO estimates that approximately 3.2 million people die each year from physical inactivity.[19,20] People who are insufficiently physically active increase their risk of all-cause mortality by 20–30%. Regular physical activity has been shown in numerous studies to cut the risk of CVD in half and significantly ameliorate CVD risk factors including high blood pressure, diabetes, and weight gain and obesity. Insufficient physical activity is currently highest in HICs, but high levels are also increasingly being seen in LMICs.
- *Harmful use of alcohol*: Approximately 2.3 million deaths occur each year from harmful use of alcohol.[11] This amounts to approximately 3.9% of all deaths in the world and over half of these deaths are from NCDs including various cancers of the gastrointestinal tract, CVD, and liver cirrhosis. Per capita consumption of alcohol is highest in HICs, although it is also high in populous areas of LMICs.
- *Unhealthy diet*: It is well known that adequate consumption of fruits and vegetables reduces the risk of cardiovascular disease as well as some cancers such as stomach and colon. In addition, most populations consume more salt than recommended by the WHO for disease prevention.[21] High salt consumption is an important risk factor for high blood pressure and CVD risk. In addition, high consumption of saturated fats and trans fatty acids is also linked to heart disease. Unfortunately, unhealthy diet is quickly rising in LMICs. For example, the amount of fat in the Chinese diet increased from 25% to 35% between 1982 and 2002.
- *Hypertension*: Elevated blood pressure is estimated to cause 7.5 million deaths each year, which represents approximately 12.8% of all deaths.[22] Hypertension is a major risk factor for CVD. Elevated blood pressure has increased across all income groups. It is generally the lowest in HICS.
- *Overweight and obesity*: Over 2.8 million people die each year as a result of being overweight or obese.[23,24] Overweight and obesity increases risk for CVD, stroke, and T2DM as well as certain cancers. Overweight and obesity are increasingly found in LMICs but are most prominent in HICs.[25] For example, in the United States, over 70% of the population is either overweight or obese. Approximately half of this population is overweight and the other half is obese. There is an increasing prevalence of overweight and obesity in young children, particularly in LMICs.
- *Dyslipidemia*: Elevated cholesterol is estimated to cause 2.6 million deaths annually.[11] This increases the risk of CVD and stroke. Raised cholesterol is highest in HICs.

94.6 OTHER RISK FACTORS

In addition to those risk factors identified by the WHO for NCDs, there are a number of other risk factors that can contribute to NCDs or are NCDs themselves.

- *T2DM*: The prevalence of T2DM has grown rapidly in the past 30 years and in many ways is parallel to the increase of overweight and obesity.[26] This is particularly prominent in LMICs. Thirty percent of people with diabetes live in LMICs. In some Pacific Island and Middle Eastern European Countries, there are age-adjusted prevalences between 19% and 25%. In the United States, approximately 11% of people have T2DM. In China, approximately

12% of people have T2DM. India and China have the largest numbers of people in the world with diabetes with 61.3 million and 90.0 million, respectively. Some studies have shown that Asian populations may have a higher risk of developing diabetes at even lower body mass indexes (BMI) because of a greater tendency for visceral obesity. There is also an increase in prediabetes. The Global Burden of Disease Study showed that 366 million people had diabetes in 2011 and almost half of these cases are undiagnosed. By 2030, the number of people with diabetes is expected to increase to 122 million. Various lifestyle medicine modalities to lower the risk of diabetes are well established including weight management, proper nutrition, increased physical activity, and not smoking cigarettes. These are discussed in more detail in multiple chapters throughout this book.

- *Infectious disease*: Healthcare providers tend to not recognize the link between lifestyle habits and practices and infectious disease. We know, however, that physically active individuals reduce their risk of various viral illnesses such as influenza and the common cold. Most recently, the link between lifestyle practices and infectious disease has been dramatically shown in the COVID-19 pandemic. Individuals who have high blood pressure or obesity are three to four times as likely to become infected with COVID-19, be hospitalized, and die from this virus.[27,28] Thus, the same types of modalities that are used to lower the risk of various metabolic diseases such as CVD and T2DM are highly relevant to lowering the risk of viral illness.
- *Alzheimer's disease and dementia*: Alzheimer's disease and dementia are increasingly a problem, particularly as the population around the world continues to age. This is particularly a problem in developed countries. Two countries where there are most individuals with Alzheimer's disease are the United States and China. In the United States, it is estimated that 4.9 million people are living with Alzheimer's disease, and in China, it is estimated that 5.4 million people are living with Alzheimer's disease.[29] The relationship between Alzheimer's disease and other forms of dementia and lifestyle factors is prominent and has been underscored by the collaboration between the American Heart Association (AHA) and the American Stroke Association (ASA) which issued the Joint Presidential Advisory on "Optimal Brain Health".[30] This Presidential Advisory recommended that individuals follow the same healthy practices recommended for reducing the risk of heart disease as a way of preserving optimal brain health and lowering the risk of Alzheimer's disease and other forms of dementia.[31]
- *Aging population*: The good news is that the average life expectancy has continued to rise throughout the world, particularly in developed regions. Average life expectancy is estimated to reach 83 years in developed regions by 2025 and 75 years in less developed regions.[32]

  While increases in life expectancy have been significant in HICs, they are also common in LMICs. For example, LMICs are anticipated to double the number of individuals over the age of 60 between 1995 and 2025. LMICs have increased the likelihood of individuals being over the age of 65 much more rapidly than occurred in more developed countries. All of the modalities of lifestyle medicine are highly appropriate for individuals over the age of 65. Once a person reaches the age of 65, they are highly likely to reach the age of 85. For all of these reasons, lifestyle modalities are highly relevant to the aging population.
- *Environmental exposures*: Environmental pollution represents a major cause of death and disease. Multiple exposures to particulate matter pollution significantly increase mortality and morbidity from CVD.[33,34] The GBD Study showed that approximately 30% of disability-adjusted life years (DALYs) come from environmental risk factors.[10] This is largely tobacco smoke, although there are other forms of air pollution prevalent, particularly in an era of global warming. It is estimated that over seven million premature deaths occur from environmental exposure. This is particularly prevalent in India and China, although it also occurs prominently now in many developing countries. Environmental exposure represents an important and relatively new frontier for the modalities of lifestyle medicine.

94.7 ECONOMIC BURDEN

The economic burden of NCDs results not only from direct costs but also from indirect costs such as loss or productivity.[35–38] In many countries, the economic burden of NCDs is between 5% and 6% gross national product (GNP). It has been estimated that indirect costs may be much more. In many countries, the cost of direct treatment of CVD is 2–3% of their GNP, and approximately double that comes from indirect expenses. The cost of obesity varies between 2% and 8% of all healthcare expenditures in both HICs and LMICs. Given that many NCDs occur in LMICs and occur in younger people than in HICs, the economic burden of NCDs, while difficult to totally compute, could be profound. By any measure, the economic burden is significant.

The economic cost of NCDs, according to the National Institute of Health, is likely to exceed $47 trillion over the next two decades. Thus, there is an enormous economic incentive to solve the issues of NCDs and lessen their impact both on health and economies around the world. By

any measure, the economic burden is significant. One of the most attractive features of lifestyle medicine modalities is that they are cost-effective solutions to the enormous economic burden of NCDs.

94.8 COST-EFFECTIVE SOLUTIONS

Strategies to find cost-effective solutions for NCDs are extremely important. These are likely to vary from country to country depending on the resources available.[39–42] However, it is clear that lifestyle medicine modalities are a highly cost-effective solution. First, there is a relatively small cost to increasing physical activity, reducing smoking levels, and improving nutrition. Moreover, lifestyle medicine modalities have the added benefit of carrying virtually no adverse effects and also impacting multiple chronic diseases simultaneously. For example, consumption of more fruits and vegetables, increased physical activity, lower rates of cigarette smoking, and lower rates of obesity all have positive impacts not only on CVD but also on many of its risk factors, including high blood pressure and dyslipidemia. Moreover, these same modalities significantly reduce the risk of T2DM and even some cancers.

94.9 PUBLIC HEALTH CONSIDERATIONS

A key component of the WHO initiative to combat NCDs involves population-wide strategies. Many of these strategies apply not only to individuals but also could be highly effective on a population-wide basis. The WHO recommends that actions should be undertaken immediately to produce accelerated results related to lives saved, diseases prevented, and high costs avoided. This is such an important area that the WHO has listed ten "best buys" in terms of the reduction of NCDs. These include the following:[42]

- Protecting people from tobacco smoking and banning smoking in public places
- Warning about the dangers of tobacco use
- Enforcing bans on tobacco advertising, promotion, and sponsorship
- Raising taxes on tobacco
- Restricting access to retailed alcohol
- Enforcing bans on alcohol advertising
- Raising taxes on alcohol
- Reducing salt intake and salt content in food
- Reducing trans fat in food and polyunsaturated fat
- Promoting public awareness about diet and physical activity including through mass media

It is clear that most, if not all, of these ten "best buys" from the WHO include lifestyle medicine modalities. The WHO also emphasizes the importance of not only population-wide interventions but also comprehensive programs that involve both individual efforts and population-wide strategies.

94.10 SUMMARY/CONCLUSIONS

NCDs have become an enormous issue around the world in the past two decades. In fact, NCDs now represent over 71% of all mortality around the world. Thus, NCDs result in more mortality than all other diseases combined.

The strategies to reduce NCDs, which are shared by the WHO and the lifestyle medicine community, include lowering the risk of various chronic diseases. The WHO has focused attention on four behavioral risk factors:

- Tobacco use
- Physical inactivity
- Harmful use of alcohol
- Unhealthy diet

These, plus other modalities that are central to lifestyle medicine are all very important. It is incumbent on physicians in the lifestyle medicine community to recognize that the impact of lifestyle medicine is important not only for individual patients but also for populations around the world. This adds a further challenge and an opportunity for those practicing in the area of lifestyle medicine.

CLINICAL APPLICATIONS

- The modalities of lifestyle medicine are critically important for the main behavioral risk factors identified by the WHO. These include the use of tobacco, insufficient physical activity, harmful use of alcohol, unhealthy diet, raised blood pressure, overweight and obesity, and dyslipidemia.
- It is incumbent on lifestyle medicine practitioners to recognize the important worldwide implications for positive lifestyle medicine modalities.
- An increasing number of lifestyle medicine organizations have sprung up around the world offering significant hope that lifestyle medicine modalities can make a major impact on lowering the epidemic of NCDs around the world.

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Part XVII

Substance Abuse and Addiction



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95 Addiction Section Introduction

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KEY POINTS

- People suffering from addiction or substance use disorders are not getting the help they require to tackle their medical problems.
- People with addiction problems are similar to people with hypertension and diabetes in that they need specialized care and diagnosis is the first step.
- All clinicians, including lifestyle medicine practitioners, need to become familiar with the signs, symptoms, diagnosis, and treatment options for those people suffering from substance use disorders.

Given that smoking is a major cause of disease leading to heart disease and cancer, two of our major killers, it is important for lifestyle medicine practitioners to be comfortable with the identification, diagnosis, treatment, and counseling strategies that are most effective for people suffering from addictions. Mokdad and colleagues pointed out that smoking was the number one "actual cause of death" in the United States in his landmark article published in JAMA in 2004.[1] On that same list of actual causes of death are alcohol and illegal drugs.

Lifestyle medicine practitioners treat patients who smoke, drink, use cannabis, and use opioids. Knowing the treatment options, identifying people in need of assistance, and recommending appropriate follow-up are all important aspects of lifestyle medicine practice. There are assessment tools that can be used before the clinic visit. In addition, there is a methodology for counseling patients that will open up the conversation for discussions about these habits that are often hidden from physicians. In many cases, patients and family members are in denial themselves. Thus, the role of the lifestyle medicine practitioner is to be a non-judgmental source of information, inspiration, and support for those individuals who are struggling to stay drug- or alcohol-free.

There are addiction specialists who have for trained years in order to effectively help people who are using tobacco, alcohol, and drugs to excess or in a way that is causing them harm physically or emotionally. Many psychiatrists, psychologists, social workers, nurses, and other healthcare professionals are focusing on this population of patients every day. Knowing clinicians who specialize in addictions, the resources available through hospital and community centers, becoming familiar with medications that may help people stay drug-free, identifying technologies that can assist patients, and understanding the value of rehabilitation centers are essential for lifestyle medicine practitioners to help their patients embrace healthy living. People might be eating a healthy diet and exercising, but they may also be drinking too much. Because substance use disorders can be missed and purposefully hidden, lifestyle medicine practitioners will be one step ahead after reading this section. This was a new section in the third edition of the textbook. It has been updated and expanded in the fourth edition. It is evidence that the editors are staying current with the times and supplying practitioners with cutting-edge information.

The naming of this field of medicine has been a source of controversy and even the definition of addiction is something that is not agreed upon by all providers and patients. The history of addictions is reviewed in Chapter 96. The currently favored term and the one used in the DSM is substance use disorders. Substance use disorders (SUDs) refer to a group of disorders that involve the compulsive and repeated use of substances that are associated with negative physical and psychological health consequences.[2] Historically, lifestyle medicine practitioners have not been routinely involved with the assessment and management of SUDs. However, in the context of the growing opioid crisis and the continued contribution of SUDs to adverse health outcomes, every clinician should be aware of the epidemiology, approach to diagnosis, and the basics of SUD treatment. While not every clinician can provide the full spectrum of SUD treatments, it is imperative that clinicians have the basic knowledge and skills necessary to identify and diagnose SUDs, provide basic treatment where appropriate, and refer to local community resources. Today, a variety of effective evidence-based pharmacologic and psychosocial services are available that healthcare providers can utilize in their day-to-day practice. Considering the degree to which SUDs are common in clinical populations, as well as the negative impact on patients, families, employers, and communities, clinicians can no longer opt out of providing these basic services to patients.

There is a long history of humans using a variety of substances for both therapeutic and recreational purposes, which will be outlined in Chapter 96 by Steve Adelman and Sanchit Maruti. The World Health Organization has recognized that substance use remains one of the most common contributing factors to premature death (in the year 2000, alcohol, tobacco, and illicit drug use contributed to 12.4% of all deaths worldwide) as well as other medical,

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psychiatric complications that reduce quality of life and contribute to a heavy economic burden through lost productivity, criminal justice costs, and healthcare costs.[3] Today, SUD continues to be a major public health problem in the United States, with over 19 million Americans ages 18 and older (7.8%) suffering from some form of SUD in 2016.[4] National epidemiologic surveys of alcohol and related conditions estimated that lifetime prevalence of alcohol-related disorders is 20.3% and drug use related disorders is 10.3% [5]. When separated by gender, males experience SUD at much higher rates (10.7% of US males) compared with females (5.7% of US females).[6] The typical age at which individuals begin to meet the criteria for a substance use disorder is during young adulthood (ages 18–25). At this age, due to the insufficient development of their frontal lobes, individuals are less able to inhibit risky behaviors and are at heightened risk of developing a SUD. Tobacco remains the most commonly used substance that is associated with considerable morbidity and mortality. While the rate of tobacco use has declined over the past several decades, 28.5% of Americans continue to endorse regular use of tobacco products.[4] More than 480,000 deaths annually are attributable to tobacco use, far overshadowing deaths from all other substance use combined.[7] Behavioral approaches to tobacco use disorder will be addressed in Chapter 97 by Ciccola and SantaBarbara. Alcohol is also frequently consumed in the United States, with 86.4% of the population consuming alcohol at least occasionally at some point in their lifetime.[8] Among those who consumed alcohol regularly in 2014, about 60.9 million (26.9% of the US population) reported binge drinking (defined as drinking more than five [for men] or four [for women] or more drinks in one occasion) and 16.3 million (7%) reported heavy drinking (defined as binge drinking on five or more days in the past month).[8] Binge drinking is an important contributing factor to injuries such as falls and motor vehicle accidents. In the same year, 6.2% of individuals 18 years and older met the criteria for an alcohol use disorder,[6] which causes additional harm to the individual by damaging all organ systems in the body, with a particular focus on the neurologic and cardiovascular systems. The approach to the diagnosis and treatment of alcohol use disorders will be presented by Chen and Slatkin in Chapter 98. Illicit drugs such as cocaine, prescribed medications such as oxycodone and benzodiazepines, and cannabis (now legal in some states) are also used frequently in the United States, with approximately 10.2% of individuals in 2014 endorsing the regular use of such substances.[6] While the use of heroin and cocaine has existed in the United States for the better part of the 20th century, there has been an alarming rise in the non-medical use of prescription medications in the last two decades.[9] This has led to an unprecedented rise in the number of overdose deaths due to misuse of prescription opioids and benzodiazepines. More recently, the misuse of illicitly produced synthetic opioids such as fentanyl has further contributed to the growing number of individuals unintentionally overdosing. The approach to the diagnosis and treatment of opioid use disorders will be covered in Chapter 99 by Dr. Volpicelli, and Bujno and Hasin will review cannabis use disorders in Chapter 100.

Unfortunately, despite the high prevalence of SUDs in the United States, addiction treatment has been largely fragmented from general medical treatment. A typical patient with a substance use disorder seeking help would not receive any substantial assistance from their healthcare provider. A typical primary care physician is well-equipped to handle most of the common illnesses that patients suffer from, including diabetes, obesity, and hypertension. In the context of the growing opioid crisis, this discrepancy in the ability of the healthcare system to help those suffering from SUDs has been exposed.

A major contributing factor for this failure stems from considering SUDs as a moral failing and criminal behavior per se, which has led to a disproportionate use of law enforcement approaches to reduce substance use. Instead of offering treatment, individuals with SUDs were punished for their substance use. Fortunately, as the scientific understanding of SUDs has increased, there has been a shift from the law enforcement approach to the public health approach. Instead of criminalizing the behavior, the growing evidence base pointed to SUD as a chronic disease, not unlike diabetes or hypertension. Treatment for SUD has a considerable impact on the individual but requires ongoing treatment and management of the underlying illness. As in diabetes treatment, there is no cure for SUD even if there is cessation of substance use. Once SUD develops, the individuals remain at heightened risk of relapse, and ongoing attempts at preventing relapse are necessary. As such, a critical component of treatment involves ensuring that patients are engaged with their treatment. One possible strategy for this is to incorporate mobile applications and smartphones to increase patient self-efficacy in managing their SUD. El-Haddad and colleagues in Chapter 102 will review the variety of psychosocial services and peer supports that patients can utilize to support their recovery in the long term.

Healthcare providers of all disciplines have historically been provided with sub-optimal education on SUDs. This meant medical schools devoted minimal time to teaching the diagnosis and treatment of SUDs and employed few faculty members who were experts on SUDs. In graduate medical education, only psychiatry residents are required to complete any rotation in addiction. To this day, internal medicine residents are not required to complete any dedicated rotation in addiction medicine. The limited exposure to addiction education as well as the limited number of preceptors and mentors experienced in the treatment of SUDs has meant that entire generations of physicians are ill-equipped to diagnose and treat SUDs once they begin practicing. As such, the chapters in the addiction section are meant to provide a succinct overview of the common

SUDs encountered by clinicians in their practice and cover the basics of assessment and treatment of these conditions.

CLINICAL APPLICATIONS

1. This addiction section clearly belongs in a lifestyle medicine textbook. It is an important topic as people with addictions often hide or mask their problems when speaking with primary care physicians or other clinicians.
2. Knowing how to recognize different substance use disorders will save the lifestyle medicine clinician time because someone trying to manage an addiction can be preoccupied with that substance (like nicotine for smokers) and thus have difficulty adopting other healthy habits.
3. It is possible that lifestyle medicine clinicians might be the clinicians that patients choose to share their addiction history with after rapport has been created and trust developed. For this reason, these clinicians need to be well-versed in substance use disorder diagnosis and treatment.

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96 History of Alcohol and Opioid Use and Treatment in the United States

Sanchit Maruti, MD, MS and Steven A. Adelman, MD

KEY POINTS

- Perceptions of substance use have evolved from widespread use and social acceptance, then to restriction and stigmatization, and now to recognition as a neurobiological phenomenon.
- The COVID-19 pandemic has had a significant impact on individuals struggling with addiction by hindering access to, and efficacy of, treatment.
- Understanding the historical basis of addiction and treatment can assist us in integrating traditional medical management with the growing knowledge of lifestyle therapeutic approaches for the well-being of the individual.

"Whereof what's past is prologue"

William Shakespeare, Scene 1, The Tempest

Human history is replete with the use of intoxicating and potentially addictive substances in various cultures in different epochs of time. Archeologic evidence suggests that alcohol has been consumed by humans over the past 9000 years and opium over the past 8000 years. These substances have been used in religious practices, recreation, and for their medicinal properties. Over the past several centuries, technological innovations, such as distillation, chemical synthetic processes, and the invention of the hypodermic syringe, have increased the potency and availability of these substances and streamlined delivery into the body. Today, alcohol and opioid use disorders are responsible for significant morbidity and mortality throughout the world. With an improved understanding of the neurobiological basis of addiction, lifestyle medicine approaches can potentially contribute to prevention and recovery.

96.1 ALCOHOL

The earliest record of excessive use of alcohol as an illness was described during the 5th century by Herodotus. At the beginning of the colonization of America, alcohol was consumed by men, women, and children throughout the day as the fresh water supply was not often safe for consumption. Colonists adhered to the traditional belief that distilled spirits were *aqua vitae* or the water of life. Over the next 200 years, alcohol was routinely consumed in general society. Between 1780 and 1830, there was a proliferation of distilleries resulting in a tripling of per-capita consumption of alcohol. Even the first president of the United States, George Washington, was actively involved in making alcohol. In fact, in 1799, the year of George Washington's death, his distillery produced nearly 11,000 gallons of spirits, making it the largest whiskey distillery in America at the time.

Despite this widespread acceptance, excessive consumption of alcohol was causing increasing concern. Early Native American tribes used plant-based medicinals to decrease cravings and induce aversion to alcohol. In 1774, the abolitionist and educator Antoine Bénézet warned of alcohol as a "poison" and in 1784, Dr. Benjamin Rush wrote the "Inquiry into the effects of ardent spirits on the human mind and body". In this work, he described the symptoms and progression of excessive alcohol use. Additionally, Dr. Rush was one of the first physicians to recognize that excessive alcohol use was an illness that required medical treatment. He believed that the properties of alcohol, rather than the choice of the individual, are responsible for the illness. He was an advocate for humane treatment and argued that individuals with this condition can be restored to full health with a return to society through proper medical treatment. These concerns and recommendations from important societal figures led to the beginning of the American Temperance movement.

During the 19th century, there emerged increasing medical evidence of the harms caused by excessive drinking, including the recognition of delirium tremens in 1813 by Dr. Thomas Sutton, the identification of the triad of ophthalmoplegia, ataxia, and confusion by Dr. Carl Wernicke, and the description by Dr. Sergei Korsakoff of memory defects and confabulation associated with chronic, excessive alcohol use. By the mid-century, there was increasing recognition of excessive alcohol use as a medical condition. In 1849, Dr. Magnus Huss compiled the chronic effects of intoxication and formulated the term "Alcoholism". Concurrently, there was growing social support for the establishment of physician-directed inebriate asylums to provide specialized residential care. In 1864, the New York State Inebriate Asylum opened, and by the late 1870s, large hospitals such as Bellevue created inebriate wards to provide care for patients in urban settings. It is noteworthy that during this time many patented medications for treating addiction contained alcohol, cocaine, morphine, or opium.

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The diagnostic term that emerged from the medical field in the 19th century was "inebriety" with further specifications based on the substance of interest.

One of the earliest addiction organizations, the American Association for the Cure of Inebriety (AACI) was created in 1870. This organization held regular meetings and published the first specialized medical journal, the *Journal of Addiction*. The founding principles of the AACI appear now to have been remarkably forward-thinking and recognized "inebriety" as a curable disease that was either inherited or acquired. They advocated for the civil authorities to support the establishment of specialized treatment facilities for the scientific treatment of inebriety in place of penal methods.[1] The growing evidence of the medical etiology of addiction encouraged the American Medical Association (AMA), which was founded in 1847, to support the creation of the American Medical Temperance Association (AMTA) in 1891. As the historian William White summarizes, "The field of addiction medicine experienced professionalism and specialization between 1830 and 1900". Thus, the approach to addiction in the United States in the 18th and 19th centuries was formed by the combined influences of medicine, morality, and social activism.[2]

Despite the medical progress, during the same time in 19th century America, momentum was building for connecting excessive alcohol use to a moral failing. In 1826, the American Temperance Society was formed with the premise of reducing alcohol use rather than complete abstinence. In 1827, Reverend Lyman Beecher published, "Six sermons on the nature, occasion, signs, and remedy of intemperance". He described the individual who excessively used alcohol as "addicted to sin". He championed the concept of abstinence on an individual and societal level. The 1830s saw the emergence of Teetotalism, which promoted complete abstinence from all alcoholic beverages. Mutual Aid Groups first started in the 18th century with early Native American recovery circles. In 1840, the Washingtonian Movement was founded by six individuals who had achieved sobriety from former alcohol use. The premise was that a fellowship of individuals could support each other's sobriety by conducting outreach to individuals who were struggling with excessive alcohol use, relying on each other, sharing their experiences with alcohol, and nurturing an environment of comradery. These principles were eventually incorporated into the Alcoholics Anonymous organization.

96.2 OPIOIDS

Opium is derived from the poppy *Papaver somniferum* and contains the opiates morphine and codeine. The first references to opium cultivation are from 6000 BC in lower Mesopotamia. Opium's use spread to different parts of the world with evidence from an Egyptian papyrus of cultivation in Egypt in 1500 BC. In 460 BC, Hippocrates noted the usefulness of opium for treating internal diseases, epidemics, and diseases of women. In the 16th century, Paracelsus created laudanum, which was a tincture of opium for the treatment of pain. In the 17th century, Dr. Thomas Syndenham, renowned as the "English Hippocrates", compounded a proprietary form of laudanum and promoted it for a variety of medical conditions. The use of opium and laudanum soon became widespread in Europe and the United States for the treatment of cardiac ailments, infectious diseases, mental conditions, and pain by patients of all ages, including children. In 1804, Friedrich Sertürner isolated morphine (after the Greek god of dreams, Morpheus) from opium, and by 1827, the Merck pharmaceutical company began the manufacturing and marketing of morphine.

In the 1850s, the work of Drs. Francis Rynd, Charles-Gabriel Pravaz, Louis-Jules Béhier, and Alexander Wood led to the creation and clinical use of the hypodermic needle. The combination of the increased potency of morphine over opium and the ability to inject the solution directly into the bloodstream catalyzed the increasing use of morphine. The discovery of the hypodermic syringe occurred just before the start of the US Civil War, and the use of injected morphine during the treatment of war injuries is reported to have resulted in addiction in thousands of veterans after the war.[3] In 1874, C.R. Wright synthesized diacetylmorphine from morphine[4] Chemists at Bayer Pharmaceuticals optimized the synthetic process and Bayer marketed diacetylmorphine under the brand name "Heroin" (from the Greek word *heros*), as a "safe, nonaddictive" alternative to morphine from 1895–1910 for pain and coughs. It is noteworthy that during this time, consumption of medications with opioids was considered normal and with minimal risk. Women were widely prescribed opioids after childbirth, or to treat "female problems" (menstrual cramps). In the 1800s, opioids and cocaine were mostly unregulated. The anthropologist Dr. Marcus Aurin writes that until the latter part of the 19th century, "It was viewed perfectly normal for individuals to take regular daily doses of opium as a 'constitutional' for vague conditions".[5] This acceptance and lack of regulation led to the development and commercialization of hundreds of patented medicines containing opioids during this time period.

96.3 ADVERSE EFFECTS OF LEGAL AND SOCIETAL CHANGES ON ADDICTION TREATMENT

The period of 1900–1935 saw a decrease in medical influence on addiction treatment in the United States as increasingly pejorative characterizations of individuals with substance use disorders led to a shift from viewing substance use as a medical condition or socially normative behavior and instead to judging it as a weakness in character and a willful, selfish choosing of sin over virtue.

In the 1890s, the Anti-Saloon League was the leading organization lobbying for prohibition in the United States. It allied with the Women's Christian Temperance Union and the Prohibition Party to support the passage of the Eighteenth Amendment to the United States Constitution

in 1919. This law made the production, transport, and sale of alcohol (though not the consumption or private possession) illegal. In parallel, there was soaring public sentiment against the availability and use of opioids. The combination of the availability of morphine and the hypodermic needle had resulted in growing opioid addiction rates in individuals. In addition, social sentiment started shifting when there were increasing cases of addiction among the immigrant population, such as railroad workers who emigrated from China. The first drug control ordinances in US history were issued in San Francisco in 1875 in an attempt to stop the spread of "opium dens".

The US government began taxing opium in 1890, and the passage of the Pure Food and Drug Act of 1906 forced manufacturers to disclose the ingredients of their products, so consumers would know the content of their medications. Shortly after, in 1909, the Smoking Opium Exclusion Act banned the importation, possession, and use of "smoking opium". Although the Act did not regulate opium-based medications, it became the first federal law to ban the use of non-medical substances. On a global level, Charles Henry Brent, an American Episcopal bishop convened the Brent Commission, which recommended that narcotics be subject to international control. In 1912, the United States and many other countries signed the International Opium Convention, which regulated the import, manufacture, and sale of morphine. Shortly afterward, the Harrison Narcotics Tax Act of 1914 was passed. This law regulated and taxed the production, importation, and distribution of opiates and cocoa products. It deemed that physicians could prescribe or dispense opioids to their patients if they kept records.

However, the moral sentiment affected medical opinion, and the US Public Health Service advocated that addiction was not a medical problem but a social one. In 1919, the AMA passed a resolution opposing outpatient treatment of opioid addiction. In 1919, the Webb amendment to the Harrison Act made offering maintenance treatment an "illegitimate medical practice" and a federal offense. During this time, many physicians were indicted under the Harrison Act and several actually went to jail. The *United States v. Behrman* Supreme Court decision in 1922 resulted in the closure of nearly all clinics treating opioid addiction, as it made it illegal for doctors to prescribe opioids to addicts under any circumstances. Thus, over the course of 50 years, the pendulum had shifted from the medical and multi-factorial perspective of addictions espoused by the ACCI to one emphasizing moral responsibility, legal regulation, and punitive consequences.

96.4 A REVIVAL OF ADDICTION TREATMENT IN THE UNITED STATES

The benefits to society of punitive legislative actions did not materialize as promised. After the passage of the Eighteenth Amendment, crime rates increased as the criminal element became wealthy from the profitable, violent, illicit market for alcohol. Prohibition started becoming unpopular across the country as the federal government and law enforcement agencies were not able to take adequate countermeasures. As a result, society became willing to reexamine and reengage with the problem of addiction. With increased awareness and support, treatment approaches were reconsidered. Publication of medical research offered physicians a voice advocating for treatment. The pendulum swung back toward a clinical perspective through a series of legislative actions and court decisions. In 1925, the *Linder v. United States* Supreme Court decision ruled that the federal government overstepped its power to regulate medicine in the Behrman case. In 1929, the Narcotic Farms Act allocated funds for the US Public Health Service to construct and operate two residential treatment facilities. Ultimately, the Twenty-First Amendment, which repealed the Eighteenth Amendment, was ratified by a majority of states at the end of 1933.

Another pivotal development in the treatment of addiction was the founding in 1935 of Alcoholics Anonymous (AA), a non-profit mutual aid society, by Bill Watson and Dr. Bob Smith. They posited that the primary purpose of the alcoholic was to "stay sober and help other alcoholics achieve sobriety". Subsequently, they published the "Big Book" and developed AA's 12-step spiritual and character development program. Although AA was not the first mutual aid group, it is the oldest and largest still operating with over two million members worldwide and 100,000 active groups. AA has served as inspiration for scores of mutual support groups that focus on specific substances and sub-populations. In 1949, the Minnesota Model (also known as the Abstinence Model) was created, which proposed the blending of professional and trained non-professional (recovering) staff who integrated the principles of AA. In addition, patients received individualized treatment plans with active family involvement in a 28-day inpatient setting. More recently, the Self-Management and Recovery Training (SMART) non-profit organization was founded in 1994 as a mutual support organization based on evidence-based scientific knowledge. SMART Recovery emphasizes the four-point program in the process of recovery including: (1) building and maintaining motivation, (2) coping with urges, (3) managing thoughts, feelings, and behaviors, and (4) living a balanced life using principles of motivational enhancement therapy (MET) and techniques taken from cognitive behavior therapy (CBT). In contrast to AA and other 12-step approaches, individual goals in SMART Recovery may include moderation of substance use rather than complete abstinence.

Starting in the 1930s, pharmacologic developments started providing hope and medical credibility to conceptualizing addiction as a medical condition. Methadone was discovered in 1937 in Germany and ultimately gained Food and Drug Administration (FDA) approval in 1947 for treating pain. By 1965, Dr. Marie Nyswander and Dr. Vincent Dole published evidence hypothesizing that heroin addiction was a metabolic condition and that methadone could be

used as a medication to treat this illness. In 1970, the FDA approved methadone for medically assisted withdrawal ("detoxification") and in 1973 for maintenance therapy. Other medications for the treatment of opioid use disorder include naltrexone which was synthesized in 1963 and FDA approved in 1984, with its extended-release injectable version receiving FDA approval in 2010. Buprenorphine was discovered in 1966 and received FDA approval for treating opioid use disorder in 2002.[6] Medications for the management of alcohol use disorder were discovered and developed over roughly the same time period, with disulfiram, a deterrent medication that increases adverse reactions to alcohol, receiving FDA approval in 1951, followed by oral naltrexone, which works to decrease craving and reinforcing effects of alcohol, being approved in 1994 and its extended-release injectable version in 2006. Acamprosate, another medication intended to decrease craving, received FDA approval in 2004.[7]

Support from state and federal governments allowed a foundation for enhancing treatment and conducting and disseminating research. The Addiction Research Center was founded in 1948 and served as a precursor for the formation of the National Institute on Drug Abuse (NIDA), which was formed by the Drug Abuse Office and Treatment Act in 1972. In 1992, NIDA became part of the National Institutes of Health (NIH). The Comprehensive Alcoholism Prevention and Treatment Act created the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 1970. In addition, in 1992, the Substance Abuse and Mental Health Services Administration (SAMHSA) was established by Congress to improve the quality and availability of treatment and rehabilitative services for individuals with substance use disorders and mental illness. The Narcotic Addict Treatment Act was passed in 1974 and it recognized the use of opioid medication to treat opioid addiction as critical and, for the first time in federal law, defined "maintenance treatment". The Drug Addiction Treatment Act (DATA), which was passed in 2000, allows providers to dispense or prescribe schedule III, IV, or V controlled substances for opioid addiction in treatment settings other than traditional opioid treatment program (OTP) settings. This has allowed patients with opioid use disorder to receive care in outpatient settings as they would for any health condition. Coverage for treatment was made easier by the Mental Health Parity and Addiction Equity Act (MHPAEA) of 2008, which required health insurers and group health plans to provide the same level of benefits for mental and/or substance use treatment and services that they do for medical/surgical care. The passage of the Comprehensive Addiction and Recovery Act (CARA) of 2016 allowed for improved access to treatment by expanding prescribing privileges to nurse practitioners (NPs) and physician assistants (PAs) until 2021.

There are several instances of government collaboration with professional organizations. The Provider's Clinical Support System for Medication-Assisted Treatment (PCSS-MAT) is an example of a national collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with the American Osteopathic Academy of Addiction Medicine (AOAAM), the American Psychiatric Association (APA), and the American Society of Addiction Medicine (ASAM). PCSS-MAT is a national training and mentoring project developed in response to the prescription opioid misuse epidemic and the availability of pharmacotherapies to address opioid use disorder.

These initiatives have led to a better understanding of the neurobiological basis of addiction. Research has outlined the processes of neuroplasticity fundamental to learning and memory. The identification of various receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-d-aspartate (NMDA), and gamma-aminobutyric acid (GABA) and their neuroanatomic distribution has been coupled with greater knowledge of the effects of neurotransmitters such as dopamine, glutamate, and GABA. Synthesizing the findings of biochemical research with behavioral studies has shed greater light on functional significance.[8] This has allowed concepts such as triggers, cravings, preoccupation, anticipation, and withdrawal to be viewed from a biological perspective.

Despite these active initiatives, a large treatment gap exists in the United States for patients suffering from addiction. In 2019, only 10% of patients with substance use disorders (SUDs) who needed treatment received it in a specialty treatment facility in the past year.[9] Addiction is a chronic condition with a significant public health impact. The incidence and prevalence of addiction can potentially be decreased by the use of evidence-based lifestyle therapeutic approaches that can help guide and empower individuals to replace potentially harmful substances with healthy habits.[10] For example, improved knowledge and skill building for stress management can have a significant effect on individuals having alternatives to alcohol and tobacco use. This can, in turn, have salient and systemic benefits for the individual and society.

96.5 COVID-19

Plagues and pandemics have had a significant pernicious effect on humanity. The plague of Justinian (541–549 AD) accounted for approximately 100 million deaths worldwide. Subsequently, 62 million individuals died of the Black Death from 1347–1351. Both of these pandemics were due to the bacterium *Yersinia pestis*. In the 1918–1919 influenza pandemic, heavy alcohol intake was recognized as a risk factor for poor outcomes.[11] As of August 2022, over one million individuals in the United States died as a result of COVID-19.

During the COVID-19 pandemic, a substantial number of Americans experienced increased psychological distress due to losses, logistical challenges, and uncertainty. Accompanying the resulting increased psychological distress was an increase in the use of alcohol and drugs as coping mechanisms.[12,13] Concurrently, there was decreased access to timely high-quality treatment. Provisional data indicate that there were approximately 100,306 drug

overdose deaths in the United States during the 12-month period ending in April 2021, an increase of 28.5% from the 78,056 deaths during the same period the year before.[14]

96.6 SUMMARY

Humans have used mind-altering substances for thousands of years for a variety of reasons. Substance use in the United States has undergone cycles of acceptance, widespread use and underappreciation of risk, and the recognition of problematic use leading to the criminalization of substances and stigmatization of users, to the legalization of certain substances and medical treatment. Access to treatment has vacillated based on cultural perceptions, social norms, legal decisions, and legislative actions. Addiction continues to pose a significant challenge. In 2019, approximately 20.4 million individuals aged 12 or older were diagnosed with SUDs in the past year. This statistic was comprised of 14.5 million individuals with an alcohol use disorder and 8.3 million with an illicit drug use disorder.[9] Additionally, there were a record number of deaths due to overdose.[14] These data potentially underestimate the prevalence of negative consequences of addictive substances since they do not include individuals whose use causes harm or increases risks but does not meet the full criteria for a substance use disorder.

The current opioid epidemic highlights the significant morbidity, mortality, and devastating economic and societal costs of this condition. However, the scientific and medical advances coupled with the economic benefits of treatment represent hope for individuals, their families, and society. SAMHSA summarizes this sentiment: "Behavioral health is essential to health; Prevention works; Treatment is effective; People recover".

CLINICAL APPLICATIONS

- Humans have utilized alcohol and opioids for thousands of years for a variety of reasons including for medical, recreational, and spiritual purposes.
- Although the use of these substances was initially accepted in society, the increased potency, widespread availability, and improvement in methods of delivery resulted in significant pernicious consequences for the individual and society at large.
- Societal perception and treatment availability have vacillated from viewing addiction through a lens of morality and deviance to the recognition of it as a treatable, chronic medical condition.
- The ongoing COVID-19 pandemic has worsened access and adherence to treatment for substance use disorders.
- With increasing personal and professional demands and increasingly limited resources, this time presents an important opportunity to utilize evidence-based lifestyle medicine approaches to prevent addiction and enhance recovery.

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97 Behavioral Approaches to Enhancing Cigarette Smoking Cessation

Joseph T. Ciccolo, PhD and Nicholas J. SantaBarbara, MS

Worldwide, more than eight million deaths can be attributed to cigarette smoking each year.[1] In high-income countries like the United States, significant strides have been made to reduce the smoking prevalence among certain segments of the population, but there are some areas where gains have been minimal. Going forward, it will be critical to identify those who are most at risk for the negative consequences of cigarette smoking, identify those who need active intervention, and inform treatment recommendations, such as what type or dose of treatment is needed.[2] Hence, the purpose of this chapter is to:

- Provide a brief overview of the health consequences and prevalence of cigarette smoking in the United States.
- Conduct a review of the literature on key behavioral approaches and strategies that have been used to enhance smoking cessation.
- Highlight the research done in various settings and across different populations of vulnerable and at-risk smokers.
- Summarize some of the most effective treatments and promising new research initiatives that are currently underway.

KEY POINTS

- In the United States, smoking remains the leading cause of preventable disease, disability, and death, with more than 16 million Americans currently living with a disease caused by smoking.
- Both pharmacological aids and behavioral strategies can help people quit and remain abstinent with some evidence that these techniques augment the effectiveness of each other.
- Technology-based interventions leveraging the ubiquitous nature of mobile phones have shown preliminary efficacy in helping people quit.
- Exercise may also help increase short-term abstinence while also improving other markers of physical health.
- Targeted behavioral interventions that build on the current and unique needs and skills of those who smoke, and are grounded in theory, will ultimately give smokers the best chance to achieve long-term abstinence.

97.1 HEALTH CONSEQUENCES OF SMOKING

The negative health effects that result from cigarette smoking are clear. Evidence shows that any exposure to tobacco smoke is harmful because it contains more than 7000 chemical compounds.[3] Indeed, smoking harms nearly every organ of the body and can cause cardiovascular disease, stroke, periodontitis, aneurysms, pneumonia, chronic obstructive pulmonary disease (COPD), asthma, erectile dysfunction, and low bone mineral density.[4] Cigarette smoking can also cause cancer of the lung, bladder, cervix, esophagus, oral cavity, larynx, stomach, kidney, uterus, and pharynx.[4] Lastly, smoking has additional adverse effects on early childhood and reproductive health, including infertility, preterm delivery, stillbirth, low birth weight, and sudden infant death syndrome (SIDS)[4].

In the United States, smoking remains the leading cause of preventable disease, disability, and death.[4] More than 16 million Americans are living with a disease caused by smoking. In total, cigarette smoking is responsible for more than 480,000 deaths per year (approximately 1300 each day), including more than 41,000 deaths resulting from secondhand smoke.[4] Overall, it is estimated that the total economic cost of smoking is more than $300 billion a year, including nearly $170 billion in direct medical care for adults.[4]

97.2 SMOKING PREVALENCE AND EPIDEMIOLOGY

In the United States, about 12.5% of the adult population (aged 18 and over)[5] and 1.5% of youths (middle and high school students) currently use cigarettes.[6] Smoking differs by demographic groups and is more common in those who are non-cisgender, a person of color, non-heterosexual, not currently married, uninsured or receive Medicaid, have not completed high school education, live below the federal poverty line, experience anxiety, and those with a disability.[5]

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97.3 RATES OF SMOKING CESSATION

Both the risk and the severity of many diseases caused by smoking are directly related to how long the smoker has smoked and the number of cigarettes smoked per day. As such, it is beneficial to quit smoking at any age.[4] More specifically, after quitting, the risk for a heart attack drops sharply after just one year; stroke risk can fall to about the same as a non-smoker's after two to five years; risks for cancer of the mouth, throat, esophagus, and bladder are cut in half after five years; and the risk for dying of lung cancer drops by half after ten years.[3]

The most recent estimates indicate that 68% of current smokers would like to stop smoking, 55.4% made a past-year quit attempt, and 7.4% were able to quit for more than six months over the past year.[7] Interest in quitting is reported to be higher among certain demographic groups, such as females, those aged <65 years, and those with a post-high school education.[7] In general, cessation rates are higher among those who participate in a smoking cessation program when compared with those who try to quit without any assistance. Unfortunately, from 2000 to 2015, fewer than one-third of US smokers used evidence-based cessation methods when trying to quit smoking. As such, the low prevalence of cessation may be related to the low use of evidence-based cessation treatments.

97.4 PHARMACOLOGICAL AIDS FOR SMOKING CESSATION

The earliest studies on smoking cessation did not recognize the addictive nature of cigarette smoking. Modern-day approaches now consider that the nicotine in cigarettes is a highly addictive drug, and this has led to a wealth of research on using medication to help smokers quit. Overall, the combination of behavioral counseling and medication has been shown to be more effective than either treatment alone.[8–10] Unfortunately, a significant proportion of those attempting smoking cessation are willing to use any type of medication. As such, it is important to recommend that all smokers wishing to quit seek out some type of behavioral support and use some type of medication (except when medically contraindicated).[8,9] Prior to describing several different behavioral approaches to enhancing smoking cessation, a clarification of the medications that often accompany treatment is needed.

Currently, there are several US Food and Drug Administration (FDA) approved first-line medications shown to help increase long-term smoking abstinence rates. These include over-the-counter (OTC) products (e.g., nicotine gum, nicotine lozenge, and the nicotine patch) and prescription-only medications (e.g., nicotine nasal spray, nicotine inhaler, sustained-release bupropion, and varenicline). When used properly, nicotine replacement therapies (NTRs) can significantly reduce nicotine withdrawal and have been shown to increase the rate of quitting by 50–70%.[11] Bupropion, an antidepressant, has also been shown to be an effective medication for smoking cessation.[12] It can reduce withdrawal symptoms and decrease nicotine's rewarding effects by blocking the reuptake of norepinephrine and dopamine in the mesolimbic system and nucleus accumbens, a key area for nicotine reinforcement.[13] Varenicline, the newest medication, has been shown to triple abstinence rates in smokers when compared with an unassisted quit att empt.[8,13,14] Varenicline attenuates the rewarding effects of nicotine and it can reduce the symptoms of nicotine withdrawal. Importantly, all of these medications can have side effects, and many of them have not been extensively studied in certain subpopulations of smokers (e.g., adolescents).[13] Given that the combination of behavioral counseling and medication is ideal, more studies on how to best combine these strategies for all smokers are needed.

97.5 BEHAVIORAL SMOKING CESSATION STRATEGIES

Extensive scientific and community resources have been used to examine ways to reduce cigarette use and increase smoking cessation. Strategies that have been used range from population-level (e.g., government-based initiatives and media-based campaigns) to individual-level interventions that have targeted a wide array of people who use cigarettes. The following review covers the various types of behavioral smoking cessation interventions that vary from minimal contact to intensive counseling. The programs described later can be classified based on the type of approach used, the population targeted, and the setting in which it is delivered. Regardless of their classification, all of the programs attempt to provide those who use cigarettes with the information and behavioral skills thought to be necessary for achieving initial cessation and sustained abstinence.

97.6 COUNSELING AND THERAPY-BASED APPROACHES

97.6.1 Individual Counseling

Individual or face-to-face counseling is a well-established method for delivering smoking cessation treatment. The treatment can be delivered by practitioners with varying levels of education and training (e.g., tobacco treatment specialists, psychologists), and it can be done in different formats, for varying lengths of time (e.g., 10–60 min sessions), and across a wide-ranging number of sessions. Individual counseling can also be combined with self-help components, medication, group counseling, and/or telephone/Internet assistance.[15] Currently, there is significant evidence to support using individual counseling, as it has been shown to increase the likelihood of quitting smoking by 40–60% when compared with less intensive treatments

(e.g., self-help without medication).[15,16] Going forward, it will be important to identify the most effective and cost-effective intensity and duration of individual counseling for smokers, particularly those who do not typically present for treatment and are hard to reach.

97.6.2 Group Therapy

Delivering a smoking cessation intervention in a group format has been used for more than 25 years, and it remains popular.[17–19] Using group therapy may be particularly helpful because it can provide members with a unique opportunity to learn about the challenges other smokers face when trying to quit. This can generate important and potentially therapeutic emotional experiences that often arise from listening to and analyzing the behavior of others.[17,20] While it is not yet clear whether group therapy is more or less effective than more intensive interventions (e.g., individual counseling), existing data indicates that smokers have a 50–130% greater chance of quitting in a group when compared with just using self-help materials.[19] Future studies will be needed to determine if group-based interventions are more cost-effective behavioral approaches for smoking cessation.

97.6.3 Telephone Counseling

A clear benefit of telephone counseling is that it can be used as a substitute for face-to-face contact to reach a large number of smokers at a much lower cost. There are two approaches to telephone counseling: proactive and reactive. Counselors use a proactive approach when they call smokers in an attempt to support a quit attempt or prevent relapse. These calls are typically made as part of a larger effort to expand the level of support given to the smoker, which may have initially included smoking cessation counseling or the provision of self-help materials or pharmacotherapy. Reactive telephone counseling occurs when a smoker calls a quit line, such as 1-800-QUIT-NOW.[21] Quit lines may be regional or national and may provide the caller with counseling at the time of the call, a future (proactive) call, mailed materials, access to pharmacotherapy, a recorded message, or a mixture of these components. Research suggests receiving a call-back from a counselor after the original call from the smoker (i.e., reactive counseling) can increase the rate of smoking cessation when compared with self-help materials or brief advice during the original call.[22] Other research has shown that proactive telephone counseling, which is more likely to reach those who may not be as ready or motivated to quit as those who call a quit line, can increase smoking abstinence in the short term; however, the long-term effect of this is less clear.[22] In addition, there is some evidence for a dose-response relationship with the number of proactive calls, with multiple calls increasing the chances of quitting over other minimal interventions such as self-help materials or pharmacotherapy (e.g., nicotine replacement therapy) alone.[22] New research should further examine the efficacy of proactive and reactive calls, including ways to standardize the number/length of calls.

97.6.4 Motivational Interviewing

Motivational interviewing (MI) was originally developed in the early 1980s as a treatment for substance use disorder.[23] It is an individually administered, client-centered counseling approach to elicit behavior change by helping individuals explore and resolve ambivalence.[24] MI seeks to reduce resistance to change by developing a discrepancy between an individual's current behavior and their values and goals. Some training is required to administer MI, but it can be delivered successfully by physicians, nurses, and other healthcare personnel. The first study to use MI for nicotine dependence was published in 1998,[25] and about 40 trials have been completed.[26] Overall, MI does not seem to be an efficacious treatment for smoking cessation. Studies have tested an array of treatment combinations, such as one to 12 session treatments, ranging in total time from five to 315 minutes.[26] Results show no significant effect of MI on smoking cessation when compared with no intervention or other types of behavioral support.[26] Future research should rigorously test standardized MI protocols, and include fidelity assessments, as many of the current studies suffer from bias and imprecision.[26]

97.7 SMOKING CESSATION IN MEDICAL SETTINGS

Considering that smoking contributes to the development of a myriad of medical problems, it is not surprising that smoking is more common in a variety of medical populations. The "5 As" smoking cessation framework (*ask*, *advise*, *assess*, *assist*, and *arrange*) is specifically designed to be applicable to brief medical visits.[8] This framework calls for all clinicians to assess smoking status at each visit (i.e., *ask*). The identification of smokers can be increased by treating smoking status as a "vital sign"[27] and building prompts into electronic medical records.[28] Having such an identification system increases the likelihood that clinicians will provide cessation interventions.[8,29] Some clinicians may worry that repeatedly bringing up smoking cessation during visits will decrease patient satisfaction; however, this does not seem to be the case.[30,31]

Providing strong, personal advice to quit (i.e., *advise*) only takes a few minutes and has clear empirical support. Specifically, physicians providing strong advice to quit can increase the likelihood of quitting even when relatively little time is spent (e.g., <3 minutes).[8] Although the absolute increase in quit rates due to brief advice may only be 1–3%,[32] the cost of advice is low and the reach is high, so its potential public health impact is great.

Discussion of a patient's willingness to make a cessation attempt at this time (i.e., *assess*) will identify patients who are currently interested in quitting and those who are not,

so clinicians should be ready to use treatment techniques for both groups.[33] For those who are ready to quit, the clinician can *assist*. Assistance strategies include developing a quit plan (including setting a quit date); recommending and/or prescribing pharmacotherapy; referring the patient to additional counseling, quit lines, or web support; providing practical counseling (e.g., problem-solving barriers to cessation); and providing social support. Notably, quit rates increase as time spent counseling increases.[8] Finally, following up in person or by phone (*arrange*) provides an opportunity to reinforce cessation or encourage another quit attempt if the patient has relapsed. Ideally, a first follow-up contact would occur within a week of the quit date and a second within a month of the quit date.[8]

For smokers currently uninterested in quitting, the "5 Rs" (*relevance*, *risks*, *rewards*, *roadblocks*, and *repetition*) provide a framework for increasing motivation and are consistent with the MI approach described earlier[8] In this framework, patients are asked (not told) about the personal *relevance* of smoking, perceived personal *risks* of smoking and *rewards* of quitting, and perceived *roadblocks* to successful cessation (for which the clinician can suggest solutions). These steps can be repeated at each visit (*repetition*). Studies have shown that the 5 Rs approach increases the likelihood of future quit attempts in those with initially low motivation to quit smoking.[34]

Integrating smoking cessation services into regular systems of medical care is ideal because when treatment is delayed or in another location, fewer patients follow through on referrals than when treatment is easily assessable.[33] Although cessation services could be integrated into almost any medical encounter (including some non-traditional contexts such as pharmacies and dental offices),[35,36] two of the most important are considered in the following sections: primary care visits and inpatient hospital stays.

97.7.1 Primary Care Visits

In the United States, it is estimated that 70% of people who smoke see some type of primary care provider (PCP) each year.[37] Thus, primary care-based cessation interventions can reach most cigarette users. In addition, PCP providers have long-standing relationships with their patients and may be in a unique position as trusted clinicians to provide influential advice that will lead to a quit attempt. It may be frustrating for the provider to repeatedly spend time discussing smoking cessation with the same patient; however, because intention and motivation to quit can fluctuate on a week-to-week basis,[38] assessing motivation to quit at every contact will catch more patients when they are ready to make an attempt. An additional advantage of conducting a smoking cessation intervention in primary care is that pharmacotherapy options can also be discussed and prescribed on the spot if the patient is ready to make a quit attempt.

Due to time and logistical constraints, many PCPs may be limited in the amount of follow-up support they can provide for a quit attempt. In fact, evidence suggests that PCPs arrange for follow-up at a much lower rate than they provide the other components of the 5 As.[39] However, it is becoming increasingly common for large primary care practices to have embedded behavioral health providers. These providers are often trained in smoking cessation[40] or could easily be trained to provide smoking cessation counseling services (e.g., through Tobacco Treatment Specialist certification).[41] Thus, PCPs may be able to refer to an "in-house" provider for continued services. When such a referral is not available, a quit line may be able to provide follow-up support. Such quit-line referrals have also been successfully integrated with primary care–based pharmacological interventions.[42]

97.7.2 Inpatient Hospitalization

Hospitalization can be considered a "teachable moment"[43] when the health effects of smoking are salient and patients are more likely to accept cessation treatment.[8] In addition, US hospitals are now smoke-free, so inpatients will likely experience temporary abstinence regardless of their desire to quit.[44] Clinical guidelines[8] indicate that smoking status should be assessed upon hospital admission and documented on the problem list and discharge summary. People who smoke should be offered NRT while in the hospital even if they are not considering quitting, as a positive experience with NRT relieving withdrawal symptoms may increase NRT use during future attempts.[8,33]

Given that hospitalized patients are acutely ill, it is particularly important to consider possible contraindications for psychopharmacology in this setting. For example, the FDA package inserts recommend that nicotine replacement should be "used with caution" for two weeks following a myocardial infarction and bupropion lowers the seizure threshold.[8] The cardiac risk of varenicline was called into question,[45] but more recent evidence suggests that risk may be lower than originally reported, for example, in reference [46]. Thus, with certain patients, inpatient providers must weigh the medical risk of prescribing pharmacological cessation aids with the benefit of an increased likelihood of cessation.

97.8 COMMUNITY-BASED APPROACHES

97.8.1 Mass Media Campaigns

Mass media, which includes television, film, the Internet, radio, newspapers, magazines, billboards, and cigarette packaging, can play a key role in shaping smoking-related knowledge, attitudes, and behaviors.[47] Mass media campaigns can be designed either to directly target individuals' behavior or to influence the social and political landscape, which can lead to a change in social norms around smoking.[48] Overall, campaigns that are theoretically based and broadcasted at a sufficient intensity (i.e., contact time with the message), frequency (i.e., number of contacts), duration (i.e., days to years), and across multiple channels (i.e.,

television, radio) have been found to be the most effective.[49] Importantly, it is somewhat difficult to isolate the specific effect of mass media campaigns, particularly when they are part of a complex set of interventions.[49] As such, the cost-effectiveness of mass media campaigns is likely high, given that they can positively influence behavior and reach large populations quickly and efficiently, but more research is needed in this area. Future studies will need to investigate the benefits of using methods of communication beyond in addition to the most common (e.g., television, radio), such as social media (e.g., Instagram), as it is becoming increasingly more effective in reaching a wider cross-section of the population, particularly adolescents.

97.8.2 Worksite Programs

There are numerous adverse effects associated with employees who smoke, such as increased healthcare costs and disability, greater absenteeism, poorer job performance, and an increased risk of injury.[50] As a result, employers may be motivated to provide support for effective worksite smoking cessation programs to offset the potential costs related to the negative health consequences of smoking.[51] There are several advantages to conducting a cessation program in such an environment, including (1) access to a large, stable population; (2) the potential for high participation and compliance; (3) a socially reinforcing network and positive atmosphere; (4) an opportunity to include a diverse or hard-to-reach population; and (5) the ability to run a program that can be tailored to the interests, challenges, and needs of a particular group.[52] To date, research has tested programs targeting smokers using individual and group counseling, self-help materials, pharmacological treatment, and social support techniques. Other initiatives tested include environmental cues (e.g., posters), financial or material incentives, and health promotion programs.[52–54] Among these, the programs that specifically target individual smokers have shown the largest effects, such as group and individual counseling, and pharmacotherapy. There is little evidence that the other methods are as helpful, but it may be that tailored programs are needed for certain subgroups (e.g., younger smokers) to be effective overall.[55] Nonetheless, more studies are needed, as participation in worksite interventions has been lower than expected, and most of the research has been conducted in traditionally stable worksites, which are becoming less common with advancing technology and increasingly mobile employees. Lastly, more data detailing the specific costs of worksite smoking cessation programs and the relevant associated potential economic outcomes such as reduced absenteeism and increased productivity are needed.[52]

97.9 TECHNOLOGY-DRIVEN APPROACHES

97.9.1 Internet-Based Interventions

In the United States, about 93% of the population uses the Internet.[56] Unlike real-time counseling via telephone and individual or group counseling, Internet-based services can potentially provide smokers with the option of finding information at any day or time they choose.[57–59] To date, there have been about 70 trials. There is some evidence to suggest that interactive and tailored Internet-based interventions, with or without behavioral support, are moderately more effective than non-active controls at six months or longer.[60] In addition, there does not seem to be a difference between Internet and other active smoking cessation treatments.[60] Future research efforts need to use rigorous evaluation methods to determine the effectiveness of Internet-based components, and examine potential mediators, such as e-mails, group chats, and other ways of engaging users and providing support during the quitting process. More information on factors, such as usability and sociability, that make people spend more time on sites or return to the sites more often will also be important to investigate.

97.9.2 Mobile Phone Interventions

It is estimated that 97% of the US population owns a mobile phone, and 85% own a smartphone.[79] As such, researchers have been examining the efficacy of using text messages and app-based interventions for smoking cessation. These interventions allow for the smoking treatment to be delivered directly to the person who smokes with minimal direct contact and to a large number of people at a very low cost. Additionally, people who smoke can engage with an app and/or receive messages anywhere they can use their phone when it is most appropriate or convenient and without threats to confidentiality.[62] To date, there have been less than 30 published studies testing phone-based smoking cessation interventions. There is a moderate amount of evidence to support the use of (automated) text messaging interventions for smoking cessation, while there is less evidence for app-based interventions.[62] Outcomes have included both self-report and biologically verified assessments. New research is needed to determine if sustained effects can be achieved over longer periods of time (e.g., greater than six months), what role apps may play, and if they can aid quitting attempts. Future research will be continually challenged by the quick turnover in technology. Studies testing theory will likely be more relevant and sustainable than those that only examine the latest and most technologically advanced gadgets.

97.10 SMOKING CESSATION IN SPECIAL POPULATIONS

97.10.1 Young Adult and Adolescent Smokers

According to the US 2021 National Youth Tobacco Survey, 1.5% of middle school students and high school students smoke cigarettes.[63] Given that 90% of smokers begin smoking before the age of 18[4] prevention and cessation initiatives are a high public health priority. There is some evidence to suggest that family-based,[64] school,[65] and peer-led programs[66] can help prevent use, but more work is needed. To date, there have been about 40 intervention studies examining tobacco (i.e., cigarettes, nicotine) cessation using a variety of approaches, including behavioral support and pharmacotherapy. Increases in the likelihood of quitting have ranged from 34–60% depending on the program, with the strongest effects being shown for motivational enhancement.[67,68] Caution is needed when interpreting these results, however, as the larger body of evidence on cessation programs for teens and adolescents is considerably heterogeneous. Few studies have used biological indicators of being quit or they defined being quit in various ways.[67–69] Other problems include biased samples, a poor description of the intervention used, and/or the use of complex intervention strategies that combine theoretical approaches.[67,68] Overall, future research will likely benefit from programs that include multiple components, specifically those that take the young person's intrapersonal (e.g., motivation, perceptions) and interpersonal factors (e.g., behavioral support) into consideration.[68] Additionally, it will be important to investigate demographic (e.g., household income) differences and long-term outcomes, and use study designs that include adequate attention control groups.

97.10.2 Minority and Disadvantaged Smokers

The tobacco industry has spent several decades targeting and marketing its products to various minority and disadvantaged groups, including Native Americans, sexual minorities (i.e., lesbian, gay, bisexual individuals), and those with low socioeconomic status (SES) (i.e., low levels of education, income at or below the poverty line, unemployed).[70–72] Unfortunately, this strategy has worked, and the rates of smoking and smoking-related death and disease are significantly higher among these groups when compared with the general population e.g., [5, 73]. As such, research investigating the unique needs of these various subpopulations is critical. To date, behavioral smoking cessation interventions have shown some success, for example, in reference [74], and several key intervention characteristics have been identified, such as using a proper level of health literacy for those with lower levels of education,[75] tailoring the intervention components for their cultural appropriateness,[76] and reducing financial burden for those with low income.[77] Moreover, multi-component interventions and those incorporating mindfulness training, financial incentives, motivational interviewing, and/or extended telephone-delivered counseling may also be particularly effective in the short term.[78] Overall, there is a great need to conduct future high-quality, rigorous research in this area, as it will help us to better understand how these populations can and will quit. It may be one of the only effective ways to reduce the current disparities that exist.

97.10.3 Pregnant Smokers

Given the negative impact of smoking on fetal development and the harmful effects of secondhand smoke on children, there is great interest in exploring smoking cessation interventions for pregnant and postpartum women. It is currently estimated that 54% of persons who smoke will quit when they become pregnant,[79] and 40% start smoking again within six months after delivery.[80] Rates of smoking are also higher among certain populations (e.g., those with less education and lower income).[80] Behavioral support has been the most widely used and promoted intervention for this population,[81] although pharmacotherapy (e.g., nicotine replacement therapy, bupropion) has also been used in combination with behavioral support or as a stand-alone treatment.[82] Recently, a Cochrane review summarized the effects of over 100 studies testing various psychosocial cessation programs including counseling, health education, feedback on fetal health, incentives for quitting, social support, and exercise.[81] Effects were shown to vary depending on the stage of pregnancy, length of time in the postpartum period, and program used, but there was relatively strong evidence to suggest that counseling, feedback, and incentives help pregnant and postpartum women quit.[81] It is important to note that even if complete abstinence is not achieved, a reduction in cigarettes smoked is also a beneficial outcome. More specifically, a significant reduction in the number of infants born with low birthweight[83] or those being admitted into a neonatal intensive care unit has been shown among women who participated in a psychosocial intervention to quit.[81] In the future, it will be necessary to test more rigorous behavior-focused interventions integrating prenatal and postpartum care.[84]

97.10.4 Mentally Ill Smokers

The percentage of individuals with a chronic mental illness (e.g., depression, schizophrenia) who smoke cigarettes has been reported to be 27–65%.[85–87] These higher rates can be attributed to an array of complex psychosocial and biological mechanisms,[88] and they ultimately contribute to the increased incidence of tobacco-related disease and premature death in this population.[89] Research suggests that traditional smoking cessation treatments that work with the general population are also effective for those with mental illness, but there may be differential effects. For example, there is some evidence that contingency management may be particularly effective for those with schizophrenia and posttraumatic stress disorder (PTSD),[90] while cognitive behavioral therapy has been shown to be helpful for those

with depression and anxiety.[91] Regardless of the type of mental illness, it is important to determine how smoking cessation treatment should be integrated with treatment for mental illness. Healthcare providers have been concerned that smoking cessation could exacerbate mental illness (e.g., via increased negative effects from nicotine withdrawal), thus, individual treatment plans based on the patient's acute responses to quitting may need to be developed. It is notable, however, that multiple well-designed studies in this area suggest that smoking cessation significantly reduces mental illness severity, for example, reference [92]. Going forward, it will be important to test the effects of smoking cessation programs in community behavioral healthcare settings, as the current research in this area is often biased with samples of relatively stable patients who have consistently attended treatment.[93] Newer studies should also consider examining innovative programs and harm reduction approaches for those who are not able to quit with standard programs.[94]

97.11 OTHER BEHAVIORAL APPROACHES

97.11.1 Exercise

The US Department of Health and Human Services promotes using exercise as an aid for quitting smoking,[8] and a wealth of clinical trial and acute laboratory-based research has examined the use of exercise as an adjunct to treatment. Overall, it appears that exercise might be helpful for increasing short-term abstinence because it can reduce nicotine cravings and many of the withdrawal symptoms that often accompany quitting, such as negative effects and weight gain.[95,96] However, the majority of studies have not shown strong or consistent effects.[95] This is likely attributable to numerous factors including insufficiently intense interventions, a lack of equal contact between the intervention and control conditions, small sample sizes and inadequate power, and poor adherence to the exercise programs. Going forward, studies will need to test the use of exercise as an explicit strategy that the smoker can use to quit. Lastly, studies should consider the impact of making multiple behavior changes (i.e., quitting smoking and beginning an exercise program) and the amount of time and effort required to change.

97.11.2 Electronic Cigarettes

Significant controversy exists over the safety and use of e-cigarettes, as there are continually new products being put on the market, and the long-term effects of use are not known. Key concerns over e-cigarette use include variability in the amount of nicotine delivered per puff, the potential for dual addiction (adding e-cigarettes to tobacco cigarettes) and increased tolerance to nicotine, low amounts of nicotine present in cartridges listed as containing no nicotine, and marketing to children and adolescents.[97]

To date, there is moderate evidence showing increased quit rates when comparing e-cigarettes with nicotine and NRT.[98] Such findings support the view of some smoking cessation scientists who have called for a harm-reduction approach, given that e-cigarettes may pose a lower carcinogenicity than regular cigarettes.[99] Nonetheless, the current scientific evidence for long-term use is inconclusive, and there is a substantial need to conduct future high-quality, well-designed, rigorous research that will examine the efficacy and safety of e-cigarettes as an aid for smoking cessation. Research is ongoing with studies exploring important factors beyond smoking cessation, such as the type of e-cigarette used, its nicotine content/delivery, and the characteristics of a typical user (e.g., demographics) and their patterns of use (e.g., frequency, duration, inhalation).[100]

97.11.3 Abrupt Quitting and Gradual Reduction

The traditional behavioral method used to quit smoking is to smoke as normal until a predetermined "quit day" and then abruptly stop using all cigarettes. An alternative approach that has gained some support is to gradually reduce the number of cigarettes smoked prior to quitting completely. This gradual reduction in nicotine intake could potentially reduce withdrawal symptoms, increase self-efficacy for quitting, and reduce the likelihood of relapse.[101,102] The value of this approach is somewhat controversial because there is concern that short-term decreases in smoking will not be maintained and that future quit attempts and motivation to quit will ultimately be undermined.[103] However, research shows that smokers using the reduction method have been able to maintain abstinence, and this technique may be more attractive to smokers less motivated to quit. In fact, a 2019 Cochrane review found no differences in quit rates when comparing the effects of abrupt quitting versus gradual reduction, and these effects held whether or not behavioral support, self-help materials, or nicotine replacement were used.[104] As such, there is empirical support to suggest that smokers should be given a choice of quitting methods.[105] Future research will need to better determine which types of smokers benefit the most from each method, and how this can help to inform future policy and intervention development.[106]

97.12 SUMMARY AND CONCLUSIONS

Worldwide, there is an urgent need to reduce cigarette smoking. This chapter has described a range of approaches and strategies that have shown promise for changing smoking behavior in various settings and across several populations. Overall, targeted behavioral interventions that build on the current needs and skills of those who smoke are the most effective.

CLINICAL APPLICATIONS

- People who smoke should be matched with a cessation program based on their preference, motivational level, and previous experience with quitting. This includes strategies ranging from low intensity (brief advice) to high intensity (medication with individual counseling).
- Given the clear role that cultural and socioeconomic factors play in smoking status, future cessation programs need to focus on the social and contextual issues that promote and support cigarette smoking. In particular, new efforts are needed to counteract the tobacco industry's long history of targeting disadvantaged groups.
- Smoking cessation programs should be incorporated into existing medical systems and community-based organizations, increasing the likelihood that these strategies will be disseminated to, and effectively used by, the populations with the highest level of smoking prevalence and greatest need for help.

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98 Alcohol Use Disorders
Diagnosis and Treatment

Chwen-Yuen Angie Chen, MD and Sara C. Slatkin, MD

KEY POINTS

- Alcohol use disorder (AUD) has a high prevalence in the United States, with substantial societal costs from its sequelae.
- Effective screening tools exist, which can be easily implemented in clinical practice.
- An understanding of the neurobiology of addiction can assist healthcare providers in diagnosing and treating AUD.
- Motivational interviewing and harm reduction are best practiced with an understanding of the stages of this disease.
- Evidence-based treatments are available for withdrawal management, prevention of return to use, and harm reduction, which includes pharmacotherapy, behavioral therapies, mutual supports, and alternative modalities.
- During the COVID-19 pandemic, alcohol use increased, which resulted in significant physical and mental health consequences, and the full extent remains to be seen.
- WHO is currently developing an action plan (2022–2030) to effectively implement a global strategy to reduce the harmful use of alcohol, as a public health priority.
- In 2023, Canada issued a final report on guidance for reducing harmful alcohol use; it is based on the principle of autonomy and a right to know the risks of use and recommends two standard drinks or less per week to avoid cancer risks.

Case Presentation

Ms. Howard is a married 48-year-old who presents to establish care in a community primary care practice. She has no specific concerns. On routine questioning, she admits to increasing her intake from one to two glasses of red wine with dinner to mostly a bottle of wine every day since the start of the pandemic. Sometimes, on the weekends, she will drink more, adding an additional cocktail or two. Upon further social history, she explains that she has been under a lot of stress as an attorney and mother of middle school twins, both of whom struggled with distance learning and now reintegration into in-person school. Her alcohol use slowly escalated because work was mostly from home and, therefore, drinking started with lunch with minimal consequences. She is now waking up in a panic at night, is slightly shaky in the morning, and has been unable to stop drinking for more than one day. She is craving alcohol daily at around 4 pm if she has not had a drink by lunch. She finds that the "Xanax" her sister gave her is helping with these shakes and anxiety episodes. Her family history is significant for her father's premature death at age 40 from a boating accident, which may have been alcohol related. On exam, she has elevated blood pressure and, on cardiac auscultation, an audible S4; she has no stigmata of chronic liver disease but has a fine tremor in her hands. At the conclusion of the history taking and the physical exam, the care provider contemplates how to assess the patient's likelihood of alcohol use disorder, how to follow up a positive screening test, and how to provide counseling and treatment to prevent disease progression.

98.1 EPIDEMIOLOGY

The Bureau of Labor Statistics reports that 1% of gross annual income is spent on alcohol in the United States; this averages to $11 per week.[1] Calculations of the prevalence of alcohol use disorder (AUD) vary greatly depending on the methods employed. Factors to consider when reviewing this information include diagnostic criteria, sample size, and sample characteristics, in particular, age and geographic location.[2]

We have chosen to cite the figures from Grant et al.; this study utilized the DSM-V classification of alcohol use disorder. In-person interviews were conducted from June 2013 to October 2014, as part of the National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III). The sample size was 36,309. Respondents were selected using probability sampling from the population of non-institutionalized civilians, over the age of 18, and in the United States. In order to determine its generalizability, the sample was compared with the characteristics noted in the American Community Survey from 2012. The following differences were noted in the Grant study sample:

- There was a greater percentage of men included
- More participants aged 60 to 69 were included
- Fewer participants in the age ranges of 30 to 39 and 40 to 49 were included

The prevalence of alcohol use disorder in the 12 months prior to the study interview was 13.9%. The lifetime prevalence was 29.1%.[3]

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As highlighted by Dr. Marc A. Schukit in an accompanying editorial, this study reveals a 49.4% increase in the prevalence of AUD, compared with a prior estimate in 2001–2002. Striking increases were noted in certain populations, including women, African Americans, participants over the age of 65, and participants aged 45 to 64.[4]

The mean age of onset was 26.2. The mean age of onset decreased with increasing severity: 30.1 for mild, 25.9 for moderate, and 23.9 years for severe. The odds of 12-month and lifetime diagnoses were higher for men compared with women. The highest prevalence was among white respondents, compared to Black, Asian, Hispanic, or Pacific Islander, independent of severity. Native American respondents though had higher rates of both lifetime and 12-month alcohol use disorder compared to the white population sampled. Regarding education level, in this sample, respondents who had attained post-secondary education had higher odds of any degree of substance use, compared with respondents who had attained up to high school level. Other identified predictors of increased prevalence included:

- Previously and never married, as compared to currently married or cohabitating
- Annual family income of less than $69,999
- Residence in an urban area
- Residence in the Western United States, compared with the South and the Northeast

The percentage of respondents with AUD in the prior 12 months who sought help or treatment was 7.7; among those with alcohol use disorder in their lifetime, the percentage was 19.8. The mean age at treatment was 3.2 years greater than the mean age at diagnosis, 29.4 years versus 26.2 years; 3.6% and 8.7% sought treatment from healthcare providers among those with 12-month and lifetime alcohol use disorder, respectively. Other common treatment sources were 12-step programs and designated outpatient and residential rehabilitation facilities.[3]

The study by Grant et al. highlights the current conflict related to alcohol use disorder: the vast discrepancy between the rising prevalence of high-risk drinking and alcohol use disorders and the percentage seeking treatment. We urge universal screening in primary care for alcohol use and, also, suggest approaching screening with the variables we have outlined above to understand the characteristics associated with higher odds of AUD. Although there has been persistence in higher rates of lifetime diagnosis of alcohol use disorder among men, it also must be noted from the Grant study that there has been an alarming increase in AUD in women as exemplified in our opening case.

It has also been established that a family history of AUD increases the likelihood of developing a use disorder and, therefore, including this in family history taking is a relevant part of screening.[5]

Additionally, we would also like to bring awareness to the case of bariatric surgery, particularly Roux-en-Y gastric bypass, which is associated with a higher prevalence of AUDs. One study showed the highest prevalence in postoperative year two.[6] The cause is only postulated, with multiple theories offered. One contributing factor may be related to the change in anatomy after Roux-en-Y. Ethanol is metabolized initially by alcohol dehydrogenase (ADH) most available in the stomach, which after the bypass procedure may be significantly diminished therefore leading to higher concentrations of ethanol being absorbed more rapidly. It is highly recommended to perform alcohol use screening in this population.[7]

98.2 NEUROBIOLOGY

98.2.1 Pharmacology of Alcohol

Ethanol, also known as ethyl alcohol, is the form of alcohol for consumption. The compound is formed from two carbon atoms and one hydroxyl group. A standard alcohol drink, in the United States, contains 0.6 fluid ounces of ethanol (Figure 98.1). Ethanol is a central nervous system depressant and may have additive sedative effects when mixed with barbiturates, benzodiazepines, or opioids, and even with some antidepressants and antipsychotics.

Alcohol is readily absorbed into the bloodstream from the stomach, small intestine, and colon, given its water solubility. It is distributed to all tissues. As muscle tissue contains 7.5 times as much water as fat tissue, individuals with larger muscle mass have larger volumes of distribution and, thus, lower blood alcohol levels; therefore, due to average body composition, men and women have startlingly different responses to the same quantity of alcohol ingested.[8] Notably though, controlling for total body water and weight, women have 20 to 25% higher blood levels than men after consumption of the same amount of alcohol; it is postulated that women have lower levels of gastric metabolism, due to lower expression of ADH.[2]

Ethanol is not a potent compound in the central nervous system; effects are not observed until the blood concentration is at least 5–10 mmol/L.

Ethanol acts by directly binding to membrane-bound ligand-gated ion channels, of which gamma-aminobutyric acid type A ($GABA_A$), N-methyl-D-aspartate (NMDA), glycine, neuronal nicotinic, and 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) are the most notable; binding is specific, and it is inhibitory at some channels and excitatory at others. It also acts on voltage-dependent calcium channels. Additionally, the compound can directly interact with secondary messenger proteins.[9]

Ethanol is primarily metabolized enzymatically in the liver. ADH degrades the molecule to acetaldehyde by first-order kinetics, or in other words, at a constant rate; further conversion to acetate is by acetaldehyde dehydrogenase. Additionally, mixed-function oxidases, including MEOS-CYP2E1, are also involved.

Pharmacodynamically, during initial ingestion, alcohol results in a state of disinhibition. With further consumption, the following are characteristics: impaired judgment,

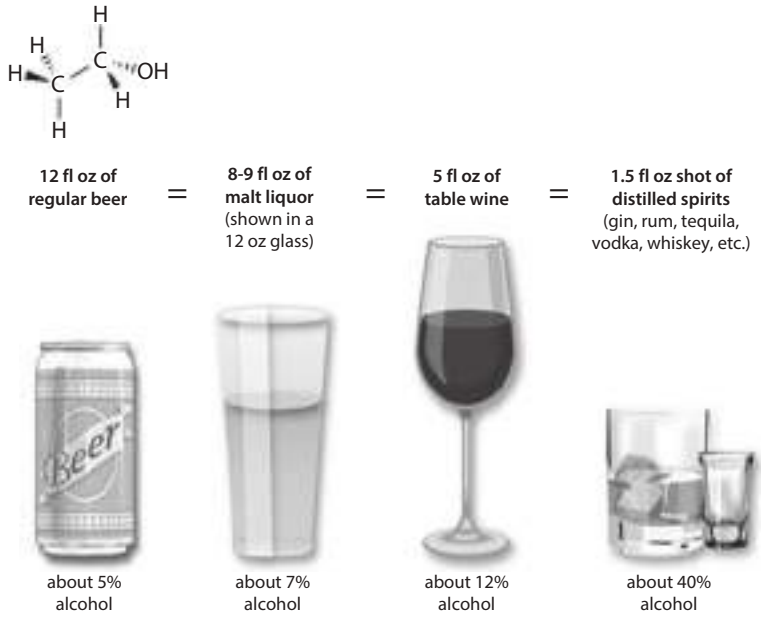


FIGURE 98.1 The chemical compounds of alcohol and a standard drink.

slowed reaction time, emotional outbursts, and ataxia. Classically known sedative and hypnotic effects are at higher blood levels (Figure 98.2). As commonly warned, alcohol potentiates the depressive effects of benzodiazepines and barbiturates if co-ingested because these agents also act on the same $GABA_A$ receptors.[2]

In summary, most notable, in terms of pharmacokinetics, is ethanol's ease of absorption and distribution, yet low potency, but diverse and specific interactions in the central nervous system.

98.2.2 Stages of Addiction

Mainstream public health publications and websites from recovery centers characterize the stages of addiction into a three-stage or a four-stage model. Additionally, central to the practice of addiction medicine are Volkow and Koob's theories.

The three-stage model is described as early, middle, and late/end. The early stage is defined by developing tolerance to alcohol; a patient may identify that his or her pattern of drinking is different from that of his or her peers. In the next phase, patients have cravings for alcohol, have symptoms of withdrawal, and suffer consequences in their personal and/or professional lives. The final stage, titled late or end, is characterized by loss of control; patients at this stage have suffered serious personal and physical consequences from alcohol use.[10]

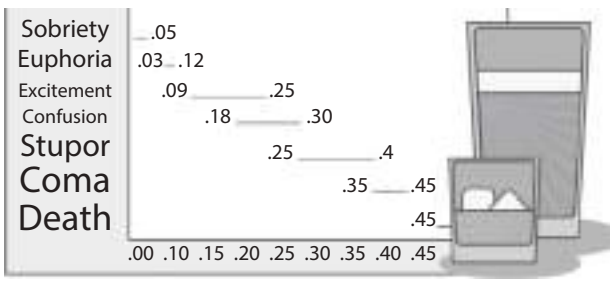


FIGURE 98.2 Stages of alcohol intoxication based on blood alcohol level.

The stages in the four-stage model are adaptive, dependence, progression, and conclusion. The first stage also includes the development of tolerance; it is also characterized by the use of alcohol as a coping strategy for challenging emotions, or more colloquially as an "escape from reality". In the next stage, the patient's amount of alcohol consumption is increased; a patient may start to plan his or her life around drinking and may make frequent excuses to consume more. The progression stage, which is similar to the third stage of the first model described, is unique for the "loss of control" experienced with respect to alcohol; drinking becomes an almost constant and solitary activity. The conclusion stage is defined by physical symptoms and serious personal and professional consequences.[11]

Volkow, Koob et al. emphasize the concept of alcohol use disorder as "an acquired disease of the brain". This brain disease model has three stages, which we summarize in Table 98.1. This model has informed critical advances in the prevention and treatment of this disease, as well as in public policy.[12]

Volkow has also taught another conceptualization to understand the addicted brain compared with a normal control. Addiction confers tremendous saliency on the substance, an overriding preoccupation, with minimal control over the drive to use. And, the memory of use, the positive associations, drives the saliency.

TABLE 98.1
Stages in Volkow and Koob's Brain Disease Model[12]

Stage	Clinical Characteristics	Behavioral Characteristics	Neural Pathways
Binge and intoxication	Pavlovian conditioning: repeated rewarding experiences with alcohol become associated with environmental stimuli	Substance-seeking behavior and binge use	Increased dopamine in the basal ganglia (nucleus accumbens and ventral tegmental areas)
Withdrawal and negative affect	Symptoms of withdrawal	Dysphoria	Desensitization of the reward circuits to dopamine and corticotropin-releasing factor dysregulation (amygdala and habenula)
Preoccupation and anticipation/craving	Inability to resist urges to use or follow through on plans to stop use	Impaired executive functioning	Impaired dopamine and glutamate signaling in the prefrontal cortex insula and allocortex

Dr. George F. Koob describes addiction and thereby alcohol use disorder as a "Reward Deficit and Stress Surfeit Disorder", complementary and supportive to Volkow's theory. He defines alcohol use disorder as: "a compulsion to seek and take a drug, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented". He highlights a transition in the disease state from impulsive use to compulsive use. This later stage is supported by circuits of negative reinforcement, used as a means to combat a negative emotional state, which is caused by dysregulation of the brain's reward circuit and recruitment of the brain's stress systems.[14] In other words, there is a reward deficit, as addiction progresses, more alcohol is required to get the same benefit, equivalent to the pathophysiologic phenomenon of tolerance. Moreover, there is also a stress surfeit, where there is an excessive sympathetic response to lack of alcohol, which is manifested clinically as withdrawal. Over time, baseline set points in the brain are reprogrammed, termed an allostatic state, in which the amount required to regain a pleasurable state is increased (more work to achieve homeostasis, the downward spiral, and, thus, a deficit is created. There becomes a new normal that is actually a perpetual state of negative emotions, which Koob often refers to as the "dark side of addiction".[13]

In summary, alcohol use disorder follows a progression from initially rewarding use into a growing tolerance. Negative emotions and physical symptoms, which include cravings and withdrawal, ensue; these states are often accompanied by costly personal and professional consequences, along with the loss of self-control, leading to more drinking. A destructive cycle is created, leading to continued and increased use of alcohol.

98.2.3 $GABA_A$ Receptors

We would like to highlight the role of $GABA_A$ receptors in the short- and long-term effects of alcohol use in the central nervous system, as they are a prominent therapeutic target. It is thought that ethanol activates $GABA_A$-associated ion currents in the mesolimbic dopamine system; thus, alcohol intake, through $GABA_A$ signaling, has a strong impact in the reward circuit of the brain, as discussed in the prior section on the stages of alcohol use. With repeated exposure to ethanol, the ion current through these receptors is diminished; additionally, the synthesis is downregulated at the mRNA level.[9]

98.2.4 Dopaminergic Pathways

As we have stressed the role of the reward circuit in the pathogenesis of AUD and discussed its activation downstream of $GABA_A$ receptors, we would like to highlight some specifics regarding these pathways and alcohol intake.

- There is a dose-dependent relationship between alcohol intake and dopamine release from the nucleus accumbens.
- The negative mood in alcohol withdrawal is associated with inhibition of dopamine action in the limbic system.[15]
- With chronic use, the persistent release of dopamine "hardwires" the amygdala; a restructured pathway is then created, the activation of which is associated with specific environmental cues related to the individual's pattern of alcohol use. Thus, the addicted brain is readied for craving, reward for use, and relapse.[16]

98.3 DIAGNOSIS

The first step, as always, is recognition, and the importance of this task is highlighted by the societal cost of AUD. The CDC estimates a cost of about $249 billion, as of 2010, averages to $2.05 per drink in expenses related to workplace productivity losses, healthcare expenses, criminal justice costs, and expenditures related to motor vehicle accidents.[17]

98.3.1 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Criteria for Diagnosis

In clinical practice, consistent with our colleagues in addiction medicine, we employ the diagnostic criteria from the DSM-5 (Figure 98.3).[18]

A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

Impaired Control

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.

Social Impairment

5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

Risky Use

8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.

Physiological Indicators

10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for alcohol
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

FIGURE 98.3 DSM-5 diagnostic criteria.[18]

Patients meet the diagnosis if at least two of the listed 11 criteria are met within a 12-month period. The sub-classifications are based on the number of criteria met:

- Mild: 2–3
- Moderate: 4–5
- Severe: 6 or more

This staged diagnosis replaces the prior DSM diagnoses of "alcohol abuse and dependence". Legal problems are no longer a criterion and "craving" has been added, as criterion 4.[19]

98.3.2 Screening Tools

We, in agreement with the US Preventative Screening Task Force, recommend screening all adults for AUD at least once a year.[20] Much of the downstream consequences of alcohol use can be prevented with screening and early intervention for any indication of problematic use. Recent Canadian guidance on alcohol use was published in 2023 (Canada's Guidance on Alcohol and Health: Final Report: www.ccsa.ca/canadas-guidance-alcohol-and-health). The report concluded that there is a continuum of risk associated with weekly alcohol use where the risks of developing cancer and other alcohol-related consequences are reduced if one drinks two[2] standard drinks or less per week.

We support the three-tiered screening approach described by Dr. Fleming, as published with the support of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), an NIH institute and an excellent reference on this topic (Table 98.2).

Level 1 consists of a single question: on any one occasion: "In the past three months, have you had more than five alcoholic drinks?"; this screening was initially proposed in 1998 and has since been repeatedly validated. Its value also lies in its brevity and ease of administration. If a patient responds yes or if time permits and a patient has admitted to alcohol use, the level 2 screen is employed, which further quantifies the patient's alcohol intake.

A more extensive screen, such as the Alcohol Use Disorders Identification Test (AUDIT), Figure 98.4, is suggested if a male patient reports an intake of more than 14 drinks per week or four drinks per day and if a female patient reports an intake of more than seven drinks per week or three drinks per day; a level 3 screen can also be used if there is high suspicion for alcohol use disorder at lower amounts of self-reported intake.[21] The AUDIT indicates harmful or hazardous drinking at scores greater than eight for men under age 60 and at greater than four for

TABLE 98.2
Three-tiered Screening Approach[21]

Level	Indication	Technique
1	All adults, annually	On any single occasion during the past three months, have you had more than five drinks containing alcohol? Positive: affirmative response
2	Positive level 1 screen OR all patients with alcohol use	1. On average, how many days per week do you drink alcohol? 2. On a typical day when you drink, how many drinks do you have? 3. What is the maximum number of drinks you had on any given day in the past month? Positive:Men: more than 14 drinks/week or four drinks/dayWomen: more than seven drinks/week or three drinks/day
3	Positive level 2 screen OR if high suspicion of misuse	Use the Alcohol Use Disorders Identification Test (AUDIT)

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

FIGURE 98.4 Alcohol Use Disorders Identification Test (AUDIT)[22]

women, adolescents, and men over the age of 60; a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.[22] For patients with a positive AUDIT, we recommend utilizing the DSM-5 criteria to further clarify a possible diagnosis of AUD.

98.3.3 Special Populations: Elderly

We would like to highlight screening and diagnosis in the geriatric population, patients over the age of 65. The disease entity is of high prevalence in this population, at least 1% to 3% but perhaps as high as 33%, as there is a substantial degree of underrecognition and misdiagnosis. Various reasons for this phenomenon have been identified including reluctance to disclose on the part of patients, lower degree of suspicion from healthcare providers, atypical patient presentation, due to multiple comorbid diagnoses, and provider lack of knowledge of diagnostic tools and criteria.

The NIAAA recommends no more than one drink per day for patients over the age of 65, as the equivalent intake

of alcohol results in higher blood levels due to unique differences in body composition; in addition to inquiring about current consumption patterns, it is crucial to determine lifetime alcohol use. The AUDIT remains a validated screening tool in this population; various experts and studies also support the use of the CAGE questions.

The consequences of underdiagnosis, and, thus, lack of treatment, are devastating in this population and include worsening of chronic diseases, commencement of and/or exacerbation of neuro-psychiatric conditions, especially dementia, and greater cardiovascular and gastrointestinal diseases. Alcohol use has been implicated in the pathogenesis of urinary and fecal incontinence, falls, syncope, heart failure, aspiration pneumonia, and malnutrition in the elderly.[23,24]

98.3.4 Special Populations: College Students

Alcohol consumption among college students is common; in one study, 40% of college students polled reported intake of five or more consecutive drinks in the past two weeks.[25] The Harvard School of Public Health College Alcohol Study (CAS) has provided significant information on the harms of binge drinking in this population. This study has correlated this behavior with lower academic performance, risky sexual behavior, and antisocial behaviors, including vandalism and those resulting in legal consequences.[26]

Effective intervention has focused on prevention, particularly on education regarding the consequences of excessive alcohol use. The NIAAA has taken a very proactive role on this topic, since 2002, and has a task force to develop evidence-based preventative strategies.[2] We highly encourage providers who treat this population to reference the NIAAA-sponsored site, CollegeDrinkingPrevention.gov, for up-to-date research and recommendations on this subject. It includes educational material for college students and parents, as well as tools for colleges to influence the culture surrounding alcohol use on campus.

98.3.5 Special Populations: Physicians

As members ourselves, we felt it especially important to include physicians in our special populations section. Throughout our careers, we have experienced and heard anecdotes of colleagues' drinking behaviors, but it may not be apparent to most in the field how pervasive this issue is and what the consequences are for the medical community.

Alcohol use disorder among physicians is common: 10 to 12% of doctors develop a substance use disorder, of which alcohol use disorder is the most prevalent, at about 50%. The specialties most at risk are anesthesia, emergency medicine, and psychiatry. The hallmarks of this disease in this population are delayed diagnosis and end-stage presentation, which is speculated to be due to high professional stigma and underreporting by colleagues.[27] We also theorize that the lack of uniformity between state-specific policies, at the level of the medical board and otherwise, may also influence the willingness of physicians to seek help depending on the risk to their professional licensure.

Thus, we encourage maintaining vigilance and sensitivity surrounding the diagnosis of AUD in this population; it affects not only patient safety and delivery of care but also the culture of wellness in our profession. We recommend becoming knowledgeable about one's local institutional bylaws around physicians' well-being and state medical board procedures on the reporting and handling of SUDs among physicians.

According to the website of the Federation of State Physician Health Programs (www.fsphp.org), at the time of this writing, there are 47 states and the District of Columbia that have a Physician Health Program (PHP); three additional states are now participating, Delaware, South Carolina, and Wisconsin, since our last publication. The states that do not have a PHP are California, Nebraska, and South Dakota. A confidential PHP where physicians can seek guidance on treatment, before significant patient care and physician health are jeopardized, is essential to an effective program. Equally important is the compassionate rehabilitation of the impaired physician who has temporarily lost their privilege to practice so that he or she may be successfully reintegrated into medical practice.[28]

98.4 MEDICAL COMORBIDITIES

Alcohol has known pathophysiologic effects on almost all body organ systems.

Regarding the brain, the following areas are most impacted: the cerebellum, the limbic system, and the cortex. The physical size of the organ has been observed to decrease, and there are known delays in neurotransmitter processing. The clinical effects include mood changes, memory loss, seizures, loss of motor coordination, impaired temperature regulation, and decreased learning ability. Additionally, the risk of ischemic stroke is increased; it has been noted, among binge drinkers, that the risk is 56% more likely.

Cardiovascular implications include cardiomyopathy, atrial fibrillation, ventricular tachycardia, and hypertension.

The most publicly known physical consequence is liver damage, which proceeds along a spectrum of disease from steatosis to hepatitis, to fibrosis, and then to cirrhosis. Additional gastrointestinal effects include acute and chronic pancreatitis, gastritis, and GERD.

There is a strong association between alcohol use and cancer risk. Cancers of the following organs have been associated with alcohol use: mouth, esophagus, pharynx, larynx, liver, colon, rectum, and breast.

Effects on the hematopoietic system are also well studied. A deleterious effect on both the adaptive and the innate immune systems has been documented. Ethanol exerts a bone marrow suppressive effect resulting in pancytopenia. It has direct effects on circulating platelets and white blood cells, which results in loss of function.

Regarding the genitourinary system, in men, there is a decrease in erectile capacity and testicular atrophy. In women, amenorrhea, decreased ovarian size, and infertility have been noted, as well as an increased risk of spontaneous abortions. Notably, also, ethanol use during pregnancy can result in fetal alcohol syndrome.[29] According to the Centers for Disease Control and Prevention and the American Congress of Obstetricians and Gynecologists, no amount of alcohol is safe during pregnancy, and alcohol use during pregnancy is a leading cause of preventable birth defects.

98.5 TREATMENT

98.5.1 Withdrawal Management

98.5.1.1 Withdrawal Symptoms and Timeframe

The first step in managing alcohol withdrawal is establishing the diagnosis, which has two criteria:

1. Recent cessation or reduction in alcohol consumption, with a history of regular, prolonged use.
2. Symptoms and signs of alcohol withdrawal, not explained by another medical illness.

Symptoms of alcohol withdrawal include hypertension, tachycardia, diaphoresis, tremulousness, dilated pupils, disorientation, hyperarousal, and seizures. Signs include anxiety, insomnia, hallucinations, paranoia, nausea, and irritability.

Alcohol withdrawal syndrome has a characteristic timeline of distinct symptoms and complications. Withdrawal symptoms, such as those listed above, begin immediately within six hours, depending on the severity, and can last up to six days. The seizure risk is highest between six and 72 hours. Hallucinations can occur between days one and seven. Delirium tremens are typically between two and 14 days.[30,31]

98.5.1.2 Inpatient versus Outpatient Setting

The American Society of Addiction Medicine (ASAM) considers the following patients to be safely monitored on an outpatient basis:

- Patients with mild withdrawal symptoms
- Patients without a history of withdrawal seizures or delirium tremens
- Patients without significant comorbid medical or mental health conditions

Additionally, ASAM advocates that patients managed in an outpatient setting have a reliable person to assist in their care, have easy access to emergency services, if required, and have regular clinic follow-up appointments.

ASAM has an extensive online resource, titled CONTINUUM, which allows clinicians to match patients to appropriate levels of care, at asamcontinuum.com.[2]

98.5.1.2.1 Use of the CIWA Protocol

The Clinical Institute Withdrawal Assessment, revised iteration (CIWA-Ar) is a validated tool for the treatment of alcohol withdrawal. It contains ten symptoms, which can be rated based on severity (Figure 98.5). The total score can then be used to guide pharmacologic treatment.[32] In clinical use, the tool is commonly embedded within the electronic health record and used in the management of hospitalized patients with alcohol withdrawal; regular assessments are then scheduled and completed by a healthcare provider, including the bedside nurse. An associated order set can then be used to administer medication, most commonly benzodiazepines, based on the total score obtained.

Several limitations are immediately apparent, even without extensive familiarity with this scoring system. The symptoms cataloged are similar to other medical and psychiatric conditions, which are often comorbid at the time of withdrawal.[33] Additionally, the scoring system is subjective, as the patients are self-reporting the severity and the tool does not include vital signs. But despite these limitations, the implementation of the CIWA-Ar protocol has been shown to limit the duration of benzodiazepine use and reduce the incidence of major complications, including severe agitation requiring restraints and alcohol withdrawal hallucinations.[34]

98.5.1.2.2 Medications in Acute Withdrawal

Benzodiazepines are the mainstay in the treatment of alcohol withdrawal. This clinical practice has been demonstrated in large clinical trials showing the superiority of this class, in terms of overall symptom management of withdrawal, delirium, and seizures, in addition to facilitating entry into rehabilitation programs, compared with other active agents and to placebo. It has also been clearly shown that the use of short-acting benzodiazepines, in particular alprazolam, and lorazepam, increases the risk of dependence and addiction to these agents, as compared with longer-acting agents, chlordiazepoxide and diazepam.[31,32]

In our clinical practice, with hospitalized patients, we use our initial assessment and subsequent trends on the CIWA-Ar assessment to guide dosing. For patients with severe withdrawal symptoms at presentation and correspondingly high CIWA-Ar scores, we start scheduled long-acting benzodiazepines, most commonly chlordiazepoxide or diazepam. We then order short-acting benzodiazepines, most commonly lorazepam, in a range to be given in response to the CIWA-Ar score.

In liver failure, lorazepam, oxazepam, and temazepam are the safest options in the drug class, due to metabolism by conjugation or Phase II metabolism that avoids the CYP450 pathway; only lorazepam is available IV.[35]

Adjunctive and alternative agents are becoming more commonly used in acute withdrawal, and thus, we would like to summarily highlight alternative regimens and rationales for their use.

Nausea and vomiting. Ask "Do you feel sick to your stomach? Have you vomited?"
Observation:
0—No nausea and no vomiting
1—Mild nausea with no vomiting
2—
3—
4—Intermittent nausea with dry heaves
5—
6—
7—Constant nausea, frequent dry heaves, and vomiting

Tremor. Ask patient to extend arms and spread fingers apart.
Observation:
0—No tremor
1—Tremor not visible but can be felt, fingertip to fingertip
2—
3—
4—Moderate tremor with arms extended
5—
6—
7—Severe tremor, even with arms not extended

Paroxysmal sweats
Observation:
0—No sweat visible
1—Barely perceptible sweating; palms moist
2—
3—
4—Beads of sweat obvious on forehead
5—
6—
7—Drenching sweats

Anxiety. Ask "Do you feel nervous?"
Observation:
0—No anxiety (at ease)
1—Mildly anxious
2—
3—
4—Moderately anxious or guarded, so anxiety is inferred
5—
6—
7—Equivalent to acute panic states as occur in severe delirium or acute schizophrenic reactions

Agitation
Observation:
0—Normal activity
1—Somewhat more than normal activity
2—
3—
4—Moderately fidgety and restless
5—
6—
7—Paces back and forth during most of the interview or constantly thrashes about

Tactile disturbances. Ask "Do you have you any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"
Observation:
0—None
1—Very mild itching, pins-and-needles sensation, burning, or numbness
2—Mild itching, pins-and-needles sensation, burning, or numbness
3—Moderate itching, pins-and-needles sensation, burning, or numbness
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Auditory disturbances. Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
Observation
0—Not present
1—Very mild harshness or ability to frighten
2—Mild harshness or ability to frighten
3—Moderate harshness or ability to frighten
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Visual disturbances. Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
Observation:
0—Not present
1—Very mild sensitivity
2—Mild sensitivity
3—Moderate sensitivity
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Headache, fullness in head. Ask "Does your head feel different? Does it feel like there is a band around your head?"
Do not rate for dizziness or lightheadness; otherwise, rate severity.
0—Not present
1—Very mild
2—Mild
3—Moderate
4—Moderately severe
5—Severe
6—Very severe
7—Extremely severe

Orientation and clouding of sensorium. Ask "What day is this? Where are you? Who am I?"
Observation:
0—Orientated and can do serial additions
1—Cannot do serial additions or is uncertain about date
2—Date disorientation by no more than two calendar days
3—Date disorientation by more than two calendar days
4—Disorientated for place and/or person

Total score:_____ (maximum = 67) Rater's initials_____

FIGURE 98.5 The Clinical Institute Withdrawal Assessment (CIWA).

Carbamazepine is a well-studied alternative agent. It is better than placebo and equal to oxazepam for mild to moderate withdrawal. It is effective in the prevention of alcohol withdrawal seizures, but it has no known activity for the prevention of delirium tremens. As compared with lorazepam, patients treated with carbamazepine in acute withdrawal had fewer protracted symptoms, and in the long term, had a lower risk of relapse.[35]

Valproic acid alone has been studied in two double-blind, randomized control trials. One study reported lessened withdrawal symptoms, a higher rate of completion, and fewer seizures, as compared with a traditional CIWA-Ar-driven protocol with oxazepam as needed. The dose used was 500 mg three times a day of week one.[37] The second study had similar results.

To reiterate the topic of anticonvulsants, to date, there are no published studies regarding the use of gabapentin in acute withdrawal.[35] There is, however, expanding clinical experience using gabapentin in high doses, 600–900 mg three times a day, as an adjunctive or stand-alone agent for the management of alcohol withdrawal; in patients requiring high doses of benzodiazepines, using gabapentin has decreased rates of delirium and shortened the duration of benzodiazepine use, with higher success of prolonged abstinence.

Electrolyte management and vitamin supplementation is another aspect of treatment in acute alcohol withdrawal. We would like to emphasize the administration of thiamine prior to the use of glucose, in patients undergoing withdrawal and with concomitant malnutrition, to prevent Wernicke–Korsakoff syndrome; we dose thiamine 100 mg IV three times daily during acute withdrawal. In hospitalized patients, the repletion of magnesium, potassium, and phosphate can be completed as needed and at least daily, pending on levels and trends.[37] Sustained abstinence from alcohol will reverse these metabolic derangements. Daily

supplementation with thiamine 100 mg, folic acid 1 mg, and a standard dose multivitamin is required initially; in our clinical practice, we prescribe a one-month supply of supplements to our patients, which we have found to be sufficient if patients maintain sobriety and have a healthy diet.[38,39]

98.5.2 Maintenance of Sobriety and Relapse Prevention

Understandably, in the acute clinical scenario, much importance is placed on executing a safe and successful detox, we argue that at least equal emphasis must be placed on developing a plan for sustained abstinence at the same time. Patients, however, are often reluctant to pursue total abstinence; the clinical interaction is improved by assessing readiness for change and by educating on the neurobiology of AUD. This may require monitoring patients through stuttering attempts at controlled drinking in order for them to be convinced of their addiction.

The highest risk of relapse is at three months and one year from the date of sobriety.[40] The following patient characteristics are associated with an even higher risk of relapse: lower level of educational attainment, more problems related to their alcohol use (including legal and psychosocial), unemployment, and consumption of large quantities of alcohol.[41]

Relapse is often a part of the process of recovery and need not be considered treatment failure. Just as one would not withdraw treatment from a brittle diabetic, one continues to treat through each relapse, welcoming the patient to develop new insights and new ways of coping with stress, managing drinking triggers, adjusting medication regimens, and addressing comorbid psychiatric conditions as indicated. It should be mentioned here as well that the risk for relapse is high in those with untreated or undertreated comorbid psychiatric conditions.

Comorbid psychiatric conditions highly associated with AUD include antisocial personality disorder, bipolar disorder, certain anxiety disorders (e.g., social phobia, panic disorder, and post-traumatic stress disorder [PTSD]), schizophrenia, and major depression.[42,43]

98.5.2.1 Pharmacologic Treatments

Currently, the FDA has approved three medications for the treatment of AUD, disulfiram, acamprosate, and naltrexone, which is approved in both an oral and depot formulation (www.niaaa.nih.gov/publications/brochures-and-fact-sheets/treatment-alcohol-problems-finding-and-getting-help#pub-toc3). There is an excellent table by Dr. Peter Friedmann which lists dosage, precautions, and common adverse events.[41] All these medications have proven efficacy in clinical trials and are greatly underutilized for this indication.

In clinical practice, through shared decision-making with our patients, we now routinely offer the use of naltrexone, either the oral or injectable form. We often initiate this medication as close to the time of detox as possible because of its growing success in reducing the risk of relapse and heavy drinking. According to the COMBINE trial, naltrexone with medication management counseling alone increased the number of abstinent days and decreased cravings during the four-month study period. The most common side effects of naltrexone are nausea and dizziness, therefore, it is recommended that patients start at a low dose, take with food, and take the medication before bedtime, for the first few days at least. There is no significant harm if patients drink while taking naltrexone. Naltrexone can sometimes cause depression and is relatively contraindicated in patients with a prior suicide history or a current or prior severe depression. The treatment team and patient need to assess the risk benefit of potential side effects versus the harms of continued drinking. If oral naltrexone is tolerated, then the month-long injectable form may be offered. Liver enzymes are monitored as naltrexone undergoes hepatic metabolism.[44]

Additional medications used for the maintenance of sobriety include those in the classes of anticonvulsants, antidepressants, and GABA agonists, which have been studied in randomized trials, but as mentioned, are not FDA-approved for this indication. Topiramate has been shown to decrease heavy drinking and increase abstinence rates. In patients with comorbid depression, selective serotonin-reuptake inhibitors (SSRIs) have been demonstrated to reduce recurrent alcohol intake. In early onset AUD, ondansetron (Zofran) has been shown to reduce consumption of alcohol as well.[41]

GABA agonists that have shown efficacy in the maintenance of sobriety include baclofen, sodium oxybate, gabapentin, pregabalin, and tiagabine. The mechanism is thought to be mediated more successfully through the B subtype of GABA and results in reduced dopaminergic-reward circuit activity in response to cues, craving, and protracted withdrawal symptoms.

We would like to comment on gabapentin specifically, given its mention in other sections of this chapter. In multiple, placebo-controlled studies, at varying doses, it has been shown to decrease the risk of relapse, reduce heavy consumption, and control craving. We commonly use the dose of 300 mg twice a day, as used in one positive study.[45]

In conclusion, multiple pharmacologic therapies have an evidence base for the treatment of AUD in the early recovery period, yet no one treatment has proven more efficacious than another.

98.5.2.2 Behavioral Treatments

It should not be understated that behavioral, non-pharmacologic treatments for AUD are necessary for recovery. These treatment techniques can be employed in the form of motivational interviewing to engage a reluctant patient in treatment, even prior to detoxification. After detoxification, these therapies are crucial for ensuring medication adherence, assessing for and treating comorbid psychiatric disease, and addressing triggers for relapse.

The following behavioral interventions have been proven effective in AUD:

- Psychotherapy, individual and group
- Behavioral therapy: aversive therapy, cue exposure, relaxation training, contingency management, and skills training (rational thinking, problem-solving, effective conflict resolution)
- Cognitive behavioral therapy, specifically identifying and changing automatic thoughts and triggers related to compulsive alcohol intake
- Family and couples therapy[46]

We would like to highlight the results of Project MATCH, a five-site study sponsored by the NIAAA; its objective was to determine patient characteristics associated with more successful outcomes with specific behavioral treatments. Three types of treatments were included: cognitive behavioral therapy, motivational enhancement therapy, and twelve-step facilitation therapy. At the one and three-year follow-ups, a consistent pattern emerged: patients with high levels of anger had better outcomes in motivational enhancement therapy than the other two treatment modalities, and patients with low anger did better in 12-step facilitation and cognitive behavioral therapy. Additionally, patients with social networks who tend to drink were more likely to have improved outcomes in 12-step facilitation. Overall, though, the conclusion, at the one- and three-year follow-ups, was that no one treatment modality was superior.[47]

We strongly advocate for clinical partnerships with behavioral health specialists, psychologists, and psychiatrists in the treatment of AUD.

98.5.2.2.1 Mutual Help Groups

Mutual help groups are a highly effective form of peer-led support to prevent relapse. Many unique groups exist and have demonstrated sustained recovery among their participants. An excellent reference on the topic is *Circles of Recovery: Self-help Organizations for Addictions* by Keith Humphreys. Featured examples, with meetings nationally, internationally, and with accessible websites, include:

- Refuge Recovery, a Buddhist meditation approach to recovery and is abstinence-based
- Smart Recovery, which is CBT-based and abstinence-based
- Lifering, which is a secular group
- Women for Sobriety
- Alcoholics Anonymous (AA)[48]

We would like to highlight AA in more detail due to its historical and cultural relevance along with its longevity and the available evidence of efficacy. On its website, AA describes the organization as: "an international fellowship of men and women who have had a drinking problem". It is non-professional, self-supporting, apolitical, and available in almost all communities. According to the AA Preamble: "the only requirement for membership is "a desire to stop drinking".

We have shared the 12 steps of AA in Figure 98.6 to increase your familiarity with the program and for your easy reference to share with patients and colleagues.[44] A specific component of the program is that new members are partnered with another member as a sponsor, who can provide mentorship throughout the process of recovery. After prolonged abstinence, members can volunteer to become sponsors, embodying the AA principle that one must "give it away to keep it". It is now common knowledge that the power of service, or volunteerism, is commonly emotionally uplifting and can reduce symptoms of depression and feelings of hopelessness, especially when one can use their own experiences to help another out of the depths of despair. This is at the heart of 12-step recovery.

Multiple trials have compared the outcomes of patients with AUD who engage in AA and those who do not, and a positive association has been demonstrated repeatedly in terms of decreasing the risk of relapse and improving psychosocial well-being. The greatest effect is seen with relatively treatment naïve patients who actively engage in all the service components of AA early in their recovery.[49,50]

The following patient characteristics have been associated with a higher rate of program completion: greater self-motivation, African American, having a formal religious background, prior attendance at formal religious functions, belief in the disease model of addiction, more social personality, and greater participation in the group's activities.[51]

In our opinion, a treatment plan for AUD is not complete without the inclusion of mutual help groups. In our practice, we strongly encourage our patients to join a group; we emphasize to patients that each mutual help group, even if part of the same organization, has its own traits and personality, therefore, if a patient has a negative experience with one group to continue their search for another.

98.5.2.4 Alternative Treatments

We would like to share some alternative treatments for AUD that have been supported by the ASAM.

98.5.2.4.1 Herbal Remedies

Isoflavone compounds, from the root of the kudzu plant (*Pueraria lobata*), have shown efficacy, in animal and human studies, in reducing the amount of alcohol consumed. One dose studied was 3 g of extract daily.

98.5.2.4.2 Acupuncture

Conventional acupuncture treatment has been shown to decrease a patient's craving for alcohol on self-reported scales. The effect is proposed to be mediated through the release of endogenous opioids.

98.5.2.4.3 Transcutaneous Electrical Acupuncture Stimulation

If patients desire a non-invasive approach, transcutaneous electrical stimulation at traditional acupoints has also

THE TWELVE STEPS OF ALCOHOLICS ANONYMOUS

1. We admitted we were powerless over alcohol—that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we *understood Him*.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed, and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we *understood Him*, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.

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FIGURE 98.6 The 12 steps.

shown efficacy, which is presumed through the same mechanism stated above.[2]

98.5.2.4.4 Brain Stimulation

Transcranial magnetic stimulation (TMS) is becoming a more widely used modality in psychiatric practice. Studies have been published, although of small sample sizes, revealing conflicting results. Some studies have shown a benefit in reducing craving and in achieving abstinence in refractory AUD.[52,53]

98.5.3 When to Refer

Addiction medicine specialists welcome referrals, and consultations can provide the following services:

- To clarify the diagnosis of alcohol use disorder
- To guide the process of detoxification
- To assist with determining the level of care required for detoxification and early recovery
- To initiate pharmacologic treatment and coordinate care with providers of non-pharmacologic treatments (including, but not limited to, psychotherapy, mutual help groups, and alternative treatments), individually tailored to patients' goals
- To develop a relapse prevention plan
- When other substance use disorders are comorbid, such as benzodiazepines and opioid use disorders

The website of the American Board of Addiction Medicine (www.abam.net) has a search tool, *Find a Doctor*, to locate a board-certified specialist in your geographic area.

98.6 AUD AND THE COVID-19 PANDEMIC

Anecdotally in our clinical practice and as published in multiple studies, alcohol use and thus risk of AUD and relapse has increased during the COVID-19 pandemic, including a 25% rate of increase in alcohol-related deaths between 2019 and 2020, which outpaced the16.6% increase in all-cause

mortality.[54] In a large, survey-based study, 75% of adults reported alcohol use on one additional day per month; women surveyed had a large increase in heavy drinking and in consequences related to alcohol use.[55] In a British survey of predominantly male respondents, of white ethnicity, with known AUD, at the start of the pandemic, 43% endorsed an increase in use and 17% with prior clinical abstinence reported relapse.[56] It is postulated that stress and isolation are the primary drivers.[57] Furthermore, it is likely that alcohol use exacerbates COVID-19 infection due to lung-specific and immune system-mediated pathways.[58] In a recently published article, there is growing evidence that even one to two standard drinks may contribute to brain volume losses.[59] What we have discovered, thus far, is that it will likely take decades to understand the impact of the COVID-19 pandemic on the prevalence and severity of AUD. As the WHO has begun an initiative for reducing the harms of alcohol use, we strongly encourage annual screening for substance use and comorbid psychiatric diagnoses as the pandemic continues and beyond, and also advise heeding the warning that there may be no safe amounts of alcohol use when it comes to cancer risk or overall health risks.[60,61]

98.7 SUMMARY

Returning to our case presentation, it cannot be emphasized enough the benefits of screening, especially during the COVID-19 pandemic. Ms. Howard drinks more than the recommended amount. Additional relevant history may be if she has experienced withdrawal or if tolerance has developed. It is important to determine if she has suffered any negative consequences from her drinking; for example, is her continued unemployment a personal choice or perhaps from the downstream changes in motivation and mood from alcohol use? How does a possible family history of alcohol use play into her risk for alcohol use disorder? As a woman, her risk for breast cancer increases with the amount of alcohol she uses, how do you counsel her? What are her thoughts on birth control if she is still capable of childbearing? What medical work-up would you want to follow after her initial visit to establish care? For Ms. Howard, it is important to include routine monitoring of her alcohol intake over time, as part of her overall preventative care, to prevent the progression of any use disorder if she has this diagnosis, or if she does not, to minimize harmful or heavy use in which she does engage.

CLINICAL APPLICATIONS

Risk Factors for AUD	Male gender, Caucasian or Native American, attainment of post-secondary education, previously or never married, annual income less than ~70,000, resident in an urban area or the Western United States, history of bariatric surgery.
Neurobiology of addiction	A progression from use that is initially rewarding but later develops into a growing tolerance and state of negative emotions and physical symptoms, which includes cravings and withdrawal and is often accompanied by personal and professional negative consequences and the loss of self-control, which sets up a destructive cycle.
Screening tools	Initial screening, of all adults, annually: On any single occasion during the past three months, have you had more than five drinks containing alcohol? If yes: assess for number of alcoholic drinks per week If male and more than 14 drinks/week or if female and more than seven drinks/week, complete the AUDIT
Treatments for detoxification	Refer to the ASAM criteria for matching patients to levels of care. Options include scheduled long-acting and as needed short-acting benzodiazepines, with the options for adjunctive use of high dose gabapentin. Utilize the hospital CIWA-Ar protocol for PRN benzodiazepine use in the inpatient setting.
Treatments for maintenance of sobriety and relapse prevention	A combination of pharmacologic and behavioral treatments. FDA-approved medications include disulfiram, acamprosate, and naltrexone (PO and IM). Behavioral treatments include individual psychotherapy, behavioral therapy, CBT, and group therapy, including mutual help groups.

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99 Diagnosis and Treatment of Opioid Use Disorders

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KEY POINTS

- Identify risk factors for opioid use disorders.
- Consider opioid use disorders when use exceeds clinical needs and is associated with medical and psychosocial adverse consequences.
- Aim to reduce opioid craving and relapse to excessive opioid use.
- Use medications such as methadone or buprenorphine for stabilization and naltrexone to reduce opioid craving and relapse.
- Encourage combined use of medications with psychosocial support.
- Make use of motivational techniques to help engagement and treatment persistence.

99.1 INTRODUCTION

The diagnosis and treatment of opioid use disorders represent an excellent example of how lifestyle medicine provides a sound foundation to better understand and treat patients suffering from this serious medical problem. The opioid epidemic in the United States has dramatically worsened in the past several years. In 2020, nearly 100,000 people died from drug overdoses, and opioids were involved in 70% of overdose cases.[1] While over-prescription of opioids may have initially contributed to the opioid crisis, highly potent synthetic opioids such as fentanyl have played an increasingly important role in opioid addiction and overdose. The risk of overdose deaths and opioid addiction can be effectively treated; however, many people cannot access evidence-based treatments.[2] The COVID-19 pandemic worsened limited access to treatment in rural, poor, and minority populations. For example, a recent study reported that drug overdose deaths in Black and Indigenous people increased by 44% and 39%, respectively, in 2020 [3].

In this chapter, I will discuss the diagnosis of opioid use disorders and help readers understand the risk factors, appropriate use of opioids, misuse, and ultimately opioid addiction. The three medications currently used to treat opioid use disorders and the integrated role of psychosocial support will then be reviewed. Finally, new digital and medical treatments will be presented.

99.2 RISK FACTORS FOR OPIOID USE DISORDERS

Opioids have an essential role in treating patients with severe pain that is not well controlled with other therapies. However, risks associated with opioid use include diversion, overdose, and addiction. In order to help reduce the incidence of these adverse consequences, healthcare providers need to be aware of the risk factors for opioid misuse. These risk factors can be broken down by looking at (1) physician prescribing practices and (2) patient characteristics and social factors associated with opioid misuse.

Physician prescribing practices often go through large cycles in which opioids are used sparingly or excessively. In the late 1990s and early 2000s, the wave of the liberal use of opioids peaked and was thought to contribute to the current opioid epidemic.[4] This wave was set in motion by reports that chronic pain was being inadequately treated and caused significant undiagnosed morbidity.[5] The advent of longer-acting opioids was widespread because it allowed patients to experience a full night's sleep or complete an entire eight-hour workday. It was thought that longer-acting opioids posed a reduced risk of addiction. Confidence in the efficacy and safety of chronic opioid use was based on limited case studies and the endorsement of medical societies.[6] In clinical research studies, the use of opioids occurs in the context of close monitoring. However, in the actual practice of opioid treatment, clinicians often prescribed many pills without sufficient follow-up visits to assess efficacy—this led to the accumulation of a large supply of unused medications, which were easily misused and diverted.

The past decade has seen a marked decline in new opioid prescriptions as new prescriptions fell about 50% from 2012 to 2017.[7] This decline is related to educational activities designed to help the prescribing clinician monitor chronic opioid use and to be especially attentive to the early signs of opioid misuse such as dose escalations, early refills, and prescriptions by multiple clinicians. One way that clinicians can improve opioid monitoring is to look at risk factors in their patients that predict opioid misuse.[8]

Short-term opioid use for acute pain does not pose a risk for most patients, but several clinical factors predict misuse when opioids are prescribed for chronic pain. Risk factors for opioid use disorder include past or current substance use

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disorders involving opioids or other drugs, including alcohol; patients with co-existing psychiatric disorders; history of trauma; and social or family environments that encourage misuse.

Clinicians can more effectively monitor patients on chronic opioid treatment using rating instruments that can predict patients at risk for opioid use disorders. A popular instrument (Table 99.1) is the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), a 24-item self-administered screening tool developed and validated for those persons with chronic pain.[9] Any individual who scores more than 18 on the SOAPP-R is rated as being at risk for opioid misuse.[10]

99.3 DIAGNOSIS OF OPIOID USE DISORDER (DSM-5 CRITERIA)

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) set the gold standard for defining when someone crosses the threshold where opioid use becomes a disorder.[11] The specific criteria can be grouped by three clusters of symptoms that center around (1) impaired control and drug craving, (2) biopsychosocial impairment, and (3) pharmacological adaptation. As Table 99.2 shows, to meet the criteria for an opioid use disorder, one needs at least two of the specified 11 criteria, with increased severity as the number of criteria endorsed rises.

The first cluster includes taking excessive doses of opioids or chronic use of opioids beyond clinical needs. Typically, attempts to cut down and control opioid use are unsuccessful. Uncontrolled use of opioids can lead to doctor shopping or other time-consuming activities to obtain opioids and excessive time required to recover from the drug's pharmacological effects. These behaviors are typically accompanied by cognitive craving and a strong desire to use opioids.

The second cluster centers around the psychosocial consequences of impaired control over opioid use. Consequences include impairment in functioning at home, at school, or at work. Opioid use continues despite impaired relationships with friends and family. Over time, much of a patient's life centers around the use of opioids, and the patient gives up time for other important activities related to hobbies, friends, family, and work. Opioid use can lead people to put themselves in unsafe situations, such as dangerous neighborhoods, to buy opioids, or engage in illegal activities to afford the cost of opioids.

Finally, the third cluster involves psychological adaptation to opioids, which can take the form of tolerance (the need to take higher doses of opioids to get the desired effect) and characteristic withdrawal symptoms that follow the abrupt discontinuation of opioid use. Clinicians often incorrectly assume that the presence of withdrawal symptoms is a cardinal feature of addiction. However, opioid withdrawal is neither a necessary nor sufficient symptom to diagnose an opioid use disorder. For example, patients with chronic pain or being treated for opioid use disorders may be on opioid agonists and experience withdrawal symptoms if their medical treatment is abruptly discontinued but will show no signs of impaired control or adverse biopsychosocial consequences of opioid use.

TABLE 99.1

Screening Tool to Assess Risk for Opioid Misuse In Pain Patients

Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0 - 14Q

Name: _____ _____ _____ _____ _____ _____ _____ _____ ___ Date: _____

The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 **= Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often**

1. How often do you have mood swings?
2. How often do you smoke a cigarette within an hour after you wake up?
3. How often have any of your family members, including parents, had a problem with alcohol or drugs?
4. How often have any of your close friends had a problem with alcohol or drugs?
5. How often have others suggested that you have a drug or alcohol problem?
6. How often have you attended an AA or NA meeting?
7. How often have you taken medication other than the way that it was prescribed?
8. How often have you been treated for an alcohol or drug problem?
9. How often have your medications been lost or stolen?
10. How often have others expressed concern over your use
11. How often have you felt a craving for medication?
12. How often have you been asked to give a urine screen for substance abuse?
13. How often have you used illegal drugs (for example, marijuana, cocaine) in the past five years?
14. How often, in your lifetime, have you had legal problems or been arrested?

Please include any additional information you wish about the above answers. Thank you.

TABLE 99.2
DSM-5 Criteria for Opioid Use Disorder

Opioid Use Disorder Diagnostic Criteria

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.

Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Specify if:

- **In early remission**: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least three months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids", may be met).
- **In sustained remission**: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids", may be met).

Specify if:

- **On maintenance therapy**: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.
- **In a controlled environment**: This additional specifier is used if the individual is in an environment where access to opioids is restricted.

99.4 TREATMENT OF OPIOID USE DISORDERS

There is a broad set of options for the pharmacological treatments of opioid use disorders. These options range from medications that fully stimulate opioid receptors (opioid agonist), and partially stimulate opioid receptors (partial opioid agonist), to medications that completely block opioid receptors (opioid antagonist). Each approach has advantages and disadvantages that will be presented below.

99.5 METHADONE MAINTENANCE TREATMENT

Methadone, a long-acting full opioid agonist, has a long history of treating opioid use disorders. Treatment involves a daily oral dose of methadone given in a specialized outpatient clinical setting. Patients are started on a small dose of methadone (10–30 mg) to relieve withdrawal symptoms. The daily dose is gradually increased until the patient no longer experiences opioid craving and the opioid receptors are saturated, so any illicit opioid will have little pharmacological effect.

Once stabilized, patients are carefully monitored during their methadone treatment by daily attendance at specially licensed clinics where the day's methadone dose is administered. These visits also include regular monitoring by prescribing clinicians to review the appropriateness of the current methadone dose with respect to withdrawal symptoms, side effects, and clinical response.

Regular urine drug screening monitors treatment effectiveness to assess for illicit opioids and other illicit drugs. Urine drug screens positive for illicit drugs should not be used to withhold methadone treatment. However, they should trigger appropriate therapeutic responses to identify if the patient's treatment needs are being met. For example, if a patient's urine sample shows continued illicit opioid use despite being in methadone maintenance treatment (MMT), it may signal that the patient needs a higher methadone

dose. There is no set rule for how long someone should stay in MMT. However, it is commonly believed that the longer a patient remains in treatment, the better the outcome.

In general, patients who are clinically stable and are being slowly tapered off MMT experience little difficulty until the daily methadone dose reaches 30 mg or less. As the daily dose drops below 30 mg, opioid withdrawal symptoms often emerge between methadone doses. Additionally, the euphoria-blocking and anti-craving effects of methadone are much diminished at this low-dose level.

99.5.1 Advantages

1. It is safer for the patient to take methadone under medical supervision than to take illicit opioids of unknown composition, thereby reducing the risk of opioid overdose.
2. Methadone is taken orally, thereby avoiding intravenous routes of administration that can lead to infections such as HIV or hepatitis.
3. To obtain illicit opioids, people often spend considerable time in risky criminal behavior, whereas methadone allows patients to focus on productive prosocial activities.
4. Methadone has a long history of clinical use. A substantial body of research shows its effectiveness in reducing HIV transmission, the death rate associated with opioid addiction, and criminal activity.

99.5.2 Disadvantages

1. Methadone is a full opioid agonist and, like other opioid agonists, leads to physiological adaptation so that after chronic use, one becomes physically dependent on methadone to avoid withdrawal symptoms.
2. Given the risk of diversion of methadone, its use is restricted to centers licensed through state and federal agencies in specialized opioid treatment programs (OTPs). These programs restrict access to methadone, so a patient in a methadone program is often required to obtain their daily dose at the center, thus leading to trips to the OTP. This daily trip can be time-consuming and restricts outside travel plans for patients who do not live near their OTP.
3. Most people on methadone do not experience severe side effects, but some of the troubling side effects include disturbed sleep, nausea and vomiting, constipation, dry mouth, decreased sex drive and difficulty having orgasms, menstrual irregularities, and weight gain.
4. The major risk associated with methadone is overdose. Overdose is a concern in the initial stages of MMT and when methadone is used in combination with other depressant drugs.

99.6 BUPRENORPHINE OFFICE-BASED TREATMENT

The use of buprenorphine to treat opioid addiction became possible with the Drug Addiction Treatment Act of 2000 (DATA 2000), which allowed qualified physicians to obtain a DEA waiver to prescribe specific controlled substances to treat addictions. Buprenorphine is a mixed agonist-antagonist with different effects depending on the opioid subtype. The mu-opioid receptor is critically important in the effectiveness of opioids in blocking pain and producing addiction. Buprenorphine partially stimulates the mu-opioid receptor. The formulation of buprenorphine used to treat opioid use disorders is typically a combination product in which buprenorphine is mixed with naloxone in a four-to-one ratio. This combination is less prone to misuse because naloxone is an opioid antagonist, so when injected or inhaled, this ingredient blocks the euphoria from buprenorphine. When taken as prescribed (sublingually), the naloxone is not absorbed and therefore does not block the effects of buprenorphine.

Buprenorphine's partial agonist effect complicates the initial induction. In cases where someone is already taking a full opioid agonist, for example, heroin or Percocet, the use of a partial agonist can precipitate opioid withdrawal. However, if someone is already in opioid withdrawal, using a partial agonist will reduce opioid withdrawal symptoms. So, to avoid precipitated withdrawal, it is recommended that the patient should refrain from any opioid use for 12–24 hours or show signs of withdrawal before the first dose of buprenorphine.

The first dose of buprenorphine (2–4 mg) is typically given in the clinician's office, where withdrawal signs can be monitored. For most patients, the next hour or two show decreasing withdrawal symptoms, but for some patients, the buprenorphine precipitates increased opioid withdrawal. Adjunctive medications such as clonidine, an alpha-2 agonist, can help decrease precipitated withdrawal symptoms. Once the patient feels stable and has a reduction in baseline withdrawal, the patient can return home with a prescription for buprenorphine and instructions to repeat the small dose of buprenorphine to relieve any subsequent withdrawal symptoms of drug craving. The dose of buprenorphine on the first day should not exceed 8 mg. Doses may be increased if needed for symptomatic relief of withdrawal symptoms or high opioid craving. Most patients are typically stabilized with a target dose of 8–16 mg daily. If side effects occur, the dose of buprenorphine should be lowered until the side effects are managed. In 2017, an extended-release version of buprenorphine (Sublocade) was introduced in which patients only need monthly subcutaneous injections.[12]

There is no clinical consensus on how long one should be maintained on buprenorphine. Like methadone, one assumes that the longer one stays on buprenorphine, the better. Consistent with the theory that some people have a natural inborn deficiency in endogenous opioid activity,

some clinicians suggest that, like treating other chronic medical conditions (i.e., diabetes, hypothyroidism), one should be maintained on buprenorphine indefinitely.

When deciding to discontinue buprenorphine treatment, it should be kept in mind that, like methadone treatment, one must slowly reduce the dose of buprenorphine to avoid withdrawal symptoms. The dose reduction rate depends on the patient's clinical needs and is negotiated by the patient and clinician together.

99.6.1 Advantages

1. Like methadone, buprenorphine effectively relieves opioid withdrawal symptoms, reduces drug craving, and reduces high-risk behavior such as sharing dirty needles and engaging in illegal activities to obtain illicit opioids.
2. Unlike methadone, buprenorphine can be used in a doctor's office without requiring daily trips to a specialized clinic for observed dosing.
3. With a small dose of naloxone, there is less chance of misusing buprenorphine to obtain an opioid "high", presumably reducing the risk of diversion.
4. Given the reduced state and federal licensing regulations, more clinicians can provide treatment for a larger pool of patients.

99.6.2 Disadvantages

1. Only available from clinicians who obtain a waiver from the DEA to prescribe buprenorphine.
2. Like methadone, chronic use creates a physical dependence on buprenorphine to avoid withdrawal symptoms.
3. Some patients find it difficult to discontinue buprenorphine because of persistent withdrawal symptoms.
4. Even with the addition of naloxone to block euphoria from injected or inhaled buprenorphine, there is still a substantial risk of diversion.

99.7 NALTREXONE AND XR-NALTREXONE

Naltrexone is an opioid antagonist used to prevent relapse to opioids in patients who have completed opioid detoxification. Naltrexone blocks opioid receptors in the brain, so opioids such as heroin or opioid pain relievers will have their pharmacological effects blocked, and the opioids will no longer produce a "high" or euphoria, thus decreasing the motivation to use opioids. The FDA first approved oral naltrexone to treat opioid use disorders in 1985, but because of poor patient adherence, it was generally not used clinically. The FDA approved an extended-release formulation in 2010 (Vivitrol). Administered by intramuscular injection, XR-naltrexone blocks opioid receptors for up to one month.

Before starting naltrexone, one must have completed opioid detoxification and preferably been opioid-free for at least seven days. One can use several protocols to safely withdraw someone from opioids without opioid medications. These protocols typically involve adding clonidine, an alpha-2 agonist, and other adjunctive medications to provide symptomatic relief.[13] Adding low doses of naltrexone early in the detoxification process may facilitate the transition to XR-naltrexone.[14]

Managing opioid withdrawal symptoms is aided by using two scales that measure the severity of withdrawal symptoms. The Subjective Opiate Withdrawal Scale (SOWS) is an 18-item scale designed to be self-administered to rate common signs and symptoms of opioid withdrawal and monitor these symptoms over time (Table 99.3).[15] The Clinical Opiate Withdrawal Scale (COWS), shown in Table 99.4, is an 11-item self-report scale that measures the severity of opioid withdrawal symptoms from the clinician's perspective.[16] The integration of clinical observations from the COWS and subjective observations from the patient's perspective gives a fair overall assessment of the severity of withdrawal.

Following opioid detoxification and a seven-day opioid-free interval, the administration of naltrexone is unlikely to precipitate opioid withdrawal symptoms. Oral naltrexone tablets, with a typical dose of 50 mg per day, can be prescribed by any physician. Medication adherence is best accomplished using the XR-naltrexone formulation of naltrexone, which is supplied as a depot intramuscular injection that the patient receives monthly in the gluteal region. After the first dose of naltrexone, the patient should be observed in the office for the next hour to observe for the presence of withdrawal symptoms. If the injection precipitates withdrawal symptoms, the use of clonidine and other ancillary medications can help relieve symptoms.

There is no recommended length of treatment with naltrexone, but as with methadone and buprenorphine, it is assumed that the longer one stays on naltrexone, the more sustained the recovery. Ultimately, the duration depends on clinical judgment and the patient's needs. Unlike methadone and buprenorphine, there is no physical dependence associated with naltrexone, so it can be stopped without the need to taper to avoid withdrawal symptoms. Patients who discontinue antagonist therapy need to be aware that after a sustained period of abstinence, there is no longer opioid tolerance. They should be mindful of the increased risks associated with an opioid overdose—especially the increased risk of death.

99.7.1 Advantages

1. Not only has it demonstrated its effectiveness in preventing relapse to drug use following opioid detoxification, but it has also been shown to decrease cravings.
2. Currently, it is the only approved medication for opioid dependence that is not a controlled substance. There is no need for a special DEA waiver for clinicians to prescribe naltrexone.

TABLE 99.3
Subjective Opiate Withdrawal Scale

Subjective Opiate Withdrawal Scale (sows)[1]

The SOWS is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extremely) and takes less than 10 minutes to complete. Patient Instructions: please score each of the 16 items below according to how you feel right now. Circle one number only.

Item	Symptom	Not At All	A Little	Moderately	Quite a Bit	Extremely
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Total score: _____ reference:

1. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two New Rating Scales for Opiate Withdrawal. 1987. *American Journal of Alcohol Abuse* 13, 293–308.

3. Naltrexone does not display abuse potential.
4. XR-naltrexone is effective for 30 days, so there is no need to take a daily dose of medication to ensure medication adherence.

99.7.2 Disadvantages

1. To prevent the occurrence of acute opioid withdrawal in opioid-dependent patients, the patients must be entirely opioid-free for a minimum of seven to ten days before starting naltrexone treatment.
2. The XR formulation is expensive, at over US$1000 per shot, but the cost is typically not paid by the patient since commercial and Medicaid insurance covers it.
3. Chronic use of naltrexone will lead to loss of opioid tolerance and increased sensitivity to opioids. This could increase the risk of opioid overdose.
4. Since naltrexone is an opioid blocker, opioid pain medications will be less effective. While pain control can often be effectively managed without opioid pain relievers, in those cases where opioids are needed, it is necessary to adjust the dose to obtain a therapeutic response.
5. Side effects from the injection of naltrexone include pain and induration.

99.8 INTEGRATION OF PSYCHOSOCIAL SUPPORT IN TREATMENT

Pharmacotherapy alone is rarely a sufficient treatment for drug addiction.[15] Therefore, clinicians have an added responsibility to patients with opioid addiction problems that go beyond prescribing medications.

At a minimum, psychosocial treatment should include the following: psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services. In addition, the patient should be assessed for comorbidity concerning psychiatric disorders, physical consequences of opioid use, family issues, legal consequences, and vocational and financial issues. Excessive use of alcohol and other drugs should also be assessed.

The frequent presence of these problems shows the key role of psychosocial services in addressing the needs of patients and improving treatment outcomes.

99.9 PSYCHOSOCIAL TREATMENT MODALITIES AND ADJUNCTS

Several modalities are offered to provide psychosocial services, such as Cognitive Behavioral Therapy (CBT). CBT helps patients identify risk factors that bring on relapse and helps teach patients more appropriate coping skills.[17,18] There is little research data to show psychotherapy works

TABLE 99.4
Clinical Opiate Withdrawal Scale

Clinical Opiate Withdrawal Scale (COWS)
Flow-sheet for measuring symptoms for opiate withdrawals over a period of time.
For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____ Date: _____ Enter scores at time zero, 30min after first dose, 2 h after first dose, etc. Times: _____ _____ _____ _____			
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120			
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* no report of chills or flushing subjective report of chills or flushing flushed or observable moistness on face beads of sweat on brow or face sweat streaming off face			
Restlessness *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds			
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible			
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort			
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks			
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting			
Tremor *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching			
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute			
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult			
Gooseflesh skin 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection			
Total scores with observer's initials			

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
more than 36 = severe withdrawal

as a standalone treatment, but it can benefit patients with co-existing emotional distress when combined with pharmacotherapy.[19] Self-help groups such as 12-step (AA or NA meetings) groups may be beneficial for some patients and should be considered an adjunctive form of psychosocial support. Alternatives to 12-step meetings include Self-Management and Recovery Training (SMART), Recovery and Moderation Management (MM), Rational Recovery (RR), and Secular Organization for Sobriety (SOS). However, it should be kept in mind that the acceptance of patients who are maintained on medication for opioid treatment is often challenged by many 12-step groups and may be a deterrent to patients adhering to medication.

An important component of any pharmacological treatment is to engage and keep patients in treatment. Motivational enhancement therapy (MET) is designed to help motivate people to engage in new behaviors that promote health. Research shows that this approach helps with nicotine and alcohol use disorders. A relatively innovative approach was derived from MET but is explicitly designed to be integrated with medical treatment. The BRENDA approach is designed to help improve treatment retention and medication adherence and can be implemented by a wide range of healthcare professionals, including those without formal psychotherapy training. The BRENDA approach is relatively easy to learn and stands for six core components that a healthcare provider addresses with each patient: Biopsychosocial evaluation; Report to the patient on assessment findings; Empathy; Needs identified by patient and treatment provider; Direct patient advice; and Assessing the patient's reaction to advice and adjusting treatment when needed.[20]

99.10 FUTURE DIRECTIONS

Challenges in delivering quality patient care limit the effective treatment of OUD. Part of these challenges involves systemic inequalities in the access to evidence-based treatments in poor and underserved areas. Limited access to care was especially prominent during the height of the COVID-19 pandemic, which contributed to the dramatic increase in opioid overdose deaths. Less than 30% of people with OUD receive life-saving medications, and fewer still receive integrated medical and psychosocial care.[21] Many patients with access to treatment fail to initiate care, and many are inconsistent or drop out of treatment prematurely. Future directions on OUD treatment focus on getting more people into treatment and then helping them to stay in treatment.

In order to help facilitate getting people to treatment, harm reduction strategies have focused on going directly to sites where opioids are sold. At these safe sites, medical personnel are available to provide naloxone in case of overdose and offer social support to help people obtain social services and medical treatment.[22] In addition, barriers to treatment are also being reduced as methadone take-home restrictions are being eased;[23] physician limits on the number of patients they can treat with buprenorphine have increased from 100 patients to 275 patients.[24] Emergency departments are offering buprenorphine onsite to overdose patients and are facilitating a "soft handshake" with local providers to help engage patients in treatment.[25]

New medicines are being developed to help medication adherence. While both naltrexone and buprenorphine have extended-release injections that provide medical coverage for a month, newer formulations, including implants, promise to increase the efficacy of the medication for six months or more.[26,27] Novel pharmacological strategies include using cannabis[28] or low-dose psychedelics such as ketamine, psilocybin, or ibogaine.[29,30]

Finally, digital technology has proven especially helpful during the pandemic as in-person visits became more difficult due to COVID-19 restrictions. Virtual visits (telehealth) are increasingly popular and have been shown to be effective.[31] A new evidence-based treatment option is the use of digital therapeutics. These online programs can deliver psychotherapy (typically CBT) to patients anywhere or anytime there is an internet connection and can be integrated with the use of medications, improving patient outcomes and retention.[32]

99.11 CONCLUSIONS

Despite challenges from treatment access, there is encouraging news in fighting the opioid epidemic. Increased attention to the harms associated with opioid misuse has reduced excessive opioid prescribing. Understanding when patients cross the line from appropriate use to having an opioid use disorder allows us to identify those people who can receive help from one of three very different medical approaches to treatment. New pharmacotherapies are currently being studied that may further aid in treating OUD. Adding psychosocial support addresses the comorbid medical and psychosocial complications of opioid use disorders and promotes a full recovery. An integrated medical and psychosocial program can help promote the effectiveness of treatment by addressing co-existing psychopathology and patient engagement. Finally, challenges presented by the opioid pandemic have encouraged new regulatory and digital strategies to further enhance treatment engagement, adherence, and retention.

CLINICAL APPLICATIONS

Practice Tips

Assess

- Opioid misuse, diversion, and addiction, particularly in chronic pain patients
- Medical and psychosocial consequences of excessive opioid use
- Opioid tolerance and withdrawal symptoms
- Comorbid anxiety and mood disorders
- Interest in medical and psychosocial treatment
- Adherence to treatment recommendations

Assist

- Understand the difference between the appropriate use of opioids to treat pain and opioid use disorder
- Discuss the advantages and disadvantages of various medical treatments
- Prescribing and monitoring appropriate medications
- Referral for self-help and psychosocial counseling
- Monitor progress in treatment in collaboration with patient needs

Arrange

- A list of other healthcare professionals and self-help groups for a coordinated care plan
- Referral to addiction specialists when appropriate
- Referral to psychologist or psychiatrist if appropriate

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100 Cannabis Use Disorder and Treatment

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KEY POINTS

- Cannabis is the most commonly used psychoactive drug in the US.
- Legalization of cannabis for medical and recreational use has led to increases in the availability and acceptability of cannabis use.
- Cannabis potency, adult use, use-related problems, and cannabis use disorder diagnoses are increasing.
- Healthcare providers, policymakers, and the general public need to be aware of the significant harms and risks associated with cannabis exposure throughout the life course to prevent potential adverse consequences of use.

100.1 INTRODUCTION

Cannabis is the most commonly used psychoactive drug in the US, with ~12% of the population aged 12 or older reporting past-month use.[1] Changes in state laws legalizing cannabis for medical and recreational use have coincided with changes in public perception of cannabis use. While adults and adolescents increasingly view cannabis as harmless,[2–4] and some can use cannabis without harm, significant risks are associated with use.[5] A major concern about cannabis legalization is that increased availability and acceptability of cannabis may lead to increases in use and adverse consequences.[6,7] Evidence suggests national increases in cannabis potency,[8] adult use[2,3,9–11] and cannabis use disorder (CUD) diagnoses,[10,12–15] with 20–30% of users now meeting criteria for CUD.[16] Healthcare providers should have information about physical, mental, and psychosocial problems associated with cannabis use, and the implications of these for clinical practice. This chapter provides an overview of the harms and risks associated with cannabis use, including CUD, and recommendations for screening, assessing, and treating CUD.

100.2 HARMS AND RISKS ASSOCIATED WITH CANNABIS USE ACROSS THE LIFESPAN

100.2.1 Prenatal Exposure

Cannabis is the most commonly used drug during pregnancy, and maternal cannabis use during pregnancy is increasing.[17,18] Between 2019 and 2020, past-month marijuana use among pregnant women increased from 5.4% to 8.0%.[1] Although many women see cannabis as a natural, safe substance to use throughout pregnancy,[19] potential risks of prenatal cannabis exposure include anemia, low birth weight, need for neonatal intensive care,[20] greater frontal cortical thickness,[21] and impaired executive functioning during childhood.[22] The American College of Obstetricians and Gynecologists recommends that women who are pregnant, contemplating pregnancy, or breastfeeding not use marijuana.[23]

100.2.2 Childhood Exposure

Cannabis exposure during childhood is often via unintended ingestion of cannabis or high-potency edible cannabis products. Acute symptoms of childhood cannabis exposure include lethargy, ataxia, dizziness, hypotonia, seizure, respiratory depression, and vomiting.[24–26] Childhood exposure can lead to the increasing need for emergency care, especially in states with legal cannabis use.[24, 27]

100.2.3 Adolescent Exposure

Concerns about adolescent cannabis use include potentially negative impacts on brain development,[28–30] educational outcomes,[31,32] cognition and IQ,[32–36] life satisfaction and achievement,[37] and risk for later addiction,[32,38,39] depression, anxiety, and suicidality.[40,41] Because common underlying causes could lead to cannabis use as well as these other outcomes, studies of early cannabis use and later impairments are not considered conclusive.[24] To gain further information, the Adolescent Brain Cognitive Development Study[42] is conducting extensive neurocognitive testing and brain imaging before children begin using cannabis and repeatedly assessing the children over a ten-year period to investigate the relationship between early cannabis use, neurocognitive development, and other developmental outcomes. Many programs exist to prevent early adolescent use, and cannabis use remains illegal for those younger than age 21 even in states with legal adult recreational cannabis use.

100.2.4 Adult Exposure

100.2.4.1 Driving Safety

Evidence indicates that Δ-9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis, impairs motor and cognitive functions required for safe driving[43,44]

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and increases the risk of injury or fatality due to driving while intoxicated.[45] Driving under the influence of cannabis (DUIC) increases the risk of fatal and non-fatal motor vehicle accidents.[24,44,46–48] Legislation prohibits driving while under the influence of cannabis, but unlike the tests and devices to detect and prevent alcohol-related driving risks (e.g., roadside breathalyzer tests), determining whether a driver is impaired due to cannabis use is complex. Detection of cannabis in biological specimens does not necessarily indicate acute intoxication, and a test like a breathalyzer has not yet been developed for cannabis. Nonetheless, various methods of roadside detection of cannabis use, including biological and behavioral measures, are being developed and tested.[49] Recreational cannabis laws (RCLs) may increase traffic fatalities[50] and medical cannabis laws (MCLs) are associated with increased prevalence of DUIC.[51] Additionally, higher intoxication levels of cannabis perceived as safe for driving correspond to frequent DUIC[52] and cannabis users may have a false sense of safety at given intoxication levels.[53]

100.2.4.2 Cannabis Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association provides specific criteria for making CUD diagnoses.[54] The earlier fourth edition (DSM-IV) included legal problems as a CUD criterion. This was removed in DSM-5 and criteria for craving and cannabis withdrawal (Table 100.1) were added.[55] To meet the criteria for DSM-5 CUD, a cannabis user must report two or more out of 11 DSM-5 criteria. CUD diagnoses are classified by severity,[54] with two to three criteria considered "mild", four to five considered "moderate," and six or more considered "severe".

Older studies indicated that cannabis users rarely become dependent,[56] leading to a present-day misconception that the risk of developing CUD among cannabis users is low.[57] However, recent national data indicate that one out of five lifetime cannabis users meet the criteria for DSM-5 CUD, and 23% are considered symptomatically severe.[58,59] CUDs are associated with many psychosocial problems and impairments in functioning.[60]

Cannabis use is clearly a precursor to the development of CUD, but in terms of causality, the etiology of CUD is complex.[61–64] Both genetic[65] and environmental factors contribute to the development of CUD. Social-ecological models of substance use[66–69] suggest that environmental factors (e.g., availability and desirability of a substance) normalize use and reduce perceived risks. These factors contribute to increases in use, and thus may also lead to increases in heavy use and the risk of developing CUD.[70]

100.2.4.3 Cannabis Withdrawal

Cannabis withdrawal is defined as three or more of the symptoms shown in Table 100.2 following cessation of prolonged use.[54] Preclinical,[71–74] clinical,[71,72,74–79] and epidemiologic[75,79] studies have established a cannabis withdrawal syndrome after cessation of use. Cannabis withdrawal is most intense during the first week of abstinence and can persist for as long as a month after use.[45,71,80–83] Up to one-third of cannabis users in the general population[75,76,79] and 50–95% of heavy users in treatment or research studies[71,78,84,85] report cannabis withdrawal. Cannabis withdrawal is moderately heritable,[86] implicating both genetic and environmental etiologic factors. In contrast to widespread knowledge of withdrawal from other substances (e.g., alcohol, opioids),[87] healthcare providers and the general public lack awareness of cannabis withdrawal.[88]

TABLE 100.1
DSM-IV and DSM-5 Criteria for Cannabis Use Disorder

	DSM-IV Abuse[a]	DSM-IV Dependence[b]	DSM-5 CUD[c]
Hazardous use (e.g., driving under the influence)	X		X
Social/interpersonal problems related to use	X		X
Neglected major roles to use	X		X
Legal problems	X		
Withdrawal			X
Tolerance		X	X
Used large amounts/longer than intended		X	X
Repeated attempts to quit/control use		X	X
Much time spent using		X	X
Physical/psychological problems related to use		X	X
Activities given up to use		X	X
Craving[d]			X

[a]One or more criteria within a 12-month period.
[b]Three or more criteria within a 12-month period.
[c]Two or more criteria within a 12-month period.
[d]New criterion added in DSM-5.

TABLE 100.2
DSM-5 Cannabis Withdrawal

A. Cessation of heavy, prolonged cannabis use (i.e., daily or almost daily use over at least a few months).
B. Three or more of these symptoms within a week after cessation of heavy, prolonged use:
   1. Irritability, anger, or aggression
   2. Nervousness or anxiety
   3. Sleep difficulty (e.g., insomnia, disturbing dreams)
   4. Decreased appetite or weight loss
   5. Restlessness
   6. Depressed mood
   7. At least one of these physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, headache
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to another medical condition or another mental disorder, including intoxication or withdrawal from another substance.

Cannabis withdrawal can be impairing[89] and cannabis or other substances can be used to relieve withdrawal symptoms. Cannabis users who experience withdrawal are more likely to have trouble quitting use[71,85,90] and have poor treatment outcomes.[78,84,89,91] Many cannabis withdrawal symptoms overlap with depressive or anxiety symptoms.[92] Thus, cannabis could be used as attempted treatment or self-medication for anxiety or depressive symptoms, but unintentionally perpetuate a chronic problem with cannabis withdrawal instead. Thus, reports of ongoing depression or anxiety among regular cannabis users warrant clinical attention and concern.

100.2.4.4 Psychiatric Comorbidity

CUDs are strongly associated with other substance and psychiatric disorders, including alcohol and nicotine use disorders, and mood, anxiety, personality, and posttraumatic stress disorders.[58,93] The associations with psychiatric disorders become stronger as CUD severity increases.[58] However, whether the relationship between CUD and comorbid psychiatric disorders is causal remains unclear.[94] A prospective study suggested that cannabis use predicted incidence of other substance use disorders (SUDs) but not mood or anxiety disorders,[95] whereas genetic research indicates that shared genetic risk underlies the comorbidity between CUD and major depression[64,96,97] or that CUD may potentially cause major depression.[98]

Cannabis use and CUD are strongly associated with psychosis,[13] with higher levels of use leading to increased risk.[24] Individuals considered ultra-high-risk (UHR) for psychosis (i.e., those with subclinical psychotic symptoms and/or genetic risk and impaired functioning) have higher rates of cannabis use and CUD and higher rates of positive psychotic symptoms (i.e., unusual feelings, thoughts, or behaviors) than nonusers.[99] Efforts to determine whether a causal relationship exists between cannabis use and psychosis have focused on long-term prospective studies, with some supporting a causal relationship[31,100,101] but debate remains.[102,103] Nevertheless, cannabis use, and particularly heavy use, is characterized as one of the strongest modifiable risk factors for developing a psychotic disorder.[104] Concerns also exist about increasing cannabis potency in a changing legal environment.[101–103] As the legalized recreational market in the US produces and distributes stronger forms of cannabis,[105,106] the public needs information on the risks associated with heavy cannabis use, including the risk for psychosis.

100.3 CLINICAL IMPLICATIONS

100.3.1 Screening and Assessment of Cannabis Use Disorder

Screening and assessment are important for detecting, evaluating, and treating CUD. Screening seeks to identify cannabis users who are at risk for or currently have problems related to use. To determine the severity of problems and inform the course of treatment, patients screened as being at risk are further evaluated through assessment.

100.3.1.1 Screening for Cannabis Use Disorder

In non-mental health settings (e.g., primary care, emergency rooms), all patients should be screened for cannabis use. Patients at highest risk for cannabis-related harms (e.g., adolescents, individuals with concurrent psychiatric or substance use disorders) and those who report problems that could be caused or exacerbated by cannabis use (e.g., mood disorders, psychosis) should be screened more frequently.[107] Patients can be screened for cannabis use with brief self-report measures or by urine toxicology tests.

Brief self-report measures provide an economical, efficient means of cannabis screening. To reliably identify those at risk prior to using more extensive assessments, brief screening measures make use of cut-off scores that balance the needs for sensitivity and specificity.[108] Studies suggest that self-reports of cannabis use are fairly accurate, as long as no adverse consequences (e.g., criminal charges) are associated with acknowledging use.[109] However, self-report typically has lower sensitivity than biological drug

TABLE 100.3
Cannabis Use Disorder Screening and Assessment Tools

	Age	Timeframe	Mode	Coverage
Timeline Followback Method[186]	Adolescents and adults	Past week–past two years	Clinician-administered; self-administered	Use patterns (e.g., number of joints smoked per day, number of days used or % days used)
Severity of Dependence Scale[187,188]	Adolescents and adults	Past year	Self-administered	Five-item scale to assess the severity of psychological dependence (e.g., worry about cannabis use, desire to stop using cannabis)
Alcohol, Smoking, and Substance Involvement Screening Test[189]	Adults	Past three months	Clinician-administered	Eight-item scale to assess use patterns and use-related problems (e.g., health, social, legal, or financial problems due to cannabis use, unsuccessful attempts to control/quit cannabis use)
Marijuana Problem Scale[190]	Adults	Lifetime	Self-administered	Nineteen-item scale to assess use patterns and use-related problems
Marijuana Smoking History Questionnaire[191]	Young adults	Lifetime	Self-administered	Twenty-one-item scale to assess use patterns and use-related problems
Cannabis Problems Questionnaire[192]	Adults	Past three months	Clinician-administered	Fifty-three-item questionnaire to assess use-related problems
Cannabis Abuse Screening Test[193]	Adolescents	Lifetime	Clinician-administered; self-administered	Six-item scale to screen for use-related problems
Cannabis Use Disorders Identification Test—Revised[194]	Adolescents and adults	Past six months	Self-administered	Eight-item scale to screen for use-related problems
Cannabis Use Problems Identification Test[195]	Adolescents and adults	Past year	Self-administered	Sixteen-item scale to screen for use-related problems
Marijuana Screening Inventory[196]	Adults	Lifetime	Self-administered	Thirty-one-item scale to screen for use-related problems
Marijuana Consequences Questionnaire[197]	Young adults	Past six months	Self-administered	Fifty-item questionnaire to assess use-related problems
Marijuana Withdrawal Checklist[198]	Adults	Most recent period of abstinence	Self-administered	Fifteen-item scale to screen for cannabis withdrawal symptoms
Cannabis Expectancy Questionnaire[199]	Adults	Current	Self-administered	Forty-five-item questionnaire to assess positive and negative cannabis use outcome expectancies
Marijuana Craving Questionnaire[200]	Adults	Current	Self-administered	Forty-five-item questionnaire to assess craving
Marijuana Quit Questionnaire[71]	Adults	Lifetime	Self-administered	Questionnaire (176-item) to assess use, use-related problems, quitting experiences, and craving

testing.[110–112] Table 100.3 shows a selection of commonly used self-report measures to screen for cannabis use and related problems.

When properly administered (e.g., observed sample collection), biological (e.g., urine, hair, saliva, blood) drug testing for recent cannabis use has the advantage of objectivity and, barring technical problems, practically 100% sensitivity.[110] However, cannabis can be detected for weeks after last use,[113] especially among chronic users, and may not indicate cannabis-related problems[114] or CUD. In addition, biological drug testing is more intrusive and expensive than self-reported measures, so it is typically reserved for screening high-risk populations (e.g., psychiatric or substance disorder patients and employees in safety-sensitive workplaces).

100.3.1.2 Assessing Cannabis Use Disorder

A positive result from self-reported or biological screening for cannabis should be followed by a review of a patient's medical history and a physical exam to identify possible medical risks and consequences of use. In contrast to screening, assessment is a lengthier, more complex process intended to formulate a diagnosis and inform treatment. A comprehensive assessment includes identification of the type, amount, frequency, and consequences of a patient's cannabis use, perception of use and readiness to change, other substance and psychiatric disorders, family history of substance use problems, and social factors that may contribute to cannabis use. A number of valid, reliable scales and questionnaires have been developed to quantify use and assess DSM-5 CUD[115] (Table 100.3).

100.3.2 Cannabis Use Disorder Treatment

A CUD diagnosis has implications for subsequent care. Treatment for SUDs in general, and for CUD specifically, is rare. Among those with current and lifetime DSM-5 CUD diagnoses, only 7.2% and 13.7% received any intervention specifically for cannabis problems.[58] In addition, despite increases in adult cannabis use and related problems, the proportion of patients who have received treatment for cannabis use has not changed since 2003.[116] Thus, CUD remains seriously under-treated in the US general population.

The US Preventive Services Task Force recommends screening for health risk factors, including substance use using the Screening, Brief Intervention, and Refer to Treatment (SBIRT) model, an evidence-based practice to identify and reduce problem substance use through counseling.[117] The SBIRT model is well-established for primary care patients engaging in risky alcohol use,[118] but its effectiveness for other substances remains unclear.[119] Nevertheless, patients in non-mental health settings should be screened for cannabis use and those identified as at risk for cannabis-related problems advised about potential harms associated with cannabis use and referred to specialized substance use treatment if needed.

Outpatient treatment for CUD is more typical but may occur in an inpatient setting if a patient is acutely psychotic, suicidal, or requires hospitalization to treat another substance use or psychiatric disorder. Psychosocial interventions for CUD are the most effective; trials of medication treatments have inconsistent or weak results.[120–123]

100.3.2.1 Psychosocial Interventions

Psychosocial interventions increase patient awareness of the negative consequences of cannabis use, enhance motivation to reduce use, manage painful feelings, and improve social skills, social support, and interpersonal functioning.[120] Randomized trials show the strongest efficacy for cognitive behavioral therapy (CBT), motivational interviewing/motivational enhancement therapy (MI/MET), and their combination.[120] CBT involves the identification and management of external triggers, thoughts and behaviors that encourage substance use, and teaches better coping skills. CBT is particularly effective at reducing cannabis use and even one CBT session can help individuals with CUD abstain from cannabis over time.[124,125] MET is a directive, patient-centered psychotherapy approach that helps individuals resolve ambivalence and increase motivation to reduce substance use through empathic, supportive counseling. A meta-analysis indicates that MI is effective in reducing cannabis use in adults and achieving abstinence from cannabis use in adults and adolescents.[126] MET combines MI with personalized feedback and education regarding patterns of substance use often.[120] MET can reduce cannabis use and the severity of CUD.[120,127] Combinations of CBT and MET are often more effective than either alone.[120] In addition, contingency management, which uses behavioral reinforcement techniques (e.g., a voucher incentive) to promote treatment adherence or abstinence, can effectively reduce cannabis use when provided in combination with CBT or MET.[120,128] However, although contingency management alone has been found to be generally effective in reducing other SUDs, evidence about its efficacy in treating CUD remains unclear.[129–131]

Individuals with CUD who lack access to structured psychotherapy may benefit from drug counseling or referral to a mutual help group like Marijuana Anonymous. Drug or addiction counseling includes individual and group sessions aiming to reduce substance use through fact-based education about use and health risks and suggestions for minimizing harm.[120] Mutual help groups for addiction aim to help individuals achieve and maintain abstinence. Based on the 12-step principles of Alcoholics Anonymous, Marijuana Anonymous is widely available and does not charge dues or fees for membership or attendance.

100.3.2.2 Pharmacological Interventions

Currently, no medication for the treatment of CUD is approved by the US Food and Drug Administration (FDA).[132] N-acetylcysteine and gabapentin have yielded the most favorable results in clinical trials, while other medications (e.g., antidepressants and anticonvulsants) have shown mixed or negative findings.[133,134]

100.3.3 Use of Cannabis for Pain

Chronic pain is common among US adults.[135–138] Prescription opioids have been widely prescribed for chronic pain[139,140] despite inconsistent evidence for analgesic benefits.[141] The serious risks of opioid use,[140,141] including physical dependence, addiction, transition to heroin use, and overdose,[142–144] have made opioids a well-known US public health crisis. Consequently, calls have been made to substitute medical marijuana for opioids[145] due to its advantages (e.g., analgesia[146] and lack of fatal overdose[147]).

Many medical marijuana patients use cannabis for pain relief, some as a partial or complete substitute for prescription opioids,[148–153] while others continue to use or abuse prescription opioids. Individuals use cannabis for pain relief in states with and without MCLs.[154,155] Enactment of MCLs has been followed by lower rates of opioid prescriptions,[156,157] hospitalizations for opioid use disorder,[158,159] overdose,[160,161] and opioids detected in fatally injured drivers.[162] However, a recent review found low/insufficient evidence that plant cannabis is an effective treatment for chronic pain.[163] Medical marijuana also has its problems, including cognitive/motor impairments,[164] other side effects,[146] and lack of standard product formulations.[165] A large-scale general population follow-up study showed that among adults with pain, those using cannabis at baseline were more likely (not less likely) to have an opioid use disorder three years later.[166] Concerns are emerging that over-reliance on medical marijuana may lead to further downstream substance problems in

the general population[166–169] and that experiencing pain is a growing risk factor for CUD.[170] Therefore, providers should inform patients that cannabis is not entirely risk-free, and can have side effects or lead to adverse health outcomes.

100.3.4 Use of Cannabis for Psychiatric Conditions

Evidence is lacking for the efficacy of cannabis in the treatment of depression or anxiety disorders,[24,146,171–173] although personal testimonies suggest that cannabis relieves depressive and anxiety symptoms.[174,175] Online product advertising may enhance the impression that cannabis can treat mood or anxiety problems (e.g., "green Prozac"[176,177]). Consistent with this, many medical marijuana patients report using cannabis to treat these symptoms.[152,153,171,178–181] However, when asked about actual symptom relief, less than half report such relief,[179] while others report that anxiety symptoms return on cessation of use,[182] suggesting that symptoms may be due to unrecognized cannabis withdrawal.[171] Several cannabis withdrawal symptoms overlap with depression and anxiety symptoms (Table 100.2). Individuals may use cannabis for short-term relief of depression and anxiety symptoms, unaware that use could perpetuate a longer-term withdrawal problem and have adverse effects on the course of depression.[183] Furthermore, some research shows that MCLs are associated with lower rates of antidepressant and anti-anxiety prescriptions.[156,157] Since evidence suggests cannabis is ineffective in the treatment of depression and anxiety disorders[24,146,171] and that use may result from confusion between withdrawal and depressive or anxiety symptoms, substituting cannabis for FDA-approved medications is a concern. Clinicians, especially those treating younger patients or patients with symptoms of mental illness, should explore with patients whether a cannabis use/withdrawal cycle may be perpetuating depressive or anxiety symptoms. Some patients may not be receptive to the idea that cannabis is contributing to their symptoms rather than alleviating them. However, continued respectful and empathic discussion and perhaps some self-monitoring may help in this regard. Efforts at cessation of use for a period of time may clarify if the depression or anxiety reflects cannabis withdrawal or is independent of cannabis use.

While some evidence indicates that cannabis has adverse effects on the course of posttraumatic stress disorder (PTSD),[184] other research suggests that synthetic oral cannabinoids may be helpful for treating some aspects of PTSD.[102] Medical marijuana is specifically authorized as a treatment for PTSD in 27 states.[185]

Since cannabis use is characterized as one of the strongest modifiable risk factors for developing a psychotic disorder, children and adolescents with a family history of psychosis or prodromal symptoms should be informed of the risks and strongly advised to not use cannabis.[104]

100.4 CONCLUSION

As attitudes and laws about cannabis use evolve and the prevalence of cannabis use increases, healthcare providers, policymakers, and the general public need to be aware of the risks associated with cannabis use. Clinicians should screen and assess all patients for cannabis use and cannabis-related problems, inform cannabis users of potential adverse consequences of use, and refer those with CUD to treatment. Additionally, further research should:

1. Identify risk factors for adverse cannabis-related outcomes and changes in such risk factors amid a changing legal and social landscape.
2. Further develop screening and assessment measures to detect cannabis use and cannabis-related problems, including CUD.
3. Provide information on the efficacy of interventions aimed at increasing awareness of cannabis risks and reducing use, particularly among those with a higher likelihood of adverse consequences.
4. Understand the relationships between cannabis use and cognitive functioning, cannabis withdrawal and psychiatric disorders, opioid use and marijuana laws (both for medical and recreational use), and postnatal outcomes related to using cannabis during pregnancy.

While much has been learned about cannabis, its use, and its consequences, further investigation is needed to expand the evidence base for clinical care aimed at preventing negative cannabis-related health outcomes alongside a rapidly evolving social and legal environment.

CLINICAL APPLICATIONS

- Healthcare providers should screen and assess all patients for cannabis use and use-related problems, inform cannabis users of potential adverse consequences of use, and refer those with CUD to treatment.
- Patients at highest risk for cannabis-related harms (e.g., adolescents, individuals with concurrent psychiatric or substance use disorders) and those who report problems that could be caused or exacerbated by cannabis use (e.g., mood and anxiety disorders, psychosis) should be screened for cannabis use and advised about potential risks more frequently.
- Patients who use cannabis for pain relief should be informed that cannabis is not entirely risk-free and should be closely monitored for adverse health outcomes, including cannabis withdrawal and CUD.
- All women who are pregnant or contemplating pregnancy should be advised about the potential risks of prenatal cannabis use in order to discourage use.

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101 Digital Health Technology for Behavior Change

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KEY POINTS

- Digital health technology is a rapidly growing field, encompassing FDA-approved prescription digital therapeutics, direct-to-consumer health apps, and social media platforms where patients exchange knowledge and experiences.
- The impact of digital health technologies has been applied and scientifically validated in a wide range of conditions, spanning from mental health and substance abuse to cardiometabolic and musculoskeletal conditions.
- It is important that digital therapeutics and health apps are built on validated principles of behavior change and lifestyle medicine.

101.1 INTRODUCTION

Lifestyle medicine stresses the importance of simple and powerful behaviors to prevent and treat diseases and requires less advanced technology than traditional medicine. Indeed, many behavior change strategies have demonstrated remarkable success in promoting healthy behaviors without using any technology.[1–4] Nevertheless, behavior change is notoriously difficult to achieve, and this chapter describes how digital health technology can support patients in their efforts.

Digital health is a discipline that includes everything from traditional healthcare services delivered over telehealth to wearable devices, innovative digital therapeutics, digital processes, decision support systems, and comprehensive digital services that integrate all of the above. The main driver of the field is the potential to increase access to healthcare, improve the efficiency of healthcare delivery, and make medicine more personalized and precise.[5] In addition, digital tools have brought healthcare into people's homes and empowered patients to take a more active role in their health and healthcare.[6]

The phenomenon of digital health builds on the underlying digital revolution, driven by improvements in data processing power and internet connectivity of mobile devices. The proportion of the world's population that had access to the Internet reached 62.5% in 2022, more than double the number in 2012; 92.1% accessed the Internet primarily via a smartphone, and the average user was online for almost seven hours per day.[7] In the United States, 93% of the population uses the Internet, and 31% of adults report being constantly online.[8,9] Digital technologies have become so intimately integrated into modern life that sociologists describe life as taking place in a mixed physical and digital presence, a "metaverse".[10]

Starting in 2020, strict lockdown measures due to COVID-19 led to increased adoption of digital health. There was a 154% increase in telehealth visits during the third week of March 2020 compared to the same period in 2019.[11]

US venture capital investment in digital health doubled to $29.1 billion,[12] and the number of health-related apps available surpassed 350,000[13] in 2021. The Center for Medicare Services has broadened its reimbursement to include remote patient monitoring and telemedicine visits, and The Food and Drug Administration has advanced its capacity to oversee and increase digital health technologies through its Digital Health Innovation Action Plan.[14]

It is difficult to generalize the impact of digital technology on health.[15] Studies have shown that digital technologies can impact the morphology of the growing brain, and others have indicated a correlation between social media use and mental health. Among adolescents, both low and excessive use of digital technology is related to decreased well-being, whereas moderate use is related to increased well-being. The impact on short-term measures of hedonic well-being is more potent than on long-term measures of life satisfaction.[16] Among seniors, there is an association between training on social media and better cognitive function, improved mental health, and improved physical well-being.[17]

This chapter describes the most critical digital health technologies and how to combine them into comprehensive digital health services. We start by discussing how health apps and wearables impact health. In the section about digital therapeutics, we describe the treatment of medical

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conditions like diabetes and depression using apps. We also touch on the emerging phenomenon of digital prescription therapeutics, software medical devices that require a prescription from a healthcare professional. We describe how healthcare professionals can use social platforms to disseminate health information and interact with patients. Lastly, we review text messaging and discuss how emerging technologies may contribute to future lifestyle medicine interventions.

An important aspect of digital health is the increasing use of electronic medical records and customer relationship management platforms to guide care processes, collect and analyze patient data, and communicate with patients over telemedicine. We have omitted these technologies since they are not primarily used to promote behavior change.

Throughout the chapter, we provide practical considerations for implementation. Whether designing a digital health service for a small practice or a large organization, adopting one digital health technology is not enough to drive success.[18,19] The user interface, ease of use, financial incentives, training, staffing, and workflow integration are essential. Lastly, services should be grounded in behavior change techniques, such as self-monitoring, positive feedback, barrier identification, or motivational interviewing.[20,21]

101.2 HEALTH APPS

A software application ("app") runs natively on a mobile, wearable, or stationary device. It can also run in a web browser. The connectedness of mobile and wearable devices makes these applications excellent vehicles for effective and efficient lifestyle interventions. This section will describe apps that impact *general health and wellness*, while the section about digital therapeutics describes those that treat a *medical condition*.

It is important to note that while some apps deliver a fully automated user experience, many include human interactions.

101.2.1 Outcomes

The evidence base for health apps is growing but still nascent. Study outcomes depend on several factors, like the underlying behavior change techniques, the technical quality, and the usability. Publications seldom report on the impact of each of these factors, making it difficult to draw systematic conclusions about why some health apps work better than others. Furthermore, mobile technology's rapid advancement and adoption have rendered many research findings out of date shortly after their publication. Nevertheless, individual studies have shown that mobile interventions can successfully encourage positive lifestyle changes and monitor adherence to a program.

Weight management and nutrition. Despite the abundance of weight management programs that offer apps, most programs rely mainly on interpersonal interactions, and there are very few high-quality randomized controlled trials (RCTs). However, a recent meta-analysis of digitized lifestyle interventions utilizing self-monitoring to promote weight loss concluded that they were moderately effective and yielded higher adherence than traditional lifestyle programs.[22] A systematic review of 41 studies concluded that automated nutrition apps had a low to medium impact on nutrition behaviors, such as caloric intake and nutrition scores, and clinical outcomes like BMI and blood lipids. Overall, evidence suggests that mobile applications may be helpful as low-intensity approaches or adjuncts to conventional weight management strategies. However, insufficient evidence supports their use as standalone intensive approaches to weight management.[23]

Physical activity. Most smartphones have embedded accelerometers that can track step counts, and GPS for tracking location to track distance. In addition, apps often implement classic behavior change techniques such as goal setting, self-monitoring, social support, feedback on behavior, and instructions. A 2017 systematic review of 21 RCTs concluded that the studied apps had a statistically significant but small effect on sedentary behavior compared with usual care and a small to medium effect on total physical activity and walking that was not statistically significant.[24]

Mindfulness and mental health. Many mobile applications support mindfulness through guided meditations, relaxation techniques, and resilience training. While these applications have become quite popular, a 2022 systematic review concluded that although studies indicate a potentially positive effect on symptoms of depression and anxiety in a non-clinical population, more rigorous RCTs are required to provide reliable evidence.[25]

Smoking cessation. According to a 2019 Cochrane review, there is moderate-certainty evidence that automated text message-based interventions result in higher quit rates than minimal smoking cessation support. However, the evidence regarding smoking cessation apps was very low certainty, and more RCTs are needed.[26]

101.2.2 Considerations for Implementation

The success of health apps often depends on whether they build on clinical knowledge and evidence-based behavior change techniques. Core features belong to clusters like "goals and planning", "feedback and monitoring", "shaping knowledge", and "social support".[27,28] Unfortunately, commercially available apps often fail to embrace established evidence. In a study of weight-loss app features, the average app included only 18.83% of the strategies included in the landmark Diabetes Prevention Program.[29] Likewise, clinical guidelines for diabetes care emphasize education on a healthy diet, tight glucose control, and the role of exercise. However, a review of 137 diabetes mobile applications showed that less than 38% included this kind of education.[30]

It is crucial to evaluate the functionality of apps diligently. The Mobile App Rating Scale can be used to analyze

an app's functionality, aesthetics, user engagement, and information quality.[31] In addition, developers should assess the risk of loss of reputation, loss of privacy, poor quality of patient data, poor lifestyle or clinical decisions, and inappropriate clinical actions.[32]

101.3 DIGITAL THERAPEUTICS

Digital therapeutics or "software as a medical device"[33] are digital tools intended to treat disease through psychological and behavior change techniques, either standalone or together with pharmacological agents. They often track biometrics using wearable sensors and utilize apps or text messaging to send information and reminders to patients. On the back end, they may include clinical assessment tools, clinician-monitored dashboards, and HIPAA-compliant data storage.[34] Many programs also incorporate remote coaching, a practical option for behavioral counseling when in-person programs are not accessible or convenient.

Digital therapeutics are available directly to consumers and are sometimes paid for by employers and health plans. Prescription digital therapeutics is a subset that requires approval by the Food and Drug Agency and is available only through a healthcare provider.

Digital therapeutics can collect a high volume of user data, ranging from traditional clinical biomarkers to personalized physiologic parameters and social patterns.[35] They can create longitudinal data sets and run analytics that provide insight into the effectiveness of specific program features.

101.3.1 Outcomes

Research on digital treatment solutions began around 2000.[36] Recent research has shown that digital therapeutics can improve access, quality of care, and safety of services.[33] The accessibility and quality of care, combined with the precision of technological advancements, have allowed digital health to transform modern healthcare practices. Digital therapeutics have improved outcomes in many areas, including COPD, asthma, substance abuse, depression, musculoskeletal pain, weight loss, and diabetes.[37–41] The constant growth of clinical trials and review papers in the digital health world reflects the potential of digital therapeutics for improved patient care.[42]

Diabetes. One online diabetes prevention program consisting of a weekly lifestyle medicine curriculum, health coaching, support groups, digital scales, and activity tracking saw participants undergo a 0.8% reduction in HbA1c after four months.[43] The study also showed significantly improved diabetes distress and medication adherence between baseline and follow-up.

Hypertension. A lifestyle modification program that delivered medically validated non-pharmacological interventions through a smartphone app showed a significantly greater reduction in ambulatory systolic blood pressure compared with a control group; 22.2% of the digital therapeutic group achieved morning home blood pressure of less than 135/85 mmHg at 12 weeks, versus 10.4% in the control group.[44]

Substance abuse. The first FDA-authorized prescription digital therapeutic was for the treatment of opioid use disorder. It resulted in improved clinical outcomes, high levels of treatment retention, and fewer hospital encounters after 24 weeks of the treatment.[45]

Mental health. Digital therapeutics for mental health have surged after the COVID-19 pandemic. A study of an evidence-based sleep and mindfulness program found decreased stress levels and improvements in mindfulness and self-compassion for college students.[37] A digital meditation program that focuses on improving mental, emotional, and social health through daily guided meditation playlists found a 14% reduction in stress and a 27% reduction in irritability after only ten days of using the program.[38]

Chronic musculoskeletal pain. Many studies have shown strong short-term improvements in pain and function,[39,46,47] and a digital health intervention incorporating physical exercise, education, and psychosocial support found that improved clinical outcomes could be maintained longer term, with 72.2% of participants achieving a clinically important difference in pain after one year, compared to 56.2% of non-participants.[40] A recent study found that individuals who used a back pain treatment app reported a significant improvement in sleep quality alongside pain reduction,[41] while others have shown improvements in mental health conditions.[46,47]

101.4 SOCIAL MEDIA

Social media are interactive technologies and digital channels that facilitate the creation and sharing of information, ideas, interests, and other forms of expression through virtual communities and networks. Some of the most popular social media websites, with more than 100 million registered users, include Facebook, TikTok, WeChat, Instagram, Twitter, Tumblr, and LinkedIn.[48] There are also health-oriented social networks, one example being "Patients Like Me", a platform where patients support each other and share personal experiences of living with a disease.

101.4.1 Outcomes

A Cochrane Review of social media interventions for different health conditions found that they may be effective in increasing physical activity and well-being. For other health outcomes, the evidence was uncertain.[49]

Social Support and Connection. Social connections are critical for overall health and healthy habits.[50] With loneliness affecting 25%–60% of older adults,[51] online options may help fill an in-person void. Online social support is precious for chronically ill or immobile individuals who can share illness-related concerns or questions with close

friends and family without straining offline relationships.[52] For people living with chronic conditions, social networks can provide a supportive space for daily self-care, a space to strengthen social ties and exchange knowledge, and a place to mobilize and raise collective awareness about illness-specific concerns.[53]

Social connections are known to influence obesity patterns.[54] A 2015 study evaluated variables that may contribute to weight loss in an online weight loss community and found that greater embeddedness in the online network was the variable with the highest statistical significance for weight loss.[55] In a survey of weight loss forum members, the major social support themes were encouragement and motivation, information, and shared experiences. Members reported that they valued convenience, anonymity, and non-judgmental interactions as unique characteristics of Internet-mediated support.[56]

Patient knowledge exchange. Online social networks can support patients in managing their health and can be valuable tools for high-quality and affordable health care.[53,57,58] As patients share their own experiences, they spread technical and medical knowledge, but also "patient knowledge" that helps others navigate day-to-day life.[52]

Decreased reliance on clinicians. Analysis of 16,492 messages from a smoking cessation network showed users took control of their cessation with various tactics, such as virtual bonfires and pledges. None of the messages mentioned the role of a physician in their smoking cessation efforts, suggesting the behavior change effort in this community was primarily self-propelled.[59]

Data collection. Patient-shared data can be collected online to create research databases. For example, a social network of ALS patients collected data on outcomes for those using litium off-label, and saw no clinical effect within the first 12 months,[60] highlighting the potential of patient-generated data to accelerate clinical discovery.

101.4.2 Considerations for Implementation

It is possible to utilize several social network mechanisms in interventions for behavior change. Network members can influence social norms by engaging in or endorsing a behavior or by rewarding or punishing others for engaging in the behavior. They can also establish communication norms that make it more socially acceptable to talk about certain health-related topics.[61]

Many affordable social media tools are available to use in lifestyle interventions, and guidelines encourage healthcare providers to engage with patients on social media. If the target audience is present on an established social media platform, clinicians may engage with them there while observing ethical guidelines. These guidelines tend to mention five moral themes: "the importance of patient confidentiality", "defamation is unacceptable", "privacy cannot be guaranteed", and "the responsibility to maintain public trust".[62]

101.5 WEARABLES

Wearable electronic devices are worn on the skin's surface, detecting, analyzing, and transmitting information concerning vital signs, movement, and the ambient environment. They have quickly become ubiquitous, and people with an interest in measuring and analyzing bodily functions has evolved from a small subculture, the "Quantified Self" movement, to a mainstream movement.

Beginning with the Fitbit in 2010,[63] wearables have evolved from simple data collection tools to extensive platforms designed to drive behavior change.[64] Wearables can provide data on users' heart rate and rhythm, oxygen saturation, blood glucose, and activity levels. They can also provide insights into users' sleep, stress levels, and mood.[64] Wearable usage has increased in the past decade, with an estimated 533.6 million shipments of wearable technology in 2021. Hearables (internet-connected devices worn on or in the ears) have recently surpassed smartwatches as the most widely used wearables category.[65] Healthcare practitioners are now beginning to adopt wearables for patient monitoring in the treatment of a growing number of medical conditions, including diabetes, cardiovascular disease, and movement disorders.[66]

Physical activity trackers are the most abundant wearables. They measure the pulse rate and have built-in accelerometers to track steps, physical activity, and sleep. Some trackers can calculate exercise performance measures like power output, oxygen saturation, and VO_2 max. Trackers and their corresponding smartphone applications are accurate to within 25% of actual step counts and can measure heart rate with less than 10% deviation. The average error for energy expenditure is around 30%.[67,68]

101.5.1 Outcomes

The general effect on lifestyle and health of the widespread adoption of wearable and sensor technologies is unknown.

Physical activity. While trackers may be able to promote physical activity in the short term, their effect on health and longevity is debatable.[69] Accelerometers are used for many clinical purposes, like measuring frailty in a geriatric population,[70] detecting falls,[71] monitoring real-world physical activity,[72] quantifying upper limb gestures in post-stroke rehabilitation,[73] and monitoring gait.[74]

Weight management. Wearable devices have been advertised to help maintain weight and a healthy lifestyle by tracking physical activity and other biometrics. Weight management programs that include wearables offer more significant and long-lasting benefits.[75,76]

Glucose monitoring. Continuous glucose monitors are applied on the skin and measure glucose levels in interstitial fluid. They provide a detailed view of glucose metabolism and collect vast amounts of data for longitudinal analysis. Use of these devices has increased since the FDA approved an easier to use type of CGM in 2017,[77] though the devices were previously adopted internationally and shown to be

accurate.[78] Studies have found that real-time continuous glucose monitoring systems can be clinically valuable, especially in reducing severe hypoglycemia in type 1 diabetes patients who may be unaware of these episodes.[79]

Mindfulness and stress. There is evidence that biofeedback from wearable devices can help reduce anxiety.[80] For example, devices can utilize electroencephalography (EEG) to enhance mindfulness training[81] or monitor stress by measuring electrodermal activity,[82] heart rate, and heart rate variability.

101.5.2 Considerations for Implementation

As devices and sensors vary, it is hard to make generalized comments about how to best design, test, and utilize them. However, Patel and colleagues present a generic outline for how to design and adapt devices to facilitate behavioral change.[83]

First, the user needs to be motivated to use the device. A survey of 6223 individuals showed that more than half who purchased a wearable device stopped using it, with one-third quitting before six months. However, 80% of over 35,000 people were still using wearable activity trackers after six months of a health insurance wellness program, which suggests that it is possible to achieve sustained use by stimulating self-motivation in a comprehensive program.[84]

Second, the device must be able to track its target behavior accurately. Multiple systematic reviews have shown that wearable devices that monitor physical activity tend to underestimate energy expenditure and overestimate sleep time.[68,85,86] The FDA provides formal regulatory guidance over medical devices and monitors the quality of devices in which accuracy is critical to patient health (e.g., continuous glucose monitors).[87,88]

Last, and perhaps most important, wearables are most effective when part of broader wellness programs involving peer groups, gamification and competition, and regular interaction with healthcare providers. Also, it is essential to display data in a way that stimulates users' motivation.[89,90]

101.6 TEXT MESSAGING

The Short Message Service (SMS) is the most widely used data application globally; 67.1% of the world's population own a mobile phone, and they open 90% of text messages within three minutes.[91,92] In addition, text messaging is part of many health apps and social media platforms.

The literature for text messaging applications is more extensive compared with other digital health technologies. The first study was published in 2002, the first systematic review in 2009, and the first systematic review of reviews in 2014.[93]

The benefits of using text messaging for behavior change are numerous. Patients perceive them as personal while being low-cost, instant, easy to use, and scalable.[93–95] Text messages can push information directly to the intended audience and are less likely to be misplaced than print materials. It is possible to precisely design messages to patients' needs, for example, by sending reminders at specific moments of decision-making. Text messages are less invasive than phone calls, and receiving text messages is associated with a small dopamine release.[93,94] Lastly, text messaging can mirror elements of in-person counseling, such as tailored advice, behavioral monitoring, goal setting, and feedback.[95]

Text messaging interventions may be particularly beneficial for low-income populations, given the ubiquity of cellular phones and the low cost of implementation. Text messaging can be cost-effective and impactful in settings with a limited healthcare workforce, limited financial resources, a high disease burden, and hard-to-reach populations.[96,97]

101.6.1 Outcomes

Text messaging has contributed to positive outcomes in many lifestyle interventions.[93] Scientific reviews have shown benefits in a wide range of conditions spanning diabetes self-management, cardiovascular disease, weight loss, physical activity, smoking cessation, and medication adherence.[26, 93, 98–100]

101.6.2 Considerations for Implementation

Various scientific reviews have investigated how to design a text messaging intervention.[94,95] Abroms et al., in particular, have specified a process that starts with understanding the critical behavior change mechanisms and goals for the population of interest. Next, determine the communication objectives of the intervention, identify appropriate behavior change techniques, and determine other theoretical constructs.

While few text-messaging studies explicitly mention behavior change theories, some programs have applied them together with the Transtheoretical Model of Behavior Change, the Health Belief Model, Behavior Learning Theory, and the Information Motivation Behavior Model.[95,99]

Other areas of consideration include:

- *The message content* may include reminders, motivational messages, educational material, goal setting, feedback, and behavior-tracking nudges. Other considerations include the length of the message,[101] the sender of the message, style of writing, cultural and linguistic appropriateness,[94,102] literacy level of the population (generally, avoid higher than the eighth-grade level for adults), and the need for translations.[95] Messages may use text, images, videos, emojis, and website links.[93,103] Standard libraries are increasingly available with empirically tested content.[94,102]
- *The frequency of messages* varies widely in studied interventions, from multiple times daily to weekly, and various recommendations exist in

the literature.[98,103–106] Some studies provide more messages during critical behavior change periods. Some only send messages at the request of users, and others vary in frequency based on their users' text habits or program adherence (e.g., a higher frequency when adherence is low).[95]

- *Interactivity.* A key consideration is whether the intervention should be one-way (provider to the patient only) or two-way (patient also sends information to provider). Bidirectional systems are likely to be more complex and resource intensive. Most studies have used some degree of bidirectional communication, but the literature is mixed regarding its benefits.[98,99,107]
- *Tailoring and personalization.* It is possible to tailor the content of messages to subgroups or even individual users. Several reviews have reported that personalized messages are more likely to catch the user's attention, be remembered, be discussed with others, be perceived as interesting, and feel personally relevant.[94]
- *Data security, confidentiality, and privacy.* Each country has laws and regulations for collecting, storing, or transmitting personal health information (e.g., HIPAA in the United States). Designers should aim to implement secure messaging systems. If using SMS, patients need to understand the privacy risk before using the service.
- *User testing.* It is vital to user-test the acceptability and effectiveness of text messaging programs.[94]

Numerous comprehensive resources are available to further assist with developing text messaging programs.

- The National Cancer Institute's (NCI) Making Health Communication Programs Work
- Pew Research Center's Internet and American Life Project provides data on technology use in various US population segments.
- The World Health Organization's Be He@lthy, Be Mobile program
- The US Department of Health and Human Services and its Text4Health Task Force
- The Johns Hopkins Global mHealth Initiative
- The PATH Mobile Messaging Toolkit

101.7 EMERGING TECHNOLOGIES

101.7.1 Multi-omics

Remarkable advancements in the speed and cost of gene sequencing technology[108] have given rise to the concept of multi-omics. This term encompasses our knowledge about the human genome, epigenome, transcriptome, proteome, metabolome, and microbiome.

There is an association between nearly 150 genetic variants and obesity, and researchers attribute half of the inter-individual variance in body size to genetics.[109] Numerous studies show that genes influence our ability to lose or gain weight.[110–112] Furthermore, genes influence metabolism, food preferences, and eating behaviors. A limited number of genes have been found that may affect exercise adherence and tolerance.[109]

Other areas of multi-omics may be relevant to lifestyle change. Epigenome-wide association studies have shown that physical activity and high-fat diets may impact weight loss by altering the DNA methylation pattern in tissues that are important for energy homeostasis.[109] Furthermore, the trillions of bacteria, archaea, fungi, and viruses that make up the gut microbiome are known to affect food processing, metabolism, vitamin synthesis, and weight regulation.[112]

Knowledge of one's multi-omic profile in itself can influence behavior. For example, identifying BRCA mutations can lead patients to undergo mastectomy, but it is unclear if this can be used to motivate lifestyle change. A Cochrane review showed little to no effect of communicating DNA-based disease risk on patients' smoking status and physical activity.[113]

Recent research has focused on developing personalized multi-omic profiles and understanding the temporal changes to an individual's omic profile. In addition to vast sequencing data, the UK Biobank subsets harbor data on cognitive function, mental health, metabolism, and activity.[114] Researchers have demonstrated that omic data collection might benefit patients in real-time by collecting serial omics profiles (including whole genome sequencing, transcriptomics, and wearables) over several years. They showcased a range of medical and lifestyle interventions adopted by the study participants based on elevated cardiac, cancer, and metabolic disease risk.[115] Understanding complex, personal biology is only possible after enumerating these rich datasets corresponding to a spectrum of wellness and disease.

101.7.2 Virtual and Augmented Reality

Both virtual and augmented reality have surged in popularity in recent years. Virtual reality (VR) is an artificial, computer-generated simulation of an environment through a headset. Augmented reality (AR) is a similar technology that adds computer-generated enhancements to reality.

There is reason to believe that these technologies may be helpful for behavior change. In 2016, an AR game called Pokémon Go (Niantic, Inc.) for iOS and Android devices led to a "population-level" surge in fitness tracker step counts.[116] By 2019, the application had been downloaded more than one billion times, and a study found that users with high interest in the game increased their activity by 26% (1479 steps/day) and were almost three times as likely to meet official physical activity guidelines.[117] Another study showed that the number of participants achieving a goal of 10,000 steps per day increased from 15.3% to 27.5%.[118] Notably, both studies reported significant improvements in sedentary, overweight/obese, and older users. Unfortunately, the

intervention results were short-lived, and the number of daily steps returned to pre-installation levels by week six.[119]

VR has made slower advances in preventing and treating lifestyle-associated diseases. Examples of situations where VR interventions have been successfully tested are respiratory therapy among COPD patients,[120] gait-training in movement disorders,[121] hand therapy after stroke,[122] and chronic low back pain.[123]

107.7.3 New Sensor Types

Miniature electronics, advances in wireless data transmission, improved optics, the steady growth of computing power, and nanotechnology are driving the development of novel wearables. A common theme is for sensors to capture standard physiological data (e.g., pulse, blood pressure, ECG, blood glucose, temperature) via a miniaturized, continuous monitor. The form factor is often novel, such as stick-on tattoos, bandages, microfibers, or minimally invasive implants.[124–126] Some sensors also promise novel physiological measurements, such as caloric intake or hydration.

The most widespread new sensor types are ECG monitors and continuous glucose monitors. The Apple Watch's single-lead EKG monitor has enabled the widespread identification of clinically actionable arrhythmias.[127,128] The Zio Patch (iRhythm, Inc) is a standalone single-lead ECG monitor that has seen widespread use to detect atrial fibrillation, especially in post-hospitalization patients after cryptogenic stroke or transient ischemic attack.[129] The FDA approved the first very-thin filament continuous glucose monitor (CGM) in 1999. Hybrid closed-loop systems that use data from a CGM to control an insulin pump are gaining popularity fast due to their superior impact on glycemic control.[130,131] The commercial success of these products demonstrates an opportunity for devices targeted directly to consumers and to organizations with a vested interest in preventing chronic disease. Possible future use cases include devices that can detect blood pressure, stroke symptoms, seizures, and pressure ulcers.

Data sharing from these new sensors to healthcare systems increases slowly due to privacy concerns, antiquated software, and lack of market incentives. Better data integration could improve patient enrollment and engagement in lifestyle change programs.

107.7.4 Artificial Intelligence and Machine Learning

Artificial intelligence (AI) is the ability of computers to mimic facets of human cognition and has the potential to influence and augment nearly every facet of healthcare. AI has already been implemented successfully in predictive medicine, medical research, epidemiology, health monitoring, medical training, and treatment of lifestyle-associated illnesses.[132,133] However, the more general incorporation of AI into conventional healthcare and consumer-focused platforms has been slow. The most rapid advances have occurred in precision oncology and AI-enhanced radiology.[134]

Machine learning is an analytical method that allows analytics software to be trained on historical data to make predictions from new data sets.[135] The capacity of the software to make predictions improves as it gets access to more data. For example, researchers trained a machine-learning

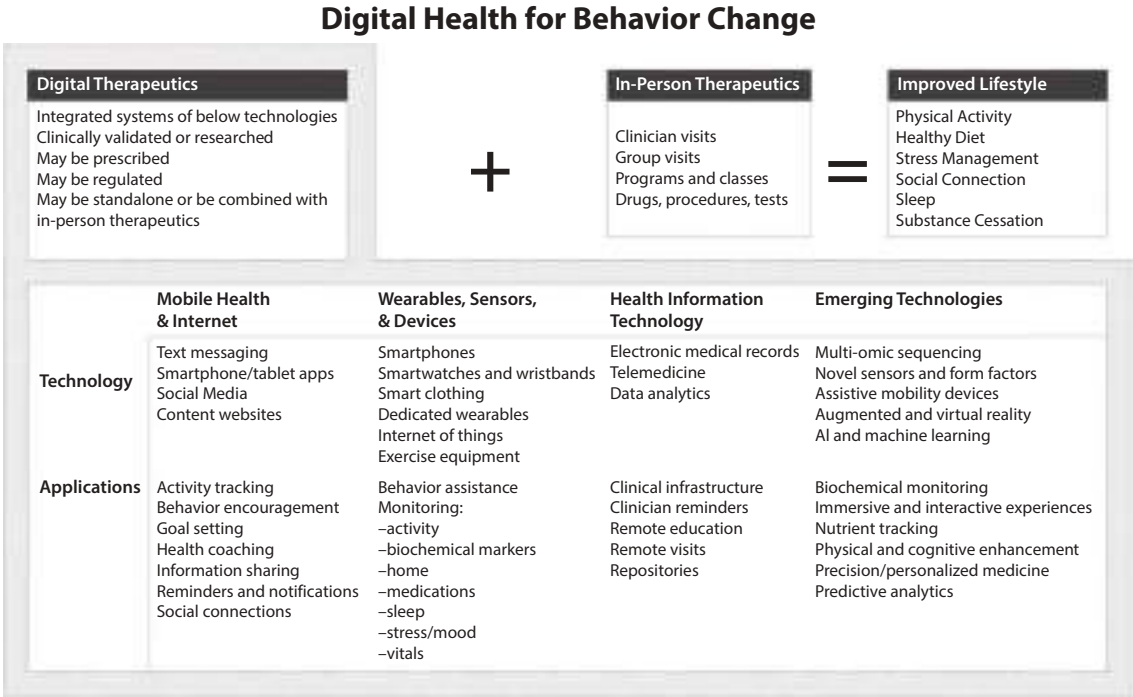


FIGURE 101.1 An overview of current and emerging digital health technologies for behavior change.

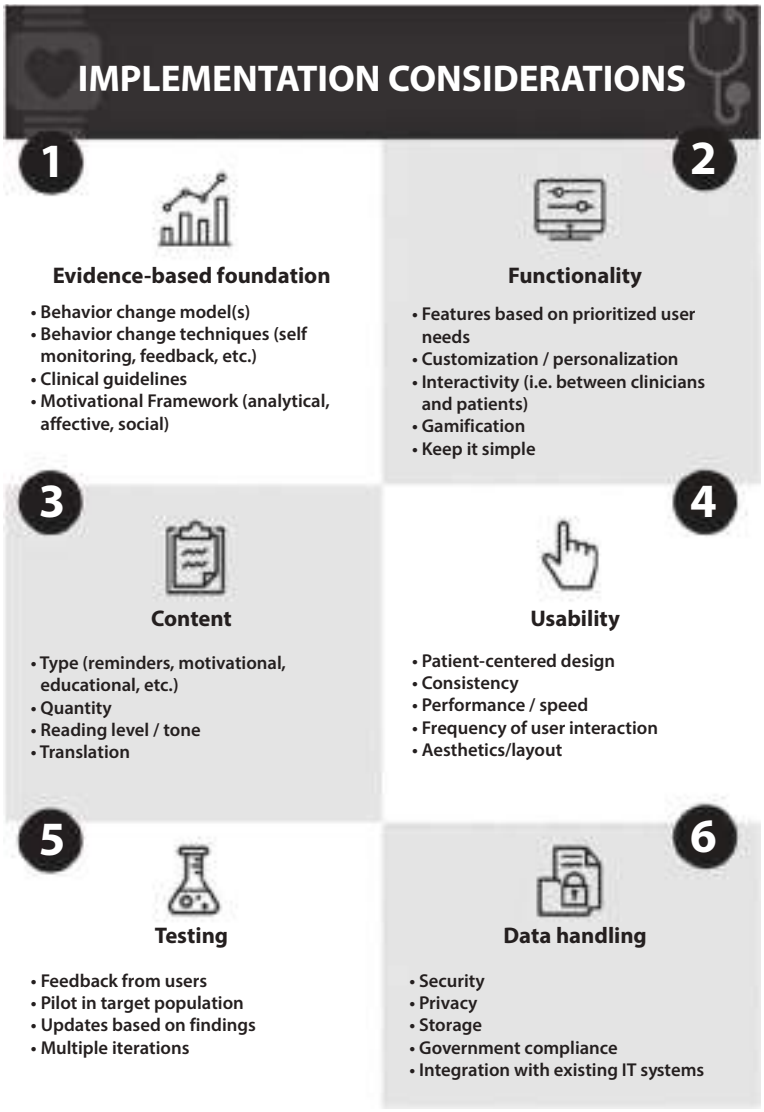


FIGURE 101.2 Multiple considerations may determine the success of digital health technology implementations.

algorithm to predict postprandial blood glucose on data from an 800-person cohort.[136] Input parameters included information from continuous glucose monitors, meal tracking, physical activity, laboratory values, and gut microbiota. The resulting algorithm successfully forecasted blood glucose levels in another group of patients. A separate small RCT demonstrated that diet recommendations based on the algorithm rivaled the impact on postprandial glucose recommendations from a human expert. Other studies have discovered novel disease comorbidities based on EHR data,[137] screened patients for atrial fibrillation from wearable data,[138] and diagnosed upper respiratory diseases such as COPD by the sounds of coughing.[139]

101.8 SUMMARY

Mobile phones, wearable devices, and social media are pervasive in our daily lives and influence our behaviors. The increasing adoption of these technologies drives the use of these technologies in healthcare. Furthermore, a shift toward value-based reimbursement models may lead providers to focus more on outcomes and costs and stimulate their demand for digital health products that monitor and encourage healthy behaviors at scale.

Even though research is lagging, there is sufficient evidence to support that digital health technologies can drive behavior change. This chapter emphasizes that digital health products should be integrated with people and processes and carefully designed to promote simple, powerful, and healthy behaviors fundamental to lifestyle medicine.

CLINICAL APPLICATIONS

- There is clear evidence that carefully designed digital health interventions can drive positive lifestyle change.

- Digital health tools can be used as standalone applications, but they are generally more successful when integrated with people and processes.
- It is important to base digital health products and services on evidence-based behavior change techniques like encouragement, goal setting, health coaching, education, and nudging, and fostering social connections.
- Self-monitoring of physical activity, biochemical markers, medication adherence, sleep, stress, mood, or vital signs can help drive behavior change.
- Whether developing a tool or using an existing one, implementation considerations include an appropriate behavior change framework, content and functionality designed for the target audience, good usability, sufficient user testing, and proper data handling.
- Digital therapeutics are evidence-based digital health programs that prevent, treat, or reverse disease. They typically combine many of the technologies covered in this chapter, are studied in clinical trials, and may require regulatory approval. Prescription digital therapeutics are a subset that requires FDA approval and are available only through a healthcare provider.
- It is difficult to predict the impact of specific digital health interventions due to their complexity. Therefore, it is crucial to validate them in clinical studies before offering them to patients.

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102 Psychosocial Interventions for the Treatment of Substance Use Disorders

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KEY POINTS

- Psychosocial interventions are an evidence-based component of treating various drug problems and addictive behaviors.
- Interventions that have proven effective include behavioral couples therapy, family therapy, cognitive behavioral therapy, dialectical behavioral therapy, community reinforcement approach, contingency management, individual drug counseling, motivational interviewing, brief intervention, 12-step facilitation (TSF), and peer support.
- Psychological interventions can be integrated into a comprehensive treatment plan at every level of care.

This chapter will discuss the evidence for psychosocial interventions for substance use disorders, describe common psychosocial interventions, and discuss how psychosocial interventions may be integrated at different levels of care for people experiencing substance use disorders (SUDs). The National Academy of Medicine, formerly called The Institute of Medicine (IOM), defines psychosocial interventions as "interpersonal or informational activities, techniques, or strategies that target biological, behavioral, cognitive, emotional, interpersonal, social, or environmental factors to improve health functioning and well-being". Psychosocial interventions can be used for drug and process addictions at various stages of treatment and different levels of care. Psychosocial interventions can prevent, identify, and treat SUDs and are useful for rehabilitation and social reintegration. Psychosocial interventions are used alone or in conjunction with pharmacotherapy, depending on the addictive disorder, the required level of care, and available evidence.

Current literature describes robust evidence for using different interventions in specific conditions. However, a significant disparity exists between the published recommendations and their application in the clinical setting. This is due to multiple factors, including:

- Difficult access to the data
- Lack of uniform training
- Insurance coverage
- Quality measurement
- The fragmentation and poor coordination between primary and specialty care

102.1 EVIDENCE-BASED INTERVENTIONS

In 2015, The National Academy of the Sciences (IOM) convened an expert committee to identify key steps to ensure the successful implementation of psychosocial interventions for individuals receiving mental health and substance use services and devised a patient-centered framework (Figure 102.1) that can be used to evaluate evidence to assist with the establishment of standards of care for people experiencing SUDs. This framework relies on continuous patient feedback to inform the overall process and feed the cycle of evidence-based intervention.[1]

Current psychosocial interventions vary tremendously, giving patients and their treatment teams a wide range of options to address their individual needs. Currently, the most commonly used interventions are behavioral couples therapy (BCT), family therapy, cognitive behavioral therapy (CBT), dialectical behavioral therapy (DBT), community reinforcement approach (CRA), contingency management (CM), individual drug counseling (IDC), motivational interviewing (MI), brief interventions (BIs), 12-step programs, and peer support. Psychosocial interventions are used across a wide spectrum of SUDs and are often used in conjunction with other substance use treatments.

102.2 COMMON PSYCHOSOCIAL INTERVENTIONS

102.2.1 Behavioral Couples Therapy

This intervention has been mainly used to treat alcohol and drug use disorders. It aims to reduce drug use while improving overall marital satisfaction for both partners. In BCT sessions, the therapist arranges a daily sobriety contact in which the patient states his or her intent to refrain from drinking or using substances that day. The patient's partner acknowledges and supports the patient's efforts to remain abstinent. The sobriety contract can also include

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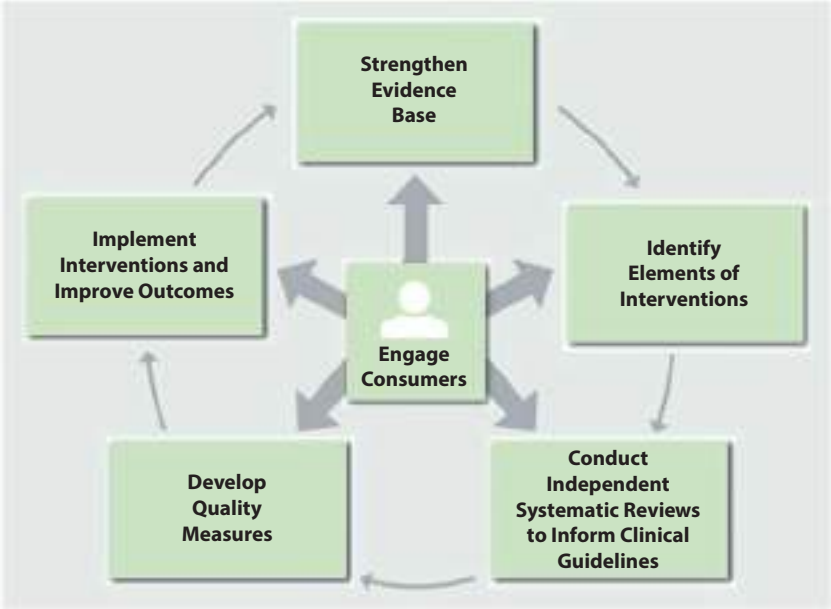


FIGURE 102.1 IOM committee's framework for developing standards for psychosocial interventions (adapted from www.ncbi.nlm.nih.gov/books/NBK321279/).

urine toxicology screens, administering medications by the partner, attending other counseling sessions, or 12-step meetings for the patient and partner. BCT uses a series of assignments to improve relationship functioning and increase positive feelings. This type of intervention also encourages shared activities and constructive communication between the partners because these relationship factors are conducive to abstinence.[2] BCT has proven effective in reducing substance use, decreasing negative outcomes associated with substance use (such as loss of job or housing and injuries), and improving partner satisfaction. Compared with individual-based treatment protocols, BCT has been more cost-effective and successful in reducing partner violence and improving child well-being.[3]

102.2.2 Family Therapy

This intervention is used to treat drug use and the harmful behaviors associated with it. Family therapy is particularly relevant during adolescence, when substance misuse may cause a variety of problems, including psychiatric symptoms, academic difficulties, and high-risk sexual behavior. A wide theoretical basis supports both family therapy and couples therapy. Family therapy is usually provided when a young person's addictive disorder, and the means of treating it, are considered best addressed using a systemic approach. Here, the underlying idea is that treating an individual in isolation would not solve the family system problems enabling or resulting from drug use. Specialists can deliver family therapies in outpatient settings or a patient's home, allowing some flexibility for the patient. Evidence in support of multidimensional family therapy and couples-based therapy in reducing drug use and related problems is accumulating. The use of family-based interventions (e.g. The Strengthening Families Program) for preventing and treating adolescent substance misuse is also well supported.[4–6]

102.2.3 Motivational Interviewing

MI is a low-intensity, patient-centered approach to addressing SUD and other psychosocial barriers based on the Stages of Change model (i.e., pre-contemplation, contemplation, preparation, action, and maintenance). Rather than prematurely pushing patients to exit their current stage, MI focuses on meeting patients in their respective stages and uses various techniques to enhance their motivation to progress to their next stage when ready. This is accomplished by employing an empathic approach to heighten awareness of ambivalence about change, promote commitment to change, and enhance patients' self-efficacy. MI employs techniques such as the OARS (Open-Ended Questions, Affirmations, Reflective Listening, and Summaries) to explore and help resolve ambivalence about substance use-related behavior. This therapeutic style seeks to elicit "change talk" from patients and a commitment to change. It offers patients standardized assessment and feedback and a collaborative structure to develop an individualized and realistic change plan.

While MI can be conducted in any setting and is often informally used in treatment settings, it is usually combined with additional interventions, such as cognitive behavioral therapy, and administered for 15 to 45 minutes for one to four sessions. Sessions lasting under 20 minutes appear less effective, and more success is associated with increased sessions.[7]

Motivational enhancement therapy (MET) goes further by providing a more structured intervention based on a greater degree of systematic assessment with personalized feedback. Involvement of a significant other is encouraged in at least one of the MET sessions.[8]

102.2.4 Brief Interventions

BIs use the collaborative conversation style of motivational interviewing to address problematic or risky drug use, usually over five to 35 periods. Personalized feedback is provided on a patient's substance use, enabling the patient to understand his or her use in relation to other people's use. In this approach, the therapist asks permission to discuss possible drug or alcohol use and provides a standardized screening questionnaire to assess the patient's substance use. The therapist then asks questions about the benefits and harms of substance use to elicit a motivation to change. In concluding the brief session, the therapist and patient negotiate a plan for change and follow-up. Brief interventions can employ several models. One such example is utilizing the "5As"—ask, advise, assess, assist, and arrange; another is the brief negotiated interview (BNI) model—raising the subject, discussing the pros and cons of substance use, providing feedback, assessing readiness for change, and action planning. The BNI model is also used in the process of Screening, Brief Intervention, and Referral to Treatment (SBIRT), which has shown strong effectiveness with alcohol as a public health approach to harm reduction. Since 2004, the United States Preventive Services Task Force (USPSTF) has recommended screening and brief interventions with adults and providing brief counseling to patients with alcohol or substance misuse. The American College of Surgeons' Committee on Trauma also requires screening and brief intervention in all Level I and Level II Trauma Centers. Individual studies, systematic reviews, and meta-analyses have found that SBIRT lowered the frequency and severity of drug and alcohol use and lowered the risk of physical trauma, as well as the length of hospital stays and the number of emergency room visits, improved overall health and substance-use-related outcomes such as housing, employment, and criminal behavior, and constituted a cost-effective approach to address a broad spectrum of use.[9–11] The evidence for drug-related BIs is less well established.[12] However, one must consider the difficulty of running long-term trials where significant reductions in drug use could be observed and the overall benefit of identifying and intervening in drug use despite the lack of available evidence for drug-related BIs.

102.2.5 Cognitive Behavioral Therapy

CBT was developed in the 1950s–1960s by American psychiatrist Aaron Beck. CBT rests upon the cognitive model, where a situation results in an automatic thought, leading to a reaction that manifests itself in three ways: an emotion, a behavior, and a physiological response. CBT further acknowledges that while automatic thoughts are specific to a situation, these may impact underlying core beliefs—a second type of cognition. Providers rely on Socratic questioning (i.e., specific guided questions to the patient) to help patients evaluate their automatic thoughts and core beliefs. According to the Beck Institute, the following are key components of CBT:

- Therapeutic alliance, which encourages a highly collaborative environment between provider and patient.
- Setting goals with patients, which can create a sense of hope.
- Following the structure of the CBT sessions, which leads to greater efficiency on the provider's end and increased understanding on the patient's end.
- Cognitive conceptualization, which allows for increased understanding by the provider of the patient's core beliefs and automatic thoughts.
- Teaching the patient to be their own therapist, which encourages independence and self-reliance.[13]

In addition, CBT incorporates structured practice outside of sessions, including scheduled activities, self-monitoring for negative automatic thoughts, and thought recording of any automatic thoughts and resulting emotions, behaviors, and physiological responses.[14]

With regard to treating SUD, CBT can prove highly effective. Over 20 years, clinical trials conducted by Carroll et al. that focused on CBT treatment for SUD showed progressively larger effect sizes for CBT over the comparison or control conditions.[15] Most approaches follow two key principles when addressing SUDs:

1. Functional analysis of drug use (i.e., understanding drug use with respect to its antecedents and consequences).
2. Skills training (i.e., coping skills, interpersonal skills, additional cognitive skills).[16]

An articulated agenda usually exists for each CBT session. The clinical discussion surrounding SUD treatment focuses on issues related to substance use, although the provider may also incorporate additional relevant topics. Compared with other behavioral approaches, CBT is a highly structured, brief intervention (12–24 weeks) organized closely around well-specified treatment goals.

102.2.6 Dialectical Behavioral Therapy

DBT was initially developed to treat those suffering from borderline personality disorder (BPD), specifically patients endorsing increased suicidality. It is now considered an adjunct treatment for several psychiatric conditions. Traditionally, treatment lasts one year and takes place in an outpatient setting, utilizing four modes: individual

psychotherapy, group skills training, out-of-session coaching, and therapist consultation team meetings.[17,18] DeCou et al. (2019) explain that there are five sets of treatment strategies in DBT, that are used in all four modalities:

1 Dialectical strategies
2 Core strategies (i.e., validation and problem-solving) including standard CBT procedures, which encompass behavioral assessment, psychoeducation, orienting to treatment rationale, contingency management, skills training, exposure, and cognitive modification strategies
3 Communication strategies (i.e., irreverent and reciprocal communication styles)
4 Case management strategies (i.e., consultation-to-the-patient, environmental intervention, consultation-with-the-therapists)
5 Structural strategies (i.e., targeting within sessions, starting and ending therapy)[18]

Patients may waver between eager voluntary engagement in their treatment and adamant refusal to cooperate with treatment guidelines and therapeutic boundaries. Providers must adapt their treatment strategy accordingly.

DBT can also be used to address SUD. Treating SUD in patients with BPD is notoriously difficult; however, opinions are split on whether to treat the SUD before the BPD or concurrently.[19,20] Evidence on the subject remains limited. In patients who do not suffer from BPD, many studies have documented the effectiveness of DBT in treating alcohol use disorder and other concurrent SUDs.[21]

10.2.7 Community Reinforcement Approach

CRA is a comprehensive cognitive-behavioral intervention for treating SUD by focusing on environmental contingencies that impact and influence the patient's behavior. The basis of this approach, formed from the foundation of operant conditioning, utilizes familial, social, recreational, and occupational events to support the individual in changing his or her drinking and/or using behaviors to achieve success in abstinence. The goal is to rearrange multiple aspects of an individual's life so that a sober lifestyle is more rewarding than one dominated by substances. CRA integrates several treatment components: building the patient's motivation to quit by highlighting the negative and positive consequences of drinking/using; partnering with the patient to create a plan for abstinence; analyzing the patient's use pattern; increasing positive reinforcement; learning new coping, problem-solving, and basic skills to obtain and maintain a job; and involving significant others in the recovery process. Two variants of CRA have been created and utilized for substance users and their families. The Adolescent Community Reinforcement Approach (A-CRA) focuses on adolescents, and Community Reinforcement and Family Training (CRAFT) involves family engagement to encourage treatment-resistant individuals to seek help.[22–24]

10.2.8 Contingency Management

CM approaches are based on behavioral principles of reinforcement that reward specific behavioral goals related to recovery. CM is not a type of psychotherapy and is a purely behavioral intervention. Either monetary or non-monetary rewards are contingent on objective evidence such as negative toxicology results, treatment adherence, or progress toward treatment goals. The most common contingencies are vouchers with monetary value that can be redeemed for goods and services, specific material prizes, or draws from a "fishbowl" that contains cards that vary in their reinforcing value from simple praise to vouchers worth $1 to $100. Schedules (fixed or intermittent) and magnitude of reinforcement vary and have implications for the overall cost of clinical implementation. Abstinence incentives have been effectively used for treating amphetamine, cocaine, alcohol, tobacco, and marijuana use disorders and are effective in patients with a wide variety of demographic, psychosocial, and substance use characteristics.[25]

10.2.9 Individual Drug Counseling

IDC is based on the philosophy that addiction is a complex disease that negatively impacts the individual physically, mentally, and spiritually. Therefore, IDC aims to address these needs in the individual holistically. IDC incorporates two important elements: endorsement of the disease model and the spiritual dimension of recovery. These elements differentiate IDC from other forms of treatment currently in use and reflect the influence of the 12-step philosophy.

IDC is distinct from psychotherapy by setting predominantly short-term goals related to addiction recovery. This treatment utilizes substantially concrete behavioral approaches and focuses primarily on the present. IDC has been developed for adult male and female outpatients with cocaine use disorder, but all of its overall tenets are appropriate for use in treating other drug addictions.

IDC is manualized and includes patient education about a biopsychosocial and spiritual approach to recovery, attention to building a therapeutic alliance, monitored drug testing, and encouragement of 12-step (e.g., Alcoholics Anonymous) participation.[26]

10.2.10 Twelve-Step Facilitation

TSF therapy aims to increase the patient's active involvement in Alcoholics Anonymous (AA) or other 12-step-based mutual help groups. This approach was systematized in a manual for The National Institute on Alcohol Abuse and Alcoholism's project MATCH and delivered as 12 sessions of individual therapy in which the therapist utilizes the AA therapeutic framework as well as cognitive behavioral therapy and motivational enhancement therapy. The therapist conveys that addiction is a chronic, progressive, and potentially fatal illness, for which the only viable therapeutic goal is total abstinence from alcohol, achieved

one day at a time by following a 12-step program of recovery. Each therapy session is divided into three parts. The first part reviews relevant events of the past week (including urges to use, drinking behavior, and recovery-oriented activities) and progress on past homework assignments. The middle portion introduces new material related to the 12 steps. The session's conclusion includes a homework assignment and developing a plan for recovery-oriented activities (meeting attendance, sponsor contact). A sponsor can be pivotal in the success of 12-step group-based approaches to SUD treatment.[27]

10.2.11 Peer Support

Historically, providers have recognized the importance of peer support in improving mental health, with several globally recognized psychiatrists, such as Vikram Patel, MD, stating that "The key to promoting youth mental health is through the strengthening of the fundamental nurturing qualities of the family system and community networks while explicitly acknowledging the rights of young people".[28] This approach recognizes how a person's peer network affects their mental health. In part, this can be done by focusing on policymaking that strengthens peer relationships to address difficulties in people's lives. Much research has been done in India and is being developed across many countries with a focus on youth and young adult populations, which translates into benefits later in life. Peer support models can improve the capacity for helping people with problems like substance use as there is a large shortage of mental health professionals and continued stigma in seeking professional help.[28]

Peer support can be divided into two broad categories: mutual aid group modalities that typically follow the 12-step model and peer-delivered recovery support services that incorporate various domains ranging from one-to-one recovery coach services to group settings. Mutual aid programs are voluntary, not-for-profit groups where people meet to discuss and address shared problems, such as alcohol, drug, or other addictions.

Participants support each other, with senior members often mentoring or "sponsoring" new ones. Prominent examples include Alcoholics Anonymous and Narcotics Anonymous. Other groups exist with similar purposes, such as SMART Recovery. In addition to helping drug users, some self-help groups support the family members of people with substance-related problems. Self-help groups are used to assist people with recognizing their drug-related problems, providing support during drug treatment, and helping users maintain abstinence and prevent relapse. These groups aim to create substance-free supportive networks around individuals during recovery and provide opportunities to share experiences and feelings. Former substance users or community peers lead these groups, which are located in various settings, including but not limited to community centers, healthcare facilities, and prisons. This model is traditionally informal and is based on a bidirectional relationship of mutual support. All members are requested to follow a single pathway for recovery guided by the 12-step literature.

Peer-based recovery services are delivered through formal structures and specialized roles that deliver services to individuals across various domains. A peer recovery coach (PRC), also called a "peer specialist", "peer mentor", or "substance abuse outreach worker in recovery", often leads the group sessions. PRCs may work as volunteers or offer paid services. In recovery community centers, they organize and lead educational, advocacy, and sober social activities. They also work in churches and other faith-based organizations, recovery homes and sober housing, the prison system, probation and parole programs, drug courts, HIV/AIDS and other health centers, and addiction and mental health treatment agencies.[29] Historically, group leaders did not typically receive formal training, but this is gradually changing.[30] Such training is not yet standardized across the country, as there is a wide range of training and certification programs, but there is a movement toward a single training model. In 2015, SAMHSA published guidelines describing peer support workers' core competencies, with the most recent list of competencies (most newly updated in 2022) detailed below as directly indicated on their website:

- **Recovery-oriented**: Peer workers hold out hope to those they serve, partnering with them to envision and achieve a meaningful and purposeful life. Peer workers help those they serve to identify and build on strengths and empower them to choose for themselves, recognizing that there are multiple pathways to recovery.
- **Person-centered**: Peer recovery support services are always directed by the person participating in services. Peer recovery support is personalized to align with the specific hopes, goals, and preferences of the people served and to respond to specific needs the people have identified to the peer worker.
- **Voluntary**: Peer workers are partners or consultants to those they serve. They do not dictate the types of services provided or the elements of recovery plans that will guide their work with peers. Participation in peer recovery support services is always contingent on peer choice.
- **Relationship-focused**: The relationship between the peer worker and the peer is the foundation for peer recovery support services and support. The relationship between the peer worker and peer is respectful, trusting, empathetic, collaborative, and mutual.
- **Trauma-informed**: Peer recovery support utilizes a strength-based framework that emphasizes physical, psychological, and emotional safety and creates opportunities for survivors to rebuild a sense of control and empowerment.[31]

Empirical evidence connecting peer support to SUD treatment is promising yet limited. Peer support might be

especially useful in substance detox units.[32] It may improve inpatient and outpatient treatment outcomes for dual-diagnosis patients. This review acknowledges that research remains limited to "specific clinical SUD populations for whom services are most commonly provided (those in outpatient, residential and transitional care settings, and recovery community centers)"[32] Peer support may also play a role in emergency departments; however, Liebling et al. state that "evidence of improved patient outcomes is needed before widespread adoption".[33] In low- and middle-income countries, peer support may be useful as a treatment to compensate for reduced healthcare personnel; however, more research is again needed.[34]

102.3 INTEGRATING PSYCHOSOCIAL INTERVENTIONS IN THE TREATMENT PLAN

Psychosocial interventions are used across the spectrum of SUD levels of care. In the 1980s, a collaborative effort created a national set of criteria for providing outcome-oriented and results-based care in treating addiction. Combined with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification of substance use disorders, the American Society of Addiction Medicine (ASAM) criteria have become the most widely used and comprehensive guidelines for placement, continued stay, and transfer/discharge of patients with addiction and co-occurring conditions.[35,36] Adolescent and adult treatment plans are developed through a multidimensional patient assessment (Figure 102.2) over five broad levels of treatment (Figure 102.3) based on the degree of direct medical management; the structure, safety, and security provided; and the intensity of treatment services provided.

Psychosocial interventions are often a component of a comprehensive treatment plan that includes medication assisted treatment (MAT), an evidence-based treatment for individuals with alcohol and opioid use disorder. FDA-approved medications are prescribed to relieve withdrawal symptoms and reduce cravings, and include methadone or buprenorphine for opioid use, naloxone to prevent opioid overdose, and acamprosate, disulfiram, or naltrexone for alcohol use disorder. Medications combined with



FIGURE 102.2 The six dimensions of the multimodal assessment (retrieved from https://www.asam.org/resources/the-asam-criteria/about).

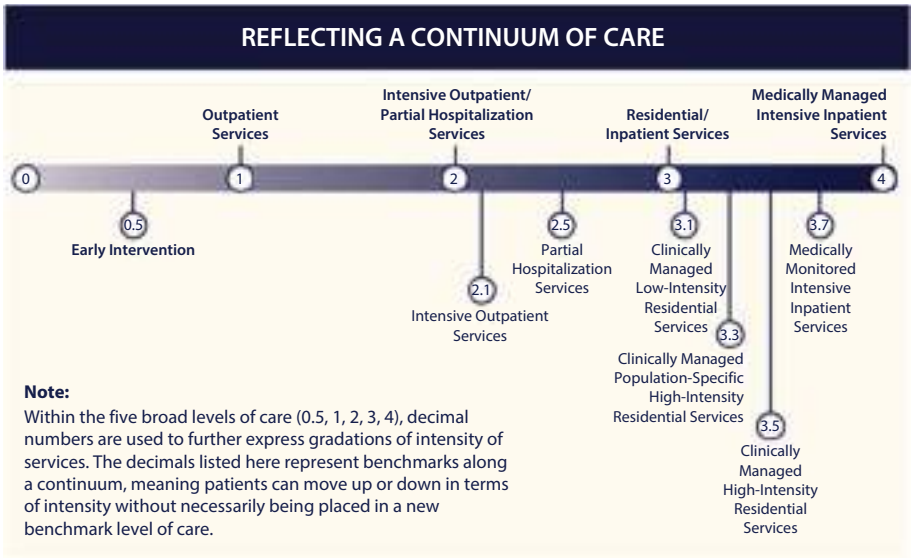


FIGURE 102.3 The ASAM levels of care (retrieved from https://www.asam.org/resources/the-asam-criteria/about).

counseling and therapy are tailored to the individual's needs to help patients sustain recovery and gain the skills needed to live a self-directed and independent life.

102.4 CONCLUSION

Psychosocial interventions are now well established as part of drug treatment and recovery processes, and ongoing research in support of their use is proliferating as they play an important role in treating various SUDs and addictive behaviors. Psychosocial interventions help individuals improve insight into their problematic substance use, progress through the stages of change, improve adherence to a treatment plan, and reinforce their achievements. Such interventions also support family members and create or strengthen social networks to help facilitate recovery.

CLINICAL APPLICATIONS

- Psychosocial interventions are an evidence-based, crucial component of treatment for substance use disorder.
- While psychosocial interventions do not replace MAT, they provide crucial tools to individuals in recovery.
- Psychosocial interventions are especially helpful in supporting family members and social networks of individuals who experience substance use disorders.

FURTHER READING AND RELEVANT WEBSITES

SBIRT: Screening, Brief Intervention, and Referral to Treatment: www.integration.samhsa.gov/clinical-practice/SBIRT
What is CBT? www.beckinstitute.org/cognitive-behavioral-therapy/
Contingency management for drug users: www.emcdda.europa.eu/best-practice/social-reintegration/drug-treatment
Cochrane reviews on psychosocial interventions: www.cochranelibrary.com/app/content/browse/page/?context=editorial-group/Drugs%20and%20Alcohol%20Group
William Miller on motivational interviewing (video): www.youtube.com/watch?v=cj1BDPBE6Wk
A session of family therapy (video): www.youtube.com/watch?v=6JjcIiCJaDo
Free courses in addiction and mental health https://aptp.nextgenu.org/all-courses/

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103 The Digital World and Addiction Treatment

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KEY POINTS

- The digital landscape for helping patients with substance use disorders has changed since the COVID-19 pandemic with newer ways to seek health education, medical attention, psychotherapy, and self-help meetings.
- Several methods are used to assess the feasibility of mobile health applications for addiction treatment. This field is emerging and may even provide increased access to care for some people.
- The commonly used apps without prescription are for counting sober days, journaling, and accessing self-help meetings. Some applications may be deceptively portrayed and, in fact, may encourage substance use, so care must be taken before subscribing.
- There is an emerging field of digital therapeutics as a prescription for people with substance use disorders to be used in conjunction with regular medical care.
- As lifestyle medicine clinicians, we should continue to advocate for using technologies for overall health, including sleep and mindfulness-based applications.

103.1 INTRODUCTION

Digital solutions are among the fastest-growing areas of delivery of healthcare access.[1] Health solutions applications are available on both Android and iPhone devices, and even in a 2017 survey, there were already more than 300,000 apps available for this purpose alone.[1] During the COVID-19 pandemic, there has been a large growth in access to mobile phone technology. An estimated 85% of all US adults owned a smartphone in 2021 compared with 35% in 2011, and nearly 97% of US adults owned a cellphone of some kind.[2] Since the COVID-19 pandemic and subsequent mandates for physical distancing, increasing numbers of transactions now occur online globally, be it shopping, banking, or even medical visits. At the same time, the social isolation during and in the aftermath of the pandemic has led to a worsening mental health situation in the United States for adults as well as adolescents.[3] Social isolation also led to defaulting to and the overuse of digital applications/appliances and associated adverse consequences like behavioral addictions, eye complications, and so on.[4]

There are many ways in which the digital matrix can both positively and negatively impact care for patients with substance use disorders. In this chapter, we will examine the overall experience of patients with substance use disorders and the technologies available for the treatment of these disorders from a holistic perspective. In addition, the chapter will review technologies and applications that are shown to be detrimental to mental health and may even worsen addiction problems.

Globally, about three million people die each year from alcohol use (5.3% of deaths).[5] In the United States, only one of every five patients with a substance use disorder seeks medical help. Opioid overdose annual deaths in the United States increased from January 2020 to January 2023 by nearly 45%, a tragically concerning increase.[6] In 2020, in the United States, only 6.5% of people needing care for a substance use disorder were able to receive substance use treatment at a specialized facility.[7] This means that a large proportion of patients seek care for addiction outside of specialized facilities or may not seek or receive help at all, contributing to the huge treatment gap that exists globally for addictive disorders.

Crucially, the treatment of substance use disorders by primary care providers, including initiation or refill of suboxone treatments, is an integral part of this approach. With increasing suboxone inductions in primary care, we hope and expect there will be enhanced access to treatment services and improved patient outcomes. In light of the addiction epidemic in the United States, there is a pressing need for easily accessible care. The statistics for overdoses, mortality, and morbidity related to substance use disorders highlight the urgency of increasing access to care.

The US Surgeon General Dr. Vivek Murthy has declared loneliness as a public health concern in the country as of May 2023.[8] It is widely recognized that loneliness can have a negative impact on addiction in numerous ways, such as exacerbating substance abuse, hindering access to recovery

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environments, and contributing to gaming addiction.[9–11] The Surgeon General is urging everyone to find ways to connect socially beyond the digital screen and use technology within apps more effectively. This call to action is expected to spur innovation both online and offline and create new communities with meaningful connections over the next few years.

Stigma is a significant contributor to the issues surrounding addiction treatment, including isolation and inadequate access to care.[12] In our practice as addiction medicine clinicians, we all appreciate the amount of courage it takes for patients to walk into our clinics. Digital tools like telemedicine and apps can be developed to help people overcome the stigma associated with addiction, whether it is self-imposed or imposed by others.[12] By making care more accessible, such digital tools can also encourage more people to seek help.[13–15]

103.2 OVERVIEW OF MOBILE APPLICATIONS AND HEALTHCARE

Before the 2007 launch of the iPhone, mobile communication was somewhat limited except in the case of the Blackberry phones.[16] Slowly, more people started using this technology, with other models that were more affordable getting introduced to the market.

Currently, many apps used in healthcare (or any other field) begin as startups. One of the key ways that these functionalities are built is that they are eventually dependent on a singular question: "What is the problem that you (or your app) are trying to solve?"[17] Given the breadth of services now available online, we can examine these applications or "Apps" in this mindset.

The term used for mobile healthcare applications is mHealth, as per the World Health Organization.[18] Given the wide variety of applications available for different purposes, there is no central governing body for their use. Over time, applications phase in and out, depending on their success.

Prior to the pandemic, addiction medicine treatment applications primarily focused on sobriety and treatment approaches. However, since the pandemic began, there has been a significant rise in demand for applications that provide access to care and allow patients to see prescribers. Even before the pandemic, multiple telemedicine startups were already striving to make care more accessible for individuals with substance use disorders. Since the COVID-19 lockdowns began, an increasing number of people have been accessing care using these modes of delivery. Across the globe, people are increasingly turning to mobile applications for convenient and cost-effective access to healthcare services. This allows people to easily manage their healthcare needs while juggling other commitments, such as work and family. Moreover, the growing availability of affordable smartphones and data plans has made this option accessible to more people than ever before.

103.3 MOBILE TECHNOLOGIES SPECIFIC TO THE FIELD OF ADDICTION MEDICINE

Applications specific to addiction medicine are available on Android and the Apple App Stores. These can range from health promotion, information, and monitoring to treatment and self-help. There are applications even designed to curb digital addictions, such as gaming, gambling, or Internet use.

mHealth applications fall into two broad categories, prescription digital therapeutics (PDTs), which require a prescription from a physician or treatment provider, or general apps available in the app store. Some mental health apps can be accessed in both ways, either with a personal payment option or covered through insurance after prescription, such as the Calm app. Notably, the demand for the Calm app was so high that it reached unicorn status in 2019.[19]

103.3.1 Health Education and Prevention Apps and Websites

Increasingly, people are accessing health information and are subject to advertising for substances on social media or other websites. In response to the COVID-19 pandemic, many in the cannabis industry began to rely heavily on social media to advertise their pop-up sales and home delivery services.[20] Similarly, efforts for prevention and information dissemination should be placed where they will have a high chance of viewership. The Health Belief Model and the Theory of Planned Behavior highlight how risk perception can change our individual approaches to experimenting with substances.[21, 22] E-cigarette companies have long claimed that they helped people quit smoking, which reduces the perception of risk, especially in the youth.[23]

A recent study in Mexico of a health information app called "What happens if you go too far" in Spanish, found it was effective in increasing risk perception of using tobacco, alcohol, and marijuana in adolescents.[24]

Universities are creating game-style versions of informational applications to help users make decisions based on real-life experiences. For instance, imagine you are a high school student on a field trip and someone offers you a pill to enhance the experience. Depending on your response, the game will progress in different directions, while also educating you about substances in general.[25]

In a study looking at web-based solutions for people who used drugs (PWUD) in New York City, it was found that nearly a third of the people accessing the pharmacies under study looked up health information through a website, and 35% of these patients also enrolled in text messaging.[26]

103.3.2 Screening

There are mobile applications that can be used for screening addictive disorders, e.g., cannabis, alcohol, and addictive behaviors. Some apps are being studied for clinical

utilization. The screening apps can detect harmful versus dependent use and can help users seek early treatment.[27–29]

103.3.3 Substance Use Disorder Diagnosis and Treatment

As previously mentioned, the number of opioid overdose cases in the United States is steadily increasing. In fact, as of January 2023, approximately 105,000 individuals died from opioid overdose within a 12-month timeframe.[6] Only 35% of US patients with a history of opioid use disorder have access to medications for maintenance treatment such as buprenorphine or methadone.[30] This makes access to telemedicine applications vital to increase access to care. With the COVID-19 emergency, the provisions of the Ryan Haight Act were relaxed and clinicians could prescribe medications for opioid use disorder using only telemedicine, without an in-person physical exam.[30,31] This increased the ease of access to treatment. Given the physical distancing for COVID-19 lockdowns, this became the new default way of providing outpatient addiction care.

When the Veterans Administration looked at the COVID-19 pandemic telehealth use, it was found that patients with access to video visits had better retention in treatment compared with those with either office-only or telephone-only consultations.[32] Patients who were non-service-connected, older, male, Black, or experiencing homelessness were less likely to have access to telemedicine in the same study. Disparities in access to telemedicine in socially disadvantaged populations exist for other specialties as well.[33] In a recent study published in *JAMA Psychiatry*, receipt of medication for opioid use disorder via telehealth increased the odds of treatment retention while it decreased the odds of having a medically treated overdose.[34]

Outside of telemedicine services, there are targeted apps for several different substance use disorders as well as non-substance or behavioral addictions.

103.3.4 Alcohol Use

Telemedicine and digital technologies have increasingly been adopted as tools to manage and treat alcohol use disorder (AUD), particularly in response to the rise in alcohol consumption during the COVID-19 pandemic. AUD, a medical condition marked by an impaired ability to control or stop alcohol use despite adverse health and social consequences, affects at least one in every 20 adults in the United States.[35] However, a small fraction of those diagnosed with AUD receive treatment, indicating a significant gap in the healthcare system.

The advent of telemedicine has begun to bridge this gap, offering accessible treatment options to individuals dealing with AUD.[36] Virtual AUD treatment programs, unconstrained by physical locations, can provide patients with customizable treatment plans tailored to their specific needs and preferences. These plans often incorporate a mix of medication-assisted treatment, group counseling, behavioral therapy, peer support, and various digital tools such as chatbots and digitized adherence and accountability software.[37] Emerging studies highlight the effectiveness of telehealth in AUD treatment, showing that virtual care interventions can successfully reduce substance use and provide timely care for individuals who would otherwise be waitlisted for treatment.

A review of the efficacy of telehealth in addiction treatment during the COVID-19 pandemic revealed promising results. The study, which included a literature review and responses from California addiction treatment providers, found that telehealth treatment was as effective as in-person treatment in terms of retention, therapeutic alliance, and substance use. The study concluded that telehealth could improve patient engagement in addiction treatment by enhancing access and convenience but recommended additional research to determine the optimal balance of in-person and telehealth services.[38]

The effectiveness of web-based alcohol e-help programs was found to reduce problematic and dependent alcohol use in the latest four-country study funded by WHO. Thus, web-based applications that can be easily transformed into mobile applications can be game changers for reducing harmful/dependent use in developing countries.[39]

Despite the promising results, further research is required to determine the optimal mix of in-person and telehealth services and how best to tailor telehealth to each patient's circumstances.

103.3.5 Opioid Use

PDTs are apps that require a prescription from a physician or treatment provider as mentioned before. Notable in this category is reSET or reSET-O. It is a PDT that utilizes cognitive behavioral therapy along with contingency management-based rewards.[40] In a pilot study, it was reported to have a high attrition rate (53%) but those who did continue to use the app gave feedback that it was a safe space to disclose any recurring substance use. This app would be prescribed along with medication services in an outpatient treatment setting. Local policies and staffing to have contingency management available in clinic can be difficult, although the app can be used without providing monetary rewards from the clinic to the patients. The app was FDA approved for clinical use in 2019 and claimed better treatment retention than care as usual.[41]

Other pilot apps are also under study, e.g., the HOPE app from the University of Virginia, which includes daily check-ins and stress management tools for patients in their medication assistant treatment (MAT) clinic.[42] MATx is a mobile app to help healthcare practitioners provide evidence-based MAT for opioid use disorders. It was developed by the Substance Abuse and Mental Health Services Administration (SAMHSA) to provide training to clinicians prescribing medications for opioid use disorder (MOUD) management.[43] Newer apps have also been developed to prevent opioid overdose by using contactless sonar technology

to detect respiratory depression and other clinical factors associated with an opioid overdose (Nand Kumar, 2019).

103.3.6 Smoking and Other Nicotine Use

Several apps are available for smoking cessation on the iPhone and Android app stores. Also, web-based information is widely available for quitting smoking. "Kick It California" is one of the most comprehensive web portals helping people quit smoking, vaping, or smokeless tobacco in a youth-friendly manner,[44] also, there is access to phone-based coaching using their portal. Their Quit Coaches help patients with a text messaging program, and there is an app-based version of this program called "no butts". Several apps are designed on CBT principles and can also have a subscription model. The "Q sense" app was evaluated for helping participants combat smoking cues and remain abstinent.[45] While participant self-report was inconsistent, the geo-tagging feature was helpful in identifying smoking locations and providing support. A randomized control trial for a Facebook-based smoking cessation intervention did not find a significant abstinence rate.[46]

103.3.7 Methamphetamine Use

A recent study using a therapy online option application called Echo-App found a significant increase in motivation to stay sober while reducing cravings for methamphetamine use.[47] The app uses a virtual image of a therapist with an interactive interface to assess depression and anxiety scores on PHQ-9 and GAD-7, respectively. The treatment module offers therapy options to the client as well. Work is in progress to look at "wearables" (e.g., smartwatches) for ecological momentary assessment of alcohol and methamphetamine use—such as heart rate and sleep duration.[48]

103.3.8 Non-Substance or Behavioral Addiction Treatment

"Smartphone addiction" is a still novel concept, with overuse of the internet or phone being under study and not included in either the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) or the International Classification of Diseases, 11th Revision (ICD-11). If it meets the criteria for inclusion, it will probably fall under behavioral addictions or non-substance use disorders. A recent study found a relationship between loneliness, depression, and smartphone addiction in college students.[49] There are several apps available for cutting back on screen time such as the default iPhone Screen Time app and Android Google Family apps. From a therapeutic perspective, writers did not find evidence-based apps for this purpose. There are several apps for general use to reduce screen time on the app store, offering various rewards such as scholarships for college students (e.g., Lock and Stock app).

Chapter co-author Dr. Kanabar did a community-based project called Screen-Win for pilot testing decreasing screen time in 2021 and found reductions in screen time by up to 30% in participants for a two-week challenge. This tool is still in the process of development.

Gambling disorder has been included in the DSM-5 and is a significant problem worldwide. Currently, there are several protocols under study for developing apps to quit gambling.[50,51]

Internet or non-Internet gaming found a place in the ICD 11. In the DSM-5 it is still a condition needing further study.[52] Given that currently it is not a billable service, there is very little insurance-based healthcare coverage and no treatment consensus available for the treatment of gaming disorder in the United States.[53] Currently, some study protocols are being developed in this area. Interestingly, an app offering virtual reality-based intervention was effective in its pilot study to cut down time spent on gaming by young adults.[54]

103.3.9 Therapy-Only Access Apps

Therapy or generally cognitive behavioral therapy-based apps are widely available and probably the most used in any mental health treatment. Apps such as Woebot, Ginger, and myStrength can be covered by insurance in many settings and help provide training in coping skills. This plays a role in increasing round-the-clock access to strategies for anxiety and mood mediation and may decrease healthcare burden to a small extent.

103.3.10 Relapse Prevention and Further Education

Counting apps are widely used by patients for recording the number of days they have been sober. Also used are several podcasts, YouTube videos, or other audiobooks available on apps such as Libby, Scribd, Kindle, Audible, or other apps for the purpose. Both clinicians and patients can listen to available information during a long commute or other pockets of time, providing excellent asynchronous learning and reinforcement of treatment principles. Several podcasts are in fact available for clinicians to follow, such as The Addiction Files, This Week in Addiction Medicine from the American Society of Addiction Medicine, and Behind the Evidence podcast.[55–57] Mutual-help groups as covered below also have their apps available for use.

103.4 MUTUAL- OR SELF-HELP

Recovery through mutual or self-help groups has been a mainstay of addiction treatment for nearly a century. Alcoholics Anonymous was started by Mr. Bill Wilson and Dr. Bob Smith in 1935.[58] Other adaptations of self-help groups and fellowships have emerged since then including Narcotics Anonymous, Al-Anon, Gamblers Anonymous, Debtors Anonymous, and so on. Other self-help groups such as Refuge Recovery, Life Ring, Women for Sobriety, and Smart Recovery have also gained traction.

With COVID-19, many self-help groups had to switch to an online mode to connect with their patrons.[59] For some with difficulty accessing video visits, this posed a new challenge. For others who could access groups, this provided new opportunities to find connections across the globe. For those with changing shift work, this increased their access to groups in different time zones, depending on when they were working that day. Interestingly, on analyzing attendance to online support groups, it was found that participants were more likely to attend if they followed more than one type of mutual support group.[60]

Outside of more traditional alcoholics anonymous type groups, applications, and online access are sometimes the only way to get peer support for more unique issues such as pornography addiction, gaming addiction, excessive Internet use, or disordered eating in early recovery.

With the COVID-19 pandemic emergency coming to an end, many of the groups have gone back to in-person care. However virtual access remains an attractive option for many. As a result, groups such as Alcoholics Anonymous now generally have online meetings available as a default. In some regions, these meetings can take on a "hop on/hop off" continuous meeting available online 24 hours a day and seven days a week. This has provided significant support to patients at a vulnerable period in their lives.

SMART Recovery, which is a cognitive behavioral therapy-based approach to managing substance use disorder, launched a SMART Track app that showed some promise.[61] People are also likely to use the internet consistently to find meetings for Alcoholics Anonymous even if they may have spotty access to smartphones.[26]

103.5 EFFECTIVENESS OF APPS: DO THEY WORK?

It is simple to say we have apps available, but it is not guaranteed that patients use them, nor (even if usage occurs) is it clear how effective they can be. Several papers in the literature look at how to evaluate applications, examining adherence, usability, and other clinical outcomes to help our patients with their substance use issues. App evaluations in their nascency were based on a Likert Scale between "Strongly Agree" to "Strongly Disagree" (Sr et al., 2015). Then came a tool for rating engagement, functionality, aesthetics, and information, which was applicable to a few apps called the mobile app rating scale or MARS.[62] In a 2019 study, most apps had a low MARS score.[63]

103.6 CONCERNS AROUND HARMFUL INFORMATION AVAILABLE ONLINE

People with substance use disorders can use internet forums, social media, and other applications to access information that worsens their use. A study of Twitter messages or tweets in 2017 found that about 49% of the tweets around opioids were for procuring illicit sources of drug use[64] In a study by Tofighi et al. reviewing apps to help treatment of addiction, they, in fact, found the converse, apps had features that would exacerbate use, such as a forum where people offered to sell drugs, features like binge drinking games, or advice to decrease the smell of alcohol.[63] Some apps also promoted increased smoking, cannabis use, or alcohol use. The app stores exercise vigilance and delete more harmful apps when detected. Recovery apps may also lack the required level of privacy protection to offer care for substance use disorders and may not be HIPAA compliant (Health Insurance Portability and Accountability Act).

It is common knowledge that on the web, information is available for addiction harm as well as treatment and does not need to be elaborated here.

103.7 LIFESTYLE AND SLEEP APPLICATIONS

Globally, about 80% of youth do not meet the recommendations of one hour of moderate to vigorous physical activity a day.[65] To encourage more physical activity in youth, apps can employ features such as notifications and rewards. A recent systematic literature review showed apps that focus on clear design, community involvement, and gamification had a higher chance of eliciting engagement and increasing physical activity in children aged four to 18 years.[65]

Sleep issues are widespread across the world, especially among smartphone users.[66,67] A Japanese app "Nenne Navi" when assigned to caregivers of young children showed benefits in decreasing sleep latency.[68]

CBT for insomnia (CBT-I) based interventions are perhaps the most famous for helping with sleep issues and may be superior to patient education alone.[69] The CBT-I Coach app from the United States Veterans Administration is available for free and has shown benefits in improving sleep for veterans with experience in combat zones.[70] Though these apps are not specific to patients with history of a substance use disorder, they can serve as effective free tools for increasing sleep.

The Calm app as well as CBT apps mentioned before also typically have an option for sleep coaching or meditation exercises that may be helpful.

103.8 RELEVANCE TO LIFESTYLE MEDICINE PRACTITIONERS.

As we inevitably create more seductive electronic and chemical addictions, we will inevitably create more useful electronic and chemical tools to combat those addictions. Lifestyle medicine practitioners should remain vigilant throughout their careers for such threats and opportunities, as they are likely to be among the most rapidly evolving variables in our practices.

Also, our patients can have a family member struggling with substance use, or personal health goals for which they need the help of such digital interventions, particularly for setting limits around alcohol, smoking, or cannabis.

Sleep, mindfulness, meditation, and mood meditation apps can speak to the other pillars of lifestyle medicine. Also, the less time we spend on our devices, the more we get to build social connections, which is an important domain of lifestyle medicine.

103.9 CONCLUSIONS

Digital approaches to increasing access to care for patients with addiction are continuously being developed and improved. After the COVID-19 pandemic, the frequency of use of telemedicine services increased, and there has been a surge of apps built for the management of addictive problems. At the same time, with increased access to technology such as wearables, contactless monitoring, tracking, machine learning, and in the future, artificial intelligence, we are likely to see an increase in the use of smartphone-based applications in healthcare, including in the care of patients with substance use disorders. This opens novel avenues for screening, diagnosis, treatment intervention, harm reduction, and monitoring for patients.

Outside the box of smartphone applications, there are also newer ways of asynchronous learning, such as audiobooks and podcasts, that can be used by clinicians as well as clients.

Great strides have occurred in using applications for psychotherapy and mindfulness, with many insurance providers approving access to digital therapeutics, text coaches, and other modalities.

CLINICAL APPLICATIONS

Accessing medical care:

- Several telemedicine startups provide easy access to medications for substance use disorders and patients can sign up using commercial insurance plans or cash-pay.
- Since the COVID-19 pandemic, most health systems have robust telemedicine options.

Accessing psychotherapy:

- Several companies now offer telehealth-only options for psychotherapy and may be contracted with insurance providers. This can make evening and weekend therapy options available for patients. There are specific therapy teaching-based applications such as myStrength that can be prescribed for patients for a set amount of time. Recently, artificial intelligence bot-based chat applications (such as Woebot) have also become available.

Accessing self-help groups:

- Applications have been developed for easier access to self-help groups such as Alcoholics Anonymous, Narcotics Anonymous, SMART Recovery, and others. They can also provide counting for sober days and easy access to online meetings.

Health education information:

- Websites such as "Kick it California" have been developed for easy access to information about smoking or vaping. Other portals where patients can seek information or access to free telephonic coaching for help with substance use issues are also available.

Prescription digital therapeutics:

- This is a new area of application development, in which notable are the reSET and reSET-O applications to be used in conjunction with medical care for substance or opioid use disorders to deliver contingency management options. These may be covered by insurance.

Lifestyle intervention applications:

- Well-rounded care for patients with substance use is essential. Text-based or chat options are available for coaching around distress tolerance and coping skills.
- Sleep applications such as CBT-I and mindfulness applications such as Calm and Headspace can help patients center on their wellness.

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Part XVIII

Lifestyle Medicine in Geriatrics



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104 How Geriatrics Principles and Paradigms Can Inform Lifestyle Medicine Practice

Jennifer D. Muniak, MD

KEY POINTS

- Geriatrics and lifestyle medicine have philosophical overlap, in that geriatricians strive for our patients to age in a healthful way, minimizing disability and premature death that is often dictated by lifestyle factors over time.
- Lifestyle medicine, as an emerging field, can benefit from the cognitive frameworks, strategies, and treatment modalities embedded in the related and more established field of geriatrics, building on previous work that made the case for geriatricians to embrace facets of lifestyle medicine.

104.1 EMBRACING COMPLEXITY AND NUANCE

Geriatricians will often joke that "if you've seen one geriatric patient, you've seen one geriatric patient". Older adult patients come into our offices not only with a chief medical concern; that concern is a metaphorical iceberg, embedded in a unique compilation of:

- Other chronic medical issues
- Structure of living arrangement (home, community, transport)
- Caregiver and social supports
- Financial resources
- Coping strategies
- Beliefs about illness and treatment efficacy
- Mental health issues

These overlapping factors to consider in the care of every older adult can seem overwhelming—many of them exist outside the reach of the prescription pad and are often rooted in the past, personal circumstances, and surrounding social, economic, and political structures (i.e., social determinants of health). Yet our training in geriatrics calls us to embrace the complexity and nuance of every patient story, producing a "complexivist" mindset, as dubbed by esteemed geriatricians Fried and Hall in a 2008 editorial.[1] They posit that geriatricians have "the cognitive skills to analyze complex health issues and establish priorities consistent with patient goals and knowledge of models of care delivery".

Case example: A geriatrician is seeing an older adult patient for a routine clinic visit who has advanced coronary artery disease, severe generalized anxiety, food insecurity, and vision impairment. Properly managing this patient will require the practitioner to consider several parallel processes: the state of each problem in isolation, the direction and velocity of that problem's change, how various problems interact with each other, and how they interact with the patient's unique set of resources and values to ameliorate them. Perhaps the most important is to connect with the patient about their perceptions of the problems and understand what is the highest priority to them.

"Complexivist thinking" (i.e., carefully holding all the interconnected facets of a patient's story in one's mind with reference to the whole) is a necessary core skill when making a diagnosis or treatment recommendation for an older adult patient. This way of thinking is contrasted to a "reductionist" model, whereby complex problems can be explained algorithmically by a collection of simpler processes. At times, reductionist thinking is necessary and appropriate, such as when a discrete problem has an equally discrete solution; but the human body rarely functions in this way, particularly when we allow ourselves the wide-angle lens of the entire biopsychosocial nature of a patient's life. Often, the application of reductionist principles in clinical medicine (e.g., making a diagnosis off a single blood test, clinical guideline, or collection of vital signs) is a cognitive shortcut that can miss crucial details and cause harm to the patient.

The field of lifestyle medicine, in a manner very similar to geriatrics, confronts complex problems that fail reductionist thinking. Practitioners need to bravely wade through the ever-changing biopsychosocial fabric of a patient's history in order to reach them and provide counsel. Only when all the relevant domains are identified and processed, will the practitioner start to have an impact.

Case example: an LM practitioner is meeting a new patient who wants to lose weight. The patient has a strong family history of obesity and has a 20-plus-year history of dieting with transiently successful 5% weight loss followed by regaining back to baseline. They have an emotionally demanding job as an ER nurse with irregular work hours and frequently will have two to three glasses of wine after

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work to unwind. They have poor social support and low feelings of competence to make change.

This patient will clearly require a holistic approach that addresses many layers of their lifestyle that are intertwined. Even digging below the chief complaint of "losing weight" could take some time: Why? Why now? Is this internally motivated? Externally? Both?

104.2 STRUCTURING THOUGHTS USING DATA-DRIVEN FRAMEWORKS

In 2016, the John A. Hartford Foundation and the Institute for Healthcare Improvement among others, came together to find a different overarching approach to the care of older adults. They realized that healthcare structures were inherently dangerous to older adult patients and that with an aging population, healthcare systems needed to rapidly adopt best practices for the care of older patients on a *consistent* basis—every older adult, at every touch point in the healthcare system. What emerged was the framework of Age-Friendly Health System (AFHS).

The framers of the AFHS understood the inherently complex and unique needs of older adult patients, as alluded to in Section 104.1. Additionally, each healthcare system has a unique culture, resources, leadership, and patient needs. Therefore, the framework needed to be flexible and easy to adapt to different clinical environments. Given this, the model focuses on major domains of care relevant to older adults and is known as the "4Ms Framework".[2]

- What Matters: Know and align care with each older adult's specific health outcome goals and care preferences, including, but not limited to, end-of-life care, and across settings of care.
- Medication: If medication is necessary, use age-friendly medication that does not interfere with What Matters to the older adult, Mobility, or Mentation across settings of care.
- Mentation: Prevent, identify, treat, and manage dementia, depression, and delirium across settings of care.
- Mobility: Ensure that older adults move safely every day in order to maintain function and do What Matters.

104.2.1 Other Uses of the Model

The 4Ms are intended to anchor the health system in best practices while still allowing for individualization based on the unique needs of the setting. While this model is rooted in quality improvement practices, clinicians, health researchers, and clinical educators have found other uses for this model, including but not limited to the framing of:

- Clinical notes (i.e., Assessment and Plan organized by the 4Ms)
- An individual didactic presentation or entire curriculum
- A research question and/or results

Each of these uses serves as a cognitive frame that encapsulates and organizes the inherent complexity and nuance of caring for older adults in a way that does not over-simplify (such as with a reductionist model).

Lifestyle medicine can similarly benefit from cognitive models that help organize the complex, multi-faceted information that comes with the territory. The six pillars of lifestyle medicine are a similarly flexible and comprehensive framework[3] to help anchor the cognitive process of a lifestyle medicine practitioner.

- Healthful eating
- Physical activity
- Stress management
- Relationships
- Sleep
- Substance use

As with the AFHS's 4M framework, the six pillars have the potential to be used in a variety of contexts within the field of lifestyle medicine: clinical work, health education (for patients and trainees), and research.

104.3 FOCUS ON PERSON-CENTERED CARE

In 2015, a team from the American Geriatrics Society collaborated to produce an evidence-based definition of person-centered care as well as its essential elements.[4] Their definition consisted of the following:

> "Person-centered care" means that individuals' values and preferences are elicited and once expressed, guide all aspects of their health care, supporting their realistic health and life goals. Person-centered care is achieved through a dynamic relationship among individuals, others who are important to them, and all relevant providers. This collaboration informs decision-making to the extent that the individual desires.

The panel went on to frame critical elements necessary to realizing this definition:

- *An individualized, goal-oriented care plan based on the person's preferences*
  Creating such a plan is the foundation of person-centered care, and first requires a thorough medical, functional, and social assessment. Understanding where one is in the present is critical to understanding where they can and want to go.
- *Ongoing review of the person's goals and care plan*
  Reassessing the care plan on a regular basis is critical to determining its effectiveness and continued alignment with the patient's goals, particularly as the patient experiences changes in their medical, functional, psychological, or social status.
- *Care supported by an interprofessional team in which the person is an integral team member*

The team must be flexible in composition and adaptable to changes in the person's health status, circumstances, and care goals.

- *One primary or lead point of contact on the healthcare team*
  Having one care provider who serves as a point of contact for the person and everyone involved in their care eases communication and facilitates continuity of care and transitions across care settings.
- *Active coordination among all healthcare and supportive service providers*
  Coordination among all providers assures that all services continue as seamlessly as possible, particularly when the person moves from one site of care (or residence) to another. The primary point of contact referenced above facilitates this.
- *Continual information sharing and integrated communication*
  Communication and information sharing may be accomplished through mechanisms such as the electronic health record and enhanced by careful listening and open communication between the person and everyone involved in their care.
- *Education and training for providers and, when appropriate, the person and those important to the person*
  Including the principles of person-centered care in the education and training of all healthcare providers contributes to their understanding of and commitment to providing person-centered care, including consistent recognition and maintenance of the person's autonomy. Health education of people receiving care and those important to them supports informed decision-making and self-determination.
- *Performance measurement and quality improvement using feedback from the person and caregivers*

  Measurable outcomes should focus on the successful implementation of care plans, evidence that the person's goals are being met, and evidence that efforts are being made to minimize difficulties during transitions between healthcare providers and across care settings.

Importantly, the panel also explored common barriers to the implementation of person-centered care at both the level of health systems and individual healthcare practitioners:

- *Inconsistent terminology*
  (e.g., "goals" vs. "preferences" vs. "values")
- *Traditional approaches to clinical practice*
  That is, established professionals can have embedded habits and philosophies of care that are difficult to change.
- *Physician workload is already high*
  A high workload limits the cognitive flexibility needed for person-centered care. This is perhaps ameliorated by the use of an interprofessional team.
- *Misaligned incentives*
  Teams that practice person-centered care may not be the beneficiaries of eventual cost savings and may be financially punished for the time and labor associated with pursuing this type of care.
- *Identifying appropriate indicators*
  Currently, it is difficult to measure success in providing person-centered care.
- *Provider concerns for risk and safety*
  When patient-centered care yields decisions that the healthcare team disagrees with and/or puts the patient at risk for death/disability, there are often ethical and medical-legal challenges to the delivery of person-centered care.
- *Lack of advance care planning*
  Older adults with cognitive impairment will often struggle to make their preferences known and therefore cannot fully engage in a shared decision-making model.
- *Lack of payment structures that span healthcare and community-based organizations*
  That is, the current healthcare system is fragmented, often failing to promote coordinated, comprehensive care for support and community-based resources that frail older adults need.
- *Lack of continuity in health records*
  That is, coordinated, comprehensive care of an interprofessional team is threatened when records are not easily accessed between health systems.

The above outline of person-centered care, while often difficult to achieve, is perhaps a critical component to the cognitive and philosophical outlook of those of us practicing geriatrics or lifestyle medicine, given our patients' complex and nuanced needs. Additional, practical applications of person-centered care to consider:

104.3.1 Health Optimization Looks Different for Different Patients, at Different Times

Geriatricians are well-versed in meeting patients where they are, optimizing based on the context and patient values. For example, a patient in a long-term nursing home unit will typically have a care plan that is palliative in nature, with the primary goals reflecting the desire to avoid pain and other symptoms and avoid unwanted interventions at the end of life. This is in contrast to a patient who might reside in a post-acute rehabilitation unit, typically a community-dwelling older adult recently hospitalized for an acute illness complicated by a functional setback and requiring intensive physical and occupational therapy. The strategy is restorative in nature with the goal being to return home and resume previously enjoyed activities.

These juxtaposed examples reveal that while strategies and goals for geriatric patients may differ based on patient circumstances, the same fundamental skillset from a thoughtful practitioner has a positive impact on both.

In a similar fashion, practitioners in lifestyle medicine need to have a flexible approach and individualized goals for patients based on their unique set of circumstances and values. One patient may need lifestyle medicine to get off medications for hypertension and diabetes and avoid downstream events of these diseases. Another patient may benefit from lifestyle medicine to avoid or delay needing any medications for hypertension and diabetes.

104.3.2 Motivation Looks Different for Different Patients, at Different Times

Attitudes around one's own health often shift throughout the lifespan, alongside motivations to make health changes. In both geriatrics and lifestyle medicine, it is essential that practitioners tap into a patient's intrinsic motivation for meeting their goals, given that sustainable, positive changes are most often dependent on the patient (± caregivers) implementing treatment recommendations.

Adolescents and young adults are more typically motivated by social acceptance and physical appearance, whereas those in middle age can be more interested in role-modeling for their children and staving off the chronic diseases (with associated burdens) that they are witnessing in their parents. Older adults may want to preserve independence or avoid future negative experiences through secondary prevention (e.g., "How do I not have another heart attack, doctor?"). By tuning in to an individual's motivational state and their readiness for change, a practitioner can more adeptly guide them in the direction of specific health behaviors.

Low motivational states are common during relapses in health goals, which are unfortunately a frequent occurrence in geriatrics and lifestyle medicine; further, these states can compound if the patient is prone to perfectionism, shame, self-doubt, or binary thinking. In these times, practitioners would be wise to avoid these psychological trappings ourselves (difficult though that may be) and instead provide empathy and validation of feelings, making space for ultimately picking up the pieces and recalibrating a path forward.

104.3.3 Triage and Make Trade-Offs

Geriatricians are well-versed in the need to triage patient health goals and carefully weigh the pros and cons of every decision we make, given the inherent medical complexity of our population in combination with reduced tolerance of most interventions; in short, we are usually looking for the path of "least potential for harm", aware that treating one problem may, in fact, make another worse. Though other patient populations may be more physiologically robust than older adults, all health practitioners would be wise to have a similar philosophy of "triage and trade-off". Particularly when it comes to lifestyle medicine interventions, patients have a limited cognitive and psychological bandwidth for behavior change that is not always appreciable (particularly when enthusiasm for change is high in the initial stages). Attempting too drastic of a change or too many changes simultaneously will set the patient up for relapse, shame, and a reluctance to re-engage. There is always a trade-off when making a change. It may not be obvious at the forefront, but it is wise to move cautiously alongside the patient in whatever field we are practicing so that we can notice and adapt to any unintended consequences that may arise.

104.4 INFLUENCE OF ENVIRONMENTAL AND STRUCTURAL FORCES UPON HEALTH OUTCOMES

> You do not rise to the level of your goals. You fall to the level of your systems.
>
> **~James Clear**

Most clinicians implicitly focus their attention on disease determinants that are rooted in pathophysiology and are directly observable during the visit by way of history, physical exam, and chart data. Especially with high patient volumes, there is little time to think about much else than these "proximal" determinants. In contrast to these, "Distal" causes of disease are rooted in systems and the environment and have traditionally been left to those in public health. Esteemed physician and medical anthropologist Paul Farmer bridged this divide in his own career, treating patients with HIV and other diseases in places such as Haiti. He became intimately familiar with systemic forces that create barriers to care for populations and can exert harm through "structural violence" that is embedded in social, economic, and political systems.[5] He called on the medical community to embrace the structural, distal causes of disease, integrating these into our care for patients in our offices.

As a group, older adults are vulnerable to poor health, elder abuse, neglect, and isolation in the absence of supportive structures. This is particularly true for those with high levels of frailty, cognitive impairment, and/or functional impairment. Whether it be a family unit, residential facility, community partner, or day program, high-functioning supports are often essential to older adults being safe and getting to experience what matters most to them. Because of this, geriatricians spend a significant amount of time during their training to understand the different resources available to older adults, how different resources interface with each other, and how to recommend the right support to the right individual. On the other hand, there is a nuanced and necessary skillset required to notice a problematic or frankly unsafe environment for older adults and disentangle them as necessary.

One exemplary care model for older adults that emphasizes infrastructure is the Program of All-Inclusive Care for the Elderly (PACE). Utilizing payments from Medicare and Medicaid, PACE provides comprehensive medical care, day programs, and social events to patients in the program. This is all done while keeping patients in their homes, although they meet the criteria for nursing home admission. PACE has positive patient satisfaction, reduces institutional care rates, controls utilization of medical services, and has cost savings to the Medicare and Medicaid programs.[6]

PACE may owe its success, in part, to its structural design. With medical care and day programming happening in the same building, there's a seamless transition from a card game to a medical checkup. Medical transportation from the patient's home to the PACE site is provided in most cases, eliminating the multitude of reasons an individual's transportation might fail them and inhibit their participation in the program. In general, individuals are going to be more successful at achieving goals when their environment is aligned with these goals. All environments encourage and discourage individual choices based on their make-up. Those who are intentional about good health outcomes will "bake in" mechanisms to decrease the energy expenditure at critical health choice points (i.e., make the healthy choice the easy choice). Unfortunately, the majority of health systems have not been as carefully curated as PACE; in fact, one could argue that mainstream healthcare is harmful to older adults and other vulnerable populations, encouraging poor outcomes by virtue of the barriers encountered by patients at every touchpoint to receive quality, affordable medical care.

All of the aforementioned six pillars of lifestyle medicine have heavy interaction with the individual's environment; therefore, optimizing those pillars will first require an assessment of how well the environment is set up to help the individual meet those goals. How well is someone going to sleep (realistically) if they are not using their CPAP for obstructive sleep apnea, if they watch TV before bed, and have an irregular sleep-wake cycle due to shift work? How well is someone going to consistently abide by a whole food, plant-based diet when the family meal pattern is based on processed animal foods?

We know from Dan Buettner's work in blue zones of healthy aging (Loma Linda, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; and Okinawa, Japan) that "9 evidence-based common denominators" of health behavior, present in the environments, appear to slow the aging process and promote healthful longevity:[7]

- Move naturally. Aim for consistent activity throughout the day.
- Purpose. Have a reason to wake up in the morning.
- Downshift. Stress may be unavoidable, but blue zones residents have regular means of self-care.
- The 80% rule. Otherwise put, mindful consumption of food and drink, without trying to be full at the end of the meal. This can mean the difference between weight maintenance and gain.
- Plant slant. Beans, including fava, black, soy, and lentils, are the cornerstone of most centenarian diets. Meat is consumed less often, and by subsets of the Adventists in Loma Linda, not at all.
- Wine @ 5. People in all blue zones (except Adventists) drink alcohol moderately and regularly.
- Belong. Most interviewed centenarians had an active faith community. Denomination did not seem to matter.
- Loved ones first. Successful centenarians in the blue zones put their families first, meaning keeping aging parents and grandparents nearby or in the home, committing to a life partner, and investing in their children with time and love.
- Right tribe. Having a social circle is important for many health outcomes, including longevity. Health behaviors are contagious!

In contrast to the blue zones, most of our environments (inclusive of home, work, and family) are not aligned with the six pillars, ranging from a little to a lot depending on a myriad of circumstances. Perhaps then, one of the precursors of making individual lifestyle medicine changes in the office should be addressing those aspects of the environment that are least conducive to the patient achieving their lifestyle goals.

Structural problems are most effectively addressed with structural solutions, yet much can be achieved by the individual motivated and adequately empowered to make changes to their environments and systems in a skillful way. Examples of practical environmental alterations for lifestyle could include:

- Taking the TV out of the bedroom.
- Having a set day and time to prepare a grocery list and shop. Negotiate meal choices outside of being hungry or short on time.
- Carving out time for exercise or social connection by putting a regular placeholder in the calendar.
- Joining a gym, sports team, or support group that has regular meetings with like-minded individuals.
- Keeping "triggering substances" out of the home (e.g., ice cream, alcohol).

In addition to adding structures conducive to health, gently exploring a shift away from less helpful structures may be needed. Here, empathy is paramount for the practitioner, given that even highly problematic environments are benefiting the patient in some meaningful way (or else they would not be there). Acknowledging this and exploring all the ways in which the patient may be actually benefiting from the problematic environment can be helpful unto itself: identification will help the patient consider meeting those needs in other ways that are more aligned with their overall goals and values.

Personal relationships often prove to be misaligned with the patient's health goals, and yet making changes in this domain can prove to be a difficult dilemma for patients and their practitioners, given what we know about the positive value of social connections[8]. Therefore, breaking away from a tribe (even in the name of one's health) can be incredibly painful, difficult, and potentially harmful to health from a social isolation standpoint. Perhaps then, in the event a patient is so motivated to make a change toward a more health-driven social network, a more gradual migration will be advisable.

104.5 LOW-TECH AND HIGH-TOUCH MODALITIES

Empathy, presence, and skillful words are among the oldest and most sacred modalities used in healing professions. Even in modern times, these attributes are often the backbone of skillful, patient-centered care. The opposite of these—"high-tech, low-touch" modalities—are omnipresent in the press and indeed can have immense benefit to patients when chosen thoughtfully. Geriatricians are often wary of adding on layers of riskier treatments for the following reasons:

- *High toxicity.* As people age, they have a higher inherent risk of medication toxicity compared with their younger counterparts.
- *Interactions and side effects.* Older patients are prone to polypharmacy, which can increase the risk of medication interactions and side effects.
- *Complexity and decreased adherence.* As the number of concurrent treatments increases, costs, complexity, and the likelihood of patients being overwhelmed will typically rise. As a result, adherence to the regimen may go down.
- *Prescribing cascade.* With every medication or intervention, there is a risk of side effects that are often difficult to differentiate from new problems; thus, patients are at risk of having a second medication prescribed to treat a side effect of the first.

While younger, healthier patients may not be as vulnerable to the above risks of medications and other risky therapies (especially in combination), they too may pay a price, and practitioners would be wise to consider low-tech, high-touch in at least augmenting the care for younger patients. Examples of such low-tech, high-touch modalities include therapies: physical, occupational, speech, cognitive behavioral, and psychodynamic; support groups, dietary coaching, and nursing care. Many of these modalities cross disciplines and are highly relevant for those practicing lifestyle medicine. They are lower risk for the patient and may be more effective for long-term positive impact, particularly when the patient is an active participant, has a therapeutic bond with the professional, and can apply skills gained during a session at other points in the future.

These modalities can be difficult for some patients to accept or stick with. Relevant patient factors may include self-efficacy beliefs, degree of cognitive impairment, depressive disorders, beliefs about time to benefit, or affordability/access to the service. Factors negatively affecting the uptake of the modality on the practitioner or systems front include low quality of the personnel, lack of availability of the service on a consistent basis, and lack of access/affordability.

Practitioners in lifestyle medicine have a particular challenge in advocating for low-touch, high-tech modalities: new lifestyle treatments are exploding onto the market at a rapid pace. Most are highly advertised, make wild claims about efficacy, and have scant if any evidence base. The lure of a "quick fix" to deep-rooted lifestyle problems can be strong for patients, and therefore it can be an uphill battle to convince them otherwise. Aspects of motivational interviewing may be helpful here, helping draw out prior experiences with "quick fix" modalities and the eventual impact.[2]

CLINICAL APPLICATIONS

- Geriatric healthcare providers are "complexivist" thinkers by nature, trained to integrate multiple layers of patient factors in making diagnostic and treatment decisions. Lifestyle medicine confronts similarly complex problems and practitioners can benefit from this way of thinking.
- Problems rooted in lifestyle medicine and geriatrics are not conducive to "reductionist" thinking, which often oversimplifies problems, and can lead to diagnostic and therapeutic errors, as well as low patient satisfaction. Given the inherent complexity of care involved with patients in the fields of geriatrics and lifestyle medicine, it is useful to have cognitive frameworks that are flexible and identify key domains of care, without oversimplifying.
- The Age-Friendly Health System 4M framework and the six pillars of lifestyle medicine are examples of such models for geriatrics and lifestyle medicine, respectively, which (because of their flexibility) can be applied by practitioners to a variety of contexts, such as clinical notes, patient and trainee curriculum, and research.
- Person-centered care is a critical philosophical and cognitive approach for practitioners in geriatrics and lifestyle medicine. Critical components of patient-centered care include having an interprofessional team with coordinated communication; frequent reassessment of the care plan based on the patient's goals/preferences/health status; ongoing data collection; and quality improvement; and attunement to individual variations in health optimization, patient motivation, and the need to make trade-offs.
- The fields of geriatrics and lifestyle medicine are inextricably linked to the environment

and structures. The ability of these structures to encourage healthful behavior will have an immense impact on the overall trajectory of the individual within that environment, and clinicians need to be aware of their patients' various environmental forces. Patients can often make changes to the structures in their own lives, setting themselves up for health-promoting behaviors.

- Low-tech, high-touch approaches to treatment often form the backbone of geriatric care models and are appropriate interventions to consider for lifestyle medicine patients as well, given the potential for long-term benefits and low toxicity.

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105 Addressing Physical Function, Sarcopenia, and Frailty through Lifestyle Medicine

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KEY POINTS

- Healthy aging is essential for maintaining mobility in older adults, which fosters an ability to maintain independence.
- The natural aging process places older adults at risk for poor mobility due to sarcopenia and frailty development.
- Nutrition and exercise interventions show promise for primary and secondary prevention of sarcopenia and frailty.
- While specific nutrients like omega-3 fatty acids, vitamin D, and protein may positively impact muscle mass and strength, dietary patterns like the Mediterranean diet may be most impactful for treatment and prevention.
- Exercise regimens should include both aerobic and resistance exercises that target older adults' activities of daily living.
- Future research needs to focus on the interplay between dietary patterns, protein supplementation, and mixed exercise routines and their impact on sarcopenia and frailty prevention and treatment to optimize healthy aging and mobility preservation.

105.1 INTRODUCTION

Preservation of physical function is a priority for older adults as it allows them to maintain independence and prevent sarcopenia and frailty. Physical independence is a key driver of overall quality of life.[1] As defined by the European Working Group on Sarcopenia in Older People, sarcopenia is the gradual loss of muscle mass, strength, and physical function.[2] Sarcopenia is a main contributor to the frailty syndrome, defined as the presence of three or more of the following components: slow gait speed, lower grip strength, low physical activity, self-reported exhaustion, and unintentional weight loss.[3] Frailty syndrome is the result of complex interactions between aging at the cellular level and the downstream impacts on muscle physiology (sarcopenia) and physical function (Figure 105.1).[4]

The progression of sarcopenia and frailty increases the risk of multimorbidity, institutionalization, and adverse health outcomes in older adults.[5,6] The negative impacts of this cycle emphasize the need for both primary and secondary prevention strategies for sarcopenia and frailty to encourage healthy aging, as defined by a recent American Geriatrics Society statement.[7] As frailty has a spectrum of phenotypes (e.g., robust, pre-frail, and frail), individualized interventions are likely needed to prevent its development or progression.[8] This need for individualization is further highlighted by older adults with both obesity and sarcopenia (i.e., "sarcopenic obesity"), where there is a need to balance weight loss and maintenance of "healthy" muscle physiology.[9,10] This chapter will discuss various approaches to the primary and secondary prevention of sarcopenia and frailty (and their overlaps) via nutrition and exercise interventions and identify areas of needed exploration.

105.2 NUTRITION

Appropriate nutrition is imperative for preventing sarcopenia and frailty and maintaining physical function throughout the lifespan. The Dietary Guidelines for Americans 2020–2025 suggest that females and males over 60 should consume 1600–2200 calories and 2000–2600 calories per day, respectively.[11] Table 105.1 highlights the composition of a typical 2000-calorie diet. However, older adults are at risk for poor nutritional intake due to factors associated with aging, such as decreased appetite (e.g., "anorexia of aging"), a blunted olfactory system, various medications, and earlier satiety due to slowing neuronal conduction.[12] Poor oral health is also a driver of inadequate intake, supported by the inverse relationship between the number of posterior teeth and consumption of a nutritionally complete diet.[13] For instance, participants with poor oral health in the National Health and Nutrition Examination Survey III lacked vitamins A and C, carotene, folate, and fiber in their diets. Furthermore, poor dietary intake is associated with chronic diseases, increasing the risk of sarcopenia and frailty. As a result, these components must be adequately addressed across the lifespan to improve the physical

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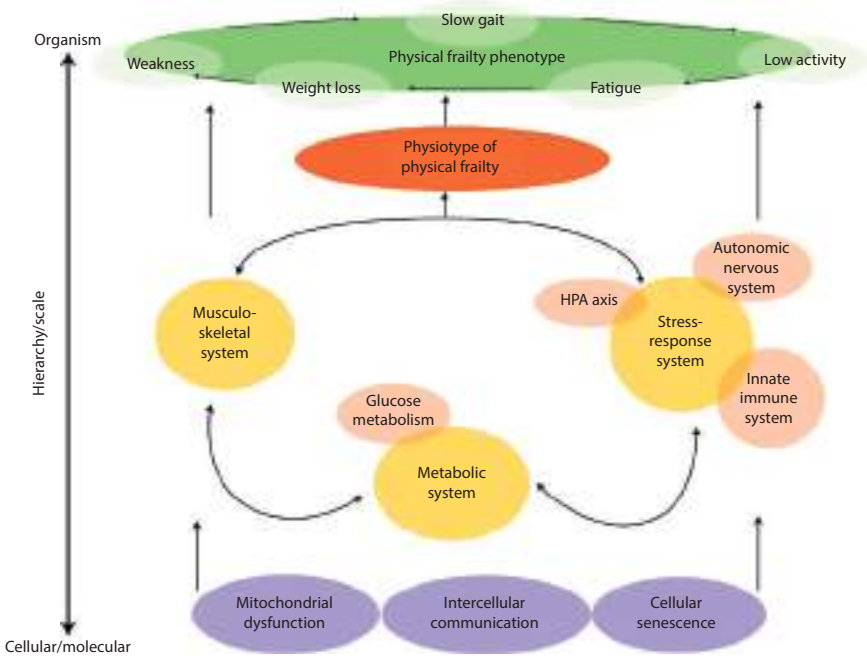


FIGURE 105.1 "A hierarchical, multiscale representation of the physiological dysregulation and likely biological drivers of physical frailty. The schema depicts the clinical syndrome of physical frailty as an emergent property, at the highest level of the hierarchy, underlain by physiological modules (systems) at a smaller scale and cellular/molecular modules (systems) at an even smaller scale. The musculoskeletal system, stress-response system, and metabolic system circles represent the three major physiological modules (systems) with the most evidence of interactions and the most evidence of a relationship with frailty. The glucose metabolism, HPA axis, autonomic nervous system, and innate immune system ovals represent submodules (subsystems) within these three larger modules. Stressors from age-related biological changes at the cellular/molecular scale, represented in the ovals with mitochondrial dysfunction, intercellular communication, and cellular senescence, likely underlie dysregulation of the physiological modules represented above, which also interact with each other. The aggregate physiotype of dysregulation (the oval containing physiotype of physical frailty) is associated with both the phenotype of physical frailty, in the top oval, and the vulnerability associated with its state" (reproduced with permission from Fried et al., The physical frailty syndrome as a transition from homeostatic symphony to cacophony. *Nat Aging*. 2021;1(1):36-46. doi:10.1038/s43587-020-00017-z).

function of older adults. Because nutritionally rich diets are important over time, we will explore certain macronutrients, micronutrients, dietary supplements, and dietary patterns as primary and secondary prevention interventions for sarcopenia and frailty.[7,11,12]

105.2.1 Protein

The Recommended Dietary Allowance of protein for adults over 18 years of age is 0.8 g/kg/day.[11] Slightly higher amounts of 1–1.2 g/kg/day and 1.2–1.5 g/kg/day are recommended by the European Society for Clinical Nutrition and Metabolism for healthy and malnourished older adults, respectively, in attempts to mitigate protein loss.[14] However, older adults are often not meeting their daily recommended dietary allowance of protein. Approximately 30% of men and 50% of women ages 71 and older do not meet their daily recommended amount.[11] Deficiencies in protein intake can lead to a metabolic deficit, leading to subsequent muscle atrophy and loss of strength.[15]

The association between protein intake and sarcopenia development is typically assessed by muscle mass or extrapolated from physical function outcomes. Lower (<0.8 g/kg/day versus >1.2 g/kg/day) protein intake was associated with loss of lean muscle mass and a higher odds ratio (2.56, 95% CI 1.01–6.50) of unhealthy weight loss in community-dwelling older adults in a longitudinal cohort study, after adjusting for caloric intake and other factors.[16] Additionally, higher protein intake was associated with a smaller reduction in grip strength for community-dwelling adults ages 60 and older in the Framingham Offspring cohort, gaining 0.52% to 0.60% strength per year.[17] Protein intake has a similar impact on the risk of frailty development. A systematic review by Lorenzo-López et al. showed that higher amounts of dietary protein (1 g/kg/day) were associated with less risk of frailty development in community-dwelling older adults.[18] Additionally, there was no significant difference based on the source of the protein (e.g., single amino acid versus whole food source). However, more recent data suggests that diets higher in plant-based protein may protect against frailty, with higher intakes of plant protein being associated with lower frailty risk (p-trend < 0.0001).[19]

Given the significant overlap in the pathophysiology of sarcopenia and frailty (e.g., muscle weakness leading to decreased strength and worse physical outcomes), recommended secondary prevention interventions are similar and

TABLE 105.1
Recommended Dietary Intake for Adults Aged Older than 50 Years of Age

Macronutrients	
Protein	10–32% of daily kcal (56 g)
Carbohydrate	45–65% of daily kcal (130 g)
Fiber	28 g
Added sugars	<10% of daily kcal
Total lipids	20–35% of daily kcal
Saturated fatty acids	<10% of daily kcal
Micronutrients	
Vitamin A	900 µg
Vitamin C	90 mg
Vitamin D	600 IU
Vitamin K	120 µg
Vitamin B_6	1.7 mg
Vitamin B_{12}	2.4 µg
Thiamine	1.2 mg
Riboflavin	1.3 mg
Niacin	16 mg
Choline	550 mg
Folate	400 µg

Recommended macronutrient and micronutrient components of a typical 2000-calorie diet for adults 51 years of age and older adapted from the 2020–2025 Dietary Guidelines for Americans.

include protein supplementation and exercise.[20] In a randomized controlled trial including pre-frail and frail older adults in Korea, 1.5 g/kg/day of whey protein supplementation led to increased appendicular skeletal mass, skeletal mass index, and gait speed when compared with 0.8-, 1.0-, and 1.2 g/kg/day supplementation amounts.[21] However, a systematic review by Cruz-Jentoft et al. yielded inconsistent results for sole protein supplementation in individuals with frailty.[22] Physical performance improved, but there was no change in muscle strength or muscle mass. The inconsistency in strength and muscle mass improvement is further supported by a randomized controlled trial where no differences in muscle mass or improvement in physical function occurred after non-protein malnourished, sedentary older men received protein supplements and testosterone injections.[23] The reasons for the negative trial were unclear as protein supplementation was ideal body weight-based; however, program adherence was self-reported, potentially confounding results.

Pairing exercise (combined [aerobic and resistance] or resistance exercises) with protein supplementation may amplify the impact of supplementation on improving muscle mass, strength, and frailty indices. In a meta-analysis by Liao et al., more significant improvements in lean body mass (standard mean difference [SMD] 0.52; $p < 0.00001$), leg strength (SMD 0.37; $p < 0.00001$), and frailty status (odds ratio 2.77; $p = 0.006$) occurred when protein supplementation (4.1–40.8 g/day) was coupled with combined or resistance exercises in community-dwelling and institutionalized frail older adults.[20] However, 40 mg daily whey supplementation paired with three times weekly resistance exercise did not lead to any statistically significant improvements in lean body mass or strength in a randomized controlled trial for older adults with mobility limitations.[24] The inconsistencies in muscle mass and physical function outcomes after protein supplementation emphasize the need for identifying which older adults will benefit from supplementation, the role of augmentation with exercise, and the appropriate supplement agent.

Branched-chain amino acid protein supplements, particularly leucine, stimulate muscle protein synthesis in older adults.[25] Leucine is found in various plant- and animal-based sources (e.g., whey). In a meta-analysis, leucine supplementation was associated with increased muscle protein synthesis when compared to controls (SMD 1.08, $p < 0.001$), making it an amino acid of interest for primary and secondary prevention.[26] There was an association between lower serum levels of branched-chain amino acids with lower skeletal muscle index and grip strength in a cross-sectional study of Norwegian adults ≥70 years.[27] Additionally, there was no defined plasma level of amino acids to identify sarcopenia and or set as a maintenance goal. Institutionalized older adults in Spain had improvements in walking time ($p = 0.011$) and muscle mass index ($p = 0.08$) with 6 g/day of leucine for 13 weeks.[28] For the supplementation amount, the PROT-AGE consensus committee recommends 2.5–2.8 g of leucine of the 25–30 g of protein consumed at each meal for healthy adults.[14] This is higher than younger adults due to the increased daily recommendation of 1.0–1.2 g/day of protein for older adults.

Both animal and plant-based protein supplement sources show promise for increasing muscle mass, with less being known about plant-based sources.[29] However, additional evaluations need to determine if plant-based or animal-based supplementation is superior for increasing muscle mass when paired with exercise and the recommended 1–1.2 g/kg/day of protein per meal. Overall, dietary protein content is important throughout the lifespan, particularly for individuals with sarcopenia and frailty, as it is required to maintain and stimulate muscle development. Additional studies are needed to individualize dietary protein amounts and types for primary and secondary prevention of sarcopenia and frailty, particularly when coupled with exercise for secondary prevention.

105.2.2 Carbohydrate

The primary energy source of an individual's diet is carbohydrates. The body uses simple sugar for energy by metabolizing simple sugars or breaking down oligosaccharides and polysaccharides. The Dietary Guidelines for Americans recommend older adults consume 45–65% of their total daily calories as carbohydrates (Table 105.1).[11] A meta-analysis examining carbohydrate intake of adults aged 45–65 years over a 25-year follow-up period demonstrated

a strong association with lower mortality in persons with a daily carbohydrate intake of ~50–55%.[30] A U-shaped curve represented the relationship between carbohydrate intake and mortality for low (<40% of daily dietary calories, pooled hazard ratio 1.20, 95% CI 1.09–1.32) and high (>70% of daily dietary calories, pooled hazard ratio 1.23, CI 1.11–1.36) carbohydrate consumption. In a cross-sectional, population-based study, dietary patterns including complex carbohydrates had lower odds of sarcopenia (odds ratio 0.25; 95% CI 0.10–0.63) and lower odds of decreased gait speed (odds ratio: 0.46; 95% CI 0.22–0.96).[31] However, future studies are needed to examine the impact of individual macronutrients, such as carbohydrates, on the risk of sarcopenia development.

105.2.3 Fat

Like protein and carbohydrates, dietary fats contribute to the energy content of the diet. Fats are the most calorie-dense at 9 kcal/g, comprising 20–35% of total daily calories (Table 105.1).[11] Dietary fats are important across the lifespan to promote cell function and the absorption of fat-soluble vitamins (A, D, E, K). Public health efforts encourage the incorporation of polyunsaturated fats versus saturated fats in the diet due to less risk of developing chronic diseases (e.g., cardiovascular disease and cancer) with diets higher in polyunsaturated fats.[32] Diets higher in saturated fats may drive the development of sarcopenia secondary to muscle inflammation and oxidative stress and are associated with an increased risk of frailty development.[33] A cross-sectional study by Montiel-Rojas et al. observed a lower risk of developing sarcopenia risk factors if polyunsaturated fats replaced saturated fats in older adult dietary patterns (β coefficient =-0.152, 95%CI −0.253, −0.051, p = 0.003).[34] However, the substitution of saturated fats with monounsaturated fats in the diet did not yield a statistically significant risk reduction of older adults developing sarcopenia risk factors. Polyunsaturated fats such as omega-3s have anti-inflammatory qualities that may have important implications for sarcopenia and frailty prevention through supplementation and dietary patterns.

105.2.3.1 Omega-3s

Omega-3 polyunsaturated fatty acids have historically been a topic of discussion within the realm of cardiovascular event prevention, acting as both a pharmacological and dietary intervention. Omega-3 polyunsaturated fatty acids include α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) and are anti-inflammatory in nature.[35] Omega-3s are found in fish, nuts, ground flax and chia seeds, and plant oils. Their anti-inflammatory activity is thought to be important for slowing muscular aging ("inflammaging"), which may be useful for both primary and secondary prevention of sarcopenia and frailty. Inflammatory markers of interest in sarcopenia and frailty include C-reactive protein, interleukin-6, and TNF-alpha.[36] In a longitudinal cohort study by Abbatecola et al., higher serum omega-3 levels were associated with better physical performance and less physical decline.[35] Similarly, in a longitudinal cohort study (5.2-year period), higher levels of ALA were associated with better knee extension in older adults (regression coefficient 5.97, 95% CI 1.17–10.8; p = 0.014).[37]

The anti-inflammatory impacts of omega-3s are inconsistent, which may be dependent on differing baseline interleukin-6 levels in older adults, as those with lower levels experienced less improvement in inflammation at similar omega-3 doses.[38] In a randomized controlled trial by Tan et al., longer duration (eight weeks versus four weeks) of omega-3 supplementation (1.5 g of EPA and 1.0 g of DHA) was associated with more successful lowering of interleukin-6, interleukin B, and TNFα levels in older adults (mean age 60.6 years) with at least one chronic venous leg ulcer.[39] These findings suggest that omega-3s may have the potential to mitigate inflammation and delay sarcopenia and frailty development. Tan et al. used higher EPA and DHA doses than in previous studies, which highlights the need for more randomized controlled trials focused on the impact of dosing on inflammation levels and physical performance outcomes, and including older adults with various chronic diseases as this may affect baseline inflammation levels.

Randomized controlled trials exploring the impact of omega-3 use coupled with exercise on muscle mass and function yielded inconsistent results. In the ENRGISE (Enabling Reduction of Low-Grade Inflammation in Seniors) trial, omega-3s did not reduce interleukin-6 levels or improve walking speed.[38] However, muscle thickness of the upper and lower extremities increased after 12 weeks of omega-3 supplementation (2 g) and three times weekly resistance training for men and women.[40] While omega-3 intervention is promising for the prevention and treatment of sarcopenia and frailty, more research is needed to identify the appropriate dose of omega-3s and exercise regimens to optimize their impact. Because dietary omega-3s are typically found in fatty fish and plant-based oils, the Mediterranean diet may be a tool for sarcopenia and frailty mitigation, which will be explored later in this chapter.

105.2.4 Micronutrients

Micronutrients are the vitamins and minerals in the foods we consume. Poor quality diets (e.g., those with limited sources of a variety of macronutrients, vitamins, and minerals) are associated with sarcopenia and frailty development.[31,41] The following section will discuss the role of micronutrients in sarcopenia and frailty prevention and treatment.

105.2.4.1 Vitamin D

Vitamin D 25(OH)D is of particular interest as vitamin D is a common supplement for osteoporosis prevention and previous observational studies suggest that vitamin D deficiency is associated with the development of sarcopenia and frailty.[42] Vitamin D acts on a cellular level at the

muscle, binding to the vitamin D receptor on the muscle and stimulating muscle growth.[43] In vivo, muscle vitamin D receptors decline with aging, leading to blunted muscle growth. Observational studies yielded inverse relationships between vitamin D, muscle mass, and strength and may predict physical decline in older adults.[44,45] In a longitudinal cohort study by Houston et al., healthy, community-dwelling older adults with a vitamin D level <20 ng/ml had worse performance on hand grip and Short Physical Performance Battery than those with a level ≥30 ng/ml at two- and four-year time points.[46] Similarly, older men in a five-year longitudinal study with 25(OH) vitamin D level <16 ng/ml and 1,25 vitamin D level <25.8 pg/ml had an odds ratio of sarcopenia of 2.53 (1.14–5.64; p = 0.02) and 2.67 (1.28–5.60; p = 0.01), respectively.[47] A randomized controlled trial by Cai et al. did not yield any clinically significant improvement in frailty status, of older adults with low vitamin D, with vitamin D supplementation (200, 1000, and 2000 IU doses) and had weak evidence for the benefits of the 4000 IU dose.[42] However, multiple randomized controlled trials support that vitamin D supplementation paired with protein (whey) supplementation may improve muscle mass in older adults.[46,48,49] Older adults with sarcopenia increased muscle mass and improved chair-to-stand performance with twice-daily whey, leucine, and vitamin D supplementation.[48]

105.2.4.2 Other Vitamins and Minerals

Sarcopenia is associated with low intake of vitamins C, D, E, and folate and low serum levels of vitamin E and carotenoids.[18] A sequential decrease in micronutrient levels has been associated with progression along the frailty spectrum, from robust to frail. A systematic review by van Dronkelaar found that sarcopenia was associated with low intake of magnesium (p = 0.015), selenium (p = 0.015), and phosphorous (p = 0.014), and calcium (highest versus lowest tertile of calcium intake OR 0.259; 95% CI 0.087–0.768, p < 0.01) intake was associated with increased muscle mass.[50] Magnesium supplementation was associated with better physical performance (handgrip change of 0.41 points, p = 0.03, chair stand change of 0.14 m/s p = 0.006, SBBP −1.31 seconds p = 0.0001) and increased muscle mass in healthy older women.

Various micronutrients also serve as antioxidants. Oxidative stress and inflammation are drivers of chronic disease with reactive oxygen species causing cellular death and clinical aging ("inflammaging").[51] Antioxidants mitigate inflammation by counteracting free radicals. Vitamins C and E are of interest in sarcopenia and frailty as vitamins C and E are associated with collagen development and muscle formation, respectively.[52] While some observational population studies suggest that vitamin C and E slow muscular aging, data is inconsistent for both primary and secondary prevention of sarcopenia and frailty.[53,54] Knowing micronutrient associations can help guide future sarcopenia and frailty screenings to include nutritional evaluations focused on particular micronutrients and direct future randomized control trials to focus on individualized dietary plans and patterns.

105.2.5 Dietary Patterns

Dietary patterns are of particular interest across the lifespan as healthy eating is important for healthy aging. Anti-inflammatory dietary patterns are associated with preserving physical function and slowing cognitive decline and include the Mediterranean and the Dietary Approaches to Stop Hypertension (DASH), which are diets rich in omega-3s and antioxidants.[55–58] The Mediterranean diet minimizes processed foods and encourages fruits, vegetables, potatoes, whole grains, beans, nuts, seeds, and extra virgin olive oil while including moderate amounts of lean poultry, fish, seafood, dairy, and eggs.[59] The DASH diet is rich in vegetables, fruits, and whole grains and low in saturated fat, sweetened beverages, foods with added sugar, and sodium.[60] The DASH diet also includes fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils. In this section, we will explore the Mediterranean and DASH diets as potential interventions for sarcopenia and frailty prevention and treatment.

105.2.5.1 Mediterranean Diet

The Mediterranean diet contains omega-3s and antioxidant micronutrients that may mitigate "inflammaging" and serve as primary and secondary prevention interventions for sarcopenia and frailty.[58] Omega-3s and antioxidants are often consumed in the form of seafood (15 ounces/week) and fruits (2.5 cups daily)/vegetables (2.5 cups daily), respectively.[59] Better Mediterranean diet adherence was associated with higher appendicular skeletal muscle mass and slowing muscular decline (e.g., less decline in gait speed and better lower limb performance).[55–58] In a cross-sectional and retrospective cohort study including older adults aged 59 to 73 years of age, each additional serving of fatty fish per week yielded improvements in grip strength for men (0.48 kg, 95% CI 0.24–0.72) and women (0.43 kg, 95% CI 0.13–0.74).[61] Similar trends were seen for frailty primary prevention in a systematic review and meta-analysis by Kojima et al., as better Mediterranean diet adherence was associated with a lower risk of frailty development.[62]

The Mediterranean diet may be a method of secondary prevention of sarcopenia and frailty through the anti-inflammatory and antioxidant properties of its food components. Despite these associations, there are no clearly defined mechanisms to specifically explain the observed benefits of the Mediterranean diet for sarcopenia and frailty but these may be related to the combination of nutrients. In areas of more Westernized diets and insufficient resources, Mediterranean diet adherence may be challenging, which will need to be taken into consideration in future research. Additionally, future research will need to explore the impact of the Mediterranean diet, and its components, as secondary prevention of sarcopenia and

frailty due to the paucity of current longitudinal data in older adults.

105.2.5.2 DASH Diet

The DASH diet has similar components to the Mediterranean diet. However, it is based on a Westernized diet that contains more refined grains (six to eight servings/day) and red meat consumption (six one-ounce servings/day).[60] Additionally, there is a focus on limiting daily salt intake to less than 2300 mg. The DASH diet was initially developed to target hypertension and led to improvements in cardiovascular disease and diabetes.[63] Like the Mediterranean diet, its anti-inflammatory and antioxidant components make it a potential approach to sarcopenia and frailty mitigation.

While few studies or reviews explore the impact of the DASH diet on sarcopenia, Perry et al. conducted a randomized controlled trial including non-frail older adults (aged 65 to 84 years) with obesity (body mass index $\geq$ 30 kg/meters^2) that consumed the DASH diet (including lean red meat) with a caloric restriction of 1800 kilocalories a day.[63] At the end of the 12-week period, there was a 6.3% ($p < 0.001$) weight loss predominantly of fat mass. Total muscle mass was reduced, hand grip strength increased, and participants maintained the same level or improved performance on sit-to-stand and gait speed. These findings suggest that the DASH diet may be a primary prevention method for older adults with a body mass index $\geq$30 kg/meters^2. Due to the preservation of lean mass during weight loss with the DASH diet, this dietary pattern may benefit individuals with sarcopenic obesity, as a special balance is needed between weight loss and muscle preservation. Cross-sectional data for community-dwelling older adults suggests that DASH diet adherence is associated with a lower prevalence of frailty (OR 0.97, 95% CI 0.94–0.99); however, there are few randomized controlled trials exploring the DASH diet as a secondary prevention method for frailty.[64] Future efforts need to explore the impact of DASH diet adherence throughout the lifespan and its impact on functional measures and body composition in older adults.

A combination of the Mediterranean and DASH diets, the Mediterranean-DASH diet intervention for neurodegenerative delay (MIND), also shows promise for slowing cognitive decline, which is of additional interest in this age cohort.[50] While the Mediterranean and DASH diets show promise for sarcopenia and frailty prevention and mitigation, the optimal dietary pattern for the prevention of sarcopenia and frailty has not yet been determined. Therefore, future research needs to explore the impact of specific dietary patterns on both primary and secondary prevention of sarcopenia and frailty.

105.3 EXERCISE

Exercise is imperative for the preservation of and improvement in physical ability in individuals affected by sarcopenia and frailty. Exercise is critically important across the lifespan as a determinant of healthy aging as it is associated with better cardiovascular health, cognition, mood, maintenance of physical function, and prevention of physical decline.[65–67] Independence is a major component of older adults' quality of life, as poor physical status negatively impacts older-adult quality of life.[68] This section will explore various exercise types and their range of impact on sarcopenia and frailty prevention and treatment.

105.3.1 Exercise Approach for Sarcopenia and Frailty Prevention and Treatment

For primary and secondary prevention of sarcopenia and frailty, older adults should engage in resistance and aerobic exercises as they age.[69,70] Both resistance and aerobic exercise directly impact muscle physiology by promoting muscle protein synthesis and are associated with the maintenance of function and cognition.[71] Aerobic activities are important for achieving the stamina needed for resistance training but have little effect on strength.[72] Resistance exercises successfully counter muscle weakness by increasing muscle mass.[73,74] The Physical Activity Guidelines for Americans recommend 150 minutes of moderate-intensity exercise weekly with resistance exercise of all major muscle groups at least twice a week.[69] Exercise programs should include combined aerobic and resistance exercises that target older adults' daily activities, focusing on large muscle groups,[75] particularly the lower extremities, as the activities of daily living heavily rely on the lower extremities. This concept is supported by better chair stand performance by older adults who participated in exercise programs that included more squat repetitions.[76] Resistance exercise prescriptions should be progressive and with a goal at least twice per week, consistent with the Physical Activity Guidelines for Americans.[69,76]

The ideal exercise intensity is unknown for sarcopenia, but a spectrum of intensities shows improvement in strength. High-intensity (e.g., three times weekly for 1.5 hours) training with resistance training and supplementation with whey, vitamin D, and calcium (versus no intervention) led to improvement in total body fat (-1.76 ± 2.08 %, $p < 0.001$), thigh lean body mass (242 ± 231 g, $p < 0.001$), leg press amount (451 ± 223 N ($p < 0.001$), and decreased abdominal fat percentage (-2.27 ± 1.89%, $p < 0.001$) in older men with sarcopenia after a 36-week intervention when compared with controls.[77] While higher-intensity resistance exercises are associated with greater improvements in strength, low- to moderate-intensity resistance exercises still show clinically significant gains.[73,74] In a randomized controlled trial comparing low-intensity (training at 40% of the one repetition maximum) versus high-intensity (training at 70% of the one repetition maximum) resistance training, there were no statistically significant differences between groups for instrumental activities of daily living and routine activities of daily living.[74] Ideally, the individual should provide maximal effort at any resistance level with exercises that show muscle fatigue at the end of the session.[78] Gradual

increases in resistance and repetitions can be guided by the individual's fatigue level, with one to three sets of six to 12 repetitions being adequate for strength gain. Ideally, rest periods between exercises cater to the individual's preference, and exercise routines should not occur on consecutive days.[69,78]

Aerobic, resistance, and combined exercise programs have shown improvements in timed up and go ($p < 0.01$), gait speed ($p < 0.01$), skeletal muscle mass index ($p < 0.01$), and appendicular skeletal muscle ($p < 0.01$) in a systematic review and meta-analysis of adults over 65 years of age participating in a randomized controlled trials investigating the aforementioned exercise regimens.[79] The exercise regimens ranged from 30–60 minutes, one to seven times a week for 8–36 weeks. Similar effects were seen in a systematic review and meta-analysis by Lu et al., as individuals with sarcopenia participating in exercise interventions (mixed training, resistance training, and whole-body vibration therapy) performed better than controls for knee extension strength ($p < 0.00001$), timed get up and go times ($p < 0.00001$), and gait speed ($p < 0.0001$).[76] These findings highlight the impact of exercise on secondary prevention of frailty and sarcopenia and the role of a combination of aerobic and resistance exercises.

Strength and functional outcomes from resistance training vary between community-dwelling and hospitalized older adults, which may result from varied study protocols and individualized responses.[80] Sáez de Asteasu et al. stratified resistance exercise response by adverse responders, responders, and non-responders to intensive exercise (five to seven consecutive days, twice daily) versus routine care for hospitalized adults.[81] The presence of adverse and non-responders emphasizes the heterogeneity of responses to exercise interventions and the need for further exploration to develop individualized programs. These varying responses may also highlight the impact of sarcopenic obesity on response to exercise interventions. For instance, older women with sarcopenic obesity had blunted strength gains with chest press (12.9% versus 8.7%), biceps curl (11.3% versus 10.3%), and leg press (50.3% versus 40.5%) when compared with women with solely sarcopenia, proposing a need for individualized therapies for this group and/or a combination of diet and exercise interventions.[82]

Although less commonly prescribed exercise regimens, yoga and tai chi show promise as methods of both primary and secondary prevention of sarcopenia and frailty and are readily available in community-based settings. In a randomized controlled trial comparing physical measures between community-dwelling older adults randomized to a ten-month tai chi intervention versus health education, the tai chi group improved their appendicular skeletal muscle mass and gait speed.[83] However, there were no changes in grip strength. Despite no changes in grip strength, this study suggests that tai chi may be a tool for sarcopenia mitigation. In a prospective cohort study of older adults with frailty residing in Singapore, those performing tai chi more than once a week had better quality of life measures and were less likely to develop pre-frailty or frailty than those who only performed tai chi zero to one time per week.[84] Yoga has not been thoroughly studied in the older adult population. Because there is some literature to suggest that yoga decreases the inflammatory markers associated with muscle aging (e.g., C-reactive protein, interleukin-6), future studies should consider including yoga as an exercise intervention.[85]

Traditionally, exercise routines are being directed face-to-face by a trained individual. With the advent of technology bringing healthcare into the home, voice assistant systems (e.g., Amazon Alexa, Google Assistant, and Apple Siri) provide a platform for the delivery of prescribed exercise programs to older adults in their homes.[86,87] Feasibility studies thus far include mostly community-dwelling adults comfortable with technology; therefore, in terms of frailty treatment and prevention, future research needs to explore applications along the frailty spectrum and consider older adults' access to voice assistant system devices and underlying healthcare disparities.

105.4 SPECIAL CONSIDERATION: SARCOPENIC OBESITY

The complexity of interactions between sarcopenic obesity and functional outcomes highlights the need for a balance between weight loss, proper nutrition, and exercise. Unlike renourishment approaches for malnutrition-related sarcopenia and frailty, caloric restriction and weight loss are pillars of treatment in sarcopenic obesity, using exercise and protein supplementation to minimize the loss of healthy muscle mass.[87] A study by Villareal et al. suggests that combined exercise with caloric restriction can achieve weight loss (9%; -8.5 ± 0.5 kg, $p < 0.001$) with preservation of muscle mass and improved strength.[88] Caloric restrictions of 500–1000 calories/day and a goal of ~0.5 kg/week weight loss are reasonable treatment goals.[87]

In attempts to minimize muscle mass loss during weight loss, protein supplementation during weight loss may mitigate the loss of healthy muscle mass; however, the optimal amount and or pattern of supplementation is unclear.[20,89] It is imperative for individuals with sarcopenic obesity to have adequate protein supplementation to promote an anabolic state after exercise, which is postulated to be 1.0–1.5 g/kg/day, being mindful of renal function at higher supplemental doses.[87] A review by Gilmartin et al. noted improvements in appendicular muscle mass and decreases in truncal fat mass and inflammatory markers in females with sarcopenic obesity after 18 weeks of whey supplementation coupled with three times weekly resistance training.[90] Similarly, a low-calorie diet (1000 kcal/day) with whey and leucine supplementation maintained muscle mass and improved strength in women with sarcopenic obesity.[91] There is currently a randomized control trial investigating the impact of different specific amino acids and exercise on sarcopenic obesity and more studies like these need to focus on individualizing

dietary and exercise routines to best balance weight loss with maintenance of muscle mass.[92] This suggests there are specific roles for specific exercise types for sarcopenic obesity treatment and a need to better understand how to maintain adequate muscle synthesis with effective aerobic exercise.

105.5 CONCLUSION

Healthy aging is an individualized experience requiring individualized approaches. Physical function has a significant impact on quality of life among older adults. Thus, identifying methods of primary and secondary prevention of sarcopenia and frailty is key to helping older adults achieve their desired quality of life. While specific diet components were highlighted within the chapter, dietary patterns combined with mixed exercise regimens will likely be most effective in reducing disease burden and improving physical function in those with sarcopenia and frailty and those at risk of developing these geriatric syndromes. We acknowledge that there are other components needed to promote healthy aging (e.g., community, mental health, cognition); however, these were deemed outside the scope of this chapter. To move prevention efforts forward, it is essential for future research to explore the impact of dietary patterns with exercise regimens, alternative exercise regimens (e.g., yoga and tai chi), and specific macronutrient and micronutrient supplementation amounts on sarcopenia, frailty, and sarcopenic obesity trajectories.

CLINICAL APPLICATIONS

- Healthy aging involves lifestyle interventions that preserve and improve mobility. Approaches to primary and secondary prevention largely overlap as a result of similar underlying pathophysiological mechanisms of sarcopenia and frailty.
- Higher protein diets (1–1.2 g/kg/day) with protein supplementation may delay the development of sarcopenia and show promise for secondary prevention when coupled with mixed exercise regimens.
- There is an urgent need for randomized controlled trials and longitudinal studies to explore the impacts of dietary patterns (e.g., Mediterranean and DASH) when coupled with exercise on sarcopenia and frailty outcomes.
- Older adults should be encouraged to engage in a combination of moderate-intensity resistance and aerobic activity for at least 150 minutes each week with a progressively difficult resistance regimen, individualized to the adult. Practicing yoga and tai chi may be beneficial for older adults.
- Individuals with sarcopenic obesity need individualized dietary and exercise regimens that optimize weight loss while minimizing the loss of healthy muscle mass.

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106 Reducing Cognitive Decline through Lifestyle Medicine

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KEY POINTS

- Cerebral atrophy is a normal part of aging, but lifestyle factors can serve to increase or decrease this rate of change.
- Mild cognitive impairment (MCI) and dementia are clinical diagnoses with structural correlates.
- MCI and dementia, including Alzheimer's type, have a strong association with vascular disease and risk factors, including diabetes, heart disease, hyperlipidemia, and stroke.
- APOE ε4 allele carriers are at significantly increased risk but this risk can still be mitigated through lifestyle factors.
- Each of the six pillars of lifestyle medicine has a role in reducing cognitive decline.

106.1 NORMAL AGING OF THE BRAIN

In order to understand what is normal and what is pathologic in regard to cognitive decline with age, one must first understand how the brain ages. Changes are wide-ranging, occurring at the molecular, cellular, vascular, and structural levels. It has been observed that the brain loses volume at a rate of about 5% per decade from age 40, with the year-to-year rate accelerating later in life. Volume loss is primarily from the gray matter, where neuronal cell bodies reside, but this is also accompanied by loss of protein and phospholipid in the brain, due in part to the loss of myelin from nerve sheaths within the white matter.[1]

Volume loss does not occur proportionally in all regions. A review of studies comparing magnetic resonance images (MRIs) of younger subjects with older subjects noted that the prefrontal cortex is most affected, followed by the striatum, and by other regions including the temporal lobe, hippocampus, and cerebellar vermis. The occipital cortex was most preserved.[2] This has important phenotypic implications as the prefrontal cortex is the primary region responsible for executive function.[3] The hippocampus is heavily involved in conscious memory formation such as learning facts or a new skill and is often noted to be particularly diminished in size in dementia syndromes. The striatal memory systems are involved in habitual processes and the systems are known to interact, as a newly learned task typically begins in the hippocampus and is then encoded in the medial dorsal striatum through practice and repetition.[4] Other changes include loss of axonal length, a decrease in the size of individual neurons, a decrease in the number of synapses, and accumulation of lipofuscin pigment, a byproduct of lipid breakdown.[5]

Another crucial mechanism of age-related cognitive change is the concept of cerebrovascular aging. The brain, receiving 15% of total cardiac output, depends on the vascular system for both the delivery of nutrients and the removal of waste products.[6] A defining feature of the cerebral vasculature is the blood–brain barrier (BBB), formed of membrane components, tight junctions, and specialized cells to prevent harmful molecules from entering the brain.[7] Regulation of flow is dynamic and achieved through smooth muscle control of arteries, long permeating arterioles, and capillary beds in response to carbon dioxide pressure in the blood (PaCO2), input from the autonomic nervous system, and other factors.[7] A number of changes occur with cerebrovascular aging. Loss of compliance of arteries occurs due to the displacement of elastic tissue with collagen and results in an increase in systolic pulse valve velocity, describing pressure exerted on the brain during systole. Endothelial cell senescence occurs, making small vessels less adaptive and thus more prone to thrombotic occlusion and oxidative damage. Luminal narrowing of the vessels and rarefaction (a loss of density) of the microvasculature have been described.[7] These processes can be accelerated by chronic oxidative stress (related to the concept of "inflammaging") and mitochondrial dysfunction inherent to multiple lifestyle and chronic disease risk factors. The downstream consequence is a loss in the above-described BBB and of the brain's ability to autoregulate, two defining hallmarks in how normal cognitive aging is superseded by cognitive impairment or dementia.

Throughout this chapter, a number of animal studies will be referenced in addition to both observational studies and randomized controlled trials (RCT) in human subjects. Dementia is known to be the endpoint of decades of accumulated damage in the brain, a time course making mechanistic study difficult in humans. Animal models are well suited to this role given shared pathogenesis in an accelerated chronology, with rodent models most commonly used.[8] A number of distinct models have been developed to mimic both normal cognitive aging and particular disease states. Such models are limited in their ability to characterize the

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full spectrum of cognitive and behavioral implications of such changes and thus complement the evidence obtainable in human studies.[8] This blended approach to evaluating evidence has previously been proposed as an optimal way to understand the relationship of lifestyle to chronic disease.[9]

106.2 DEFINITIONS

106.2.1 Cognitive Domains

The cognitive activities of the brain are often organized into functional "domains". While domains are not mutually exclusive, they are often handled by distinct parts of the brain and thus are a useful way to conceptualize both the function and dysfunction of cognitive processes. These domains include sensation, perception, motor skills and construction, memory, executive functioning, processing speed, and language/verbal skills. Executive function encompasses tasks of planning and problem-solving and involves complex coordination of inputs from other cognitive domains.

106.2.2 Age-Associated Memory Impairment

Most individuals can expect to experience age-associated memory impairment (AAMI) through normal aging. This is thought to be primarily due to changes within the hippocampus and the frontal and temporal lobes of the cerebral cortex.[10] Of the four types of memory—episodic, semantic, procedural, and working memory—episodic and semantic memory are most affected by AAMI, collectively known as declarative or explicit memory. Episodic memory refers to memories associated with events in personal experiences, such as a college graduation, a memorable birthday, or a successful day at work. These memories include information on the time and location of the episode. Semantic memory refers to general accumulated world knowledge, such as universal facts or concepts not unique to an individual's own experience.[10] Nondeclarative or implicit memory is generally preserved in normal aging but can be affected in the disease state. This includes procedural memory, a form of long-term memory involved in the performance of actions and skilled tasks such as tying shoes, and working memory, a short-term form of memory that facilitates the performance of complex tasks.

106.2.3 Mild Cognitive Impairment

Mild cognitive impairment (MCI) is defined by more severe changes than those expected with normal aging but an absence of functional impairment. MCI often affects cognitive domains that are preserved in normal aging and often shares a mechanistic cause with dementia, such as accumulation of tau proteins and neurofibrillary tangles or cerebrovascular disease. The incidence of MCI increases in each decade after age 60 and carries an estimated 15% yearly risk of progression to frank dementia.[11] Cognitive function is screened for by various scales (such as the Montreal Cognitive Assessment, Mini-Mental State Examination, and St Louis University Mental Status scale) and score cutoffs have been employed in distinguishing probable MCI from dementia but ultimately it is the presence or absence of functional impairment due to cognitive decline that distinguishes the two conditions.[12]

106.3 RISK FACTORS FOR COGNITIVE DECLINE AND DEMENTIA

An increase in the incidence and prevalence of cognitive impairment and dementia has been noted consistently year to year in the United States.[13] Given higher prevalence per age cohort, increased life expectancy alone cannot account for the increase. As is the case with many of the diseases discussed in this text, it has been increasingly recognized that many modifiable lifestyle-related risk factors influence the risk and extent of cognitive decline.

The 2020 Lancet commission identified 12 potentially modifiable risk factors for accelerated cognitive decline and dementia. These were estimated to have a weighted population attributable fraction (PAF) for dementia of 39.7%, meaning approximately 40% of dementia cases were calculated to be due to these risk factors.[14] They are summarized in Table 106.1. These factors will be discussed further in the context of the six pillars of lifestyle medicine in the next section. This list is not exhaustive of all modifiable risks.

The greatest non-modifiable risk factor and greatest risk factor overall for cognitive decline is age with risk approximately doubling every ten years of life from age 60.[15] Among genetic risk factors, the APOE ε4 allele is the most well-known. Strength of association has varied widely in the literature but has been generally estimated at a two- to three-fold increase in dementia for individuals with one allele and 8–12 times greater risk for those with two alleles.[16,17] Approximately 25% of people carry one copy of

TABLE 106.1
Top 12 Modifiable Risk Factors Identified by the Lancet Commission

Lower education level
Hearing loss
Traumatic brain injury
Hypertension
Alcohol abuse (>21 drinks per week)
Obesity (body mass index ≥30)
Smoking
Depression
Social isolation
Physical activity
Diabetes
Air pollution

APOE ε4 and 2–3% carry two copies.[18] This association is true for both MCI and dementia. A number of additional genetic risk factors have been identified including but not limited to mutations in amyloid precursor protein (APP) on chromosome 21q, Presenilin 1 (PSEN1) on chromosome 14q, and Presenilin 2 (PSEN2) on chromosome 1q.[19] These are associated with early-onset Alzheimer's disease in particular. The APOE ε2 allele has been found to be associated with a decreased risk of cognitive decline.[20] This was demonstrated in a number of case-control studies and more recently reinforced in analyses of multiple centenarian genetic databases.[21]

The above-described factors contribute to the cumulative risk of cognitive decline in an individual. A number of factors and activities can conversely mitigate the risk. An important concept to define in this context is "cognitive reserve". Cognitive reserve can be defined as an individual's resilience to cognitive aging.[22] This concept will be referenced throughout the remainder of this chapter.

106.4 SIX PILLARS

106.4.1 Nutrition

The consequences of the standard American diet accelerate cognitive aging in a number of ways. Broadly, cerebrovascular aging is accelerated in the same contexts as systemic cardiovascular disease, through chronic inflammation, oxidative stress, and atherosclerosis. The Honolulu Aging Study, best known for characterizing the types of lesions seen on brain autopsies in sufferers of dementia, also noted that Japanese Americans had a considerably higher rate of cognitive impairment than inhabitants of mainland Japan, thought to be in large part due to dietary and other lifestyle differences.[23] Dementia rates in China have been found to increase in correlation with rising obesity rates in China, as Western influence continues to impact diet.[24] Additional disease-specific pathways have been noted. In a study of Drosophila flies and in vitro neuroblastoma cells, it was noted that increased insulin resistance leads to increased tau phosphorylation and thus decreased clearance from the brain through insulin receptor-dependent kinases.[25] In a 2016 study of rats, exposure to a "Western-style diet" (characterized as high in fat and sugar) compared with typical chow-fed rats was associated with increased permeability of the BBB with a dose-dependent relationship to time of exposure to the Western-style diet.[26]

A number of epidemiological studies have demonstrated an association between low dietary omega-3 fatty acids (O3FA) and risk of cognitive impairment. Docosahexaenoic (DHA), a type of O3FA, has been noted to produce neuroprotective metabolites and participate in neuroprotective signaling pathways. It also has been found to limit the production and accumulation of tau proteins and phosphorylation of β amyloid.[27] A recent randomized controlled trial comparing serum and CSF DHA levels found that APOE ε4 carriers experienced a lower rise in CSF DHA after DHA consumption, further supporting the protective role of DHA in cognitive aging.[28] Clinical trials have thus far failed to strongly support a real-world benefit of supplementation of O3FAs. A Cochrane review of three RCTs including 4080 participants aged 60 or older found no differences in cognitive function scores in those receiving O3FA supplements versus those receiving placebo for a minimum of six months.[29] While results may have been influenced by the length of the treatment period or age at treatment, at this time data is insufficient to recommend supplementation. Thus, whole food sources of O3FAs should be recommended. These are rich in fatty fish such as salmon. Plant-based sources include flax seeds, chia seeds, brussels sprouts, and walnuts.[30]

Numerous vitamins and micronutrients have been studied with regard to cognitive decline. Vitamin D has been noted to be protective through a variety of mechanisms. Vitamin D, a steroid prohormone, is known for its primary role in regulating bone health and serum calcium but has been increasingly recognized for its antioxidant and anti-inflammatory roles. Vitamin D crosses the BBB and receptors are present on neurons in multiple structures of the brain. It has been found to promote the production of nerve growth factors (NGF), an important neurotrophic factor.[31] In rat studies, this has been correlated with increased hippocampal volume. Other roles of vitamin D in the brain include regulating various neurotransmitters, reducing tau phosphorylation, reducing the formation of amyloid oligomers (which are more difficult to clear from the brain), and promoting clearance of neurotoxins. While a causal relationship is difficult to demonstrate, numerous observational studies have found an increased prevalence of vitamin D deficiency in individuals with cognitive decline and dementia and have correlated low vitamin D levels with brain volume loss, particularly in the hippocampus.[31] Animal studies have noted a decrease in NGF and glial-derived neurotrophic factor in rats born to vitamin D-deficient mothers and in young rats exposed to a transient vitamin D deficiency. Impairment in attentional tasks was also noted compared with control group rats.[32] B vitamins have also been shown to be protective against cognitive decline. B12 is well known to be associated with dementia and demyelination leading to the syndrome of subacute combined degeneration. B12, B6, and folate have additionally all been found to decrease homocysteine levels, a molecule associated with cognitive decline.[33] An RCT randomized subjects with above average homocysteine level to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B12, and 20 mg vitamin B6 versus placebo for two years and demonstrated reduced homocysteine levels and improved scores in measures of semantic memory, episodic memory, and global cognition in the intervention group.[34]

A 2014 review published in the journal *Neurobiology of Aging* proposed seven dietary and lifestyle guidelines based on available evidence for the prevention of cognitive decline.[35] These are as follows. (1) Minimize intake of saturated and trans-fat due to the strong association

of dyslipidemia with cognitive decline. (2) Vegetables, legumes, fruits, and whole grains should replace meat and dairy as these foods were found in the Chicago Health and Aging Project to be associated with a reduced risk of cognitive decline. (3) Vitamin E should come from foods rather than supplements, as dietary sources (such as leafy greens, nuts, and seeds) have been associated with decreased risk but supplements have not. (4) Daily recommendations of B12 should be reliably met and levels should be checked regularly due to many factors that may impair absorption. (5) If using multivitamins, ones without iron and copper should be chosen unless directed by a physician as studies have linked excessive iron and copper intake to cognitive decline in some individuals. (6) Consider avoiding exposure to aluminum, including through cookware and antacids, as, while evidence is not yet definitive, increased prevalence of Alzheimer's disease has been noted in areas with higher aluminum content in water and aluminum has been noted in brain biopsies of individuals with the disease. (7) Incorporate aerobic exercise equivalent to 40 minutes of brisk walking four times per week. The benefits of exercise are discussed separately in this chapter.

Several diets have been trialed in relation to cognitive decline, with the Mediterranean diet being the most studied. A 2016 systematic review noted the consistency in which studies have demonstrated a linear relationship between adherence to a Mediterranean diet and performance on cognitive scales. A lower incidence of cognitive impairment was also noted in longitudinal cohorts.[36] In 2015, a diet combining the Mediterranean and DASH diet, the Mediterranean-DASH diet intervention for neurogenerative delay (MIND), was published. Differences from the standard Mediterranean diet included an increased emphasis on berry consumption and leafy green vegetables and a framework of ten brain-healthy and five brain-unhealthy foods. These are summarized in Table 106.2. In a cohort of 960 participants, adherence was associated with a slower decline in global cognitive scores as well as in multiple domains. This was described as the equivalent of being 7.5 years younger in age, in terms of the rate of decline between the highest and lowest quartile for compliance. The highest adherence group was found to have a 35% risk reduction for cognitive impairment, and the moderate adherence group had an 18% risk reduction. Mediterranean and DASH diet compliance scores were also measured and found to have a protective effect but a weaker association than that observed with MIND adherence.[37]

A 12-year prospective case-control study (n = 842) published in 2021 sought to further characterize food and microbiota with a protective effect against cognitive decline through serum analysis.[38] Metabolite analysis was done and modeled against performance on multiple cognitive tests. A protective association was found from multiple metabolites of polyphenols (found in deeply colored fruits and vegetables and in green tea), cocoa, coffee, mushrooms, and wine (including resveratrol), supporting plant-based nutrition. The artificial sweeteners acesulfame and saccharin and elevated serum alcohol were found to be associated with increased risk.[38] A particularly rich polyphenolic compound that deserves special mention is curcumin, found in the spice turmeric. Curcumin has potent anti-inflammatory effects in part through modulation of the transcription factor NF-κB, an important regulator of inflammation. Animal studies have found a dose-dependent decrease in markers of oxidative stress within the hippocampus and early human studies have found improvements in mood, attention, and working memory, though optimal dosing remains to be determined.[39]

TABLE 106.2
Food Groups Classified as Brain Healthy or Unhealthy in the MIND Diet Study

Brain healthy
Green leafy vegetables
Other vegetables
Nuts
Berries
Beans
Whole Grains
Fish
Poultry
Olive Oil
Wine
Brain unhealthy
Red meats
Butter and stick margarine
Cheese
Pastries and sweets
Fried and fast food

106.4.2 Exercise

Exercise is one of the most potent tools to combat both long-term cognitive decline and improve mood and cognition day to day. In addition to the numerous benefits to cardiovascular risk which as discussed informs risk of cognitive decline, exercise has been shown to improve functioning across numerous cognitive domains. Numerous interventional trials have demonstrated a slowed risk of cognitive decline in older adults exposed to exercise in multiple geographic regions.[40] Aerobic exercise has been more strongly supported in the literature. A randomized trial assigning previously sedentary older adults aged 60–74 to either a walking program or a stretching and toning program found that only the aerobic group (walking) showed improvement in cognitive tasks of executive function after six months. A 5.1% increase in VO_2 max was also noted, a measure known to correlate with improved cognition.[41] Findings were corroborated in a later study comparing a 12-week aerobic exercise program, consisting of 40 minutes three times

weekly of progressive activity (beginning with walking and progressing to running by the end of the trial period) with one hour, three times weekly stretching sessions, and found improved executive function measured by the Wisconsin Card Sorting Test and improved heart rate variability, thought to reflect general cardiovascular fitness, in only the aerobic exercise group.[42]

Exercise exerts its benefits through a variety of mechanisms including angiogenesis, neurogenesis, and synaptogenesis. Animal studies have demonstrated an increase in BDNF, a crucial neurotrophic factor, and insulin-like growth factor 1 (IGF-1) in the CSF.[43] Exercise-induced increase in BDNF was found to not only reduce loss but even increase hippocampus volume in MRI studies. Loss of hippocampal volume is one of the hallmarks of cognitive aging. More recent studies have found an increase in brain activity as measured by functional MRI as well.[44] A 2018 animal study found that aerobic exercise led to increased expression of Klotho in the brain and kidney, a gene involved in the clearance of reactive oxidative species.[45]

The benefits of exercise in cognition are not limited to primary prevention. A systematic review of 46 randomized trials explored the effects of exercise in individuals with a pre-existing diagnosis of MCI or dementia.[46] Exercise was found to be beneficial for global cognition and in particular cognitive functions including working memory and, less strongly, language. In other studied domains, studies often did not show an improvement from baseline but did show a slower decline in function compared with controls, supporting a disease-modifying effect. Behavioral problems were significantly reduced as assessed by the Neuropsychiatric Inventory. While specific protocols varied widely between studies, noted trends included a greater benefit from aerobic training than from resistance training and a greater benefit with increased intensity of training. It was also found that those with more severe cognitive decline had a more pronounced benefit in global cognition attributed to the expected faster rate of decline at more advanced stages during study periods. Observed adverse events were few and all but one trial noted a greater than 60% attendance rate in exercise classes. Overall meta-analysis of data found a 44% reduction in decline in global cognition compared with controls.[46]

106.4.3 Stress

The importance of stress management has gained recognition in slowing cognitive aging. The allostatic load model postulates that chronic stress leads to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid release.[47] This glucocorticoid excess has downstream effects including disruption of cellular metabolism through glutamate accumulation, increase in insulin resistance and other risk factors of cerebrovascular aging, and disruption of BDNF expression via epigenetic changes. Over time, this has been shown to lead to hippocampal volume loss, leading to cognitive decline and decreased ability to respond to emotional distress. In mouse models, increased plasma cortisol has also been shown to result in accelerated amyloid-β plaque deposition, further increasing the risk for cognitive decline.[48] This is mechanistically related to increased amyloid-β production due to neuronal excitation and increased formation of oligomers and plaques through HPA-mediated pathways.[49]

Meditation has been shown to protect against hippocampal volume loss. A study comparing 50 meditators with 50 controls found increased hippocampal volume in a dose-dependent relationship with the number of years of meditation. This was particularly pronounced within the subiculum region of the hippocampus, important in the regulation of stress, thus suggesting a protective role against stress hormone release and neurotoxicity.[50] Other benefits noted in the literature from mindfulness-focused interventions have included improved attention, increased working memory, and improved performance on tasks of executive function.[51] While protocols varied, there is sufficient evidence to recommend prioritizing stress reduction in general according to patient preferences.

106.4.4 Substances

The negative impacts of smoking on the circulatory system are well documented and cerebrovascular aging is no exception. Analysis of a ten-year cohort from the Whitehall II study noted an accelerated cognitive decline in tests of memory, reasoning, and fluency in male middle-aged smokers. The mean age at first assessment was 59. Effect size was 20–50%. Of note, differences were not seen in females or in those who had stopped smoking at least ten years prior. This may be due to the later onset of diseases of aging in women in general. It also highlights the importance of early smoking cessation.[52] A prospective British study of adults between 43 and 53 years of age found an increase in cognitive decline in midlife in tasks of verbal memory and visual search speeds, with a greater divergence from non-smokers in older participants. Regression predicted this trend would continue later in life.[53]

Shedding light on the mechanisms of these changes was an animal study in which rats were exposed to doses of oral nicotine and cigarette smoke approximating doses used by humans for short-term (four weeks) and long-term (12 weeks) durations. Observations included a dose-dependent increase in anxious and depressive behavior, cognitive interference, neurodegeneration, and DNA damage in the cerebral cortex. Molecular and signaling changes included increased oxidative stress, overexpression of BDNF and dopamine, increased tyrosine hydroxylase, and downregulation of ascorbate (which plays an antioxidant role) and nuclear erythroid factor 2 (Nrf2, a transcription factor involved in resilience against oxidative and metabolic stress).[54]

Data from the Whitehall II cohort was also analyzed with regard to alcohol's effects on cognitive decline in early old age. The mean age in this analysis was 56 years with

5044 men and 2099 women included. Light and moderate use (defined in the study as under 20 g daily) was not associated with accelerated cognitive decline in men but heavy consumption, ≥36 g/day was associated with accelerated decline in all domains. In women, impact was noted at ≥19 g/day on average.[55] One standard drink contains roughly 14 g of alcohol. Thus, patients wishing to minimize the risk of cognitive decline should be advised to drink no more than one standard drink daily for women and no more than two for men. Findings were supported by an analysis of eight-year cohort data from the Ginkgo Evaluation of Memory Study. This included 3021 participants with a mean age of 72 with or without a diagnosis of MCI. Heavy alcohol use (≥14 drinks weekly) was associated with a rate of cognitive decline and a 72% increased risk of progression from MCI to frank dementia in those with MCI at the start of the study. This effect was not modified by the APOE genotype. An increased risk was not observed for alcohol use within recommended limits.[56]

Mechanisms of alcohol's effects on the brain include upregulation of glutamate, and down regulation of GABA and dopamine. This leads to, among other effects, accelerated cell apoptosis in the CNS. The metabolite of alcohol acetaldehyde is also known to be directly neurotoxic. Excess alcohol consumption has also been shown to lead to an increase in pro-inflammatory cytokines and oxidative stress. The effects of thiamine deficiency also bear mentioning given impaired absorption and malnutrition in chronic alcoholism including Wernicke syndrome, characterized by acute ataxia, confusion, and ophthalmoplegia, Korsakoff syndrome, characterized by chronic anterograde amnesia, and Marchiafava–Bignami syndrome, causing seizures and alterations in consciousness due to damage to the corpus callosum.[57] Structural changes on autopsy and imaging study have included volume loss, fiber tract degeneration, cerebellar atrophy, thinning of the corpus callosum, and loss of pyramidal cells in the frontal cortex.[57]

106.4.5 Sleep

The CDC estimates that 35% of all adults and 26% of those above the age of 65 get insufficient sleep, defined as under seven hours nightly on average.[58] This figure has consistently been found to be higher in those suffering from cognitive decline.[59,60] Seen alongside this trend is an exaggeration of age-related sleep changes, including earlier sleep phase, increased fragmentation of sleep, and decrease in slow wave sleep.[61] Disrupted sleep is both a cause and consequence of cognitive decline. Several studies have linked poor sleep to deficits in domains including memory, attention, and executive function in both the short and long term, as well as to increased prevalence of behavioral symptoms.[62,63] Sleep is also known to be crucial in memory formation and thus poor sleep across the lifespan can be surmised to decrease cognitive reserves.[64] One meta-analysis found a 53% increased risk of all-cause dementia in those with insomnia.[65] Research correlating polysomnography with MRI and lumbar puncture noted an increase in CSF amyloid β in cognitively normal older adults with disrupted slow wave sleep, further supporting the link between poor sleep and cognitive decline.[66]

Sleep, among many other roles, serves to facilitate the clearance of neurotoxic substances from the brain. This has been described as the "glymphatic system", a perivascular system in which metabolic waste products are cleared from the CNS. In addition to sleep duration and quality, alcohol consumption, exercise, omega-3 consumption, diet, and chronic stress have all been found to influence glymphatic clearance.[67] In addition to amyloid β, increased levels of tau and various inflammatory markers have been shown to be increased in those with sleep deprivation. In an animal model, amyloid β was also shown to directly impair melatonin synthesis in the pineal gland and interfere with melatonin receptor signaling.[68] Sleep deprivation has also been shown to decrease levels of BDNF, thought to be in part due to disruption of the hypothalamic-pituitary-adrenal (HPA) axis.[69] Thus, prioritizing sufficient high-quality sleep is essential in reducing cognitive aging. A summary of measures to support sleep hygiene is found in Table 106.3.[70]

106.4.6 Relationships

Social interactions are among the most cognitively challenging scenarios one can have day to day and the role of relationships and socialization has been shown to improve cognitive reserve. A 2020 meta-analysis analyzed data from 31 cohort studies exploring the link between social relationships and cognitive decline found that poor social relationships increased the risk of cognitive decline, with a 1.11 odds ratio noted.[71] A 2022 analysis of Framingham Study cohort data found a hazard ratio of 1.54 for ten-year dementia risk for those noted to have loneliness at least three days per week as noted on the Center for Epidemiologic Studies Depression Scale. The hazard ratio was even greater in those without APOE ε4 alleles. Loneliness was also associated with impaired executive function, lower total cerebral

TABLE 106.3
Lifestyle Modifications to Support Healthy Sleep

Sleep Hygiene Measures
Avoid nicotine use
Avoid alcohol before bed
Exercise regularly
Manage stress
Reduce evening blue light exposure
Reduce noise at night
Go to sleep and wake up at consistent times
Avoid meals within two hours of bed
Refrain from electronic use in bed
Avoid caffeine in the afternoon
Seek sunlight exposure on waking

volume, and increased white matter injury on MRI, suggesting a role in pathogenesis.[72]

On a day-to-day basis, a study explored how daily social interactions related to the results of mobile cognitive testing and found that an increase in daily interactions and interactions that were rated as more pleasant led to improved cognitive performance on the same day and subsequent two days. Higher interaction scores across the study period predicted higher average cognitive testing scores as well.[73] These supports emphasize positive social interaction as both a preventive and a therapeutic measure relating to cognitive decline.

106.5 HEARING LOSS

The role of hearing loss in accelerated cognitive decline deserves special mention. One of the 12 modifiable risk factors highlighted by the 2020 Lancet commission as noted above, hearing loss in midlife was associated with a relative risk of 1.9 for dementia, tied with depression late in life for the highest risk.[14] This was defined by a threshold of 25 dB loss and a dose-dependent response was noted for worsening loss. While the mechanism is not fully known, a prospective cohort study of middle-aged adults with mean follow-up of 19 years noted that in subjects without baseline cognitive impairment, those with hearing loss demonstrated an accelerated loss of temporal volume on MRI.[74] Several hypotheses have been proposed. The cognitive load hypothesis postulates that untreated hearing loss causes the brain to divert energy toward auditory perception, at the expense of other cognitive processes, leading to accelerated neuronal degeneration.[75] The psychosocial hypothesis theorizes that hearing loss leads to increased depression and social isolation, two known independent risk factors for cognitive decline.[76] While there is an association between hearing loss and depression, a 2017 systematic review found that the status of hearing loss as a risk factor remained when such factors were controlled for.[77]

Fortunately for those experiencing hearing loss, the use of hearing aids has been repeatedly shown to greatly mitigate the risk of cognitive decline. A 25-year prospective cohort study of 1289 older adults (≥65) with hearing loss and 2290 with normal hearing at the start of the study found an association between hearing loss and dementia, depression, and disability only in those who were not using hearing aids.[78] An 18-year study of adults over 50 with cognitive testing every other year found a decrease in the rate of deterioration of immediate and delayed recall starting from the initiation of hearing aids.[79]

106.6 FINGER STUDY

A comprehensive multimodal intervention was tested in the Finnish Geriatric Intervention Study to Prevent Cognitive Decline (FINGER). This double-blind RCT targeted older adults aged 60–77 who were identified to be at risk for cognitive decline as defined by a CAIDE score of at least six and a cognitive score at the mean or slightly below level expected for age. Participants were assigned to either a multidomain intervention including diet, exercise, cognitive training, and monitoring and treatment of vascular risk factors or to a control group receiving general health advice: 1260 participants were randomized and followed over two years. Significant differences were noted in the primary outcome of overall cognition on neuropsychiatric testing as well as secondary outcomes including executive function, processing speed, BMI, dietary habits, and physical activity. The intervention group had good adherence and a low incidence of complications.[80] The promising results of this trial led to the formation of the World-Wide FINGERS network with representation from research teams in over 40 countries to expand clinical research of similar multidomain approaches in combating cognitive decline in different populations.[81]

CLINICAL APPLICATIONS

- Western-style diets characterized by high saturated fat and sugar intake and low fresh fruit and vegetable intake have been repeatedly implicated in accelerated cognitive decline. Diets rich in fruits, vegetables, dietary fiber, and omega-3 fatty acids such as a whole-food plant-based diet, the Mediterranean diet, and the MIND diet should be recommended.
- Exercise has been shown to both protect against cognitive decline and improve memory in those already experiencing cognitive decline, with aerobic exercise having the strongest benefit.
- Stress management protects against cognitive decline through regulation of the hypothalamic-pituitary axis.
- Sleep is vital for the brain's ability to clear toxins, with chronically inadequate sleep leading to accelerated amyloid deposition and cerebral volume loss.
- Healthy social interaction is vital to developing cognitive reserves.
- Hearing loss should be diagnosed and treated early as hearing loss in middle age is associated with cognitive decline later in life.

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107 Medication Management in Older Adults

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KEY POINTS

- Medication management in older adults is a balance between evidence-based treatment guidance and shared decision-making related to a patient's healthcare goals, taking into account the benefits and risks of each medication.
- Medication harms can occur due to the physiology of aging in the presence of chronic conditions, healthcare systems in which the patients are provided care, and breakdowns in patient and medication safety as part of the medication use process.
- Deprescribing is the systematic process of identifying and providing supervision to discontinue medications when existing or potential harms outweigh benefits.
- Medication management, with a focus on deprescribing, supports the other "Ms" of the 4M model, namely, mentation, mobility, and what matters most.
- Future research will focus on the interaction between lifestyle medicine and deprescribing to determine the best approaches to integrating these two interventions to optimize outcomes.

107.1 INTRODUCTION

Medication management in the older adult population requires balancing evidence-based treatment guidance with shared decision-making. This is even more important when there is a significant lack of representation among older adults in medical research. When there is inadequate evidence for the treatment of certain conditions in older adults, and limited guidance from medical societies, medical management becomes a balance of benefits and risks. It is the intersection of the art and science of medicine. Given the broad scope of medications used in the older adult population, the focus of this chapter will be limited to those who are community-dwelling rather than in congregate settings such as hospitals, skilled nursing and long-term care facilities, and inpatient psychiatric facilities. However, the application of the 4Ms of Age-Friendly Healthcare Systems from the Institute of Healthcare Improvement,[1] as described in Chapter 104, has relevance to all patient care settings. This chapter discusses one of the 4Ms, namely, medication. The adoption of the principles of deprescribing will be discussed.

DEFINITION

Deprescribing is the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits. It is supervised by a healthcare professional with the intent of reducing polypharmacy and improving outcomes. It is not denying care, but rather a patient-centered risk mitigation strategy, where thoughtful discussion occurs between the care team and patients and their caregivers on the balance regarding the risks or harms done by continuing a medication, compared with stopping it.[2]

107.2 PROBLEM—THE WHAT AND THE WHY: FACTORS THAT CAUSE MEDICATION-RELATED HARMS IN OLDER ADULTS

Many factors either by themselves and/or in conjunction with others contribute to medication-related harms in older adults. These factors can be broadly divided into the physiology of aging in the presence of chronic conditions, healthcare systems in which the patients are provided care, and breakdowns in patient and medication safety as part of the medication use process.

107.2.1 Polypharmacy

Prescribing medications for various ailments leads to polypharmacy, defined as greater than five chronic medications, or hyper-polypharmacy, greater than ten chronic medications for greater than 90 days.[3] A systematic review of polypharmacy stated that its causes are complex and conflicting, however, there are notable increased associations in terms of adverse drug events (ADEs), disability and functional decline, frailty, multimorbidity, and malnutrition.[4] According to the Centers for Medicare and Medicaid Services (CMS), the average number of prescriptions over a ten-year period has increased per beneficiary. Patients who take ≥4 medications and ≥10 medications are 21% and 50% more likely to experience falls, respectively, as

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well as at higher risk for avoidable healthcare utilization (emergency care, hospitalizations, rehospitalizations, long-term care) and mortality.[5] Multiple factors increase the risk for polypharmacy in older adults and are broadly categorized into patient-specific (e.g., multiple chronic conditions, mental health conditions, cognitive impairment, care under multiple specialists) or health system-related (e.g., poor communication between care providers or care transitions, prescribing to meet quality metrics, and use of automated refill systems).[6] When an older adult has multiple chronic conditions, the likelihood of polypharmacy and hyper-polypharmacy is increased.

107.2.2 Changing Physiology Affecting Medications in the Older Adult

As a person ages, many homeostatic and physiologic functions continue to change in tandem with their overall health and the severity of chronic conditions. Historically, most medications were small molecule compounds, but increasingly, many medications are biological and immunotherapies that could elicit targeted cellular responses. There are four components to be generally aware of when addressing medications in the older adult: pharmacology, pharmacokinetics, pharmaceutics, and pharmacoepidemiology.

Pharmacology or more specifically, pharmacodynamics, refers to what the medication does in the body; the site of action; specific or non-specific receptors or proteins affected. The physicochemical properties of medications are what lead to the intended effects of the medication(s). Pharmacokinetics is what the body does to the medication—absorption of the medication; distribution to the site(s) of action(s); metabolic transformation by various pathways; and elimination from the body. Some medications are prodrugs and require metabolic pathways in order to become active while others can have more active metabolites than the parent compound. Both pharmacology and pharmacokinetics exhibit inter- and intra-patient variability.[7]

Pharmaceutics is the science of formulating a medication for optimal delivery: either systemically, topically, a targeted delivery to the site of action, or delayed or sustained release formulation that enables the medication to be delivered over a period of time. The end product may require special instruction(s) for preparation and administration. This can add to the complexity and cause end-user errors if not properly instructed. A particular formulation of a medication, along with the pharmacokinetic profile can affect how long it takes to achieve maximum concentration (Tmax), the maximum concentration (Cmax), and how long the medication persists in the body, also known as area under the curve (AUC).

Pharmacoepidemiology is the known effects—both intended and unintended—of a specific medication or class of medications based on length of exposure often not studied as part of randomized controlled trials (RCTs) that were conducted for the medication's approval process. This typically happens months to years after the medication has been on the market, and it provides real-world evidence of the benefits and risks associated with medications beyond the RCTs. More often than not, this is where long-term negative impacts of medications on the human body are ascertained, which can further add to the complexity of the aging process. Furthermore, long-term exposure to multiple medications and their interactions may worsen the response of each other as well as cause damage to the human body.[8]

In an aging person, adrenergic receptor density changes, and function of baroreceptors and venous valves within the cardiovascular system also have notable changes. The blood–brain barrier may also weaken with age, allowing for more medications to pass through, increasing the exposure to the central nervous system (CNS). Medications may have enhanced effects on these receptors, increasing an older adult's likelihood of adverse drug reactions (ADRs) due to changes in blood pressure, heart rate, respiratory rate, and/or cognition. The liver utilizes a complex system of a family of enzymes for the metabolism of all chemicals, including medications called cytochrome P450 (CYP450). There are many isoenzymes with some of these displaying genetic variations that affect the capacity of medication metabolism. Of the two key enzymatic processes, CYP450 is responsible for the oxidation and reduction (Phase I) stage of the medication metabolism. This capability significantly declines with age. Phase II is responsible for chemical modification that increases the ability for the medication to be excreted by the kidneys. This typically remains intact with age. The liver also has synthetic functions such as the production of clotting factors, and proteins such as albumin and globulins. Many medications are bound to circulating proteins such as albumin, which affects distribution to sites of target and/or storage in tissue. Medications that are highly protein-bound in a person with reduced synthetic capacity in the liver may result in higher concentrations of unbound medication leading to accumulation and subsequent additive effects in the body. Glomerular filtration rate tends to decrease by 10 ml/min per decade after 40 years of age. Certain chronic conditions such as hypertension and diabetes can further reduce renal function. Structural as well as age-related changes affecting kidney function will result in slower elimination of the medication, accumulation in the bloodstream, and enhanced effects or toxicities at other sites. Furthermore, some medications may cause direct toxicity to the kidneys, resulting in acute kidney injury.

107.2.3 Medication Safety

Medication safety is an evolving field within patient safety and has been challenging to study due to inadequacy of research methodology, lack of documentation in patient medical records, organizational culture, and many other reasons. However, mandates from accreditation organizations as well as local and state requirements are enforcing patient and medication safety through continuous quality improvement within healthcare organizations. Furthermore,

the adoption of electronic health records (EHR), with computerized prescriber order entry (CPOE), has allowed for better data collection around both patient and medication safety. This data now exists within an organization or a local, state, or national registry, which can be used for both research and quality improvement practices.

A 2016 study estimated that medical errors contributed to more than 250,000 annual deaths in 2013 based on the coding of the diagnoses at the time of death.[9] This data, when compared with the National Center of Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), made death due to medical errors the third leading cause of death. A 2017 joint report from the Institute for Healthcare Improvement (IHI), National Patient Safety Foundation (NPSF), and the University of Chicago showed that 41% of 2536 patients who responded to a survey had experienced a medical error, of which 59% was a misdiagnosis.[10] A misdiagnosis may lead to inappropriate treatment(s). The Institute for Safe Medication Practices (ISMP) has a national database of medication errors reported by individual practitioners as well as healthcare organizations. The ISMP has compiled a list of high-alert medications, those responsible for the highest likelihood of errors that can cause harm, temporary or permanent, or be fatal in patients. The high-alert medication lists vary based on the site of care (e.g., hospitals, long-term care facilities, or ambulatory/community). In the ambulatory/community setting, the medications of greatest concern for the geriatric population are opioid analgesics, antithrombotics/anticoagulants, insulin formulations, sulfonylureas, anticonvulsants, cancer chemotherapeutic agents (especially oral), and immunosuppressants.[11]

The medication use system typically includes five distinct components per the Food and Drug Administration (FDA): prescribing, packaging/re-packaging, dispensing, administering, and monitoring. Even though many studies show a significant variation between propensity for errors committed in each component, the prescribing component contributes the most to errors and downstream medication-related problems.[12] This stage requires a lot of patient education and discussion of benefits, risks, and expectations of treatment, as well as lifestyle-related factors to allow for shared decision-making to treat a medical condition with an appropriate medication. A potentially inappropriate medication (PIM) may be prescribed if a comprehensive review of ailments is not conducted, an inappropriate diagnosis is made, or if a thorough assessment of patient-related factors such as medication adherence and persistence, administration techniques, ADRs, and even treatment cost burdens is not completed. A PIM may also be started as a trade-off if the patient is unwilling or incapable of making lifestyle changes necessary to treat a medical condition with a high response rate to modifiable risk factors. Furthermore, a prescribing cascade (Figure 107.1) can be introduced when a patient complains about a new problem that may be attributable to a new ADR, for which a new medication is prescribed, and this cycle continues to be repeated in subsequent encounters. At this stage, it is important to weigh the comparative benefits and risks of initiating medication(s). Implementing CPOE and utilizing pharmacists' ability to intervene and educate providers and patients has been shown to reduce errors at the point of prescribing.[13]

Adverse drug reactions (ADRs) are unintended or excessive effects of a medication. In some cases, these ADRs are tolerable, such as a dry cough with an angiotensin-converting enzyme inhibitor (ACEI), yet still should be noted by both the patient as well as their providers. However, when the ADRs become excessive and impact a patient's quality of life, they often need to be addressed with alternative options.

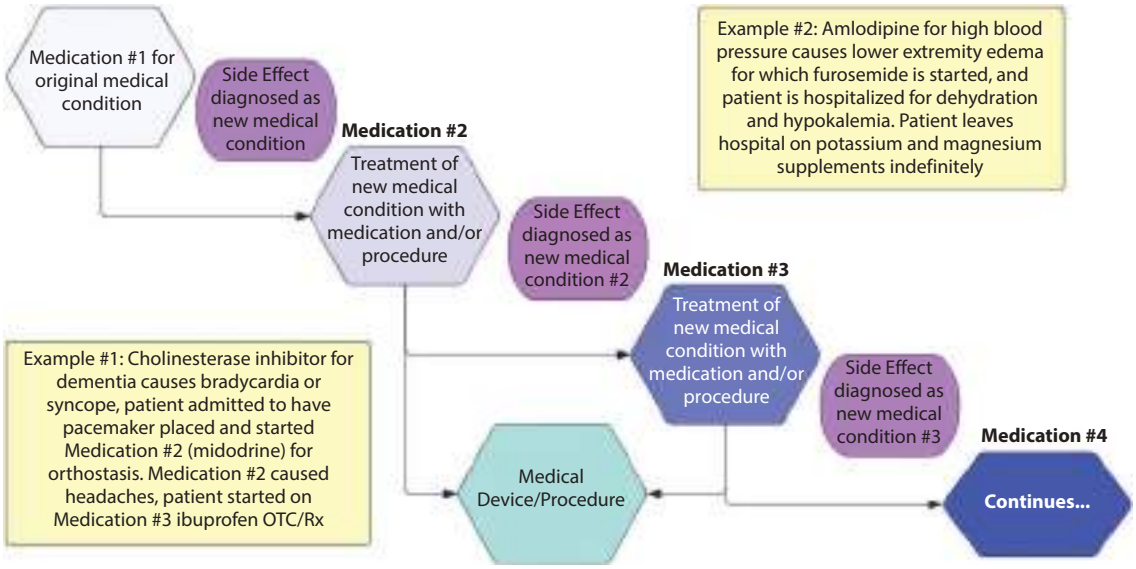


FIGURE 107.1 The prescribing cascade that leads to polypharmacy (adapted from Rochon PA, Gurwitz GH "The prescribing cascade revisited". *Lancet* 2017;389:1778–1780).

Other stages where errors are especially important in the medication use process are administering it to oneself or by a caregiver to the patient. Monitoring of therapy, both for expected outcomes (i.e., benefits) balanced with ADRs (risks), with appropriate laboratory and genetic tests (i.e., precision medicine), may help the older adult achieve their health goals. Thorough patient education is necessary across all aspects of the medication use process including the dispensing component.

107.2.4 Intensification of Medical Guidelines

Guidelines are usually coordinated and published by medical organizations to manage a chronic medical condition in a standardized manner. They establish the standard of care, which may be used as a target for assessing the quality of care provided to a patient. This is especially helpful when a patient has an acute exacerbation of a chronic condition such as hypertensive urgency/emergency, congestive heart failure, asthma, chronic obstructive pulmonary disease (COPD), diabetes, and so on. Standardization can help unify the approach to medical care, reduce inefficiencies, and may help reduce healthcare costs. The downside of standardized guideline-directed therapy could be its inability to take patients' goals, beliefs, and wishes into the decision-making process. Furthermore, a significant lack of older adults (>65 years of age) participating in RCTs further adds to the lack of appropriate inclusion and treatment recommendations established in guidelines. Although some guidelines consider co-occurring chronic conditions (e.g., diabetes and hypertension), often guidelines are mostly disease-specific, intensify based on disease severity, and do not take into account the presence and severity of other chronic conditions.

Therefore, the management of a chronic medical condition occurs in a silo, i.e., treating to a number or a goal and/or to meet performance measures for quality of care. Since most of the guidelines run in parallel with each other, it increases the likelihood of them being applied in a mutually exclusive manner, especially in the setting of having multiple specialists, without a provider who is coordinating care and complexity. This increases the risk for aggressive management which may lead to polypharmacy and hyper-polypharmacy.

When comparing key guidelines for chronic care management, the balance of intensification versus deintensification of treatment must be ascertained. Based on a study of seven of the largest medical guideline developers in the United States, it was found that the majority of them focus mostly on the intensification of treatment (79%) in comparison with the deintensification of treatment (21%).[14] The authors cited the major reason for this is that the majority of guidelines utilize data from RCTs to generate recommendations for treatment and its intensity. Another reason was inconsistency with the balance of benefit to harm, i.e., the number needed to treat (NNT) versus the number needed to harm (NNH). This imbalance is what is not accounted for when metrics are utilized to measure the performance of the quality of care provided.

For example, treating a patient with essential hypertension to a goal of 120/80 mmHg or less, without untoward side effects is based on the guideline goal-directed therapy. This was demonstrated in previous randomized controlled trials over the decades and re-demonstrated in the Systolic Blood Pressure Intervention Trial (SPRINT).[15] The SPRINT series of RCTs was focused on understanding long-term outcomes of intensive versus less intensive blood pressure control in people over 50 years old. While the SPRINT series of trials demonstrated cardiovascular benefit in many, including those with mild cognitive impairment, and reduced brain lesions in the intensive treatment arms of the SPRINT-MIND cohort, the message that is often missed is that only one-third of the patients were >75 years old, and the majority of the participants were generally healthy for their age, as frailty was not assessed.[16] Furthermore, the earlier blood pressure was controlled, the better the intended outcomes with an enduring effect. However, the results may not be generalizable to older people with multimorbidity and frailty. A recent observational study by van Dalen et al showed that blood pressure associations with incident risk for dementia followed a U-shaped curve based on age strata and the very elderly fared better with looser control than the younger.[17] In light of such evidence, should we continue to aggressively manage an older adult's blood pressure to <120/80 mmHg in the presence of multimorbidity and frailty?

In another example, how would we manage a 69-year-old male patient who has type 2 diabetes with an A1C of 9.5%, stage III CKD (eGFR <60 ml/min), with a blood pressure of 152/86 mmHg who is morbidly obese (BMI 38 kg/m2), newly diagnosed with Stage 1 (NYHA) or Stage A (ACC/AHA) heart failure and an ejection fraction of 45%? This person also has osteoarthritis of both knees, states he is in pain, his mood is horrible, and he has trouble falling asleep at night. Which guideline-directed therapy should we access first? How do we prioritize our treatment goals? Where does lifestyle fit in? If we follow the guidelines as they are written, this patient would be on three to five medications for the management of his type 2 diabetes, three to five medications for his hypertension and heart failure, and to meet performance measurement quality metrics, required to be on a statin medication. It is now possible to see how by following guideline-directed therapy, following quality metrics, and treating pain and mental health, it is conceivable to see him on 15 medications. Furthermore, some of these medications may cause side effects, which may result in additional medications to treat them, possibly creating a prescribing cascade. There is a significant risk for polypharmacy and hyper-polypharmacy. In such a patient, would offering options through lifestyle medicine provide additional help while enabling them to deprescribe some medications along the way?

107.3 HOW TO ASSESS IF A PROBLEM EXISTS

A systematic approach that aligns with the Medication component of the Age-Friendly Health Systems (AFHS) from the IHI should be utilized with patients that will help identify patients at risk for drug-related problems (DRP), as well as a comprehensive review of their medical conditions, procedures, and medications, and the patient's health goals. The key drivers are appropriate assessment and determining a solution, which can include medication(s) as long as there is a proper indication, a favorable benefit-risk ratio, and the medication does not interfere with the other three Ms: What Matters, Mobility, or Mentation across care settings.[1]

Many providers encounter patients who already have medication regimens. In such cases, we must assess for drug therapy problems (DTPs).

> Pro Tip: This offers the opportunity to work in an interprofessional manner with trainees (students, residents), nurses, and especially pharmacists. The goal is to make it as simple and seamless as possible in your practice. See Table 107.1.

In addition to the assessment process to identify DTPs, there are additional tools that help identify if certain therapies or regimens a patient is receiving provide low-value care. Table 107.2 shows selected Choosing Wisely recommendations that pertain to geriatric populations regardless of care setting. For the sake of simplicity, only recommendations pertaining to community-dwelling older people were included. To learn more about additional recommendations in the geriatric population in acute, post-acute, and long-term care, refer to the Choosing Wisely website (www.choosingwisely.org) to learn about medication use recommendations by the American Society of Consultant Pharmacists (ASCP), the American Society of Health-Systems Pharmacists (ASHP), and the American Medical Directors Association (AMDA).

During the care process, the other three elements of the 4Ms are typically reviewed in detail: what matters to the patient and their caregivers/family members; their mentation; and their mobility. High-risk medications as defined by multiple stakeholder organizations (IHI, ISMP, AGS, etc.) typically include psychotropic agents (benzodiazepines, antipsychotics, sedatives, tricyclic antidepressants), opioids, anticholinergic agents (especially antihistamines like diphenhydramine), and muscle relaxants. These medications not only affect mentation but can increase the risk of falls, especially in those with frailty.[25] Deprescribing them to either the lowest dose, or completely tapered off, is ideal and safe for patients. To align this with "What Matters", the care team should ask the patient and/or their caregiver about what is the most important thing they would like for their care team to help them with, both short-term as well as long-term. Medications that affect mentation can cause drowsiness, impair cognitive function, and cause significant mood disturbance, all of which may impair their gait, and hence, mobility. They may experience a fall as a result and require additional medical attention due to fractures and/or physical/occupational therapy. Each aspect of the 4Ms is intertwined with the other. If a patient's mentation is significantly affected, it may impair their ability to communicate what matters to them the most.

The 4Ms process encourages creating both deprescribing champions as well as algorithms and guidance within the organization. By putting continuous quality improvement processes in place, there may be an adequate amount of real-world experience that could be published and shared with other institutions that are looking for guidance and support in their efforts to create an age-friendly healthcare system.

107.4 HOW TO FIX THE PROBLEM

According to a review in the American Association of Family Practice on polypharmacy, deprescribing starts with judicious prescribing, i.e., an off-ramp must be deliberated along with the on-ramp when initiating medications (Table 107.3).

When caring for patients with existing extensive medication regimens, an algorithm by Scott et al. (see Figure 107.2) can help determine which medication(s) to consider deprescribing.[26] A thorough assessment should include appropriate indications for medications; identification of any existence of prescribing cascades; balancing actual or potential harms over benefits; evaluation of current symptoms; benefits of medications present in the lifespan remaining of the patient; as well as treatment burdens.

Certain medications cannot be immediately discontinued and will require a slow withdrawal or taper to minimize any withdrawal reactions due to physical and/or psychological dependence on the medication, as well as the symptoms they may have been trying to control. This applies especially to psychotropic, antiepileptics, and neuroleptic medications; opioid analgesics; antihypertensive agents, antidiabetic agents, adrenergic agents, and immunosuppressants. Since this is unique to each medication and/or medication class, it is outside the scope of this chapter. Instead, please refer to the resources section.

107.5 COLLABORATION IS KEY TO SUCCESS

Successful deprescribing initiatives focused on the medication component of the 4Ms model require partnership with all stakeholders, especially pharmacists. As the breadth and scope of practice of pharmacists continue to grow and evolve, it is important to include them in the care process of deprescribing. Pharmacists will also need to work with other members of the care team to better understand how medications may be influential on a patient's mobility or mentation. There is extensive literature on pharmacists playing key roles in providing deprescribing initiatives through their usual practice during patient care encounters.[27–29]

TABLE 107.1

Process to Identify Drug Therapy Problems in Patients with Polypharmacy

Task	Tools (Examples)
1. Perform a thorough medication reconciliation to ensure all medications are appropriately accounted for	• Electronic Health Record (EHR) • Reviewing and reconciling multiple sources of medical records
2. Assess adherence and understand barriers to adherence such as costs, concerns about side effects, or commitment to chronic care management	• ASK-12 Questionnaire[20] • Medication Regimen Complexity Index (MRCI)[21] • Review of prescription fill/refill records, claims, or utilization
3. Identify drug-drug interactions (DDI)	• Available databases already available in EHRs or online at your institution (eMicromedex, UpToDate, Dynamed, etc.) • Serious DDIs include QT prolongation, coagulation/bleeding, psychotropic medications, serotonin syndrome
4. Identify drug-disease interactions	• For example, NSAIDs use in CKD or CHF
5. Identify overtreatment and/or accumulating therapies	• Duplicate therapies • Additive effects (e.g., BP control, anticoagulation/antithrombotics) • ChoosingWisely Initiatives (www.choosingwisely.org)
6. Identify high-risk drugs in older adults ○ Both criteria help identify high-risk drugs and disease states ○ Assess if medications are appropriately prescribed	• American Geriatrics Society Beer's Criteria[24] • STOPP/START Criteria[22]
7. Identify the use of herbal supplements and OTC products ○ May need to identify drug-herb interactions	• Efficacy and benefits can be reviewed on the Memorial Sloan Kettering herbal database (Free) (www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs) • Natural Medicines database (subscription required) https://naturalmedicines.therapeuticresearch.com/
8. Identify medication monitoring for safety and efficacy, as well as adverse drug effects the patient may be experiencing	• Best practice alerts in EHRs • Professional guidelines
9. Assess if any medications are eligible for deprescribing, the patient requests it, and/or the risk-benefit ratio is no longer favorable	• Clinical pharmacist consult for CMM (if available)

ASK-12, Adherence Starts with Knowledge, 12-item questionnaire; STOPP, Screening tool for older person's prescriptions, identifies PIMs; START, Screening Tool to Alert Treatment Prescription, identifies potential prescribing omissions; CMM, comprehensive medication management. Adapted from references [18] and [19].

TABLE 107.2
Selected Choosing Wisely Recommendations for Medication Use in Geriatrics

Sponsoring organization	Recommendations	Rationale
AGS	Do not use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia.	Inconsistency of benefits and increased risk for falls, cognitive impairment, sedation, stroke, and death.
AGS	Avoid using medications other than metformin to achieve hemoglobin A1c <7.5% in most older adults; moderate control is generally better.	A1C control <7% is associated with an increased risk for hypoglycemia and mortality. Given the long timeframe to achieve the theorized microvascular benefits of tight control, glycemic targets should reflect patient goals, health status, and life expectancy. Reasonable glycemic targets would be 7.0–7.5% in healthy older adults with long life expectancy, 7.5–8.0% in those with moderate comorbidity and a life expectancy <10 years, and 8.0–9.0% in those with multiple morbidities and shorter life expectancy.
AGS, AMDA	Do not use benzodiazepines or other sedative-hypnotics in older adults as the first choice for insomnia, agitation, or delirium.	Large-scale studies consistently show that the risk of motor vehicle accidents, falls, and hip fractures leading to hospitalization and death can more than double in older adults taking benzodiazepines and other sedative-hypnotics.
AGS, AMDA	Do not use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.	Cohort studies have found no adverse outcomes for older men or women associated with asymptomatic bacteriuria. Antimicrobial treatment studies for asymptomatic bacteriuria in older adults demonstrate no benefits and show increased adverse antimicrobial effects
AGS	Do not prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.	Although some RCTs suggest that cholinesterase inhibitors may improve cognitive testing results, it is unclear if it is clinically meaningful. It is uncertain whether these medicines delay institutionalization, improve quality of life, or lessen caregiver burden. No studies have investigated benefits beyond a year nor clarified the risks and benefits of long-term therapy. AMDA also has similar recommendations
AGS	Avoid using prescription appetite stimulants or high-calorie supplements for the treatment of anorexia or cachexia in older adults; instead, optimize social supports, discontinue medications that may interfere with eating, provide appealing food and feeding assistance, and clarify patient goals and expectations.	Megestrol and cyproheptadine are on the AGS Beer's Criteria and ineffective for weight gain. Mirtazapine can stimulate appetite with modest weight gain but should only be used if a patient has clinically diagnosed depression.
AGS, ASCP, ASHP	Do not prescribe a medication without conducting a drug regimen review.	Similar recommendations also come from pharmacy organizations (ASCP and ASHP) as well as AMDA. This is to reduce the risk of polypharmacy.

AGSP, American Geriatrics Society; ASCP, American Society of Consultant Pharmacists; ASHP, American Society of Health-Systems Pharmacists; AMDA, American Medical Directors Association. Adapted from Choosing Wisely Website: www.choosingwisely.org.

107.6 THE INTERPLAY BETWEEN RESEARCH AND REAL-WORLD EVIDENCE

Since much of the deprescribing initiatives and the attention to the details of medications in the 4Ms model is based on quality improvement in the care delivery process, balancing safety with what matters to our patients, it is important to note that the preponderance of research in terms of randomized controlled trials is still an emerging science. The first place to start research on deprescribing medications is with patient safety or quality improvement projects within health systems.[30,31] Usually, this research shows identification and quantifiable reductions in harmful or inappropriate medications.[32] They can expand from there to qualitative research including various stakeholders such as providers, patients, and caregivers to understand what they value in this process.[32–35] One of the largest qualitative studies conducted by Green et al. involved attitudes toward language used in deprescribing medications based on clinical vignettes in the elderly ≥65 years. In both scenarios, the patients preferred language of side effects over questionable clinical efficacy to help them consider having their medications deprescribed.[36]

The Shed-MEDS, D-Prescribe, and OPTIMIZE trials are examples of pragmatic real-world approaches to patient-centered care processes conducted in a traditional

TABLE 107.3
Considerations for Judicious Prescribing

Before starting any new medication ask:

- Are there underlying causes for the issues or symptoms the patient is experiencing that should be addressed first?
- Is the new medication/treatment necessary for the patient's condition?
- Are there nonpharmacologic therapies that can be considered? This is a place where lifestyle medicine may serve an impactful role.
- Are there preventive measures that can be tried first?
- Are there benefits? Are there proven outcomes? When will the benefit be seen?
- What are the risks?
- What are the patient's/caregiver's goals of therapy?
- What are my goals (as the primary care provider) of therapy?
- What is the patient's estimated life expectancy when considering age and comorbidities? Will the patient be alive long enough to experience any benefits?
- Have I discussed this with the patient for shared decision-making?
- Is the patient adherent to currently prescribed medications? Can the patient adhere to this medication?

Consider the complexity of regimen and any visual, dexterity, or cognitive impairments the patient has.

- Can the patient afford this medication?
- When starting any new medications, consider it a trial rather than a permanent addition.

Follow-up with the patient in a timely manner after adding medications.

Assess for effectiveness and safety at follow-up visits.

- When renewing refills, consider the benefits vs. the risks of continuation (long term and short term).

Adapted from reference [19].

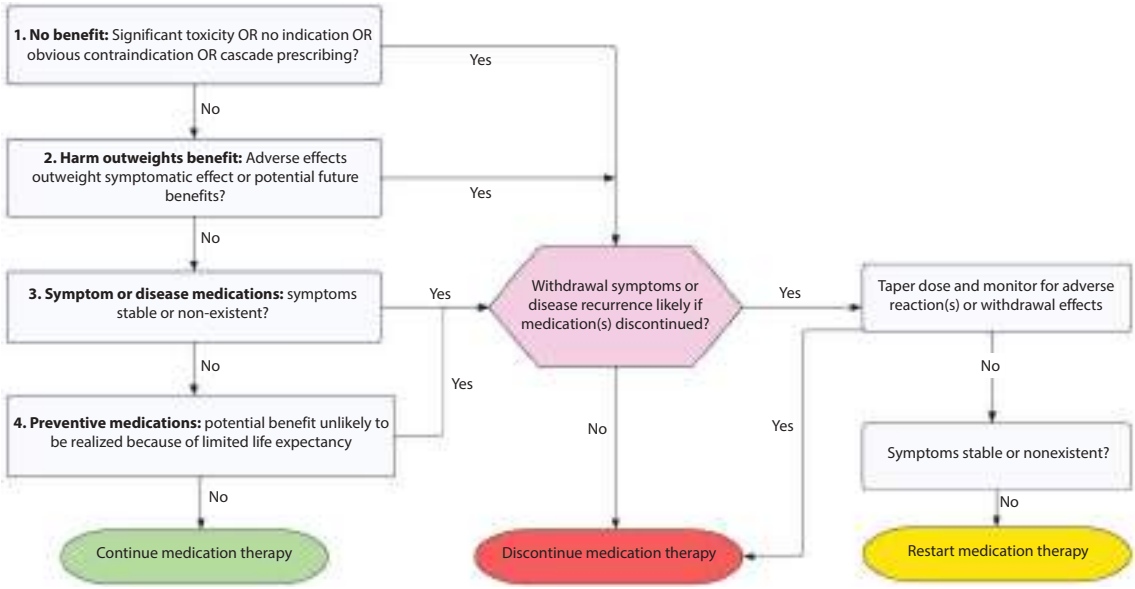


FIGURE 107.2 Deprescribing algorithm (adapted from Scott et al. *JAMA Intern Med* 2015;175(5):827–834.

randomized controlled trial setting.[37–39] The Shed-MEDS trials were conducted on patients ≥50 years of age discharged from a hospital to a post-acute care (PAC) facility such as a skilled nursing or inpatient-rehab facility. The patients were followed up at 7, 60, and 90 days post-discharge from the PAC with a primary endpoint of percent reduction in the total number of medications. Secondary endpoints included the number of medications associated with geriatric syndromes, drug burden index, medication adherence, the prevalence and severity of geriatric syndromes, and functional health status.[37]

The D-Prescribe trial was conducted in Canada and focused on pharmacist-led educational programming for the elderly population in the community pharmacy setting.[37] The patients were randomized at the pharmacy level and received educational materials that discussed options for deprescribing medications based on the American Geriatrics Society Beer's Criteria of PIM versus usual care. At the end of six months, more patients had their medications deprescribed in the pharmacist group (43%) versus the usual care group (12%). Both of these studies demonstrate that not only can the construct of the 4Ms

model be applied in different care settings, but so can the interventions.

The OPTIMIZE trial was a cluster randomized RCT that targeted outpatient clinics in an integrated healthcare delivery network over 12 months. Patients and their providers were provided with educational information to deprescribe unnecessary or risky medications in 3012 patients ≥65 years of age with dementia or mild cognitive impairment with at least one additional chronic condition and taking ≥5 chronic medications.[39] Patients and clinics were randomized to receive deprescribing education (1433) versus usual care (1579). While this study showed modest increases in deprescribing in the intervention group compared with the usual care, it demonstrated the manner in which the education is delivered and who is delivering it. Since clinics and providers were aware that their patients may receive this information, having the intervention come directly from the provider or care team rather than research study education materials could have had an impact on the rates of deprescribing.

Successful research can drive practice when helping patients make decisions that matter to them. As a result, many such trials are currently being undertaken for deprescribing interventions. The United States Deprescribing Research Network (www.deprescribingresearch.org) is a great place to start reviewing studies in progress as well as new research opportunities.

107.7 QUESTIONS AND FUTURE DIRECTIONS

Most of the research is focused on what happens when medications are deprescribed safely under appropriate circumstances taking into consideration risks versus benefits, patient beliefs and expectations, as well as overuse or low-value care. The research is still in its infancy when two approaches are combined into one—lifestyle medicine and deprescribing. How can deprescribing be utilized as a tool in lifestyle medicine in a systematic way?

As patients are encouraged, coached, and enabled to make healthier choices in mitigating, preventing, or even reversing their chronic medical conditions, what is an optimal dose of each component of lifestyle medicine—diet, healthy activity, restful sleep, managing stress, reducing risky behaviors/substances, and positive social connectedness—individually or in a combination? How would we study the individual effects of lifestyle as medicine interventions in patients who are on concurrent medications and the impact of deprescribing them in a stepwise process? Which medications should we start with first, and which ones should be reserved to deprescribe last? Where does deprescribing fit in with biologic therapies and immunotherapies in autoimmune conditions? This is where there is a need to blend both the art and the science of medicine into something practical and useful for our patients.

CLINICAL APPLICATIONS

- Managing medications in older adults requires balancing what is known from research and evidence-based guidelines with the patient's goals of care.
- Polypharmacy is defined as taking more than five chronic medications, and hyper-polypharmacy is defined as taking more than ten chronic medications for greater than 90 days. It is associated with an increased risk of adverse drug events, falls, functional decline, healthcare utilization, and mortality.
- A prescribing cascade can occur when a patient experiences a new problem that may be attributable to a new adverse drug reaction and is treated with a new medication to address that reaction. This can compound the risks of polypharmacy.
- Guidelines are usually targeted toward single chronic conditions, and do not take into account the complexity of the older adult, which may include multiple conditions and individual patient goals. This may lead to an increased risk for polypharmacy. Furthermore, they are often based on studies that have not enrolled frail older adults, so the findings are not applicable to a frail and complex older patient.
- Appropriate prescribing requires determining that there is a proper indication for a medication, a favorable benefit-risk ratio, and that the medication does not interfere with the other three Ms: What Matters Most to the patient, Mobility, or Mentation.
- A framework for considering deprescribing includes identifying appropriate indications for medications; identifying the existence of prescribing cascades; balancing actual or potential harms over benefits; evaluating current symptoms; determining benefits of medications based on life expectancy; and understanding treatment burdens.

SELECTED RESOURCES

- ChoosingWisely: National Initiative to reduce low-value care while improving safety and outcomes: www.choosingwisely.org/
- Cochrane Library Special Collections: Reviews of Deprescribing of Specific Medication Classes: www.cochranelibrary.com/collections/doi/SC000054/full
- Deprescribing.org: Canadian Deprescribing Network conducting research and providing specific algorithms for deprescribing: https://deprescribing.org/
- United States Deprescribing Research Network (USDeN): Network of research and implementation science dissemination of deprescribing

initiatives, including opportunities for research grants: https://deprescribingresearch.org/
- American Medical Director's Association (AMDA): Drive-2-Deprescribe Initiative in post-acute and long-term care facilities: https://paltc.org/drive2deprescribe

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108 What Matters: Geriatrics, Lifestyle Medicine, and Palliative Care

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KEY POINTS

- Palliative care is holistic care for those with complex, chronic, or terminal illnesses. It addresses the physical, functional, psychological, practical, and spiritual consequences of a serious illness.
- The goal of palliative care is to discover what gives meaning to people's lives in order to create a plan of care to support them in improving their quality of life and meeting their goals.
- The goal of palliative care is to support the patient and all who love and care for them. This includes supporting patient autonomy and patient empowerment for informed consent in all medical decisions.
- Lifestyle interventions can help palliative care patients and other older adults achieve what matters to them, including personal growth, achievement of life milestones, maximal possible self-sufficiency, satisfaction with life, and symptom management.

108.1 WHAT IS PALLIATIVE CARE?

Palliative care is the care of patients with chronic illness, often multiple complex chronic illnesses, or terminal illnesses. It is care of the whole person and centers itself on what matters to the patient, their goals of care, and relief of suffering. For an older person receiving palliative care, improving their self-efficacy, and personal or spiritual growth is often as important as maintaining their functional status and relief of the symptoms of their disease.

> *Palliative care focuses on expert assessment and management of pain and other symptoms, assessment and support of caregiver needs, and coordination of care. Palliative care attends to the physical, functional, psychological, practical, and spiritual consequences of a serious illness. It is a person- and family-centered approach to care, providing people living with serious illness relief from the symptoms and stress of an illness. Through early integration into the care plan for the seriously ill, palliative care improves quality of life for the patient and the family.*
>
> Source: National Coalition for Hospice and Palliative Care, Clinical Practice Guidelines for Quality Palliative Care, Fourth edition, 2018.[1]

Six principles are central to providing optimal palliative care: clarifying goals of care; improving quality of life; identifying the unit of care as the patient and all who love and care for them; recognizing that the patient's path through illness and care is unique to them; documenting the patient's condition, options, decisions, interventions, and needed supports in a plan of care; and planning to support the patient with the interdisciplinary team across healthcare settings. These principles are listed in Table 108.1 and are further described below.

108.2 PATIENT AUTONOMY AND GOALS OF CARE

A typical goal of care, what matters most, is the improvement of quality of life, regardless of prognosis. The goals of care will typically reflect the individual's values about what represents an improved quality of life. This allows a level of freedom to prioritize the patient's autonomy and choices, rather than reflexively following the standards of care that may no longer be appropriate to the patient's age or stage of disease.

The Age-Friendly Health Systems initiative defines "What Matters" as "knowing and aligning care with each older adult's specific health outcome goals and care preferences including, but not limited to end-of-life care, and across settings of care".[2] The "What Matters to Older Adults Toolkit" produced by the Institute for Healthcare Improvement (IHI) Age Friendly Healthcare initiative has concrete steps a clinician can take to hold productive and supportive conversations with their patients at appropriate touch-points in their care. This patient care, as described by the IHI, is consistent with high-quality palliative care goals-of-care conversations and may serve as an accessible entry point for clinicians unfamiliar with goals-of-care conversations.

What matters most to patients often becomes starkly transparent as the patient's internal resources are exhausted by illness or treatment, consistent with the IHI

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TABLE 108.1
Six Principles of Palliative Care:

- Clarify goals of care
- Improve quality of life
- Identify the unit of care as the patient and all who love and care for them
- Recognize that the patient's path through illness and care is unique to them
- Document the patient's condition, options, decisions, interventions, and needed supports in a plan of care
- Plan to support the patient with the interdisciplinary team across healthcare settings

recommendation to explore "what matters" with a change in health status or during chronic disease management. As repeat hospitalizations and multiple medical visits consume more of a patient's time and energy, the options for refocusing efforts on quality of life often become more attractive to patients. This may mean less stringent medical control over their clinical conditions, such as hypertension or diabetes. This may also lead to choices to limit invasive interventions or hospitalizations. It may also mean, for some patients, the choice to discontinue all or most conventional medical interventions for chronic or terminal illnesses. When possible, an in-person, linguistically, and culturally competent interpreter is invaluable in any circumstance where the patient and clinician do not share a common primary language and culture and where goals of care or treatment are being discussed or decisions are being made.

The goals of care discussion often reveal what matters most to patients, their values, and what gives their life meaning. These goals may be as concrete as going on vacation at the beach, living to see a grandchild graduate, being able to walk their daughter down the aisle at her wedding, being able to walk to the bathroom independently, having less pain, or completing one last road trip. Or the goal may be as amorphous as improved sleep at night, less anxiety about the future, a deeper connection to the Divine, or self-forgiveness. It may also be an open-ended goal that can never be completed, such as continuing to provide resources that keep their family from becoming homeless. When eliciting and documenting the goals of care, it is helpful to have an openness to the full range of patient priorities: physical, emotional, social, and spiritual. Specificity in documenting the individual goals and what matters most to them with concrete examples or quotes can be exceedingly helpful for the continued appropriate care of the patient.

Guidance on eliciting and documenting these goals of care is provided in the IHI "What Matters to Older Adults Toolkit". Common questions that are more commonly used in palliative care, and not contained in the "What Matters" toolkit, are questions such as: "If you knew you had only a short time left to live, where and how would you want to spend your time?" and "What is an unacceptable quality of life/death for you?" Other tough questions may include, "If you are unable to return to your prior level of functioning/place of residence, what care do you want to receive, from whom?" Many of these questions are based on both the need for care planning and clinical experience working with patients who are facing tough decisions. In addition, there exists an acknowledged potential for personal growth or development in the setting of the suffering experienced by many palliative care patients, often referred to as post-traumatic growth. Such personal growth may be a goal of the patient and more easily achieved when the patient's suffering is managed or relieved.[3–5]

108.3 DEFINING QUALITY OF LIFE

The patient's capacity to achieve these goals is often limited by their terminal illness or complex or severe chronic disease. With limited intrinsic resources, choosing interventions becomes a balancing act of figuring out which interventions have the greatest chance of improving the patient's quality of life with the least burden to the patient. For instance, pulmonary patients who are in chronic hypoxic respiratory failure are not typically good candidates for intensive inpatient physical rehabilitation, though they may welcome information about eating a low-inflammatory diet, "eating the rainbow" with a wide variety of fruits and vegetables as part of their own engagement in their health and well-being,[6] along with cessation of tobacco and breathing exercises to reduce anxiety due to dyspnea. Massage and passive or supported range of motion may also help decrease musculoskeletal pain associated with decreased mobility. All of these modalities can improve symptom management, and thereby improve the patient's quality of life and opportunity for post-traumatic growth, which can further aid in achieving even more of their goals of care. Finding out from the patient what is important to them to address first, and any larger goals, can aid in developing an effective plan of care.

There are numerous measures of quality of life in advanced disease used in clinical research. Some of these measures are disease-specific and some are more general, applying to all patients, including those with severe or chronic illness. The clinician's perspective is determinative in the formulation of most instruments used to measure quality of life. However, the responses are frequently highly subjective and may change as disease or debility progresses. As Davis and Hui point out in their article from 2017:

> Patient perspectives when queried about QOL include the following perspectives: Fulfillment of personal goals, good control of physical symptoms, emotional well-being, the

> ability to lead a normal life and maintain a sense of self, sociability (role within the family and society), existential and transcendent fulfillment, finding meaning in life, adaptability or resiliency, changing values or recalibration of goals with the disease trajectory.[7]

Alleviating physical symptoms and improving functional status can provide the conditions necessary for the exploration of other goals. It could be said that the real work at the end of life begins when the physical suffering abates. This work can involve the deep and important work of attaining social, psychological, and spiritual peace or growth. The team must remain sensitive to what matters to the patient to provide or facilitate the most appropriate support for these goals.

108.4 THE UNIT OF CARE

Choosing the interventions that are likely to have the greatest effect on quality of life often leads to involving the patient's family, friends, and care providers. For an effective plan of care, the unit of care is often the patient and all who love and care for them. For instance, one of the most effective interventions for comfort in end-stage cardiac disease or end-stage liver disease is decreased sodium intake. This can be the difference between a bounce-back to the cardiac care unit after a trip to a fast food restaurant or decreased dyspnea with improved lower extremity edema at home on fewer medications. For this intervention to be effective, the patient and all who care for the patient need to be aware of how important it is and what it means. A home visit that reviews foods immediately present can be a useful intervention for patients, family, and caregivers, with an opportunity to educate about the milligrams of sodium in a serving or container. For many patients, this is not the first time that they have heard this, but the recognition that they are running out of disease-directed treatment options appears to focus many patients on taking back control over this part of their medical condition. Even then, it remains a shared decision-making process, with openly discussed, respectful plans for the management of increased symptoms when the patient chooses not to follow the recommended nutritional interventions. These variations in the plans of care are often for special events, like family celebrations or holidays, where the patient prioritizes the goals of reconnecting or celebrating their connection with those they love. For those patients, fully recognizing their autonomy may involve finding alternative ways for them to improve their symptoms, such as elevation of their legs, lymph drainage massage, temporary increases in their medications, or walking in a pool to relieve lower extremity swelling. Informing the patient of these potential interventions and working with them, and their caregivers, to create the least burdensome plan of care can support the patient's sense of self-efficacy, which may have a unique contribution to quality of life.

Older adult patients living in care facilities sometimes face additional challenges and have additional benefits. Many care facilities do not offer heart-healthy meals, such as low sodium, Mediterranean diet, vegan, vegetarian, or DASH diet options. Other options that are often difficult for patients to navigate in facility settings are changes such as avoiding all dairy or a low-fat diet to treat chronic diarrhea or abdominal discomfort. Many older adults with chronic diarrhea or irritable bowel syndrome demonstrate symptomatic improvement with the avoidance of dairy or the addition of lactase with dairy-containing foods.[8] Likewise, older adults, especially those with biliary dysfunction or status post cholecystectomy, may see relief of diarrhea with a reduced fat diet. Coordination of these interventions can involve the patient's other clinical care providers, as well as family members and other patient advocates, with the patient designating the person they would like to have involved in the efforts on their behalf. Other interventions that often benefit from facility participation include restorative aid services for light exercise or range of motion, physical therapy, occupational therapy, music therapy, art therapy, religious services/observances, social events, exercise classes, dances, and organized outings. With the patient's goals always as the guiding principle, care facilities may have, or know how to access, many elements of robust lifestyle interventions.

108.4.1 Alternative Decision-Makers

At times, due to individual patient preference, culture, language, or health condition, patients may indicate they wish to designate an alternative person to receive their health information and make decisions about goals of care and interventions or they may lack the capacity to make some or all decisions. The designation of an alternative decision-maker may have been made prior to the patient's inability to make decisions or be made by state law in some states and situations. Substituted decision-making is frequently utilized by asking the alternative decision-maker to explain what they believe the patient would have wanted if the patient could choose for themself. Alternatives to substituted decision-making include the best interest of the patient based on community norms and narrative techniques emphasizing patient dignity and individuality.[9] State law varies in how alternative decision-makers are designated and the extent to which they are empowered to make decisions for a non-decisional patient.

In the situation where the patient is capable of making medical decisions and is deferring to another or desires the assistance of another in making medical decisions, as long as the patient's designation is clearly made when provided privacy to express their sincere wishes, it is often not necessary to burden the patient with every detail of their condition and options for treatment, if they designate that information to be given to another person. State law may vary in how these designations are viewed. Formulation of care plans with the patient and their caregivers is an example of the type of shared decision-making common to palliative care medicine.

In all circumstances, the patient should be encouraged to define the important relationships in their lives. The patient

designates who is important, how they should be addressed, and what access they should have to medical information. As the IHI "What Matters" toolkit points out, the level of formality and type of address with the patient should have also been elicited, so as not to offend the patient. When referring to people important to the patient, a husband should not be referred to as a "significant other" and should be addressed with the formality with which he is introduced. A rabbi is not a "priest". And an unrelated person of a certain age may be an aunt, not a "friend of the family". This can make explicit charting more important, and it is an important step in honoring and supporting the patient's goals of maintaining important relationships and social roles. Enjoyment of these relationships is often a primary goal for patients when they are asked about what makes their lives sweet, or if they are asked about how they would like to spend their time if they knew it was limited.

108.5 INDIVIDUALIZED PLANS OF CARE AND WALKING THE PATH WITH THE PATIENT

There is a recognition that the patient's path through illness and care is unique to them. This requires recognition and communication of all options for treatments and interventions, including those of lifestyle medicine, as part of informed consent for their care plan. Formulation of care plans with the patient and their caregivers is an example of the type of shared decision-making common to palliative care medicine.

108.5.1 What Matters: Maslow's Hierarchy as a Bidirectional Cycle

Maslow's hierarchy is typically depicted as a pyramid built on a broad base of essential needs, such as our physiologic needs, with our needs for safety, then love and belonging, following as less foundational, and abstract problem-solving representing the fulfillment of our self-actualization. (See Figure 108.1.) In palliative care, these dimensions of life demonstrate themselves to be a more self-reinforcing bidirectional cycle, with gains in each area supporting gains in the next. An example would be problem-solving frequently aiding the patient in solving difficulties such as access to food, fluids, or the bathroom. Frequently, increased connection to others is seen to lead to gains in all categories, making the lifestyle medicine pillar of positive connections to others clearly key to achieving the highest quality of life for most patients. Having noted that, there is still a level at which patients do need food, shelter, care, and safety before any palliative plan of care can be effective, therefore the palliative care plan of care must include and accommodate preferences for living and caregiving environments as well as the realities of the need for care and available resources of the patient and their family.

108.5.2 Independence

Almost all older adults who receive palliative care services have previously lived independently. Continuing or regaining this independence in driving, living in one's chosen home or community, and completing one's activities of daily living independently is often a goal of older adults. Assisting older adults in creating a plan of care that provides nutrition, exercise, rest, reflection, and sleep, and supports their relationships can assist the older adults in achieving their highest goals of care. Even in older adults with advanced illness, mild-moderate routine physical activity is frequently observed to both bring joy as well as support their independence and there is some indication that it may restrain cancer progression.[10] Examples of activities that patients enjoy that appear to support their continued

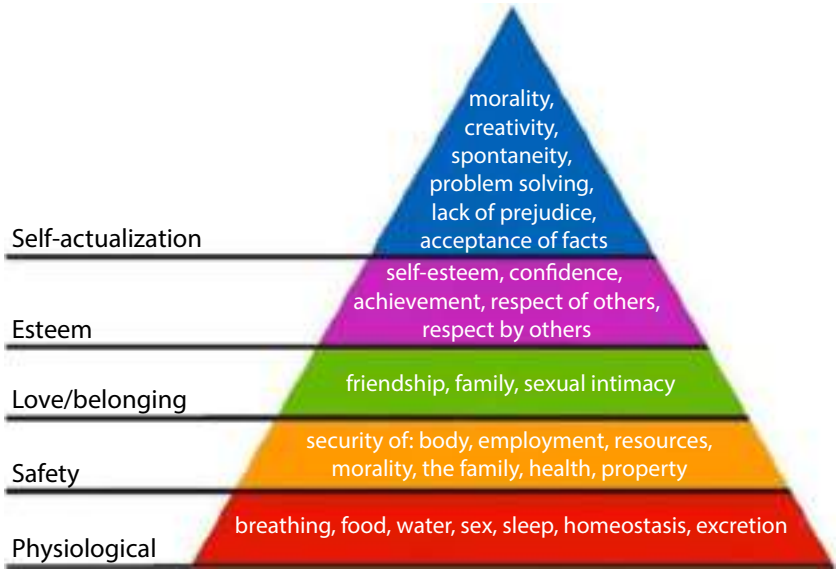


FIGURE 108.1 Maslow's hierarchy.

well-being include gardening, walking (even short distances), and running errands, such as grocery shopping.

Provision of food, shopping, and cooking are aspects of daily living that are essential to wellness and independence. Accommodating changing nutritional needs, nutritional recommendations, and capacity for self-care may force older adults to reexamine their habits, creating both opportunities and barriers to lifestyle interventions. As a source of comfort, having familiar foods may be important to the older adult, at times to the extent that even effective nutritional lifestyle interventions may not be consistent with the older adult's goals of care. In addition, community-based nutritional support, such as community food banks, congregate meal sites, and Meals-on-Wheels cannot typically accommodate specific nutritional requests.

When the plan of care cannot safely include the older adult remaining fully independent, their relationships with others often become how, where, and from whom they receive care. This can be a shift for older adults who have previously defined themselves as care providers. The decline in an older adult's ability to fulfill their activities of daily living can be a source of shame. Those who have highly prized their independence and may have believed themselves invulnerable to disability seem to be at increased risk of shame about the need for assistance in activities of daily living, such as eating and toileting. From Brene Brown, "Far from being an effective shield, the illusion of invulnerability undermines the very response that would have supplied genuine protection".[11] According to Brene Brown, the antidote to shame is resilience, and resilience comes from connection. The connection the older adult often forms with their care providers, whether friends, family, paid caregivers in the home, or custodial care providers can be that antidote to shame. Supporting the adult in creating, renewing, and strengthening these relationships is often key to their sense of well-being and adjustment to their changing social roles and physical status.

108.6 PLAN FOR SUPPORT ACROSS MULTIPLE CARE ENVIRONMENTS

The stress of severe chronic or terminal illness can be addressed through many of the interventions of lifestyle medicine, including meditation, spirituality, positive connections to others, and exercise. Support for these healthy lifestyle changes can take many forms, both within the formal medical system, including hospice, as well as in the broader community. Of particular note, as demonstrated by the meta-analysis by Sawatski 2002[12] there is a significant relationship between engagement in spirituality and quality of life. Per Lindberg 2003,[13] the improvement due to meditation and spirituality extends even to those older adults with dementia and may extend to those in nursing home care. There is a long tradition in hospice of providing spiritual comfort to those enrolled in hospice through regular interactions with a hospice chaplain. The hospice chaplain is considered so important that, per Medicare guidelines, a chaplain is a required member of the hospice care team to formulate and regularly review the plan of care. Many non-hospice hospital-based and home health-based palliative care services have adopted the tradition of providing spiritual care due to the improvement observed in quality of life when older adults and those who love and care for them are supported by chaplains.

108.6.1 Symptom Management

Another requirement of the Medicare benefit which informs palliative care provided in the United States is the requirement of hospices to prioritize treatment for pain, nausea, constipation, and anxiety. As comprehensive lifestyle treatment of these symptoms is widely researched and reported, what will be reviewed here are the modalities that have been commonly observed to provide quick benefit in the alleviation of these symptoms in patients at end of life or with severe disease or disability.

108.6.2 Management of Total Pain

Pain management is often equated with medications, both in the minds of patients and medical professionals. The armamentarium of analgesic medications seems to grow each year, with increasing sophistication in the use of opioid and non-opioid pain medications, each with their specific targets of therapy and side effects. It is outside of the scope of this chapter to address the treatment of symptoms through medication and procedures. However, there are non-pharmaceutical methods of relieving pain that patients and caregivers can incorporate into their lives to relieve some of the pain and distress of prolonged debility and illness.

Addressing any difficulties with sleep, anxiety, emotional pain, and spiritual pain also shows benefits in treating physical pain. Until the other aspects of suffering are addressed, physical pain frequently cannot be adequately alleviated. In palliative care and hospice medicine, there is a concept of "total pain" put forward by the founder of the modern hospice movement, Dame Cicely Saunders. The concept of total pain refers to suffering in the physical, psychological, spiritual, and social domains.[14] The suffering in each domain is understood to amplify the suffering in the other domains. This is part of the reason for the interdisciplinary aspect of hospice and palliative care medicine. It is not uncommon for clinical social workers and chaplains to work extensively with patients and their families to address current and past sources of non-physical suffering. All care providers, especially the nursing staff and physicians, can support treatment of the total pain, often by as little as offering a hand to hold or an ear to listen. These small acts of kindness and attention allow patients to make human connections that are an essential part of the high-touch medicine of palliative care.

The first and foremost intervention for physical pain that patients frequently note is that they want to get out of bed

and move around. This can require the direct assistance of physical therapy, restorative aid services, nurses, or attentive family members or friends. The goal is not exercise, per se, it is movement to relieve muscle spasms and joint pain due to immobility, as well as the pain of pressure injuries. Physical therapy and occupational therapy can be key in helping patients safely return to a level of activity that allows patients to do those things that matter the most to them. Even in patients who cannot rise from bed, range of motion exercises and massage can aid in increasing the patient's sense of well-being and are often reported to decrease pain. Integration of a moisturizer massage into a bed-bound patient's daily hygiene routine appears to provide significant comfort to patients, as well as maintaining the health of their skin. Positioning for support and comfort can include not only pressure relief but also specific pain-relieving postures such as 90/90 positioning: 90/90 positioning involves the patient lying on their back or side with a fully supported 90-degree flexion at hip and knee to relieve nerve compression and pain in the lumbar spine for patients with lumbar spinal stenosis or dysfunction. Restorative stretches and restorative yoga may also improve quality of life for some patients. There are specific yoga options that can be appropriate even for people who would not be capable of typical yoga. These options include chair yoga and therapeutic yoga, including integrated movement therapy, a yoga therapy method that helps people make behavior shifts to move toward optimal well-being.

Anti-inflammatory foods and a plant-based diet, especially for inflammatory arthritides such as rheumatoid arthritis and psoriatic arthritis, appear to benefit patients relatively rapidly.[15] Many patients report benefits even with modification of their diet, rather than a complete change in their diet. As addressed elsewhere, management of the pain and progression of multiple sclerosis can be profoundly impacted by dietary choices. The benefits of anti-inflammatory foods or diet are often remarked by patients to be especially notable in morning stiffness and pain. It is not unusual to hear from someone that they are now able to walk downstairs or do other daily tasks with far less pain. One of the changes encouraged is the use of turmeric in food, tea, or golden milk for relief of pain, with the use supported both by patient reports and multiple studies,[16] always with a dash of black pepper to improve absorption. The typical recipe for golden milk, based on plant-based milk with turmeric, pepper, ginger, and sweet spices for additional flavor, may also be helpful for discomfort due to muscle pain and osteoarthritis pain, with research showing specifically the pain-relieving benefits of ginger and turmeric.[17,18]

Meditation, mindful breathing, prayer, and mindfulness in some form are frequently used by patients to treat physical as well as emotional and spiritual pain prior to any instruction by clinicians. In systematic reviews of the research, the use of mindfulness meditation and mindfulness practices has been shown to improve pain, depression symptoms, mobility, functional status, and quality of life.[19,20] Some of the forms these practices take at the bedside of a chronically or severely ill person are the use of breath awareness, breathing techniques, guided imagery, progressive relaxation, singing, prayer, and other techniques that can be easily taught or reinforced at the bedside. The reinforcement of these techniques can be undertaken by all members of the care team, giving the patient more support in actively managing their own pain.

108.6.3 Nausea and Vomiting

Another common source of suffering for patients with severe or terminal illness is nausea. There are myriad sources and types of nausea, including nausea associated with anesthesia, chemotherapy, cancer, radiation therapy, medications, gastroparesis, autonomic changes, constipation, intracranial pressure, heart failure, renal failure, and liver failure. Multiple classes of medications address multiple receptor classes associated with nausea: histaminergic, serotonergic, dopaminergic, and cholinergic. The most potent and commonly used medications for acute nausea are the dopaminergic (haloperidol, olanzapine) for general nausea and the serotonergic (ondansetron) for chemotherapy-related causes, with the mixed receptor phenothiazines (prochlorperazine) and antihistamine (promethazine) used more commonly for chronic or general nausea. All of these medications, with the exception of ondansetron, commonly cause sedation, which is often undesirable by patients. It matters for most patients that they are awake, aware, and able to interact with those around them. Utilizing non-pharmacological treatments for nausea can reduce the need for sedating medications and give the patient control over their symptoms.

Once again, breathing techniques have been shown to bring rapid relief to some patients with postoperative nausea, as well as chronic, recurrent nausea. The technique used by Sites et al.[21] for their research on the treatment of postoperative nausea utilized a pattern of breathing with three seconds of inhalation, three seconds of holding, then three seconds of exhalation, repeated three times. This pattern was found to bring rapid relief, typically after about five minutes, with and without aromatherapy with peppermint. The use of peppermint, other mints, and ginger has long been advocated for the treatment of nausea, with many patients reporting improvement with the inclusion of these foods in their diets or the use of mint teas or ginger-containing lozenges, foods, and drinks.

Reduction in the fat content of meals has also been reported to reduce dyspepsia symptoms, including nausea.[22] The usual advice is to eat small frequent meals, low in fat, and high in easily absorbed carbohydrates. Examples frequently used are culturally appropriate comfort foods, such as rice soup or porridge, noodle soups, and other food combinations with high water content, moderate salt, and starches. This can also include cold foods, such as applesauce and sorbet if desired by the patient. The mechanism of the relief seen may be in part due to the relief of dehydration, as these are all foods that support more rapid gastric

emptying and fluid absorption. For many families, where the cultural tradition could be expressed as "food is love", the ability of the family or other caregivers to support the patient in this way can be an invaluable source of comfort to both the family and the patient.

Increasing fluids with sparkling water may be especially helpful in decreasing dyspepsia, including nausea, as well as constipation.[23] Other sparkling drinks are not as effective in the research, though many patients and families do report improvement with ginger ale or ginger beer, as well as home remedies such as clear sodas. As nausea triggers can be very individual, so can the alleviating foods and drinks. The important message for the family and other caregivers is to honor the patient's desire whether or not to eat or drink, especially if it is related to the natural and normal decrease in oral intake at the end of life.

At this point, caution is warranted as some patients with a history of an intra-abdominal process, such as tumor or adhesions, may have either a partial or complete bowel obstruction as a cause for nausea with vomiting and subsequently no desire to eat or drink. If there is vomiting of unknown cause despite no oral intake, or in the setting of a known intra-abdominal process, bowel obstruction must be ruled out prior to the initiation of other interventions. Treatment of these conditions is outside of the scope of this chapter, though a low residue (low fiber), high fluid content diet may help maintain a patent bowel after restoration of bowel function in a patient with risk for continued or recurrent partial bowel obstruction.

108.6.4 Constipation

As oral intake and mobility decrease, one of the natural consequences can be slowed gastrointestinal motility and dehydration, leading to constipation. Constipation itself can increase nausea, as well as bloating and abdominal discomfort. This makes constipation a high priority for treatment for many patients. Many patients choose to stop medications that can cause constipation, including opiates. Helping patients understand the many other medications that may be playing a role in increasing their risk for constipation can help the patients achieve their goal of relieving their discomfort due to constipation. Common offending medications are the anticholinergics, which include prescription medications as well as over-the-counter sleep medications, urinary frequency medications, and allergy medications. Many of these patients are also noted to be on supplemental iron, calcium, diuretics, anticonvulsants, or antiparkinsonian agents that may contribute to their constipation. Helping the patient consider what matters most to them is a dynamic process that may lead to decreasing or stopping some medications or supplements, or to the use of other interventions or medications to increase bowel motility.

For patients who are tolerating a full diet, encouraging increased fluids and fiber, especially soluble fiber through the inclusion of more whole grains, vegetables, and fruits, can be effective in helping relieve constipation not caused by medications. Increased fluids and fiber are often most difficult to initiate when patients are in custodial care, such as assisted living facilities and nursing homes. For patients who are fully dependent on others for access to fluids, it may be beneficial to clarify with the facility that each caregiver who enters the room should offer fluids with every entry to the room. One frequently well-tolerated, time-honored intervention is prunes, which has been shown to be more effective than supplemental psyllium.[24] This intervention also has the advantage of being commonly available to nursing home residents.

Finally, abdominal massage is a time- and nursing resource-intensive intervention that is effective in stimulating bowel motility. When elderly residents of a nursing home were provided daily 30-minute abdominal massage for symptomatic constipation, significant improvement was seen in constipation, quality of life, physical disability, psychosocial discomfort, anxiety, and satisfaction with treatment.[25] Even patients whose constipation is a result of opiates may benefit from abdominal massage, with improvement noted in discomfort, stool consistency, quality of life, and number of bowel movements.[26] For patients and their care providers, solving the issue of constipation may represent a return to the cyclical nature of care of older adults, typified by problem-solving, relationship building, and management of resources to support the patient in what matters most to them.

108.6.5 Anxiety, Insomnia, and Depression

For patients facing severe chronic illness or terminal illness, some of the primary forms of suffering observed are disturbances of mood and sleep. Medications used to treat pain and other physical symptoms, such as opiates, may also increase the risk of depression and disturbed sleep. While some patients come to this stage in their lives with prior diagnoses of clinical depression, anxiety disorders, post-traumatic stress disorder (PTSD), insomnia, or other mood or psychiatric diagnoses, all patients are at risk for changes in mood and coping. It is not uncommon for patients to experience and express grief, anger, sadness, worry, existential anxiety, helplessness, regret, shame, guilt, loss of meaning, and demoralization. When persistent, these symptoms may meet the criteria of adjustment disorder. Patients, family members, and caregivers also frequently cope with stress related to changing roles, changing functional status, finances, family relationships, disease changes, treatment-related stress, and stress due to physical symptoms.

The use of screening instruments for depression and anxiety can be difficult in patients with severe or life-threatening illnesses due to the inclusion of somatic symptoms in many screening tools. These somatic symptoms may be associated with mood changes, though not necessarily indicative of a primary clinical depression or an anxiety disorder. One of the most effective depression screening

tools used is a simple two-question screening that is 97% sensitive and 67% specific in the general population:[27]

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

In practical application with severely ill patients, the question about anhedonia is far more sensitive for differentiation between sadness or grief and clinical depression. For seriously ill patients who are still capable of joy at the presence of a grandchild or the sun on their face in the garden, the use of antidepressants is unlikely to be helpful. Often these patients have not had a chance to do anything that interests them or brings them pleasure for a prolonged period, though they can report joy at imagining the possibilities. In that visualization, they may even begin to have relief of hopelessness or demoralization.

Cognitive strategies that are commonly used to relieve depressed mood and anxiety in seriously ill people include prayer, guided imagery, progressive relaxation, meditation, counseling, and cognitive behavioral therapy. Other strategies that are successful for select people include music and art therapy, touch therapy or massage, exposure to natural sunlight in the morning, gratitude journaling, and working with someone to record their life story. Exercise and movement have even been shown to improve depressive symptoms and improve function in patients with chronic illness.[28] The variety of these interventions reflects the work of the interdisciplinary team and provides increased opportunity to find an intervention that is successful for the specific patient and family.

Many of the interventions for the treatment of depressed mood and anxiety are also effective in treating insomnia. Some of the most reliable responses are seen with exposure to morning daylight, cognitive behavioral therapy, and physical activity.[29]

Other strategies encouraged to improve sleep include avoidance of caffeine and alcohol, as well as avoidance of other psychostimulants or recreational drugs. However, some patients do report improvement in the quality of their sleep with CBD or marijuana, the use of which is now decriminalized in many states. For patients who have delayed onset of sleep, rather than unrefreshing or interrupted sleep, bedtime routines typically recommended for other people also often work well for older adults with severe illness. Specific additions to the usual bedtime routine that have been observed to be effective are online recordings, often accessed through phone apps, for guided sleep meditations, bedtime stories for adults, and music or ambient noise designed to help the person relax and mask sounds that might otherwise interfere with initiation or maintenance of sleep. Similar to gratitude journaling, another strategy that has been successful for some patients is the development of a habit of recalling three positive things that occurred during the day for which the person is grateful.

Of particular note, anxiety is frequently relieved with open and honest discussion about medical conditions and prognosis with the patient and family. Addressing fears about the physical dying process in particular can relieve not only anxiety but also hopelessness and demoralization. Reassurance that the patient and family will continue to be supported on their journey, whether or not they accept any or all medical, surgical, or lifestyle interventions offered, can go far in supporting a sense of control and hope.

108.7 DOCUMENTATION OF THE PLAN AND GOALS OF CARE

Documentation of the plan of care, including what matters most to the patient, their current condition, options, decisions, interventions, and support needed are essential to the process of continued interdisciplinary and cross-specialty communication.

The most effective plan of care is only as effective as the communication across care environments and care providers. At times, this may require a commitment to the education of care providers on the requirements and effectiveness of lifestyle interventions. This may also provide an opportunity for family members and other care providers to seek information or referrals to discuss their own disease risk and lifestyle interventions. A list of accessible resources can be helpful in these situations.

Complete and explicit documentation of what matters, ideally in the patient, family, and caregivers' own words, can also protect the patient from inappropriate care and interventions. This can be achieved through advance directives, a durable power of attorney, a POLST (Physician's Order for Life Sustaining Treatment), or other legal documents appropriate to the jurisdiction and goals of care. Such explicit documentation of the patient's goals of care, and any changes, can also be essential in prioritizing interventions to achieve an improved quality of life. All healthcare providers can assist in this documentation, though it is often a task requested of the members of the palliative care team.

108.8 HOSPICE AND PALLIATIVE CARE INTERVENTIONS IN PULMONARY AND CARDIAC DISEASE

Hospice and palliative care has a greater than 30-year history in the United States. According to the report of the National Hospice and Palliative Care Organization,[30] the principal diagnosis categories that have grown the most since 2014 are stroke, respiratory, and circulatory/heart; while cancer remains the most common diagnosis class, it no longer represents the majority of patients. Those patients who are admitted to hospice with a primary cancer diagnosis frequently also have cardiac and pulmonary comorbidities amenable to lifestyle interventions for improvement in their quality of life.

108.8.1 Lung Disease and Dyspnea

According to the research of Keranis et al.,[31] a randomized trial demonstrated the benefits of increasing fruits and vegetables by one serving per day in the progression of symptoms of COPD. In practical terms, this can mean that a patient who is suffering from severe, chronic dyspnea with advanced COPD, may feel better and, in some cases, live longer than patients who continue to eat a standard American diet. For some patients who feel these effects, they come to crave fruits and vegetables while they associate them with improved ease of breathing. In some patients who adopt this change, weight loss has been observed, which is common in end-stage pulmonary patients due to the caloric demands of their disease process. The advice to balance the intake of fruits and vegetables with higher calorie foods as tolerated, such as avocado, nuts, non-dairy ice creams, and other treats, has typically been well-received.

Breath-based meditation practices, augmented with the use of a pulse oximeter for some patients, have also resulted in decreased patient distress due to dyspnea. Practically, this can look like the nurse at bedside demonstrating pursed lips breathing or square breathing, or it can be the physician using a pulse oximeter and demonstrating that a slowed exhalation breathing pattern improves oxygen saturation and decreases heart rate. Chan and Lehto[32] demonstrated in their research that an eight-week one-hour mind/body meditation course led to improvement in emotional and physical symptoms associated with COPD for most patients. This is consistent with what is seen in one-on-one interactions in the clinical context where the intervention may be more intense, if less systematic.

Home-based pulmonary rehabilitation, specifically including an exercise component at least four times per week, was noted by Gefine[33] to improve health-related quality of life, general fatigue, and anxiety and depressive symptom scores after pulmonary rehabilitation in frail COPD patients with hypoxic respiratory failure. These and other positive effects on functioning were seen at eight weeks and the benefits were particularly notable at eight months in patients who were more frail at the onset of the research.

Finally, whether it is the theobromine, as suggested by some research,[34] or simply the comfort of the sugar content or taste, many patients find the use of dark chocolate to be useful for treating mild-moderate cough, as an alternative to opiates or other cough suppressant medications.

108.8.2 Heart Failure

The final common pathway for many cardiac diseases is heart failure of some type. Heart failure is somewhat unique among the common pathways of terminal illness in that management of the symptoms of heart failure not only improves quality of life but is also frequently consistent with prolonging life. Avoidance of heart failure exacerbations, fluid overload, symptomatic tachycardia, symptomatic bradycardia, hypotension, angina, and severe hypertension are all desirable strategies to improve quality of life. Many of these symptoms are amenable to dietary changes, changes in daily routine, and changes in physical activity.

The current AHA/ACC/HFSA guideline for the management of heart failure were released in May 2022. The classifications of heart disease within the guidelines are both based on the left ventricular ejection fraction and the degree of symptoms, with special attention paid to the increasingly recognized heart disease due to amyloidosis. These guidelines emphasize the importance of palliative care in the treatment of patients at all stages of heart failure. The goal of this recommendation is enhanced communications, prognostication, symptom management, anticipatory guidance for patients and families, and advance care planning with shared decision-making about medically reasonable treatment options.[35]

The symptoms of heart failure that are frequently managed by palliative care or hospice are dyspnea, orthopnea, edema, fatigue, hypotension, angina, nausea, and orthostatic hypotension. Many of these symptoms are secondary to volume overload and are amenable to sodium restriction for a large proportion of heart failure patients. The degree of necessary and tolerated sodium restriction varies, with a common hospice recommendation being 2 g of sodium per day until comfort is achieved, at the same time that the diuretics are titrated for maximum effect and comfort. Recent pilot studies have supported using an even more stringent 1.5 g sodium per day limit to improve quality of life.[36,37] The extent of sodium restriction and how consistently it is followed is clearly a personal choice for patients when they have access to a reduced sodium diet. However, when what matters to the patient is a 4th of July barbecue or Thanksgiving turkey dinner, then it is not uncommon to aid the patient and family in planning for an increased need for diuresis surrounding these events.

For those patients who are able to make the adjustment, the number needed to treat with a Mediterranean Diet in the known presence of coronary artery disease after a myocardial infarction is just 30 for mortality and 18 for repeat MI.[38–40] For those patients who are more familiar or comfortable with the DASH diet, they are encouraged in making those changes. The DASH diet is also recommended in the AHA/ACC/HFSA 2022 guidelines. Most importantly for symptom management, the patients who make positive changes in their diet frequently report more rapid and sustained relief of their heart failure symptoms.

Other lifestyle interventions that appear to improve nocturnal orthopnea and lower extremity edema are elevation of the legs to the level of the heart for as much of the day as tolerated, with or without spiral compression wrapping and lymph drainage massage. Patients frequently report improved sleep and daytime fatigue when both orthopnea and nocturia are improved with more intensive daytime treatment of lower extremity edema. Some patients have also reported improved lower extremity edema with water aerobics or walking in waist or chest-height water.

Optimizing fluid status is often also beneficial to patients with hypotension or orthostatic hypotension. Older adults often benefit symptomatically from a higher blood pressure and heart rate, with an observed decreased risk of falls and fatigue. Through optimization of cardiac function and medication management, it is not uncommon to allow the systolic blood pressure of an older adult to rise above the usual target range for younger adults. Many researchers, including Masoli[41] in a study in 2020 of more than 400,000 frail adults above 75 years old, have found that the lowest mortality risk was at a systolic blood pressure of 140–160 and diastolic of 80–90. Elderly advanced heart failure patients appear to do well symptomatically with blood pressure at the lower end of that range. Some patients have treatment of their heart failure limited by hypotension despite optimization of their fluid status by all means acceptable to the patient. While managing symptoms and side effects of medications, beta blockers and other medications that decrease the heart rate of older adults are often titrated to allow an increased heart rate, including in the setting of atrial fibrillation.

Avoidance of tobacco is also recommended, with all of the other interventions for relief of dyspnea described above in the pulmonary section.

Finally, meta-analyses have shown that cardiac rehabilitation improves functional capacity, exercise tolerance, and health-related quality of life. Many older adults with cardiac disease need to start low and go slow with increasing their physical exertion. The guidance of either a formal cardiac rehabilitation program, inpatient rehabilitation, or home health rehabilitation can benefit patients in regaining and sustaining the highest quality of life possible.

108.9 SUMMARY: WHAT MATTERS

Lifestyle medicine interventions can improve quality of life consistent with the goals of palliative care. The intensity of the interventions or the forms of the interventions may need adjustment for frail and debilitated patients. At all times, with informed consent, the patient's goals—what matters to the patient—must guide the plan of care.

CLINICAL APPLICATIONS

- Palliative care:
  - Is holistic care of those with complex, chronic, or terminal illness, addressing the physical, functional, psychological, practical, and spiritual consequences of a serious illness.
  - Discovers what gives meaning to people's lives and creates a plan of care to support them in improving their quality of life.
  - Supports the patient and those important to them, including supporting patient autonomy and patient empowerment.
- Lifestyle interventions:
  - Contribute to the care of palliative care patients and other older adults by helping them achieve what is meaningful to them, including personal growth, achievement of life milestones, maximal possible self-sufficiency, satisfaction with life, and symptom management.

Palliative lifestyle interventions include:

- Targeted nutritional interventions, when available and consistent with what matters most to the patient.
- Movement adapted to patient condition and goals.
- Mind–body exercises, targeted breathing exercises, and spiritual practices for the management of total pain and suffering.
- Improved sleep and mood with cognitive strategies, mindfulness, and physical activity.
- Limiting or avoiding the use of alcohol, stimulants, and nicotine to improve symptoms, including mood disturbances, insomnia, dyspnea, and cardiac symptoms.
- Support for positive patient relationships with others as essential to meeting patient needs and achieving what matters most to the patient at all levels of self-actualization.

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109 Healthy Aging: Impact of Loneliness and Social Isolation

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She could be lively only in the midst of life; in isolation she dwindled to a shadow.

—— **Stefan Zweig,** ***The Collected Stories of Stefan Zweig***

KEY POINTS

- Loneliness and social isolation are increasingly part of the aging experience.
- Loneliness and social isolation among older adults are influenced by many factors, including sociodemographic attributes, available social resources, and health status—both physical and mental.
- Increasing evidence suggests that perceived social isolation or loneliness is a major risk factor for physical and mental illness in later life.
- Social engagement is a key feature of healthy aging.
- Promoting resilience and high-quality social relationships throughout the lifespan appears to be vital to healthy aging.
- Although our understanding of the effectiveness continues to develop, clinical and social interventions exist for clinicians to implement and promote.

109.1 INTRODUCTION

From July 12 through July 16, 1995, the city of Chicago experienced an unprecedented heat wave, with daytime temperatures ranging between the low 90s and low 100s (Fahrenheit) and nighttime temperatures in the low to mid-80s. On July 13, the daytime temperature reached 106°F, and, with the extremes of humidity, the associated heat index reached 120.[1] During this one week, Chicago experienced at least 700 excess deaths, most of which were classified as heat-related. Those at greatest risk of dying from the heat were people with medical illnesses who were socially isolated and did not have access to air conditioning. In an analysis of the experience, the US Centers for Disease Control noted that "People, especially elderly people, who live alone and do not have networks of social contacts" were at particularly high risk. "During the summer heat wave of 1995 in Chicago, anything that facilitated social contact, even membership in a social club or owning a pet, was associated with a decreased risk of death".[2]

The Chicago heat wave and others like it[3,4] dramatically illustrate the vulnerability of socially isolated older adults to major environmental stressors, but there has also been much work done to better understand the many mechanisms by which social relationships affect health and how the promotion of social connectedness may enhance health and quality of life across the age span.[5]

Since at least the 1980s, social isolation and loneliness have been recognized as having deleterious effects on the health of older adults, rivaling other risk factors that are well-recognized by the medical community.[6] It has become increasingly clear that loneliness and social isolation have a major influence on physical health, mental health, and healthy aging. We now find ourselves in an era in which 25–29% of adults over the age of 70 report feeling lonely[7] and up to half of Americans have only one person or no one to discuss personal matters, especially losing their ties to local neighborhoods and groups.[8] Thought leaders and social commenters refer to our current state of affairs as an "epidemic of loneliness"[9] or a "Loneliness Crisis".[10] Whether a crisis, an epidemic, or merely a sign of the times, it is clear that loneliness and social isolation are increasingly part of the experience of growing old and that social relationships (or lack of social relationships) matter to healthy aging.

109.2 DEFINITIONS: LONELINESS AND SOCIAL ISOLATION

Loneliness and social isolation are distinct concepts: individuals can be lonely without being socially isolated; experience both loneliness and isolation; or be socially isolated without feeling lonely.[11,] How people define loneliness and social isolation is important because it influences how clinicians may measure these concepts. Loneliness has been conceptualized in several different ways but is frequently viewed as a perceived discrepancy between one's desired and actual social relationships.[12] Domains of loneliness include social loneliness (perceived lack of a wider social network) and emotional loneliness (the absence of a specific desired companion). Feelings of loneliness are not synonymous with being alone but rather involve feelings of isolation, disconnectedness, and not belonging.[13] Researchers

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have distinguished loneliness from the experience of solitude. The latter reflects a state of social isolation that involves voluntary distancing from one's social network, whereas loneliness is involuntary and more closely associated with deficits in the perceived quality of one's social interactions.[14] Other constructs of loneliness include a perceived deprivation of social contact, perceived social isolation, or a lack of people with whom to share emotional and social experiences.[15]

Social isolation, on the other hand, has, for many, been more difficult to define. Social isolation and social disconnectedness refer to an objective state rather than the subjective experience of loneliness. Social isolation reflects an individual's lack of contacts or ties with others, such as family, friends, acquaintances, and neighbors.[16] It can be conceptualized as a measure of a person's integration and meaningful communication with their community, friends, and family. Constructs of social isolation include the objective experience of being alone, a lack of meaningful social ties, or a lack of integration with social networks.[17]

While these concepts of social isolation and loneliness appear to overlap, research shows that there is only a moderate association between loneliness and social isolation.[18] Individuals vary significantly in how their social circumstances elicit feelings of loneliness. The quality of the individual's social relationships is a stronger predictor of loneliness than the quantity of social contacts.[19] Some people can live what feels to them to be an isolated experience even when around others. Individuals who have a rich and forgiving social environment have more opportunities to meet their emotional need for social connectedness and belonging. For others, loneliness becomes inescapable, and they may need more help making the connections necessary to feel safe, secure, and content with life.[20]

109.3 MEASURING LONELINESS AND SOCIAL ISOLATION

There are several widely used self-report tools to measure loneliness. These include the UCLA Loneliness Scale and the De Jong Greifeld Loneliness Scale. Measures of loneliness and social isolation are of practical significance to any clinical effort to identify those at risk and to assess interventions to mitigate loneliness and/or social isolation. The UCLA Loneliness Scale and the dJG Loneliness Scale have demonstrated reliability and validity, but they have been designed primarily as research tools, and further study is needed to understand their use in older adults.

UCLA Three-Item Loneliness Scale[21]

This scale is comprised of three questions that measure three dimensions of loneliness: relational connectedness, social connectedness, and self-perceived isolation.

1. How often do you feel that you lack companionship?
2. How often do you feel left out?
3. How often do you feel isolated from others?

The scale generally uses three response categories:

Response	Score
Hardly ever	1
Some of the time	2
Often	3

Scoring

Least lonely 1 2 3 4 5 6 7 8 9 Most lonely

A broader range of approaches have been used to measure isolation, including the size of an individual's social networks, levels of social contact, marital status, and household composition.[22] Most of the validated tools measure the size, closeness, and frequency of contact between the individual and their social networks. These tools have been designed primarily for use in research, and include the Lubben Social Network Scale, the Duke Social Support Index, and the Social Disconnectedness Scale.[23] None of these tools have been designed and tested for use in clinical settings and there is an opportunity for research to understand the most effective strategies to identify and measure loneliness and social isolation in the clinic.

109.4 AGING, LONELINESS, AND SOCIAL ISOLATION

Older people are particularly vulnerable to social isolation and loneliness because of common age-related changes and losses. Experiences of loneliness and social isolation are not uniform across the life course: individuals may become lonely or isolated in old age, be lifelong isolates, or experience loneliness and/or social isolation because of a triggering event.[24] Loss of one's partners and friends through death, deteriorating health, institutionalization, and loss of social roles through retirement are common experiences for older adults. There is evidence that emotional closeness in relationships increases with age, but at the same time, the number of social relationships decreases and life events triggering disruptions in ties increase (e.g., death of a parent, death of a spouse, children leaving home).[25] Variables found primarily in cross-sectional studies to be associated with loneliness in older adults include the following: female gender, non-married status, older age, poor income, lower educational level, living alone, low quality of social relationships, poor self-reported health, and poor functional status. Psychological attributes that have been associated with loneliness include poor mental health, low self-efficacy beliefs, negative life events, and cognitive decline. [26] Women may be at greater risk for loneliness than men because of their longer life expectancy and higher burden of many known risk factors. Additionally, women may more readily admit their feelings of loneliness in comparison with men, which can help account for the higher levels of loneliness observed.[27] These individual factors are compounded by social changes that include reduced intergenerational living, greater geographical mobility, and the rise in one-person households.[28]

There are also community and societal factors impacting an individual that can increase their vulnerability to social isolation and loneliness.[29] These include at the community level, high levels of neighborhood crime, high residential mobility, limited opportunities to participate in social activities, and limited access to services and public transport. Society risk factors include the experience of social discrimination or social marginalization, lack of social cohesion, and social norms that discourage activity.[30]

Risk Factors for Social Isolation and Loneliness Among Older Adults[31–34]

Sociodemographic Factors

- Being 75 or older
- Living alone
- Female
- Being a caregiver
- Limited financial resources
- Cognitive vulnerability
- Sensory Impairments (vision and hearing)
- Language barriers
- Having no children

Life Transitions

- Health decline
- Physical disability
- Losing the ability to drive
- Losing a partner

Relationship Level Factors

- Poor quality personal relationships
- Little contact with friends or family
- Personal relationship conflict, disruption, or dysfunction

Community Level Factors

- High levels of neighborhood crime
- High residential mobility
- Limited opportunities for participation in social activities
- Limited access to services and transportation

Societal Level Factors

- Experiencing discrimination and social marginalization
- Lack of social cohesion
- Social norms that discourage activity

109.5 SOCIAL ISOLATION AND LONELINESS: IMPACT ON HEALTH IN OLD AGE

A growing body of evidence indicates that perceived social isolation and/or loneliness are significant risk factors for physical and mental illness in later life, with an impact on par with other known risk factors such as obesity or tobacco use. One meta-analysis of the literature investigating the association between social relationships and mortality found that individuals with adequate social relationships have a 50% greater likelihood of survival over 7.5 years compared with those with poor or insufficient social relationships.[35] The experience and consequences of loneliness and isolation vary with socioeconomic status and culture, but the association with the lowering of broad-based morbidity and mortality appears consistent. Loneliness or the perceived absence of positive social relationships has been linked to diminished longevity, particularly among older individuals in whom declining economic resources, illness, widowhood, and impaired mobility may result in increased risk for social isolation.[36] Unfortunately, most of the available evidence has been generated through cross-sectional studies, which have limited ability to inform the direction of the association between loneliness and social isolation and health. [37] Causal linkages remain modestly uncertain, but loneliness and isolation have been found to be independent predictors of mortality[38] and are associated with a myriad of physical and mental health problems. Their linkages to chronic diseases, declining function, and any number of adverse physical and mental health problems warrant individual attention, clinical attention, and public health attention. Physical health problems associated with loneliness and social isolation include elevated systolic blood pressure, less restorative sleep, diminished immunity, reduced function, cardiovascular disease, and impaired cognitive performance.[39] Loneliness is also associated with hopelessness, depressed mood, lower levels of well-being, psychological distress, psychiatric morbidity, and depression. Loneliness is also a predictor of suicide among older adults.[40]

Adverse Health Outcomes Associated with Loneliness and Social Isolation[34–39]

Physical Health

- Higher mortality
- Elevated systolic blood pressure
- Cardiovascular disease
- Sleep disturbances
- Reduced immune function
- Impaired cognitive function
- Impaired physical function

Mental Health

- Higher levels of hopelessness
- Depressed mood
- Psychological distress
- Increased suicide risk

Compared with our understanding of risk factors such as smoking and obesity, we know much less about the mechanisms through which loneliness and social isolation affect health.[41] There are two prevailing proposed mechanisms by which social relationships may influence health: the stress-buffering model and the main effects model. The stress-buffering model hypothesizes that real or perceived social resources "buffer" the individual from the deleterious influence of stressors on health. The main effects model proposes that high-quality social relationships have a more direct protective effect on health through mechanisms that are not explicitly intended to be supportive. For instance, social relationships may directly or indirectly encourage or discourage healthy behaviors that lead to better health

outcomes.[42] Emerging research has identified candidate neurobiological mechanisms, which include changes in neuroendocrine, cardiovascular, and inflammatory stress responses; elevated vascular resistance, and hypothalamic-pituitary-adrenocortical activity. However, there are significant gaps in our understanding of the impact of loneliness and social isolation on healthy behaviors, social resilience, and any underlying biological mechanisms. [43]

One area of study has been the impact of loneliness and social isolation on healthcare utilization. Both have been implicated in patterns of increased healthcare utilization. Socially isolated and lonely adults are more likely to undergo early admission to residential or nursing care. They have increased physician utilization and have been independently associated with higher rates of emergency hospitalizations and re-hospitalization within one year of discharge.[44]

109.6 REDUCING LONELINESS AND SOCIAL ISOLATION

A key question that remains open to discussion is whether loneliness and social isolation can be alleviated among older adults and whether alleviating these life experiences leads to improved health outcomes. Many factors that reduce loneliness and social isolation are cross-cultural (living with a spouse or partner), but others are culturally bound (e.g., discrimination and social marginalization). Sustainable solutions may need to be culturally appropriate and hinge on the degree to which an intervention improves an individual's social environment and social interactions. [45]

A variety of interventions have been directed toward alleviating loneliness and social isolation in older adults. These interventions have attempted to improve social skills (e.g., through social recreation), enhance social support (e.g., via mentoring, home visits), increase opportunities for social interaction (e.g., telephone outreach, nonverbal communication), and/or address maladaptive social cognition (e.g., psychological reframing or cognitive behavioral therapy).[46]

Researchers have developed six types of interventions that have been explored at a variety of levels: working with individuals, working with groups, service provision, technology-based, neighborhood, and social structures[47]. The heterogeneity of interventions and the multiplicity of measurement tools and outcome measures, alongside poor methodological quality and a focus on subgroups of the population, have all limited researchers' ability to draw definitive conclusions about the effectiveness of interventions.[48] Yet, because of the high prevalence of loneliness and social isolation in older adults and the suffering they cause, clinicians, health systems, and communities are in a perfect position to develop and test methods that identify loneliness and isolation and take steps to mitigate their ill effects.[49]

It is beyond the scope of this review to provide an exhaustive list of interventions and proposed approaches, but any number of specific examples can be found in the medical literature. These include the following approaches.

- Group-based interventions that target a specific group and focus on a shared interest (or on education) and include older individuals in the planning process.
- Improving access to "gateway services" such as transportation and technology that can improve social connectedness.
- "Befriending" approaches where volunteers or paid companions provide one-on-one outreach to high-risk individuals or those identified as socially isolated or lonely.
- Treating sensory deficits (vision and hearing loss) to improve the quality of social interactions.
- "Social prescribing" in which healthcare providers link patients with existing social services programs or facilitate those linkages. These services include volunteer opportunities, community groups, and faith-based organizations.

Models of Social Prescribing[50]

Model 1: Information Service

This service is an information-only service, with advertising and directory access to SP in a primary care practice

Model 2: Information Service and Telephone Line

This service advertises SP on leaflets and noticeboards in a primary care practice. Based on this information, patients can self-initiate a telephone discussion with a worker

Model 3: Primary Care Referral

Primary health care professionals assess patients during consultation and refer them to SP services if appropriate, for example, if patients have non-clinical issues and require psychosocial support. Referrals to SP services are opportunistic.

Model 4: Practice-Based Generic Referral Worker

Primary care patients can be referred by health workers or self-refer to an SP link worker. Clinics are held in the primary care setting so that they can act as a "one-stop shop".

Model 5: Practice-Based Specialist Referral Worker

A specialist worker works from primary care practice and patients can be referred through primary care referral or self-referral. Direct advice and specific services, such as Citizens Advice,[51] may be offered, as well as referral or signposting onwards.

Model 6: Non-Primary Care-Based Referral Worker

Patients are referred to an external referral center by primary care practice staff, offering one-to-one facilitation, for example, an outreach service or community-based resource center.

- Support groups that facilitate social interactions and/or focus on shared common underlying causes of social isolation such as bereavement or widowhood.
- Group activities to promote healthy behaviors or physical activities such as the US Department

of Veterans Affairs GeroFit program[52] or the SilverSneakers® fitness program for older adults.[53]
- Cognitive behavioral therapy may be useful in helping people suffering from loneliness to reframe the way they think about their relationships, their assumptions about others' views, or their expectations of success in overcoming loneliness.[54]
- Health system and payer-based, population health strategies that integrate communication technology engagement, befriending programs, and social hubs with community health workers to help people found to be socially isolated and engage them with social resources.

Though there is strong evidence that loneliness and social isolation pose a risk to the health of older adults, the evidence for effective interventions to mitigate their adverse effects is limited. The evidence base is, however, growing and there are numerous examples of interventions—both simple and complex—that are ripe for study and implementation.[55]

109.7 ENGAGED AND BEFRIENDED: IMPLICATIONS FOR HEALTHY AGING AND LIFESTYLE MEDICINE

In their influential archetype of successful aging, Rowe and Kahn proposed a three-part model in which one of the three key components is active engagement with life. Life engagement is a complex, multidimensional concept, but the Rowe and Kahn model emphasizes social interaction and productive activity. [56] The literature on loneliness and social isolation supports this emphasis and prioritization of social interaction as key to healthy aging.[57] There are numerous challenges to an engaged, supported, and socially fulfilling life across the lifespan. These include personal barriers, geographic barriers, social barriers, built environment barriers, and the inevitable losses experienced across the course of a life lived into old age. But opportunities abound to mitigate these challenges and there are many examples to follow. There are built environments and age-friendly communities that support social engagement and interaction. There are cultures of social engagement like blue zones, which promote quality relationships through active engagement with community, friends, and family. There are group activities, learning opportunities, and communities of faith that can open doors for those suffering from social isolation and loneliness or those who are at risk (which may be all of us). And there are our personal heroes who develop and nurture multigenerational relationships that are supportive and fulfilling and offer social support and resilience across their lifespan.

CLINICAL APPLICATION

- Evidence indicates that perceived social isolation and/or loneliness are significant risk factors for physical and mental illness in later life, with impact on par with other known risk factors such as obesity or tobacco use.
- Clinicians should consider assessing their patients for self-perceived loneliness and social isolation.
- Although a developing science, interventions to mitigate loneliness and social isolation exist for clinicians to implement and/or promote as mitigation strategies.

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110 Caregivers: Bringing the Invisible Patient to the Forefront

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KEY POINTS

- Caregiver burden is defined as the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical, and/or spiritual functioning.
- Many risk factors put caregivers at risk for burden, including female sex, low education level, residing with the care recipient, higher number of hours spent caring, and caring around transitions (e.g., hospital to home).
- The health outcomes of caregiver burden are substantial and include increased risk of depression, anxiety, social isolation, financial stress, weight loss, and death.
- Healthcare providers need to improve caregiver recognition and implement screening tools for caregiver burden.
- Resources exist to help with screening and educating caregivers to improve caregiver well-being and quality of life.
- Public policy is working at a national level to help gain recognition for caregiver burden and address it as a public health initiative.

110.1 INTRODUCTION

As Americans are living longer lives, many live more years with chronic, complex, medical conditions.[1] Management of multimorbidity is a lot for an individual to manage and often needs the support of a caregiver. The caregiver role is common, as one in six Americans can be classified as a caregiver for people over the age of 50 years.[2] Caregivers are prominent and crucial for the well-being of care recipients, yet they are under-recognized. Caregivers have been called the "Isolated Army"[3] or the "invisible patient".[4] Their under-recognition combined with the challenging task of being a caregiver leaves many caregivers stressed, strained, or burdened. This chapter outlines the importance of the public health issue of caregiver burden, including epidemiology, risk factors for burden, and potential health outcomes, and it provides screening tools and resources for the caregiver. Addressing caregiver burden involves principles that align with lifestyle medicine. It is a collaboration that requires the active participation of healthcare providers, their patients, and any caregivers involved in patient care.[5] Healthcare providers can use lifestyle medicine principles to recognize stressors in caregivers and provide individualized support.

110.2 EPIDEMIOLOGY

Caregiving is defined as providing any type of care to another person. Caregivers provide both physical care and emotional care to the care recipient.[6] Care recipients need ongoing assistance with everyday tasks on a regular or daily basis because of chronic illnesses or disabling conditions.[7] Caregivers provide as much as 90% of the in-home long-term care needed by adults in the United States, with their lost wages amounting to approximately $522 billion annually.[6,8] Older adults are the demographic that requires the most caregivers. In fact, 76% of care recipients are over the age of 65 and 25% are 85 years or older. As of 2020, one in six Americans, or 42 million Americans, are caregivers to someone age 50 or older. Additionally, 24% of caregivers care for more than one person. Sixty-one percent of caregivers are women and 62% of caregivers have another job aside from their caregiver role. Non-Hispanic Whites make up most caregivers to those 50 years and older (61%), followed by Hispanic/Latinx caregivers (17%) and then African American caregivers (14%). Five percent of caregivers are Asian American and Pacific Islanders and 3% are another race/ethnicity. Ten percent of caregivers 50 years and older served in the United States Armed Forces and 7% self-identify as LGBTQ.[2]

The average age of a caregiver is 50.1 years old with 56% over 50 years old and 20% over the age of 65. Most older caregivers are providing care to a relative (89%). The caregiver is often providing care to a care recipient who is a parent or relative who is 75 years old, male (60%), and who has multiple chronic medical conditions that are both physical and/or emotional. Memory problems also make up 35% of care recipient conditions that require caregiving. A majority of caregivers 50 years and older have health insurance that is usually provided through an employer.[2]

By 2026, the baby boomers will be in their eighth decade of life, and starting at this age, older adults need the most support and services for performing their activities of daily living (ADLs).[9] ADLs include bathing, dressing, ambulation, toileting, and feeding. Instrumental activities of daily

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living (IADLs) are more complex than ADLs and include food preparation, laundry and housework, transportation, telephone use, and managing finances.[10] Caregivers on average assist with 1.7 ADLs and 4.4 IADLS. Additionally, most caregivers aid with medical/ nursing tasks (59%).[2]

Not only do caregivers help with physical and emotional support in the home, but they are often their care recipient's advocate with healthcare providers, community services, and government agencies. In fact, 56% of caregivers report taking on the role of advocate. Women caregivers are more likely to communicate with care professionals (69%) than men and African American and Asian American caregivers are more likely to advocate than White caregivers (63% and 66% vs. 53%).[2]

Perhaps because of increased longevity, caregivers are spending more years in their caregiving role, with 28% providing care for five years or more as compared with 24% in 2015.[2] Most caregivers spent over 20 hours per week working to provide care and 20% of caregivers spent more than 40 hours a week providing care.[4] In the care recipients' last year of life, most caregivers spent up to 66 hours per week caregiving.[11] Many (37%) care recipients cohabit in their caregivers' households. Three in ten caregivers for those 50 years and older provide care on their own without help from anyone else.[2]

110.3 ABOUT CAREGIVING AND CAREGIVERS/CAREGIVER BURDEN

110.3.1 About Caregiving

Caregiving responsibilities include healthcare decision support, care coordination or management, medical and nursing tasks, physical care, emotional support, homemaking, and transportation.[6] Caregivers provide any type of care to another person informally and 90% do not receive financial compensation.[6,12,13]

There are many positive aspects of caregiving. Caregivers may feel emotionally rewarded because it can affirm family ties, honor past service the caregiver received from the person who now needs care, and save family resources.[4] Caregiving is associated with personal satisfaction in caring for another and providing comfort, feeling useful and needed, and may provide more meaning and purpose to life.[3] However, the role is highly individual and it can have a multidimensional toll on the caregiver.[14]

110.3.2 Terminology

Although there are significant associations with stress in the caregiving role, the term caregiver burden is controversial for its negative connotation. Many caregivers may prefer to be asked about their reflection on caregiving rather than the burden of it. A more positive term may be carepartner, especially when they are the spouse of the care recipient. This terminology puts caregivers at the same level as the care recipient instead of in a hierarchy with the care recipient. Instead of asking a caregiver about "burden", it may be wise to use the word "challenges" instead. This chapter uses the terms caregiver and burden throughout, but newer terms may come into favor.

The Healthy Caregiver Phenomenon explains that caregiving (without strain) is associated with decreased mortality. This may suggest that healthier persons are more likely to take on the caregiving role, or that the sense of purpose in the caregiving role may have a positive effect.[8]

110.3.3 Definition of Caregiver Burden

The definition of caregiver burden, or caregiver strain, was established in 1986. Zarit and colleagues coined the term caregiver burden to be, "the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical, and spiritual functioning".[4,8] Within the domains of physical, mental, and psychosocial health, the spectrum of stressors for caregivers can range from personal caregiving, chores around the home and transportation needs, to medical care, social care, advocacy, and financial support.[4,15] The strain of caregiving is significant to those caring for chronically ill older adults.[4] However, caregiver burden is not a one-size-fits-all definition, as many caregivers have different capacities for caregiving and different thresholds for feeling stressed or "burdened".[15] Ultimately, caregiver burden not only affects the caregiver but also the perceived quality of care from the recipient and may add to recipient anxiety.[3,16]

110.4 RISK FACTORS FOR CAREGIVERS AND POTENTIAL HEALTH OUTCOMES

110.4.1 Risk Factors

Although there are known benefits to being a caregiver, there is evidence of potential negative health outcomes when the caregiver role becomes very challenging. One-third of all caregivers describe a high burden of care.[3] There is increased stress and strain if the caregiver is not given the choice to assume the caregiver role. Less than half (47%) of caregivers 50 years and older report choosing to be in the caregiver role. Other risk factors for negative health outcomes for caregivers include:[2,4]

- Lower level of education (associated with the highest levels of caregiver burden in many conditions)
- Female sex (twice that of men)
- Low level of education
- Residing with the care recipient
- Higher number of hours spent caring
- High or increasing care needs
- Caring around transitions (e.g., hospital to home)

Caregivers who have an annual household income of less than $50,000 provide more care than those with higher incomes (26.4 hours a week versus 20.1 hours, on average).

Caregivers of color report higher weekly hours of care than White caregivers.[2]

110.4.2 Potential Health Outcomes

Health outcomes of caregiver burden include: [4,17]

- Depression
- Anxiety
- Social isolation
- Financial stress
- Weight loss
- Suicide

Many caregivers have other employment, and there is a significant risk that the caregiving role may take priority over regular employment. Perhaps most alarming is that caregiver burden is identified as an independent predictor of mortality. In fact, compared with non-caregivers, caregiver burden increases the risk of death by 6.3%.[4]

110.5 CARING FOR PERSONS WITH SPECIFIC CONDITIONS

Compared with younger care recipients, older care recipients are more likely to have memory problems or long-term health conditions, while younger care recipients more commonly have emotional or mental health issues or short-term physical conditions.[2] Multimorbidity, or having multiple chronic medical conditions, is also prevalent among care recipients. On average, caregivers are caring for recipients with 1.7 chronic conditions.[2] It is important to study caregiver burden in the context of specific chronic illnesses, as knowing the primary disease of the care recipient can help predict caregiving challenges. Caregivers should partner with physicians in the care of patients to understand the individual approach to specific illnesses. However, physicians alone cannot be the only source of support. An interdisciplinary collaboration, often with social work colleagues at the forefront, is crucial to creating individualized care plans to address caregiver burden.[4]

The following will investigate specific caregiving roles for two chronic illnesses: dementia and cancer. This section will also discuss caregivers with chronic illnesses and the role caregiving has on their own self-care.

110.5.1 Dementia

Caregivers report that 35% of their care recipients have memory concerns.[2] When asked the main challenge of caregiving, 4% of caregivers report that Alzheimer's or other dementias are the care recipient's main challenge.[2] Challenges include behavior disturbances, intense physical tasks, and continued monitoring of care recipients.[3] However, caregivers not only have to manage the disease and associated memory and behavioral changes but also have to manage the loss of the relationship with the person their care recipient used to be.[18]

Dementia patients require more help with their ADLs compared with those without dementia.[2] Support groups or psychoeducational interventions for caregivers of individuals with dementia are helpful to prevent and manage caregiver burden.[3,4] Education through home and telephone-based sessions provides positive supports and tools for caregivers.[3] Multicomponent interventions including education and resiliency training can reduce caregiver burden and improve quality of life.[19] Pharmacologic interventions (that manage the patient's dementia or dementia-related behaviors) reduced caregiver burden.[4] Preferable to medications, caregivers for dementia patients who practiced self-compassion and emotion-focused coping strategies, such as acceptance and emotional adaptability, had lower depression and anxiety.[18]

110.5.2 Cancer

More than half of informal caregivers provide care for older cancer patients (over 65 years).[16] They must provide cancer-specific care, such as monitoring for treatment side effects, managing side effects, and administering medications.[3,20] In one cohort study looking at caregiving for cancer patients, half of the caregivers felt ill-prepared to care for their care recipient's cancer-specific needs and a quarter of those caregivers reported low confidence in the quality of care they provided.[20]

Since cancer is so diverse and personalized, interventions and supports should also be personalized and scalable to reduce caregiver burden across the cancer trajectory. However, with the unpredictability of cancer, many caregivers express concern with the lack of control over their care recipient's illness. Most cancer caregivers are not prepared for the intensity of their role. Caregivers report 22% worse physical health secondary to caring for a cancer patient although they reported good overall quality of life. Twenty-eight percent of caregivers who are caring for their spouse with cancer reported psychological distress.[16]

Cancer patients with greater symptoms or poor performance status resulted in caregivers reporting lower quality of life. One study of lung cancer patients revealed when patients had more symptoms (physical or psychological), it resulted in increased caregiver burden.[16,21]

A meta-analysis of psychoeducational interventions, skills training, and therapeutic counseling for caregivers of cancer patients showed caregiver burden was reduced, but the improvements in caregiver burden were lost with time.[4] Digital engagement and technology-based interventions include:[16]

- Smartphone applications
- Websites
- Multimedia
- Electronic health record patient portals
- Online peer support network
- Visual mobile system
- Online symptom reporting system

These resources provide information facilitation, caregiver social support, and multicomponent caregiver support. A review of this technology showed that these technology-mediated interventions improved cancer caregiver outcomes, including knowledge, self-efficacy, caregiving satisfaction, burden, emotional well-being, and quality of life.[16,22]

Studies have shown that an interdisciplinary palliative care team, educational sessions, and self-care plans, helped reduce the caregiver burden in caregivers for cancer patients.[23]

110.5.3 Caregivers with Chronic Conditions

By nature of the prevalence of chronic disease and the older average age of most caregivers, caregivers may have their own health issues that they must juggle while caring for their care recipients.[2] We know that a caregiver's health and well-being are critical to providing quality care and allowing for the care recipient to remain at home.[3] Most (74%) of caregivers over the age of 50 report that caregiving has not affected their own health, however, 21% of caregivers report that their health is worse from providing care and 5% of caregivers feel their health has improved with caregiving.[2]

When caregivers are burdened, they have a higher risk of serious illness and are less likely to engage in preventative care for themselves.[3] One paper details caregivers with diabetes and the potential toll caregiving takes on managing their own diabetes. The study revealed that when caregivers are strained, they have lower medication adherence with their diabetic regimen. The rationale is that caregivers have less time to manage their own health and well-being when they are caring for another person.[8]

110.6 SCREENING CAREGIVERS

There is a lot of room for improvement in caregiver screening. Only one-third of caregivers recall being asked by their provider about their role; even fewer are asked about what they need to help themselves.[12] In order for providers to manage any issue, it needs to be brought to the provider's attention. Many caregivers may not think to direct the time and attention of the patient's provider to the caregiver's needs. Therefore, healthcare providers need to initiate the conversation to improve recognition of the caregiver burden.

Many resources are available to help providers ask caregivers the most appropriate questions. Questionnaires can help identify caregivers and then determine the level of stress experienced. By simply asking these questions, providers may make caregivers feel seen and supported.

Assessment of caregivers should be performed by a primary care provider or another healthcare team member. These assessments should be triggered once a caregiver is suspected or a patient has an illness that requires a high degree of care or care that the provider can identify needs additional support. Ideally, caregivers and care recipients should be interviewed together and separately to get more accurate responses.[3]

Initial screening questions:[6]

1. Do you provide care to another adult loved one? Who is the adult (friend, spouse, etc.)?
2. Do you feel strained when you are around your loved one?
3. Do you feel you have lost control of your life since you started providing care for your loved one?
4. How burdened do you feel caring for your loved one?

Screening questions to assess caregiver well-being:[15]

1. Can you tell me how you are doing with your caregiver responsibilities?
2. Are there times when you need help but are hesitant to ask?
3. Do you know about community resources that could help support you as a caregiver?

There are many different screening question templates. Table 110.1 has information on different options. It is

TABLE 110.1
Caregiver Burden Screening Tools and Questionnaires

Resources:	How to Access:
The American Psychological Association[6]	www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools
The Hartford Institute for Geriatric Nursing[6]	consultgeri.org/try-this/general-assessment/issue-14
Caregiver Self-Assessment Questionnaire (online; self-assessment)[6]	www.healthinaging.org/tools-and-tips/caregiver-self-assessment-questionnaire
Zarit Caregiver Burden Interview[26]	Zarit, S. H., Reever, K. E., Back-Peterson, J. Relatives of the impaired elderly: correlates of feelings of burden. *The Gerontologist*. 1980;20:649–655.
Table 2 of Adelman et al. titled, "Topics and Selected Questions for Caregiver Assessment" [4,26–28]	Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS. Caregiver burden: A clinical review. *JAMA*. 2014;311(10):1055
The CARE Framework [29]	Holliday A, Quinlan C, Schwartz A. The hidden patient: The CARE framework to care for caregivers. *Journal of Family Medicine and Primary Care*. 2022;11(1):5. doi:10.4103/jfmpc.jfmpc_719_21

advised to use the template that works best for the provider in terms of length and detail.

110.7 ADDRESSING CAREGIVER BURDEN USING THE PILLARS OF LIFESTYLE MEDICINE

Caregivers want information from their healthcare providers about caregiving and self-care.[2] Most (63%) caregivers report interest in obtaining more information on or help with caregiving topics. Despite that, fewer than 30% of caregivers report that healthcare providers have asked them about what they needed to care for their recipient and 13% report that healthcare providers have asked them what they need to care for themselves.[2] As patients need to be engaged and motivated to promote good health, their support system, which may heavily rely on caregivers, must also be enthusiastic and invested.[5]

110.7.1 Pillars of Lifestyle Medicine and Caregiver Burden

The pillars of lifestyle medicine have been studied to evaluate their relationship to caregiver burden. The results of the findings are discussed here:

- *Tobacco.* It is unclear if tobacco use is associated with caregiver burden.[8] However, there is evidence that when caregivers are stressed, they are more likely to use tobacco.[24]
- *Alcohol and other substances.* Similar to tobacco use, binge drinking was seen in stressed caregivers for cancer patients.[24]
- *Nutrition*. Surprisingly, the literature suggests that some caregiver strain resulted in higher adherence to the Mediterranean diet.[8] Increased adherence may be due to caregivers eating similar diets recommended for their care recipients as caregivers may not have time to prepare separate meals for themselves if they are overwhelmed.
- *Physical activity.* Many caregivers 50 years and older (17%) report high physical strain as a result of caregiving.[2] Caregivers with diabetes have lower levels of physical activity.[8] Enrolling in aerobic exercise programs has been shown to reduce caregiver burden and depression.[25]
- *Weight*. Caregiver burden is associated with weight loss.[4] Two possible mechanisms include 1) caregivers may have unintentional weight loss because they are too consumed with caregiving responsibilities to eat enough calories or 2) caregivers may be healthily losing weight because, as mentioned above, they may be eating more healthily.
- *Stress*. Caregiving was reported to be highly emotionally stressful for 36% of caregivers 50 years and older.[2] Stress was directly related to the number of hours spent caregiving and was increased when caregivers were balancing another job while caregiving.[4] Caregivers have increased stress if they are African American, make less than $30,000 per year, co-reside with their recipient, provide care to spouse/partner, or have difficulty affording services for their care recipient.[2] Many caregivers are unpaid and many report increased financial strain (42%).
- *Sleep.* Caregivers have higher rates of insomnia compared with non-caregivers.[3] Many caregivers of cancer patients (23%) report not sleeping enough to feel rested.[24]
- *Emotional well-being.* Caregiver burden increases anxiety, depression, suicide, and death.[3,4] Loneliness is reported in 21% of caregivers 50 years and older.[2] Interestingly, 51% of caregivers feel their role as caregivers gives them a sense of purpose or meaning in life.[2]

Table 110.2 presents examples of available resources to address caregiver burden within each pillar of lifestyle medicine.

There are many other resources for caregivers aside from the above-described. There are many technological resources and apps to help caregivers. AARP.org has many of these options available. Technology ranges from using programs to help organize lists and calendars to websites that help order transportation services without a smartphone.[3]

110.8 CURRENT PUBLIC POLICY TO ADDRESS CAREGIVER BURDEN

Public policy can shape the future of the psychosocial and financial burdens of caregiving in the United States. Most developed countries offer mandatory paid leave, and the United States is starting to show an interest in providing more support to caregivers. The Family and Medical Leave Act now allows employees to take up to 12 weeks of unpaid leave to provide caregiving needs. In nearly every state, care programs, mostly supported by Medicaid, exist for informal caregivers to be paid for the services they provide.[3]

Below are some other advocacy initiatives supportive of caregivers:[6]

1. The Recognize, Assist, Include, Support, and Engage Family Caregivers Act (RAISE) (https://acl.gov/sites/default/files/about-acl/2018-10/PLAW-115publ119%20-%20RAISE.pdf).
2. The RAISE Act, which became law on January 22, 2018, created the RAISE Family Caregiving Advisory Council, managed by the Administration on Community Living (ACL).
3. The ACL webpage for the Advisory Council is https://acl.gov/programs/support-caregivers/raise-family-caregiving-advisory-council.

TABLE 110.2

Using the Pillars of Lifestyle Medicine to Address Aspects of Caregiver Burden[10,30]

Lifestyle Pillar	Resources for Caregivers:
Tobacco	*Smoking cessation*: CDC: www.cdc.gov/tobacco/quit_smoking/index.htm The American Lung Association: www.lung.org
Alcohol and other substances	*Alcohol use reduction/cessation*: Alcohol reduction: www.rethinkingdrinking.niaaa. nih.gov/thinking-about-a-change/strategies-for- cutting-down/tips-to-try.aspx Alcoholics Anonymous: www.aa.org/
Nutrition	*Access/ resources to adhering to the Mediterranean diet*:[5] oldwayspt.org/traditional-diets/mediterranean-diet/ Mediterranean-diet-resources • Schedule meal delivery by family, friend, or organizations:[15] www.mealsonwheelsamerica.org/ *Cookbook*: *Blue Zones Kitchen: 100 Recipes to Live to 100*, by Dan Buettner
Physical activity	*Set up the right environment to thrive:* AARP age-friendly communities: www.aarp.org/livable-communities/network-age-friendly-communities/ Blue zones replications:[5] www.bluezones.com/services/blue-zones-project/#section-2 *Exercise*: Health Moves: home-based exercise program: www.ncoa.org/resources/program-summary- healthy-moves-for-aging-well/ Go4Life: www.nia.nih.gov/health/exercise-physical- activity NCOA: recommended exercise programs (Active Choices, Health Moves) • Virtual exercise classes through youtube.com
Weight	• Refer to resources in the nutrition, sleep, and stress sections.
Stress (including financial stress)	*Respite services/day programs*: Eldercare locator: https://eldercare.acl.gov/ National Adult Day Services Association: www.nadsa.org *Help with transportation*: Area Agency on Aging:[6] http://n4a.org/about-n4a/?fa=aaa-title-VI • Utilize telehealth and mail order pharmacies[15] • Early involvement in palliative care for patients with serious illnesses[3] *Financial/legal support*: National Academy of Elder Law Attorneys: www.naela.org/findlawyer National Alliance for Caregiving: www.caregiving.org/resources
Sleep	*Sleep hygiene*: • Aim for seven to nine hours of restful sleep www.cdc.gov/sleep/about_sleep/sleep_hygiene.html *Phone applications*: • Avoid screen time but use a smartphone to access applications that have guided meditation before bedtime (Headspace, Sleepio, or Calm). *Respite*: National Institute on Aging: www.nia.nih.gov/health/what-respite-care
Emotional well-being	*Books*: *The Soul of Care*, by Dr. Arthur Kleinman *The Gerontologist* volume on caregiving: "Aging—It's Personal" (https://academic.oup.com/gerontologist/issue/57/1) Caregiver support groups (in-person or online):[15] Family Caregiver Alliance: http://caregiver.org Online resources for caregivers: AARP's Prepare to Care: A Planning Guide for Families[31] (www.aarp.org/home-family/caregiving/) Alzheimer's Association tools (useful for caregivers managing care recipients of any disease): www.alz.org/care/alzheimers -dementia-online-tools.asp American Cancer Society: www.cancer.org/treatment/caregivers.html

4. SAGECAP is an expansion of SAGE which provides support and advocacy for lesbian, gay, bisexual, and transgender older adults. SAGECAP was launched to support caregivers. The focus is on New York City and Baltimore (www.sageusa.org /resource-category/caregiving/).

110.9 CONCLUSION

Caregiving is a common role for Americans and although many caregivers are comfortable in their roles, many experience stress and feel unsupported. When caring for patients, healthcare providers need to improve on recognizing

caregiver burden. Individualized approaches to supporting caregivers can be taken based on healthcare providers' practice, the needs of the caregiver, and the health of the care recipient. Many concerns from the caregiver can be addressed using lifestyle medicine approaches. More information, resources, and policies are available now more than ever on supporting the caregiver, and healthcare providers can enable caregivers to improve their quality of life, which will translate to better care for patients.

CLINICAL APPLICATIONS

- Caregiving is defined as providing any type of care to another person and caregiver burden is defined as the extent to which caregiving has a negative effect on the caregiver.
- Caregiver burden increases depression, anxiety, stress, suicide, and death.
- Existing questionnaires and tools can be utilized to increase healthcare provider screening and the recognition of caregiver burden.
- Many resources exist to help caregivers who are experiencing caregiver burden and newer resources rely on technology to address burden.

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Part XIX

Health Promotion



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111 Introduction to Health Promotion and Lifestyle Medicine

Jane Ellery, PhD and Dee Edington, PhD

KEY POINTS

- Evidence shows that health promotion and lifestyle medicine practices can positively impact patient health. Encouraging patients to make meaningful changes is difficult, but highlighting the value of the investment, using motivational interviewing, and introducing appropriate digital applications can help nudge them toward healthier behaviors.
- Environments matter, and our built environment typically detracts from rather than promotes good health. Working collaboratively to reshape our environments, including diverse teams of professionals and the individuals who will benefit from the intended changes, is key to behaving differently.
- Changing behaviors to encourage healthier living will require a collective effort. As physicians become more adept at using digital tools, and at working with both traditional and non-traditional health professionals in workplace, school, and community settings, new tactics for change will emerge.

This health promotion section is a primer for physicians who are committed to lifestyle medicine in service of their patients. You are likely in this field of health and healthcare because you are passionate about helping others. By focusing on a lifestyle medicine approach to your practice, you are taking steps to introduce and encourage lifestyle changes when appropriate. This step beyond more traditional medical therapies is not an easy task in a medical system that financially supports physicians who do things *to* sick people instead of rewarding practices that promote good health. Our collective challenge is to shift both thinking and practice so we develop a new system that also champions doing things *for* people, *with* people, and empowers people to do things *by themselves*. The chapters in this section will help you think through this *to…for…with…by* strategy.

First, we have to make sure that people stop getting worse! Dr. Dee Edington's landmark book, *Zero Trends: Health as a Serious Economic Strategy*,[1] reminded us that everyone needs to stop getting worse before we can start getting better. By bringing together insight from years of research and data collection, this book expanded our understanding of the benefits of active living and good nutrition. It presented evidence to support how being active, eating well, connecting with others, and creating built and social environment conditions that allow us to take action on our intentions and aspirations are important to healthy living. We also know that different people have different needs when it comes to physical, social, and environmental health and that they have varied resources and opportunities available as they work to adopt healthier habits.

Actions taken on behalf of patients when they have acute, immediate needs are an important part of the healthcare continuum. Doing things *to* people in our emergency departments, crisis management centers, and operating rooms is imperative to survival; and these actions represent a valuable part of our *to…for…with…by* strategy that is not addressed in this health promotion section. The remaining categories, *for…with…*and *by*, come into play when you work with your patients to co-produce long-term solutions that support the primary, secondary, and tertiary prevention needs often associated with health promotion and lifestyle medicine practice.

The chapters in this section focus on evidence-informed thinking designed to help you expand your practice strategies in ways that will allow you to view your patients as a compilation of everything that they have experienced up to that point in their lives and everything that they experience each day in their current environment. We must treat the whole person. We also must encourage change in ways that make sense in the world in which your patients live, keeping in mind that their worlds likely look very different from how you experience the world.

We may not have definitive answers for you, but we can share what we have learned. Our hope is that you can take this knowledge, build on it, talk with your patients and peers, and find meaningful opportunities to have a positive impact on your patients. Here are highlights of how each chapter contributes to this.

In Chapter 118, Parkinson and Doyle introduce a concept of population health that has emerged at the intersection of public health and medicine. They remind us to move beyond viewing wellness and health promotion efforts as an investment in reducing the cost of medical treatment. Instead, we should view our health and wellness-related efforts as an investment in the value these initiatives bring to individuals and the contributions each individual brings to the world. They also highlight the opportunities that

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emerge when considering epigenetics, the microbiome, and neuroplasticity; the importance of the mind–body connection; and the role that our built environment and our personal choices play in our overall health.

The Ellerys expand on built and social environment concepts, in Chapter 114, to encourage co-produced change and a shift in thinking that includes a focus on salutogenesis and a sense of coherence in addition to our more traditional pathogenic concentration. This involves shaping the environment in ways that inspire a good life in a safe and nurturing setting as well as promoting activities that help people keep from getting sick. It also encourages diverse teams of practitioners, including planners, employer groups, and individuals who are working to make the changes, to come together to develop and deliver interventions. This chapter closes by drawing attention to the United Nations Sustainable Development Goals and the Healthy People 2030 Social Determinants of Health and how the principles presented in these collective visions can provide guidance as we think about healthier living.

Pitts and Schultz focus on behavior change in Chapter 112 by helping us understand what motivation is and how we can cultivate it among patients. They introduce us to the importance of intrinsic motivation and a compassionate frame of mind as we work to serve our patients. They also remind us of the value of being fully present and authentic during patient counseling, while allowing the voice of each individual to be part of the plan for change. One recommendation to enhance motivation is to use a collaborative, goal-oriented style of communication called motivational interviewing. This approach respects a patient's interests, values, and concerns. It also helps patients maximize their autonomy and freedom of choice while clarifying their strengths and aspirations.

In Chapter 117, Katch reminds us that biological variability is real and that many factors impact the magnitude of response to interventions. We often blame individuals for being non-compliant; however, age, disease conditions, ethnicity, concomitant medication, environmental variables, and genetics can also play a role in how individuals respond to treatment. He highlights the importance of the language we use and encourages us to adjust modalities if the expected positive responses are not achieved under the current treatment plan.

Chapter 113 highlights the rapidly changing digital technology landscape. Chown, Thibodeau, and Kirby draw our attention to the idea that technology can help us individualize our patient care approach. With digital innovations revolutionizing healthcare and allowing us to intervene in new ways, access to data and analytic tools provides predictive opportunities that were not available to us in the past. Wearable technologies provide new opportunities for personalization and for patient-centric care, and phone applications and websites provide participatory opportunities for our patients. Together, these digital tools can help bring health promotion, prevention, and wellness strategies to the forefront of our work, giving lifestyle medicine physicians new tools to use as they nurture individual behavior change efforts.

In Chapter 116, Shultz provides additional support for built environment change and for using technological innovations for measurement and communication. She also advocates having physicians take a more active role in health promotion. To do this, she encourages lifestyle medicine practitioners to consider the issues of health behaviors, environment, values, and culture while overcoming barriers such as disease orientation, reimbursement policies, and conflicting recommendations. As physicians become more adept at using digital tools, and at working with both traditional and non-traditional health professionals in workplace, school, and community settings, new tactics for change will emerge.

In Chapter 115, Burton provides a perspective on international health and lifestyle. As he recaps the emerging severity of chronic disease throughout the world, he reminds us that smoking and outdoor air pollution contribute to morbidity and mortality across the globe. Additionally, the World Health Association predicts depression will be the top cause of worker disability globally by the year 2030. He brings his chapter to a close by highlighting effective strategies that involve culture changes, health literacy, and a healthcare system that includes prevention, early detection, and healthy behavior change initiatives that can positively impact non-communicable diseases.

As a further insight into the potential of lifestyle change practices, we would like to draw your attention to reports and writings compiled by two recent Surgeons General, Dr. Vivek Murthy and Dr. Jerome Adams. In 2021, Murthy released *Protecting Youth Mental Health: The US Surgeon General's Advisory*,[2] stating, "If we seize this moment, step up for children and their families in their moment of need, and lead with inclusion, kindness, and respect, we can lay the foundation for a healthier, more resilient, and more fulfilled nation".[2] His related popular media book, *Together: The Healing Power of Human Connection in a Sometimes Lonely World*,[3] shares the value of connections and highlights three types of loneliness. These include: (1) intimate/emotional loneliness, a longing to share a mutual, trusted bond; (2) relational/social loneliness, a longing for quality friendships and social support; and (3) collective loneliness, the longing for a network or community of people who share a sense of purpose. Cultivating connections among individuals of all ages will start to help minimize our feelings of isolation and help mitigate the negative impact this isolation has on our health and well-being.

Also released in 2021 was the first Surgeon General report on economic prosperity, *Community Health and Economic Prosperity: Engaging Businesses as Stewards and Stakeholders—A Report of the Surgeon General*.[4] In releasing this report, Adams shares that "As a physician, I understand that health happens in communities. The fact is, our environment shapes the opportunities we have, and a lack of opportunity can mean poor health, education,

family and career outcomes".[5] The report focuses on how communities can become places that nurture health, wealth, and well-being and how businesses can help create value for themselves and their communities by helping create the conditions that will allow people to thrive. Highlighted in this report are robust examples of how diverse organizations and individuals can join together to strengthen community health and increase opportunities for all.

Collectively, we have to commit to finding solutions that will allow our patients to move past outsourcing the responsibility for their health to others, even if that is what our current healthcare system promotes. The chapters that follow can guide your thinking as you explore opportunities for evidence-informed, systems-based changes to help create the social and environmental conditions that will allow your patients to live meaningful, healthy lives.

CLINICAL APPLICATIONS

Action	Benefit
Work with your patients to find changes that fit their understanding of the world.	Involving your patients in developing plans that fit their worldview is an important consideration. Coaching, nudging, and reshaping environments can lead to lasting, meaningful change.
Individualize treatment plans.	Everyone is unique, lives under varied conditions, and responds differently to proposed treatments. Working together to find digital tools and using motivational interviewing as you co-produce individualized treatment plans empowers those who will benefit from taking action.
Think globally, act locally.	Following evidence presented across the globe is important in managing and mitigating the impact of poor lifestyle choices. However, all solutions are local, and the current physical and social environments will need to be considered when encouraging action for change.
Encourage connection and involve non-traditional partners.	As humans, we are built for connections, yet we live in environments that lead to deep isolation with most change tactics taking place in "silos". Intentionally developing intimate, social, and community relationships helps bring meaning to our lives and makes life worth living.

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112 Motivation as Medicine

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KEY POINTS

- While many factors influence unhealthy behaviors, intrinsic motivation is the active ingredient for a successful lifestyle change.
- Physicians are uniquely positioned to play an important role in helping patients create conditions for the motivation that can drive the lifestyle change process.
- Deep listening, compassion, and motivational interviewing are strategies that can strengthen the healing relationship between physicians and patients.

112.1 INTRODUCTION

By changing four aspects of the American lifestyle—poor diet, sedentary lifestyle, obesity, and smoking—we could see an 80% reduction in heart disease, a 90% reduction in diabetes, and a 60% reduction in cancer.[1] It is this powerful impact of lifestyle that led David Katz, Founding Director of Yale University's Prevention Research Center, to proclaim that "lifestyle is medicine".[2] While people face many challenges when attempting to improve health-related behaviors, a big factor is motivation—and physicians can be powerful motivators of positive change.[3] There are many ways physicians can help their patients find the motivation to live healthier lives, and medical practice guidelines recommend lifestyle counseling. Yet many physicians do not counsel patients on their lifestyles, and even when they do, they have varying degrees of success.[4]

112.2 BEHAVIORS

Behaviors are driven by numerous determinants including personal beliefs, attitudes, and motivation, as well as social, economic, cultural, and environmental factors. Unhealthy behaviors become habits by repeatedly meeting an immediate need. For example, people smoke to relieve stress and anxiety or eat poor or too much food for comfort or convenience. There is no lack of available information on healthy lifestyle choices. This is one of the most common frustrations of anyone in the health and wellness field. Unhealthy or risky behaviors have a significant impact on today's all too common chronic health conditions, but helping patients make behavioral changes can be a huge challenge. While many people want to lose weight, for example, they often have ambivalence or even animosity toward making actual lifestyle changes. Of course, it is not enough to know that change is needed or even wanted. Dropping old behaviors and persisting with new behaviors in spite of the biological, emotional, cognitive, environmental, social, and cultural forces that challenge our resolve is one of the most profound trials in life and one of the most promising opportunities for the practice of lifestyle medicine.

112.3 MOTIVATION

The Oxford English dictionary defines motivation as: "A reason or reasons for acting or behaving in a particular way. Desire or willingness to do something; enthusiasm". But motivation is nuanced in subtle but important ways. Self-determination theory (SDT)[5] is about human motivation and a core set of human needs that, when met, contribute to living a full and healthy life and make a primary distinction between autonomous motivation and controlled motivation. Autonomous motivation is what a person chooses to do for themselves while controlled motivation involves acting out of a sense of coercion or pressure. Autonomous motivation is associated with deeper learning, greater flexibility and creativity, and greater persistence in behavior change efforts.[6]

According to SDT, people are more autonomously motivated to change their diet or quit smoking if they believe it will help them achieve a valued health outcome. The more autonomous and self-determined the motivation for a behavior, the more likely it will be to persist. Controlled motivation includes the classic "carrot" or "stick" incentives. Telling patients that they will live much longer if they stop smoking (carrot) or using fear tactics like telling them to stop smoking or risk dying of lung cancer (stick) can both be experienced as very controlling. Both involve external pressure or coercion, and both can undermine individual autonomy. Because the impetus for these behaviors is external, it does not feel authentic and fully integrated.

There are two types of autonomous motivation: intrinsic motivation and fully internalized extrinsic motivation. Intrinsic motivation involves doing things purely for their own sake. When we are intrinsically motivated, we function with a high degree of autonomous motivation and we endorse what we are doing and operate at a high level of self-awareness. We understand ourselves in relation to the world at that moment and operate authentically.

Fully internalized extrinsic motivation is different but just as important as intrinsic motivation. As we all know, the realities of life require that we often do important things that we do not find inherently interesting and enjoyable.

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Under certain conditions, these external demands can become internalized and integrated into who we are. Integrating an extrinsic prompt is an active process that people must do for themselves and involves identifying the importance of the behavior and integrating it into who they are as human beings.

112.4 EXTRINSIC TO INTRINSIC MOTIVATION

The transition from controlled (extrinsic) to autonomous (intrinsic) motivation can be difficult. Physicians must understand what blocks or erodes a patient's motivation and how to create conditions for successful behavior change. They must also understand what fuels motivation and help patients cultivate their own autonomous and self-determined motivation to engage in healthier lifestyles. This is a skill that is fast becoming a core part of the practice of lifestyle medicine.

By adopting a need-supportive approach, physicians can help patients adopt and internalize healthier lifestyle behaviors. Studies have shown that autonomy support by health care practitioners affects patient motivation and health behaviors, including smoking abstinence,[7] weight loss,[8] diabetic glucose control,[9] and medication adherence.[10] Autonomy support includes asking about and recognizing the preferences and perspectives of patients, offering them choices about treatment options, and giving them relevant information while taking care not to use too much pressure or be too controlling.

112.5 WILLPOWER

In addition to motivation, patients need willpower (i.e. self-control or self-regulation) to choose and maintain healthy habits. Willpower is the energy or will to do the positive things that some part of us does not really want to do, or resist doing negative things that some part of us really wants to indulge in. A popular theory describes willpower as a muscle that can become fatigued if it is overused, but also strengthened through exercise.[11] Many things deplete that source of willpower energy on a daily basis including lack of sleep, resisting temptations to snack, focusing on difficult mental tasks, dealing with difficult people, and many other tasks that require self-control. When depleted, dieters are more likely to eat poorly[12] and smokers smoke more.[13] Habits require less energy, so they are an important strategy for conserving willpower.[14]

112.6 PHYSICIAN INFLUENCE AND STRATEGIES

In the traditional doctor-patient relationship, physicians are seen as experts, and their role is to give advice or administer some form of treatment to the patient. The role of patients often includes being passive recipients of advice and faithfully executing physicians' recommendations. This approach can be felt as controlling and results in passivity or resistance from patients. Likewise, simply giving patients advice to change can be unrewarding and ineffective. Developing strong interpersonal relationships with patients is crucial to effective lifestyle medicine. Physicians must be fully present and authentic in their patient counseling because patients can feel it when physicians truly care about them. They can tell when they are genuinely heard and understood, and when their preferences and needs are respected.

Having a compassionate frame of mind during encounters with patients is also critical. Compassion is at the heart of quality medicine and is comprised of two components: 1) feeling for another person who is suffering and 2) being motivated to help them. Treating patients compassionately has wide-ranging benefits, including improved clinical outcomes, increased patient satisfaction, and enhanced information gathering.[15] Cultivating compassion could be better incorporated into medical training. Physicians can be trained to see patients with a greater sense of generosity, ask what might be driving and supporting patients' poor behaviors, or identify their willingness or ability to change.

Genuinely curious listening is another important part of developing a strong connection with patients. Active listening involves factual listening to learn new information, empathetic listening to see through another person's eyes, and generative listening, which requires setting aside one's own agenda and connecting with the conversation.[16] This type of listening can transform people and their motivation to change. Helping patients tie behavior change to some greater purpose in their lives is also helpful. If patients can name for themselves how the behavior change can help serve a greater purpose they care about, intrinsic motivation will be stronger.

Motivational interviewing (MI) is another approach to enhance patient motivation to change poor lifestyle behaviors. This is a collaborative, goal-oriented style of communication focusing on the patient's point of view, and respecting their interests, values, and concerns.[17]

MI has been effective for many types of change including hypertension control[18] and increased intake of fruits and vegetables.[19] The principles of MI include understanding and accepting patients' perspectives and situations, emphasizing any incongruity between present behavior and goals, changing strategies to assist patients with change, and supporting patients' confidence in their ability to make changes or achieve goals. With MI, physicians work to maximize patient autonomy and freedom of choice, while minimizing resistance to change. They help patients clarify their strengths and aspirations (goals), explore their values, develop their own reasons for change, and collaborate with patients to outline effective change strategies.

MI involves four processes that may occur simultaneously. These include engaging (establishing a connection), focusing (clarifying the direction that a change goal might take), evoking (eliciting a patient's own motivation for change), and planning (details about when and how to change). MI is achieved by developing five communication

skills. These are: asking open-ended questions, affirming the patient's personal strengths and resources, reflective listening which restates what was shared, summarizing the discussion and insights, and offering advice in line with the patient's perspective and needs.

Powerful ways to deepen intrinsic motivation to change unhealthy lifestyles is to help patients tie behavior change to some greater purpose in their lives: engage in empathic and compassionate inquiry to determine what matters most in patients' lives; look for what animates them, what they care most about; help patients name for themselves how the behavior change can help serve this greater purpose; and help patients purposefully connect to their purpose and values in the moment of temptation and bring to mind the short-, moderate-, and longer-term consequences of their actions. Eating the donut may feed an immediate emotional craving (short-term), but sap the energy needed for spending quality time with family later in the day (moderate-term), undermine a goal to finish that long overdue project, or shed the two pounds that would help them feel better in the long-run.

112.7 CONCLUSION

Lifestyle medicine physicians can play a large role in helping patients make healthy lifestyle choices such as regular exercise, adherence to preventive services, consuming a healthy diet, and other behaviors. One important factor is developing intrinsic motivation rather than extrinsic motivation for behavior change. Some strategies for doing that involve understanding the nature of motivation and situational barriers that exist. Deeper healing relationships can be developed through active listening, motivational interviewing, strengthening willpower, and improving compassion. Overcoming the traditional doctor-patient dynamic of giving generalized advice to a patient who is resistant to control is challenging. Forming stronger bonds with patients requires a genuine caring attitude that is conducive to helpful conversations and counseling so that physicians and patients can work together to make plans for improving health behaviors.

CLINICAL APPLICATIONS

- Physicians can be supportive guides that help strengthen patients' motivation to change unhealthy lifestyle behaviors with a better understanding of the nature of motivation and the fundamental human needs that fuel it.
- Embracing a need-supportive approach to helping patients adopt and internalize healthier lifestyle behaviors is key.
- Using motivational interviewing methods can help patients cultivate their own autonomous and self-determined motivation to engage in healthier lifestyles.
- Helping patients understand and strengthen their willpower and more wisely choose their willpower battles can be aided by deep, curious, and authentic listening during patient encounters.

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113 Hybrid Health Promotion: Patient-Centric Digital Tools to Support Healthier Lifestyles

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KEY POINTS

- Advancements in technology, along with the COVID-19 pandemic, have resulted in significant growth and innovation in digital health, including in workplace health and wellness programs.
- Digital healthcare (including telehealth and telemedicine) will continue to remain an important part of the healthcare system.
- Healthcare providers should learn about and promote digital health technologies as a facet of healthcare, especially due to its accessibility, simplicity, and more frequent capacity to influence positive health behaviors.
- Healthcare providers can leverage digital tools from the private sector to supplement care for the best interest of their patients and the broader healthcare system.

113.1 INTRODUCTION

Digital health is a broad term that encompasses technologies and their application in health, including e-health, m-health, telehealth and telemedicine, wearable devices, digital therapeutics, and health information technology.[1,2] The addition of digital health to existing health infrastructure had been slowly evolving for many years, due in part to a lack of funding and resistance—primarily from healthcare providers. However, the COVID-19 pandemic accelerated change and led to a substantial increase in innovation and utilization.[6] Although continued growth of digital health relies on a multi-sectoral effort that spans local to global levels,[4] trends strongly suggest that it will strengthen its position as a vital aspect of the health ecosystem, as evidenced by its inclusion in major organizational roadmaps such as The World Health Organization Global Strategy on Digital Health 2020–2025.[40] Digital tools can supplement the care clinicians provide and may establish better methods of healthcare planning, delivery, safety, and quality.[5] Thus, knowledge and recognition of digital health technologies are essential for all healthcare practitioners.[6]

Societal challenges, especially attaining buy-in from existing institutional healthcare stakeholders, have been asserted to be a bigger challenge to adoption than the scientific or technological challenges.[7] Recent evidence supports this as a large proportion of clinicians recognize that digital health is the future but have concerns about how it changes the role of the clinician and the way care is delivered.[6] Irrespective of opinions toward digital health, it is *happening* and many health professionals and patients across the globe are embracing health applications and devices. As stated by Dr. Keith Horvath in reference to artificial intelligence (AI), the following could be more broadly applied to digital health technologies: "AI is not going to replace physicians, but physicians who use AI are going to replace physicians who don't..."[8] Staying current on this frontier is crucial for physicians practicing lifestyle medicine.

113.2 INNOVATIONS IN DIGITAL HEALTH

Investments in digital health have escalated, and new opportunities for innovation within the digital health space have been realized. In fact, the first half of 2021 saw almost $15 billion in venture capital investment in the United States—nearly two times that of the entire 2019 year.[9] The top three funded clinical indications were mental health, cardiovascular disease, and diabetes.[9] Heavily prioritized due to COVID-19 restrictions was virtual care, such as telehealth and telemedicine services, with reports of usage approximately 40 times higher than pre-pandemic levels.[3,10] An increase was also seen in AI applications within healthcare and services, such as digital diagnostics to detect health conditions, as well as wearable technologies and wellness apps.[6,11] Many health and wellness services thought not to be adaptable to remote settings were reimagined, an example being virtual fitness solutions. As such, expected trends in digital health include further uptake of AI and machine learning, telehealth and telemedicine, augmented and virtual reality, wearables and Internet of Things (IoT), and wellness apps.[12–14] Importantly, these innovations can be delivered in various ways, from primary care physicians to workplaces/work plans and communities. Taken together,

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innovation in digital health provides new methods for accessing and delivering health support and services.

Advancements in digital health technologies should not only increase availability and access but should also give rise to additional avenues for user engagement. A popular method for increasing health engagement is gamification, which is the application of game design elements to motivate positive health behaviors.[15–17] Benefits of gamification in health and wellness, as noted by Johnson et al. (2016), may include the following: intrinsic motivation for lasting health behavior change; broad accessibility and everyday life fit of smartphones and wearables; appeal of games; applicability for different health conditions and risks; cost-benefit efficiency; and support for overall well-being through accomplishment and engaging relationships with others.[15] The inclusion of gamification is well-represented in health and wellness programs, whose shift toward technology-focused solutions to improve structure and delivery preceded COVID-19.[18] Digital health companies are filling this need by delivering engaging digital experiences that employ gamification to support individuals on their health journeys. For example, Carebook Technologies creates meaningful and engaging experiences from health assessments to interventions that integrate health challenges, self-directed programs, and coaching with digital tools, such as wearables and digital therapeutics. Such digital health and wellness programming allows individuals and organizations to prioritize action, track progress, and evaluate impact over time in a more accessible, personalized, and data-driven manner. Engagement is a typical metric for the success of health and wellness programs, and as more individuals and organizations adopt hybrid and remote solutions, continued research and development in this space will lead to further innovation in digital health technologies.

113.3 DIGITAL HEALTH: GAINS AND BARRIERS

Digital health offers many gains to individuals, organizations, communities, and systems. With projected challenges of population health and health systems that range from healthcare provider shortages to growing aging populations and increases in chronic condition prevalence,[19,20] an opportunity exists for the private sector to play an important role in the complex web that is the healthcare system.[21,22] Over the last few decades, successful programs have arisen when multiple sectors have joined forces. An example that led to effective health promotion initiatives was the collaboration between CoreHealth Technologies (part of the Carebook family) and the Government of British Columbia (Canada). ActNow BC utilized CoreHealth's technology as the central hub for programs and communications to run and track a province-wide activity challenge, as well as to pilot an Integrated Health Network with allied health teams. Advantages to these alliances are continuing to be explored, as seen from patient-centered medical homes (US), which act in sharp contrast to more traditional siloed care that typically lacks continuity and is oftentimes incomplete. Considering that 90% of healthcare leaders agreed that patients are looking for integrated journeys instead of single services,[23] the implementation of digital health is beneficial for population health and health systems at large.

Over the years, health solutions have become more encompassing of the whole self by assuming a holistic approach that considers multiple dimensions of health and wellness targeting nutrition, physical activity, smoking cessation, sleep, financial well-being, stress, mental health, and communicable and non-communicable diseases.[24,25,26] By ensuring people have access to timely, personalized, and accurate lifestyle and health information—along with the tools to help them build healthy habits—digital tools establish ways for individuals to think about their health more often and be empowered in their health and wellness decision-making.[4] For healthcare providers, the relationship with patients will continue to transition to a partnership in health instead of the previous paternalistic approach.[6] In this way, digital tools can supplement the care of healthcare providers by not only augmenting the interventions that would be promoted for preventing and/or managing chronic conditions but also by helping to serve as a conduit for improving health literacy and accessing care.

Debate about whether digital health technologies support health equity has ensued, especially when compared with traditional brick-and-mortar facilities. However, evidence to date has shown positive impacts on health equity. Digital health technologies are becoming easier to use and more accessible for patients and has shown positive impacts on the healthcare they have received. According to a 2021 survey of US adults conducted by the Pew Research Center, 85% own a smartphone while about 75% own a laptop or computer, and these percentages generally remain high across demographic variables.[27] For individuals who do not have access to technology, hospitals and healthcare organizations have initiated opportunities to provide it to those in need.[28,29] By expanding reach, existing barriers, such as lack of transportation for those who live in rural areas, may be mitigated by reducing the need to be in person.[3,4] Additionally, research has shown that the continued uptake of AI and machine learning applications for healthcare providers, such as decision-support tools that utilize large databases encompassing diverse symptom presentations, increases the capacity for individuals to access adequate care with reduced bias.[11] Ultimately, digital health technologies can support health equity and the sustainability of an already strained healthcare system.[30]

Barriers to digital health exist, ranging from strategic alignment and leadership to governance, capacity, change management, and solution design.[5,31] Perhaps unsurprisingly, the challenges are not considered to stem from technology but rather policy.[5] Systems-level decisions must be made that outline regulatory compliance especially as it relates to health data, education and training for healthcare providers and patients/users on appropriate usage, cost and remuneration,

and appraisal of digital tools.[5,31–33] For patients/users, common concerns include health data privacy and user-friendliness of the technology.[33] Additionally, even though 70% of clinicians agreed that the widespread use of digital health technologies will enable the positive transformation of healthcare, about the same percentage feel that it will be a challenging burden.[6] Concerns raised by clinicians include difficulties preserving the quality of care in virtual settings (i.e., demonstrating empathy virtually), as well as increased responsibility and feeling overwhelmed by new technology and mass amounts of data.[6,33] By co-designing and developing digital tools that center on patients/users and communities, the barriers to digital health, such as access and education about its use, can be mitigated.[34,35] In order to fully attain the positive outcomes of digital health technologies, challenges to its growth are necessary considerations in order to carefully integrate digital tools into existing or updated health systems and avoid creating additional barriers to health.

To ensure gains are attained and barriers are overcome, insights about experiences using digital health technologies are vital to meet the diverse needs of users and providers. The patient/user experience is exceptionally important, and it is what 90% of clinicians believe has driven change in the last decade.[6] Data thus far have shown positive user experiences across various digital health technologies. The US Nationwide Telehealth Impact Survey found that 79% of respondents were satisfied with their telehealth visit and 73% expect to continue receiving virtual healthcare services in the future, with high satisfaction across ages, insurance types, and locations (i.e., urban, suburban, or rural).[36] Positive experiences have also been shown among a variety of non-clinical digital health and wellness services, such as coaching. HealthFitness, a Trustmark company that builds and manages comprehensive fitness solutions for leading companies and organizations with options that extend beyond fitness to address total well-being, received valuable feedback on the benefits of their virtual coaching:

> My coach kept me *accountable* with my sleep and financial goals, giving me a *realistic target date* to achieve them by and *checking in regularly* to support the challenge. I felt the check-ins were extremely valuable to my success…
>
> Coach Michele was great! I have come a long way. It has made a *big difference in my lifestyle*, and my coach helps out very much. No matter what my questions were, Michele was always able to assist me. She made me feel like we have known each other for years…
>
> Katie has been fantastic! I knew what I need[ed] to do, but *just getting started is the hardest part*. Having Katie in my corner has been so helpful for me to *maintain consistency* with my goals!

Moreover, healthcare providers' experiences of digital health have also proven positive, especially in terms of improving efficiency and effectiveness in diagnosing, treating, and supporting patients.[6,11,37] A survey of healthcare providers at the height of the pandemic found that 80% indicated telehealth improved the timeliness of care and almost 70% were motivated to increase the use of telehealth in their practices.[38] Of leaders in healthcare, 61% identified that their main purpose in providing digital health services is to improve well-being by improving health outcomes.[23] Essentially, the primary goal for healthcare providers when utilizing digital health technologies is to adopt tools that help them help their patients better. As more digital health tools are created, these insights will be invaluable to inform further development and enhancement for the best interests of patients/users and care providers.

113.4 FUTURE OF DIGITAL HEALTH

The future of digital health is promising for all stakeholders across industries. From healthcare providers to scientists, technology experts to patients/users, there is an opportunity to redefine how health promotion is supported. The growth of digital health and its capacity to be as positively impactful as possible is dependent on patient/user-centered, multisectoral collaboration.[4] With the opportunity to provide improved care and protect health systems and healthcare providers from further strain, digital tools are important to pursue and implement. Our hope is that digital health is carefully embedded in the healthcare system, and—similar to public health—it is woven into the structure of health systems seamlessly and is not necessarily "seen" if it is functioning effectively.

One way that digital health can be integrated into existing healthcare systems is to align with a vision of healthcare known as "P4 medicine," which has been promoted for many years by Dr. Leroy Hood and advocates of systems medicine.[7] Having thought to emerge from the intersection of systems biology and systems medicine, consumer-driven healthcare and social networks, and the digital revolution, the four Ps in P4 medicine are predictive, personalized, participatory, and preventive.[7] Digital health technologies are already aligning with the four Ps. First, digital tools can lead to more predictive data via AI and machine learning applications that can be used to support clinical decisions and lifestyle changes. For instance, blockchain personal health records and AI can help increase access to health data and decision-making support for patients and healthcare providers. Additionally, digital health allows for more personalization, which means individual health needs can be directly addressed in a patient-centered manner that considers multiple dimensions of health and meets people where they are at. Further, digital tools allow patients to be more active participants in their health, which not only increases patient health literacy and engagement in their healthcare decision-making but also alters the patient-healthcare provider relationship in such a way that is collaborative instead of paternalistic. Finally, digital health brings prevention to the fore through early identification and management of risks, while also supporting people further along the health continuum.

As digital health continues to expand, it will become more important to appraise its benefits in order to determine opportunities for improvement. To do so, frameworks have heavily focused on return on investment (ROI);[32]

however, there has been a shift toward inclusion of value on investment (VOI) to evaluate quantitative and qualitative outcomes, such as patient/user satisfaction, time and cost efficiencies, improved productivity, increased engagement, and reduced health risks.[18,32] Health systems have been encouraged to create measurable, accountable, and scalable key performance indicators to evaluate success.[39] To evaluate digital health technologies across all stakeholders, a heavy reliance on community involvement will be needed to move the digital health ecosystem forward.

113.5 CONCLUSION

Beyond diagnosis and throughout intervention prescription that takes place in clinical settings, healthcare practitioners are in a unique position to influence lifestyle for improved health and well-being in a way that is predictive, personalized, participatory, and preventive. Digital tools are multidimensional and accessible and can augment existing care or emphasize areas of concern that may not have been previously known. Digital health is an aspect of the healthcare system that will continue to grow; therefore, learning about, acknowledging, and sharing digital tools serves the best interests of patients and healthcare providers alike. The strain on the healthcare system relies on being able to adequately support patients with all available resources. Thus, the future of health and health promotion includes digital health.

CLINICAL APPLICATIONS

As a physician, partner with your patients by	Benefits
Embracing lifestyle as medicine	Taking small steps in building new habits can have a significant impact on health risks and chronic condition management. Empowerment of patients by building self-efficacy through learning and iterative attempts to change behaviors that are not based on success vs. failure but on a journey to better health.
Supplementing your practice with digital health technologies	Provide education, encourage lifestyle change through habit formation, support disease management, and integrate remote patient monitoring through appointments and prescriptions. If patients use health and wellness apps, they can utilize this information during appointments (i.e., tracking trends of lifestyle and biometrics when relevant).
Acknowledging and promoting engagement in digital health technologies (through the workplace, community, etc.)	Encourage patients to utilize their workplace benefits and/or access community services and tools: • Completing health assessments and onsite screening • Participating in programs and challenges • Accessing allied health professionals and/or health coaching • Reimbursement for therapeutics, medical devices/wearables, etc.
Keeping pace with current and emerging digital health and wellness applications	Recommend personalized applications that are built with a targeted patient in mind (age, sex, gender, lifestyle, condition, accessibility, etc.) Leverage curated libraries that contain objective, expert evaluation based on usability, clinical value, supporting evidence, and data rights: • APA • ORCHA • PsyberGuide • MindTools • Therappx

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114 Community as a Catalyst for Healthier Lifestyles

Jane Ellery, PhD and Peter Ellery, PhD

KEY POINTS

- Diverse disciplines contribute to a theoretical foundation that supports a community-engaged change process to enhance health and wellness.
- A shift from pathogenic thinking to salutogenic thinking opens up new opportunities for meaningful change.
- Placemaking is a place-led, person-centered approach to community development, and it can have a positive impact on lifestyle, wellness, and healthy decision-making.
- Involving those who are to benefit from services in the development and delivery of those services has the best chance of resulting in coherent, sustainable change.

114.1 INTRODUCTION

Communities across the United States are beginning to embrace an economic development strategy that focuses on creating great places for people to live and work.[1–3] "If tax breaks were the old recipe for economic development, creating vibrant neighborhoods that can attract people from near and far is the new one".[1] This change represents a seismic shift in economic growth and development. It also offers the medical community an excellent opportunity to expand health and healthcare delivery options beyond the prevention, management, and treatment of disease models often used today. Lifestyle medicine's focus on addressing the underlying lifestyle causes of a disease, and not just the signs and symptoms of it, epitomizes a step in this direction. According to the American College of Lifestyle Medicine:

> Lifestyle Medicine is the therapeutic use of evidence-based lifestyle interventions to treat and prevent lifestyle related diseases in a clinical setting. This approach empowers individuals with the knowledge and life skills to make effective behavior changes that address the underlying causes of disease.[4]

Unfortunately, even when individuals have the knowledge and skills needed to make healthier choices, their environments often prevent them from following through on those behaviors, making healthier lifestyles difficult to sustain. By forming meaningful relationships between medical professionals and the numerous organizations that work to promote economic development and community revitalization, communities can be reimagined and redesigned to promote health rather than detract from it. If the goal is to have a healthy citizenry, then involving members of the community in the creation of healthy places makes it easier for medical professionals to encourage active, vibrant lives for those in their care.

So where do we start as we rethink our approach to improving health and wellness in communities? The purpose of this chapter is to explore the idea that health and wellness can be impacted by something as simple as where you live and how involved you are in your community. To do this, we will:

- Discuss theoretical connections between place, health, and engagement
- Briefly examine sense of coherence (SOC) and generalized resistance resources (GRR)
- Identify opportunities for physicians to co-produce healthy lifestyle changes with their patients

After reading this chapter, you should have a better understanding of the value that comes from expanding beyond the pathogenic, disease-mitigating perspective of health that is too pervasive among medical and health professionals. Incorporating the salutary factors that encourage health and prosperity, especially when strategizing around community-level interventions, provides new opportunities for impacting community health and wellness through placemaking and community development. These place-led, person-centered, salutogenic initiatives transition the focus of our thinking from how to keep individuals from getting sick to bringing people together and shaping the environment so that it promotes a good life that is lived in a safe and nurturing way.

114.2 DETERMINANTS OF HEALTH, SENSE OF COHERENCE, AND CO-PRODUCTION

The lifestyle medicine movement encourages physicians to prioritize lifestyle changes over medical interventions when working with patients.[5] This approach is well matched with efforts in public health and health promotion that are centered around the determinants of health. Community-level

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FIGURE 114.1 Healthy People 2030 Social Determinants of Health.

initiatives that focus on systems and environmental changes are being deployed across the country to make the healthiest choices the easiest choices.

According to the World Health Organization (WHO), determinants of health can include the social and economic environment, the physical environment, and a person's individual characteristics and behaviors. WHO notes that the "context of people's lives determine their health, and so blaming individuals for having poor health or crediting them for good health is inappropriate. Individuals are unlikely to be able to directly control many of the determinants of health".[6] Based on a US population, Healthy People 2030 further defines social determinants of health as "the conditions in the environment where people are born, live, work, play, worship, and age that affect a wide range of health functioning, and quality-of-life outcomes and risks". They identify five domains (see Figure 114.1) including economic stability, education access and quality, healthcare access and quality, neighborhood and built environment, and social and community context.[7]

Enhanced healthcare access and quality will continue to be the primary focus of the medical community. At the same time, advocating to expand efforts beyond those specific to disease prevention and risk reduction to also focus on determinants of health is a valuable step forward for lifestyle management professionals. Additional opportunities for meaningful change emerge when practitioners also consider health within the context of an individual's overall life, and a salutogenic orientation facilitates movement from a pathogenic, disease-focus to a salutary, life-enhancing approach.[8,9] Interestingly, as part of his salutogenic thinking, Antonovsky regularly expressed concern that those who have adopted the concept of lifestyle change too often focus solely on risk factors for diseases like smoking, lack of exercise, poor nutrition, unsafe sex, and exposure to injury. While these are important areas to address, this myopic focus keeps intervention strategies squarely within the context of a pathogenic orientation.[8] In contrast, Antonovsky encourages us to focus on engaging in life experiences that help create consistency, load balance, and participation in decision-making.[10,11]

114.3 A SENSE OF COHERENCE AND GENERALIZED RESISTANCE RESOURCES

Just as pathogenesis looks at the origins of disease, salutogenesis explores and promotes the origins of good health and prosperity for individuals. In Latin, the root *salus* represents safety, salvation, and welfare.[12] Antonovsky developed a central construct for salutogenesis that he termed *sense of coherence* (SOC). SOC is determined by the degree to which individuals perceive their lives to be meaningful, manageable, and comprehensible. In a salutogenic context, Antonovsky defines meaningful as the extent to which individuals feel that life makes sense emotionally and that the problems and demands of life are both welcome and worthy of commitment and engagement. Manageable refers to the extent to which individuals perceive that resources are both available and adequate to meet the demands being placed on them by

the environment. Comprehensible is viewed as the extent to which individuals are able to make cognitive sense of the information that they are exposed to within a specific context or environment and the degree to which that information conforms with their worldview.[10]

In addition to SOC, Antonovsky constructed the concept of *generalized resistance resources* (GRRs). GRRs afford individuals the capacity to deal with stressors and situations that can impair health and that represent "phenomena that provide one with sets of life experiences characterized by consistency, participation in shaping outcomes, and an underload-overload balance".[10] Overall, GRRs refer to the characteristics of a person, a group, or a community that facilitate an individual's ability to cope effectively with life's stressors. They can be personal as well as environmental, and both material and non-material in nature. Examples include knowledge and intelligence, individual genetic traits, social support networks and personal ties, cultural stability, and money. GRRs provide an individual with the attributes needed to comprehend, manage, and find meaningfulness in life. In contrast, the absence of GRRs, also referred to as *generalized resistance deficits* (GRDs), can lead to chronic or endemic strain that can negatively impact an individual's health.[10,13–16]

While individuals may have access to the resources available within a specific context, and the ability to use those resources, they also need to be able to draw on GRRs that help them navigate the decision-making processes they encounter each day. This suggests that the availability of adequate resources is essential to moderating the stresses and strains of daily life. Unfortunately, a substantial portion of our society lives in areas that have limited access to the resources they need and few opportunities to develop personal resources of their own. This makes achieving a strong SOC difficult and may lead to the adoption of suboptimal health behaviors. This conceptualization supports the data analytics that identify zip codes as useful predictors of health and longevity[17] and highlights the need for developing both personal and community resources.

114.4 CO-PRODUCING HEALTHY CHANGE

In our quest to live healthier lives, having a strong SOC is an important step. Additionally, people benefit from experiencing a sense of involvement where they feel engaged and valued. While Antonovsky's research highlights the benefit of individual participation in decision-making processes, the importance of involvement is further enhanced when the life's work of political scientist and Nobel laureate, Elinor Ostrom, PhD, is considered. Ostrom explored the co-production of services while examining the polycentric governance of resources that many individuals share and use in different ways (often referred to as the Commons).[18] Co-production describes a relationship where professionals and citizens share power and work together to deliver public services.[19] This concept emerged in the late 1970s to counter the predominant theories of the time that recommended massive centralization, and it continues to receive periodic attention when working to identify opportunities for community-level change.[20] Co-production involves individuals who are impacted by public services in the development and delivery of those services, lending support to the construct of involvement/engagement.

The association between health, engagement, and community is also apparent in the conceptualization of *high-level wellness* offered by Halbert Dunn, MD, PhD, in the 1960s. While working as Chief of the National Office of Vital Statistics, Dunn encouraged medical and public

health practitioners to explore the factors responsible for good health instead of focusing solely on disease and disability. Dunn's recommendation for a new way of thinking about health was "rooted in the changing demographic, social, economic, and political character of civilization".[21] The four factors that he identified as contributing to this need are highlighted in Table 114.1.

When considered collectively, the works of Antonovsky, Ostrom, and Dunn offer an interesting perspective. Although originating from different disciplines, their theoretical underpinnings provide support for new ways of thinking about health and wellness that are finally reaching

TABLE 114.1

Dunn's Four Factors Contributing to the Need for a New Way of Thinking about Health

1. *It is a shrinking world*. Communication time has shrunk to the vanishing point. Knowledge of events can span the world in seconds and can be known to the masses in a matter of hours. Travel time from the farthermost reaches of the earth has diminished from years and months to a matter of days and hours.
2. *It is a crowded world*. Turned loose in an all-out assault upon disease and death, the medical and health sciences have brought about generally falling death rates without a corresponding reduction in birth rates. The consequent "epidemic" of population growth has reached towering proportions in many parts of the world and brings with it new health problems arising from population pressures and the scarcities of materials and living space.
3. *It is an older world, in terms of its people, productivity, and resources*. A consequence of the revolution brought about by the health sciences is that relatively more people live to an older age. The per capita demand for the output of the economic and productive machinery is steadily advancing. Consequently, it is probably a fallacy for us to assume, as so many of us have done, that an expansion in scientific knowledge can indefinitely counterbalance the rapidly dwindling natural resources of the globe.
4. *It is a world of mounting tensions*. The tempo of modern life and its demands on the human being and his society are steadily increasing with no corresponding readjustment and strengthening of the inner man and the fabric of his social organizations.



Goal 1. End poverty in all its forms everywhere
Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
Goal 3. Ensure healthy lives and promote well-being for all at all ages
Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
Goal 5. Achieve gender equality and empower all women and girls
Goal 6. Ensure availability and sustainable management of water and sanitation for all
Goal 7. Ensure access to affordable, reliable, sustainable and modern energy for all
Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
Goal 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
Goal 10. Reduce inequality within and among countries
Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable
Goal 12. Ensure sustainable consumption and production patterns
Goal 13. Take urgent action to combat climate change and its impacts
Goal 14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
Goal 15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
Goal 16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
Goal 17. Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

FIGURE 114.2 Sustainable Development Goals, United Nations (source: United Nations; seewww.un.org/sustainabledevelopment/wp-content/uploads/2019/01/SDG_Guidelines_January_2019.pdf for guidelines for use).

the forefront of intervention strategies.[22] Henry Ford has been quoted as saying: *Coming together is the beginning. Keeping together is progress. Working together is success.* As we consider opportunities for future change consistent with the theoretical foundation presented in this section, coming together, keeping together, and working together become key to identifying successful interventions.

114.5 TAKING ACTION

Changes that combine a salutogenic focus with community involvement and co-production models can be initiated by physicians, mayors, urban planners, and many others in communities across the country and throughout the world. Ideally, diverse disciplines will come together to help

realize this change, because it will take everyone working together to create an environment where the healthiest choice is also the easiest and most accessible option. Opportunities for meaningful, community-level change can come in many forms. The shared vision and needs presented in the United Nations' Sustainable Development Goals (Figure 114.2) provide a springboard for thinking about community-level change opportunities.[23] These 17 goals were adopted by world leaders in September 2015 and provide a unique call to action for all countries interested in working to promote prosperity while protecting the planet. They recognize the value of building economic growth while addressing social needs, climate change, and environmental protection.[23]

The connection between Goal 3, *ensure healthy lives and promote well-being for all*, and lifestyle medicine practice is easy to envision. Building on a salutogenic, co-production orientation, ending poverty (Goal 1), achieving food security (Goal 2), providing quality education (Goal 4), empowering women and girls (Goal 5), promoting decent work for all (Goal 8), and reducing inequities (Goal 10) all work to decrease GRDs and enhance GRRs. Built environments can be restructured to ensure that the healthiest choices are also the easiest choices through managing water and sanitation (Goal 6), accessing modern and clean energy (Goal 7), building a resilient infrastructure and fostering innovation (Goal 9), and making human settlements inclusive, safe, resilient, and sustainable (Goal 11). The remaining six goals are equally important because they foster sustainable, natural environments, and global connectedness.

Communities can positively impact individual health and community wellness by adopting change strategies that are engineered to intentionally enhance GRRs and nudge people toward healthier decisions using globally identified improvement goals. This approach can also enhance SOC by helping everyone involved understand how what they are working toward fits within the bigger picture of what is happening in the world around them.

Involving citizens in the change processes is also important to address when working toward co-producing change. Placemaking refers to a collaborative approach to planning, designing, and managing public spaces, and it inspires people to collectively reimagine and reinvent public spaces.[24] Embodying Ostrom's views related to governing the commons, placemaking involves the people living in the community in the process of maximizing the shared value of public spaces. With a focus on designing communities around how people experience public spaces and not just thinking about transportation, buildings, and open space, placemaking "facilitates creative patterns of use, paying particular attention to the physical, cultural, and social identities that define a place and support its ongoing evolution".[24] Placemakers approach community change by facilitating activities that involve individuals in the community and that encourage open conversations about the use of public and open spaces. These activities contribute to an understanding of the needs and aspirations that the people living and working in a community have for both specific spaces and for their community as a whole. The emotional connection that develops between everyday citizens and the places that they share encourages them to take ownership of the public spaces and contribute to the continuous development and activation of these places.[22,25–27]

The importance of thinking globally but acting locally comes into view. While we can learn a lot from others throughout the world, individuals can only make healthier decisions when local conditions support healthier actions. Involving those who are to benefit from services in the development and delivery of those services through placemaking and other participatory approaches has the best chance of resulting in coherent, sustainable change.

114.6 SUMMARY AND CLINICAL APPLICATIONS

As physicians embrace a salutogenic orientation within the context of community to encourage more positive behaviors among their patients, unique opportunities for developing and providing resources that lead individuals toward healthier decision-making will emerge. Based on the foundational thinking presented in this chapter, Table 114.2 represents five strategies that physicians and other lifestyle management professionals could consider as they work to nudge their patients toward happier, healthier lives.

TABLE 114.2
Lifestyle Management Strategies for Physicians

1. Learn about the community and the offerings available to your patients so you can connect individuals with meaningful opportunities for change and the resources they will need to help them grow and develop.
2. Collaborate with local agencies (including community planners, public health practitioners, corporations, social service agencies, and local non-profit groups, to name a few) to ensure that necessary resources that are not currently available in the community are strategically developed, deployed, and accessible.
3. Look beyond standard lifestyle factors like smoking, nutrition, exercise, and injury prevention to also include housing and safety conditions, neighborhood design, resource availability, and community cohesion.
4. Listen carefully to your patients so you gain insight into the context of their life situations and include them in the development of care plans.
5. Work with your patients to co-produce individualized lifestyle plans that bring their current internal resources together with available community resources to create the best opportunities for success.

When it comes to our communities, we often find ourselves living in places that limit our ability to act in ways that support healthy living. By recognizing that where you live impacts your health and wellness, community change efforts have now emerged as an important intervention strategy. Working together, physicians, planners and developers, employer groups, and even citizens themselves can be involved in the creation of great places for people to live, learn, work, and play. This will take new ways of thinking and doing for physicians, but lifestyle medicine will be a key leader in this change effort.

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115 International Health and Lifestyle

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KEY POINTS

- Non-communicable diseases (NCD) are a global issue accounting for about 71% of all deaths around the world.
- Over 80% of all premature NCD deaths globally are the result of cardiovascular diseases, cancers, respiratory diseases, and diabetes mellitus.
- The modifiable health risk factors for NCDs globally include tobacco smoking, excessive sodium intake, alcohol misuse, and physical inactivity.
- WHO predicts depression will be the top cause of worker disability lost time globally by the year 2030.

115.1 OVERVIEW

Health and well-being is a global issue for countries, multi-national employers, and other stakeholders who are focusing on the health and productivity/performance of their populations. Communicable as well as non-communicable diseases vary in prevalence and importance from country to country. Communicable diseases include a wide range of bacterial, viral, fungal, and protozoan infections. For example, the reported number of COVID-19 global pandemic deaths between January 1, 2020, and December 31, 2021, was almost six million. However, the actual number of COVID-19 deaths has been estimated to be from 18.2 million to over 20 million.[1,2] The pandemic has been associated with a decline in global life expectancy for the first time since 1950, by 0.92 years between 2019 and 2020 and by another 0.72 years between 2020 and 2021.[3]

This section will focus on non-communicable diseases (NCDs), which are chronic diseases resulting from a combination of genetic, physiological, environmental, and behavioral factors including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes among others. NCDs result in the death of 40 million people around the world each year and account for about 70% of all deaths. The cumulative economic impact to the global economy is estimated to be $30 trillion by the year 2030 according to an analysis by the World Economic Forum and the Harvard School of Public Health. NCDs like heart disease can develop in emerging market countries in much younger populations. For example, in India, people aged 25–35 years old have nearly five times the prevalence of heart disease compared with American workers of the same age. American workers tend to develop heart disease in their 40s, 50s, and 60s. The United Nations (UN) has adopted 17 global goals for sustainable development. The good health and well-being goal is to reduce premature mortality from non-communicable diseases by one-third by 2030.[4]

Four medical disorders (see Table 115.1) account for 71% of all premature NCD deaths globally and about 85% of these deaths occur in low- and middle-income countries.[5]

Fifteen million global non-communicable disease deaths (Table 115.2) occur in relatively young adults, ages 30 to 69 years old. The risk factors for these medical conditions include poor diets, physical inactivity, high blood pressure, elevated blood glucose, abnormal blood lipids, and obesity. Cardiovascular disease in large part is attributable to metabolic risk factors (e.g., cholesterol, blood pressure, overweight/ obesity, blood glucose) and is the leading cause of premature NCDs. Cancer accounted for 23.6 million new cancer cases, 10 million deaths, and 250 million disability-adjusted life years (DALYs) in 2019 in 204 countries.[6] In 2019, cancer was second to cardiovascular disease-related DALYs but the leading cause of death.

The United Nations and The World Health Organization announced a goal of a 25% reduction in NCD mortality by 2025 among persons ages 30 to 70 years old.[7]

TABLE 115.1
Global Deaths Associated with Chronic Diseases

Disorder	Global Deaths Annually
Cardiovascular diseases (heart attacks, stroke, etc.)	17.9 million
Cancers	9.3 million
Respiratory diseases (chronic obstructive pulmonary disease, asthma, etc.)	4.1 million
Diabetes	1.5 million

TABLE 115.2
Global Deaths Associated with Health Risks

Health Risk	Global Deaths Annually
Smoking and secondhand smoke	7.2 million
Excess salt/sodium intake	4.1 million
Alcohol misuse	3.3 million
Physical inactivity	1.6 million

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- Fifty percent of at-risk people receive drug therapy and counseling to prevent heart attacks and strokes.
- Eighty percent availability of affordable technologies and medications to treat major NCDs.

Despite this continuing dramatic global shift from communicable diseases to non-communicable diseases, especially in lower-income countries, the healthcare systems in poor countries are not prepared for these new challenges.[8,9]

Because people in lower-income countries do not generally have access to preventive and primary care, diseases like vaccine-preventable cervical cancer, complications from diabetes, and hypertension are more likely to develop. Such diseases will result in avoidable morbidity and mortality, especially in the working-age populations.

115.2 HEALTH RISK FACTORS MEASURED GLOBALLY

The Organization for Economic Cooperation and Development (OECD) includes 34 member democratic countries that report comparable data on key indicators of health. Key health risk factors they report include the percentage of the adult population that are smokers, alcohol consumption, overweight/ obesity, and air pollution-associated deaths. Most countries do not report desirable results for one or more of these health risks.[10] Air pollution may cause six to nine million premature deaths worldwide annually by 2060. Outdoor air pollution contributes to the morbidity and mortality of non-communicable diseases.

115.3 MENTAL HEALTH/ ADDICTIVE DISORDERS

Mental health and addictive disorders are common, affecting more than one billion people globally, and represent 19% of all years lived with disability and an estimated 7.4% of the world's measurable burden of disease.[11,12] The World Health Organization (WHO) predicts depression will be the top cause of worker disability globally by the year 2030.[13] Mental health disorders have a peak onset of incidence in the working-age population and therefore have a significant impact on individual's productivity during the peak of a person's career. They are often underdiagnosed and undertreated, resulting in potentially avoidable medical costs, absenteeism, disability, and lost on-the-job productivity (presenteeism). The financial investment in mental health treatment services has been lagging globally.

The WHO European Ministerial Conference on Mental Health was held in 2005 and endorsed the statement "No health without mental health", which emphasized the important linkage between physical and behavioral health.[14]

Internationally, as in the United States, there is an insufficient number of quality mental health providers. The lack of mental health providers is a major barrier to providing adequate behavioral health services in low- and middle-income countries. For example, more than 75% of persons with serious mental illness in less-developed countries do not receive adequate mental health treatment.[14] Appropriate treatment is compounded by the lack of mental health medications in many countries and the cost of these drugs may be prohibitively expensive to much of the population.[15]

115.4 ALCOHOL

Alcohol use disorder (AUD) was the seventh leading risk factor for both deaths and DALYs in 2016. It has been associated with deaths due to infectious diseases, intentional and unintentional injuries, digestive disorders, cancer, and other non-communicable diseases.[16] In the past, light to moderate intake of alcohol was thought to be associated with a lower risk of cardiovascular disease compared with either abstinence or heavy drinking. However, research now indicates that any amount of alcohol use on a regular basis is associated with an increased risk of cardiovascular disease, including hypertension, coronary artery disease, myocardial infarction, stroke, heart failure, and atrial fibrillation.[17,18]

115.5 TOBACCO

Smoking is the single most important avoidable health risk factor in OECD countries and globally. Almost 170 countries signed a tobacco control treaty adopted in 2003 by the WHO. The prevalence of smokers in a population varies from country to country Approximately six million people die globally each year related to smoking including five million from the direct effects of tobacco and over 600,000 who were exposed to secondhand smoke.[19] Smoking is a major risk factor for the development of cardiovascular diseases and several types of cancers. In addition, smoking is a major risk factor for developing respiratory diseases such as chronic obstructive pulmonary disease (COPD).[20] Smoking during pregnancy is associated with the development of low-birth-weight babies.

Many governments, employers, and other organizations offer smoking cessation programs in many countries. Several governments as well as employers prohibit smoking in the workplace because of the health hazards to others from passive inhalation of tobacco smoke. Medications that support smoking cessation are also available but may be cost-prohibitive to people in low- and moderate-income countries.

115.6 OBESITY

Overweight and obesity is known to be a risk factor for numerous health conditions including hypertension, high cholesterol, diabetes, cardiovascular diseases, respiratory conditions, musculoskeletal diseases, and several cancers.[21] The most commonly used measure of overweight and obesity is body mass index (BMI). BMI is defined as an

individual's weight in kilograms divided by their height in meters squared. Overweight is defined as a BMI of 25.0 to 29.9 and obesity as a BMI of 30 and over.[21] This classification may not be appropriate for all ethnic groups who may be at increased risk at lower or higher BMIs. For example, the Asian population is considered by the WHO to have an ideal BMI of less than 23. The prevalence of overweight/obesity in several countries is summarized in Table 115.3. Researchers reported that in 2015, a high BMI contributed to four million deaths and 120 DALYs lost globally.[22]

Governments and employers in many countries are beginning to address the epidemic of obesity through education and other initiatives. Employer initiatives have included offering healthier food choices in workplace cafeterias and vending machines, workplace-based weight loss programs, and even medications that assist in weight loss as part of a comprehensive approach to weight loss. Governments such as Mexico and India have instituted taxation on sugar-sweetened beverages (SSBs) to help lower the incidence of obesity and type 2 diabetes, while others have mandated the display of food calorie counts in restaurants and the construction of walking and bicycle paths to promote physical activity.

115.7 PHYSICAL ACTIVITY

There is now overwhelming evidence on the benefits of regular physical activity including its positive effects on health and well-being.[23] It is now considered the fourth leading risk factor for global mortality. Both the WHO and the US CDC recommend adults aged 18–64 years old do at least 150 minutes of moderate-intensity aerobic physical activity per week or at least 75 minutes of vigorous-intensity aerobic physical activity per week or a combination of the two.[24] Additional benefits may be gained from 300 minutes per week of moderate physical activity, 150 minutes of vigorous physical activity, or a combination of both. The WHO has also recommended reducing sedentary behavior, although they provide no specific guidelines. Any amount of physical activity can be beneficial, and it is important in achieving physical and duration activity goals. However, only about one in five Americans meet the Centers for Disease Control and Prevention physical activity guidelines.[25] Physical activity has been associated with:

- Decreased all cause-mortality,[3] CVD, high blood pressure, stroke, type 2 diabetes, metabolic syndrome, colon and breast cancer, and depression.
- Less risk of hip or vertebral fracture.
- Heathier body mass index.

Physical activity, both recreational and non-recreational, has been associated with a lower risk of mortality and CVD events for people in low-, middle-, and high-income countries. However, more workers are performing primarily sedentary jobs, which has been associated with increased mortality and morbidity.

Several interventions have been used to promote physical activity by governments and in the workplace, including:

- Urban planning to include walking, cycling, and other forms of physical activity which are accessible and safe.
- Facilitating active transportation to work (e.g., walking and cycling). In many US cities, Mexico City, and others, rental bicycles are available for transportation.
- Including bike and walking paths on employer office campuses.
- Worksite fitness centers are available to employees in various countries at little or no cost.
- Coaching employees on developing a physical activity program.
- Employee activity competitions with incentives that might include pedometers to measure steps taken per day. A common goal is 10,000 steps per day.

115.8 COUNTRY-SPECIFIC HEALTH AND WELL-BEING PROGRAMS

There are a number of organizations that offer resources for organizations that develop health and well-being programs tailored to the needs of a particular country. They include

TABLE 115.3
Health Risk Factor Prevalence in Selected OECD Countries[10]

Country	Smoking (percent smoking daily)	Overweight/Obese (BMI 25 and over)	Alcohol Consumption (liters/capita)	Deaths per 100,000 Population (outdoor air pollution)
Canada	10.3%	59.8%	8.0	10
US	10.9%	73.1%	8.9	15
UK	15.8%	64.2%	9.7	21
France	24.0%	49.0%	11.4	20
Israel	16.4%	50.9%	3.1	27
Japan	16.7%	27.2%	7.1	31
Poland	17.1%	56.7%	11	73
All OECD countries	16.5%	56.4%	8.7	29

TABLE 115.4
Responsibilities of Stakeholders

Stakeholder	Prevention	Detection	Treatment
Government/employers	Anti-tobacco policy Reduction in salt intake Food labeling High-sugar beverages Promotion of physical activity Alcoholic beverages	Awareness of NCDs, signs and symptoms, early detection	Access to affordable medications
Clinicians	Education of patients on health risk factor reduction (e.g., smoking cessation)	Screening and detection of health risk factors	Evidenced-based treatment of health risk factors and NCDs
Health care system	Detection and treatment of NCDs (e.g., blood pressure and blood sugar control)	Screening and detection of health risk factors	Evidenced-based treatment of health risk factors and NCDs

ministries of health, health education and advocacy organizations, the WHO, OECD, and employer wellness councils/organizations among a growing list of others.

Data is important to determine the major health risks and medical conditions for a particular country and for an organization to determine, plan, and evaluate the effectiveness of country-specific interventions. The types of data that are available vary greatly from country to country. Population health data may include biometric risk factors (blood pressure, body mass index, glucose), vaccination rates (influenza, hepatitis, childhood immunizations, etc.), the prevalence of chronic diseases (diabetes, depression, asthma, cancer, high blood pressure, heart disease, etc.), and the prevalence of lifestyle health risk factors (alcohol misuse, overweight / obesity, physical inactivity, stress, etc.)

115.9 APPROACH TO PREVENTION AND CONTROL STRATEGIES

There are three components to comprehensive effective strategies for the prevention and control of NCDs in countries including:

- Cultural, which encourages people to make and maintain healthier choices.
- Health literacy to educate people on how to improve their health.
- Healthcare, which focuses on early detection and the management of health risk factors and NCDs.

Table 115.4 summarizes the responsibilities of various stakeholders in addressing NCDs.

115.10 CONCLUSIONS

All countries are now interdependent in the growing global economy. With the ease of global travel, there are constant threats of communicable diseases such as has occurred in recent years with SARS-COVID-2, Ebola, Zika, drug-resistant tuberculosis, human immunodeficiency virus (HIV/AIDS), and a long list of others. However, the increasing prevalence of NCDs is negatively affecting the health and productivity of country populations and the global economy.[26]

It is important for international healthcare providers and countries to place a higher priority on health promotion and disease prevention in order to reduce modifiable health risk factors that lead to NCDs and mortality. Many countries including the United States and Mexico have made remarkable progress over the past few decades in reducing smoking. However, these same countries have relatively high rates of overweight and obesity, which continue to increase at an alarming rate.

It is essential that healthcare providers, governments, employers, and others implement evidence-based interventions to address the worldwide epidemic of NCDs for the global economy to prosper. Global- and country-specific actions will be needed to achieve the WHO goal of a 25% reduction in the rate of premature death from NCDs.

CLINICAL APPLICATIONS

- Health risk factor targets for blood pressure, cholesterol, blood glucose, and body mass index may vary by country from the generally accepted targets in the United States.
- While risk factor screenings are generally covered by private and government-sponsored health insurance in the United States, such coverage varies significantly internationally.

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116 Future Directions of Health Promotion: The Role of the Physician

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KEY POINTS

- Health can be defined as a complete state of physical, mental, and social well-being, and not merely the absence of disease or infirmity; moving the population to thriving, healthy, high-performing, and sustainable outcomes requires earlier and consistent interventions.
- Health promotion professionals, including physicians, must understand the environments in which patients live and work and what connections are needed between the clinical system and changes that are easily supported by communities.
- Health promotion can utilize technological innovations in wearable technology, communication portals, and other tools to more easily support and encourage healthy lifestyles.

116.1 INTRODUCTION

Wellness is defined by the Oxford English Dictionary as "the state of being in good health, especially as an actively pursued goal", and its usage has gone from approximately zero in 1950 to a word used every day in a multitude of ways by 2022. Internet search queries for "wellness" increased 20% year over year from 2018 to 2020[1] and interest in health promotion continues to grow today. The Global Wellness Institute estimated that worldwide spending on wellness in 2020 was $4.4 trillion, including categories as diverse as physical activity, personal care and beauty, wellness tourism, healthy eating, public health, prevention, complementary medicine, personalized medicine, and more.[2]

Health promotion programs, activities, and environments aimed at improving wellness occur in many settings today.[3] Each person may exist in several overlapping settings—home, community, workplace, and physician's office—and individuals may receive different messages in each of these settings. In the workplace, the health promotion message and expected outcomes have traditionally focused on behavior change and the positive impact of healthy lifestyles on healthcare and disability costs, time away from work, and job performance. On the other hand, community and physician-provided health promotion messages may focus on improving healthy behaviors in order to prevent morbidity or mortality or prescribing medicine to combat a wide range of health conditions.

Health and wellness are influenced by contextual and environmental factors, which is why a multi-site approach to health promotion encourages interventions and wellness messaging across the social, cultural, and physical places in which people live, work, and play. This approach has been popularized and applied to health-promoting schools, cities, workplaces, and even islands. What logically follows this approach is a range of actions intended to address the physical, social, organizational, and cultural factors influencing health in any given environment.

Settings such as the workplace or physician's office are more than just convenient locations for reaching target groups; they are also social systems that can support health and provide avenues for changing societies, not just individuals. The types of outcomes expected from working in this way include changes in environments, policy, skills, and organizational processes, as well as changes related to specific health problems. This approach to health promotion and wellness does not preclude a focus on specific health issues. Such an integrated approach ensures greater coordination in negotiating with stakeholders and compiling resource materials and may reduce duplication of effort and competition between programs.[4]

116.2 WELLNESS REAL ESTATE

One area of health promotion that is growing in popularity is wellness real estate. These are planned homes and communities designed to support healthy lifestyles. The COVID-19 pandemic sparked a trend for people to work from home more than ever, allowing them to choose a place to live that is independent of their worksite. This trend also triggered more interest in wellness real estate, which seeks to blend home, work, wellness, and a focus on nature. These wellness developments include new technology and building designs to create "well" environments. Examples include places that put mental and spiritual health at their center such as Gravity in Columbus, OH, communities centered on farms such as Agrihood in Santa Clara, CA, and multi-generational age-in-place communities such as Cantina near Austin, TX. It is easy to see how lifestyle medicine physicians can integrate into these communities

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to support the health-promoting lifestyles their residents are seeking.

116.3 TOOLS

Technology innovation occurs in all areas of life and health promotion is no exception. Wearable technology designed to inform and promote health is commonplace today. Patient portals are another advancement that allows patients and care providers to aggregate information such as test results, prescriptions, and messaging in one place and ease collaboration among providers while giving patients direct access to their health and wellness metrics. Other devices such as wireless blood glucose meters and smart pillboxes continue to improve patients' abilities to manage their own health. Electronic medical records (EMR) can play a key role in helping physicians address health promotion among their patients. EMRs can prompt certain information about family history or suggest a measurement of exercise as one of the vital signs.

116.4 BEHAVIOR CHANGE

A core principle in health promotion is making the healthy choice the easy choice. Putting this motto into practice requires removing barriers that individuals face when trying to live a healthy lifestyle. This requires that physicians really get to know their patients; looking closely at exercise levels and home life or environmental factors that cause strain and identifying sources of problems rather than just the problems themselves. One challenge to health promotion in any setting is that the ability to achieve health behavior improvement is dependent on an individual's willingness to implement change consistently.

Behavioral design may help people find useful tools and tactics for making healthy lifestyle changes. It also helps determine how able and ready a person is to make a change and what triggers are most likely to instigate that change. If patients are resistant to change, physicians can enlist the expertise of others by looking at what the community can offer. There may be diet- and exercise-tracking apps, free nutritional and wellness counseling, cooking classes, sports clubs, and even community or church groups that could help patients make positive lifestyle changes once they leave the physician's office.

Work in the field of behavioral economics has led to a better understanding of the role of emotions and intuitions in shaping decision-making. While intuition and emotions can serve important functions, they can also bias decisions in several important ways. Insights from the field of behavioral economics have relevance for the future of health promotion. By understanding the social, cognitive, and emotional influences on decision-making and behavior, it will be possible to develop more effective initiatives and approaches. In the future, physicians need a way of understanding how to measure environmental determinants and how to speak to patients about them. The health promotion field must find a way to effectively relate to each patient individually to ascertain how they can fit healthy habits into their everyday routines, and then identify what changes individuals are willing to make. Then those changes can be simplified to guide patients through monitoring their own actions against an overall goal. Resistance to change is to be expected. Instead of challenging this resistance, respect it and encourage patients to drive toward their own goal-oriented solutions.

116.5 PHYSICIANS' FUTURE ROLE IN HEALTH PROMOTION

A major aspect of any health promotion program is the involvement of physicians because they have high credibility on health issues. In a healthy city or community program, physicians can contribute by sitting on advisory boards or networking with community leaders. Outcome measures will continue to focus on health behaviors, risks, and disease prevention but will also expand to include the impact of additional elements such as well-being, emotional health, psychology, and organizational health on the health of individuals and populations.

Tomorrow's physicians, insurance plans, and best practice guidelines have to re-orient their mindset from the traditional treatment of illness and disease to the promotion of good health and wellness, which is much more than the absence of disease. In health promotion, physicians must consider the issues of health behaviors, environment, values, and culture while overcoming barriers such as disease orientation, reimbursement policies, and conflicting recommendations to take a more active role in health promotion.

The importance of integrating health into the environment and culture is one of the most important future trends in health promotion. Some studies indicate that the culture of an organization or population has the potential for a larger impact on the health of an employee population than the health promotion programming offered by that organization.[5–7] The current model of health promotion will continue to evolve with the integration of psychology, organizational health, technology, integrated medicine, and other fields over time.

The American Medical Association (AMA) states that "health promotion should be a collaborative, patient-centered process that promotes trust and recognizes patients' self-directed roles and responsibilities in maintaining health".[8] They also recommend several things that physicians can do to promote health and wellness. These include:

- Staying up to date on evidence-supported preventive care guidelines and encouraging patients to comply with appropriate vaccinations and screenings.
- Educating patients about modifiable health risk factors.
- Dialoguing with patients about circumstances that impact chronic conditions or wellness such as

transportation, work/home environment, and support systems.
- Delegating health promotion activities to other professionals or community resources as needed.[5]

Further guidance from the AMA is for physician groups and medical schools. These include:

- Including health promotion and disease prevention training in medical school, residency, and continuing education.
- Advocating for health and wellness in schools, workplaces, and communities.
- Supporting or contributing to research for disease prevention and health promotion.

To evolve, the field of health promotion must embrace a new set of measures and metrics for success and apply better methods for measuring the impact of initiatives. Although sometimes hotly debated, the more traditional indicator of a program's value has been return on investment (ROI). However, an improved understanding of what works best and for whom is dependent on measures of the overall value of more comprehensive population-level strategies. This will require adopting a thoughtful framework for understanding the environmental and cultural factors that can influence all individuals in a population. It will also require a new set of metrics that help connect the environment and culture and the leading and lagging indicators of the impact on health and well-being.

To carry the field forward, program planners should continuously assess the support for health in their environments and cultures, track both participation and engagement in programs, and measure self-directed behavior change. The value of traditional health risk assessments can be improved by adding measures of positive outlook (e.g., resilience, optimism, perceived control) and by regularly measuring changes in these important precursors to health. Advances in technology make it possible to more frequently monitor and report on these and other important outcomes with minimal burden on the population.

116.6 CONCLUSION

For the medical community to be successful in helping promote health in the population, it is crucial to approach prevention differently. To ultimately produce good health, we must make investments in the personal lives of patients—understanding the environments they live and work in and what connection is needed between the clinical system and changes that are easily supported by communities. We have an opportunity to help the primary care system promote change among individuals, empowering them to restore and maintain healthy lifestyles, and we have tools available to help us guide the necessary conversations to effect change.

CLINICAL APPLICATIONS

- Tomorrow's physicians may have to re-orient their mindset from the traditional treatment of illness and disease to the promotion of good health, which is so much more than just the absence of disease.
- It is important to bridge the gap between the medical model of the physician's office and the individual's experience in the home, workplace, and community.
- Physicians should learn successful methods to assist patients in sustainable behavior change and make use of the latest technologies such as wearables and patient portals to automatically monitor and encourage good health with more consistent communication between providers and patients.

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117 "Responders" and "Non-Responders" in Exercise Studies

Victor L. Katch, Professor Emeritus

KEY POINTS

- Humans exhibit large individual variability in response to exercise training. Some experience larger improvements, while others exhibit either no or negative responses.
- Individual responses to exercise training result from a combination of "true" inter-individual differences, intra-individual differences (within-subject biological variability), and measurement error.
- Biological variability is a fact of life and can be ascribed to many factors including genotype, nutritional status, lifestyle habits, and individual history of exercise training.
- The extent to which a non-response to exercise training is true or false, static or changing, probably depends on exercise modality and what metrics are being observed.

117.1 INTRODUCTION

Establishing an effective individual or group program to improve health outcomes is never perfect. Research on the effectiveness of different intervention strategies that include "structured lifestyle interventions" to increase individual and group success is mixed.[1–8]

Most structured interventions include group or individual education meetings, behavior change techniques, self-monitoring, written information, or even telephone and online counseling. Now, there has been a flood of new "wearable" technologies that, when paired with a smartphone, can track, report, and prescribe all sorts of performance and health information metrics as well as provide extrinsic motivation techniques. Each of these interventions is thought to be an effective tool for enhancing outcome measures used to justify program goals and program funding.

Decisions regarding program effectiveness are based on group comparisons using statistical tests of significance. Deciding whether an observed difference between two sets of data should be interpreted as simply a reflection of "sampling error" (null hypothesis) or a "real effect" (alternate hypothesis), statisticians have devised the t-test, the F-test, the Chi-squared test, and so on. The underlying philosophy of these tests is that the established critical magnitude of the t, F, and x^2 that divides statistical significance from non-significance is a value that yields a 5% (or 1%) probability in support of the null hypothesis.[9]

While these probability tests are appropriate when reporting group differences in research journals and may give insights for the development of "best practice" guidelines, they do not explain the wide array of individual responses to different exercise/diet interventions. Researchers often report such variations by reporting standard deviations or standard errors—which is important, of course—but gives little insight into both quantifying and understanding individual variations to specific outcome variables.[10]

117.2 INDIVIDUAL RESPONSES TO EXERCISE ARE VARIABLE

In the exercise area, initial studies exploring the individual response to aerobic training were published in the mid-1980s. In one important study,[11] ten monozygotic twin pairs were recruited to participate in a 20-week endurance training program, with pre- and post-intervention measures of maximal aerobic power (VO_{2max}) and ventilatory aerobic threshold (V_T). Results showed training increased post-training measures by 12% for VO_{2max} and 20% for V_T, but there was considerable variation among subjects. The magnitude of improvements in VO_{2max} ranged from 0 to 41%. Subsequent studies replicated these initial findings.[12,13] In another study from the same group, 720 subjects underwent a 20-week aerobic training program, completing a battery of pre-training and post-training tests.[14] Again, results showed significant individual variation for VO_{2max} expressed in $mL \times kg^{-1} \times min^{-1}$ with some subjects experiencing improvements of over 1000 ml $VO_2 \times min^{-1}$!

Similar results have been reported in resistance training studies[15–18] and studies examining other exercise modalities, such as sprint interval training.[19,20]

It has been shown that about 10% of subjects demonstrate an adverse response to exercise training—i.e., subjects exhibit a post-test change greater than twice the technical error of measurement, in the negative direction. Such findings are problematic—if certain individuals cannot improve—or, even worsen their health or fitness following exercise training, the implication is that for some people, exercise may be ineffective, potentially even increasing their disease risk.

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117.3 NON-RESPONDER, RESPONDER, SUPER-RESPONDER

Interestingly, just as some experience adverse effects to an intervention, there are those who respond as expected (responder) and those who might be considered super-responders—those who respond way off the charts. Sometimes an individual is a non-responder to one intervention and a super-responder to another intervention, and it is nearly impossible to predict the outcome. This not only becomes important when reporting research findings but also in the clinical setting where an individual can become disappointed and discouraged with their post-test scores and are labeled a non-responder.

If an individual is truly a non-responder, they should receive urgent attention, particularly with respect to diet and exercise intervention strategies. Researchers need to determine if non-responders would revert to a more positive response if exposed to more individualized intervention strategies.

117.4 TERMINOLOGY IMPORTANT

The term "non-responder" has been employed to describe those who fail to exhibit positive changes following an intervention.[21,22] This term, however, may promote a misleading perception that exercise is not universally beneficial, which goes against the well-established dictum of the positive effects of regular exercise training on reducing obesity risk,[23] enhancing cardiometabolic health, increasing function in the elderly,[24] improving mental health,[25] and reducing the risk of various disease states.[26]

It may entirely be possible that for an individual any observed non-response to exercise training is modality-specific. That is, subjects exhibiting a non-response in one modality may well show a positive in another modality. In other words, improvements and non-responses are not systematic.[20,27,28] That non-response may be modality-specific points to whether or not training responsiveness to any given intervention is a permanent or a temporary phenomenon. If a given intervention were to be repeated using the same population, would the same individuals also classify as non-responders with a different exercise modality? Since exercise intervention studies tend not to be repeated using the same subjects, this issue remains unresolved. Thus, it is not clear whether a non-response or an adverse response to one exercise modality remains static and unchangeable when repeated with another modality.

Therefore, it may be preferable to label individuals exhibiting no measurable improvement in a given variable as those who "did not respond", rather than "non-responders".

117.5 ARE NON-RESPONDERS (DID NOT RESPOND) COMMON?

In most studies, a "did not respond" result is common, particularly in drug intervention studies. Listings of adverse drug reactions that occur are ubiquitous.[29] This is an admission that sometimes during drug testing, someone (or many) individuals experience adverse drug reactions.

The prevalence of adverse responses in exercise studies is not often considered nor well reported, as we all assume that everyone responds to exercise in about the same way, but to different degrees. As research shows, this is not true.

A recent study[30] looked at the prevalence of adverse responses across six well-known and highly cited exercise intervention studies that tested exercise effects on different cardiometabolic risk factors. Adverse responses ranged from 8.3% for exercise training-induced changes in fasting insulin to 13.3% for changes in high-density lipoprotein levels. About 7% of participants experienced adverse changes in two or more biological risk factors consequent to exercise training.

117.6 COMPLEXITIES OF THE NON-RESPONDER PHENOMENA

There are many reasons people do not respond as expected to an intervention. We often blame the individuals for being non-compliant, the most often cited reason for a null response.[31] When non-compliance is ruled out, we look for other explanations like age,[32] disease conditions[33] ethnicity,[34] concomitant medication use,[35] and environmental variables.[36] Also, recent studies reveal a far greater impact of genetics in determining the magnitude of inter- and intra-individual responses to various classes of drugs and different types of exercise and nutrition interventions.[22]

One of the best examples of variable response to an intervention is in clinical weight loss studies. Aside from the growing reliance on drugs, the standard weight-loss prescription primarily includes calorie restriction of some kind, (high carb, low carb, no carb, etc.). Sometimes caloric expenditure (exercise) is included. But either one of these interventions or in combination is only effective for about 5% to 15% of the population.[37] What then can explain the large number of people who fail to respond to the exercise (and diet) intervention? Obesity and overweight is actually a collection of different conditions each with distinct etiologies and a shared spectrum of symptoms reported by individuals. No wonder there is such diversity in responses between, and perhaps, within individuals!

117.7 INTRA-INDIVIDUAL DIFFERENCES (BIOLOGICAL VARIABILITY)

An often-neglected aspect of understanding the phenomenon of non-responders is the little-appreciated fact that most individuals' biological response to an intervention is variable from time to time. In fact, the inherent tendency of an individual to biologically vary is common for all human variables and may in fact constitute the largest source of variability in a data set. Biological variability should not be treated the same as technological error, which can be

controlled to a certain degree. In contrast to technical error, biological variability is not controllable, although it may be increased or decreased under certain conditions (e.g., disease training). Biological fluctuation has theoretical importance in and of itself. It also becomes important, however, when evaluating changes due to an experimental intervention. For example, suppose an individual started a new exercise program to help reduce elevated cholesterol level, from say 300 mg×dl^{-1} to below the recommended 200 mg×dl^{-1} level. Research shows that tested cholesterol of 300 mg×dl^{-1} is really only an estimate of the "real" value. In most experiments of this type, usually, one cholesterol test is taken before and following the intervention. Little mention is ever provided regarding the error range for an individual cholesterol test. Test-retest cholesterol testing reveals a reliability of about r = ≤92 for cholesterol and its subfraction estimates, depending on the lab, techniques, fasting versus non-fasting, and age,[33,38–40] with a standard error of estimate of about ±8%. In other words, the measured cholesterol of 300 mg×dl^{-1} will fluctuate between 276 mg×dl^{-1} and 341 mg×dl^{-1} for any individual. This is termed intra-individual differences, within-subject variability, or biological variability.[41–43]

Biological fluctuations result from many factors related to how the body responds from time to time and day to day. Biological variability for cholesterol, for example, is based on intrinsic factors related to liver synthesis and tissue utilization, as regulated by genetic factors and their interactions with extrinsic factors like time of day, age, gender, time of year, biological set point, type of food in the gut, and even psychological set. For exercise responses, biological variability is probably influenced by the same variable set but would also include variability in the percentage and type of muscles activated for different types of exercise (aerobic versus glycolytic-dependent exercise). Some individuals exhibit greater and some lower levels of biological variability, depending on the variable being measured. Finding the extent of biological variability for any individual requires multiple tests on the individual and the ability to obtain accurate estimates of equipment and other measurement errors. This is seldom done or reported.

Many examples of measuring biological variability have been reported in the literature, but its magnitude and effects on clinical results and the designation of responders and non-responders are often overlooked[44] but need to be considered.

VO_{2max} and other cardiovascular variables[43,45,46] measuring biological variability can have a large impact on study interpretations, often resulting in faulty conclusions, particularly with respect to identifying the presence of non-responders. For example, in one study[46] biological variability for VO_{2max} was estimated to vary within a range of ±5.6%, 68% of the time, and 98% of the time it could vary within a range of ±11.2%, regardless of whether or not there is an experimental treatment effect, as determined by hypothesis testing. This represents a rather large effect, stated in these terms, when compared with the range of VO_{2max} changes reported resulting from physical training.[47] This biological variability could certainly mask the identification of "true" non-responders. The magnitude of biological variability has also been reported for other cardiovascular metrics used to evaluate exercise training effects.

CLINICAL APPLICATIONS

- There are large individual variations in response to exercise training, with some subjects experiencing larger improvements than others while others appear to exhibit either no or a negative response to exercise training.
- Individual responses to exercise training are a combination of "true" inter-individual differences, intra-individual differences (within-subject biological variability), and technical measurement error.
- Biological variability is a fact of life and can be ascribed to many factors including genotype and individual history, among other factors.
- The extent to which a non-response, i.e., non-responder, to exercise training is true or false, static or changing, probably depends on exercise modality and the metrics being analyzed.

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118 Health Promotion: History and Emerging Trends

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KEY POINTS

- Understanding the historical schism between "medicine" and "public health" informs the creation of a new era of integration acknowledging the social determinants of health.
- Multidimensional, integrated models are required to achieve population health objectives.
- Defining the value of wellness, health promotion, and disease management programs requires a shift from narrow medical cost "ROI" to a comprehensive employer and societal "VOI".
- Understanding the transitions from wellness to well-being, health, and productivity.
- The future is now: emerging trends, technologies, and transdisciplinary research offer a promising way forward for impactful population health initiatives.
- Accelerating clinical alignment should embrace the growing science and practice of lifestyle medicine.

118.1 INTRODUCTION: HISTORICAL SCHISMS AND A NEW ERA OF INTEGRATION.

The roots of "health promotion" conceptually derive from the early 20th-century historical schism between *clinical medicine* (treatment of the individual patient) and *public health* (prevention of disease in populations).[1] As defined in the 1979 Report of the Surgeon General, *Healthy People*, health promotion "seeks the development of community and individual measures which can help … [people] to develop lifestyles that can maintain and enhance the state of well-being".[2] The core scientific models of medicine are best represented by Koch's postulates, which define a deterministic, linear proof for an organism to cause disease.[3] Public health has at its core the paradigm of multifactorial interaction described by the epidemiological triad of "agent-host-environment" to understand disease causality.

Similarly, the division between mental and physical health in the 20th century created a philosophical and practice separation of the *mind* (behavioral and psychological health) from the *body* (medical specialties with ever-narrowing fields of expertise). The *epidemiology* of both medical care costs and public health were historically uninformed by the principles and practice of the science of *economics*. Environmental, architectural, policy, and social psychological (how *individuals* impact and are impacted by *groups*) influences were similarly disconnected from an integrated framework that could explain why individuals and populations behave as they do (or do not) with respect to health, care, costs, performance, and productivity. Emerging science now provides new insights and integrated models can define systematic approaches and best practices to improve "population health".

118.2 INTEGRATED MODELS OF POPULATION HEALTH

The goal of having the longest life possible without suffering premature death, disease, or disability has been termed the "compression of morbidity".[4] It is a useful and compelling epidemiological construct that is understood broadly and sought by individuals and organizations who strive for a healthy and productive life. Both international and US population-based studies and models acknowledge the primary contributory role of social determinants of health which traditionally were inadequately addressed in early health promotion programs whether they be sponsored by private (employer) or public (health agency) entities.[5–8] The Robert Wood Johnson Foundation multiyear effort said it succinctly and best, "how long and well we live is determined by where and how we live, learn, work and play".[9] Early health promotion programs emphasized an individually focused, behavioral, and biometric risk-based approach that was often delivered largely out of context from the community, employer, or organizational culture and determinants of health. As the appreciation of the multifactorial causes of healthy and unhealthy behaviors grew, the terms "culture of health" and "well-being" emerged as better expressing the complexity, comprehensiveness, and more person-centric vision of the goal of health promotion. As more research indicated that the root causes of poor health, excessive medical costs, and lost productivity costs (absenteeism, injuries, disability, workers' compensation) were similar and focused on subpopulations of individuals with elevated health risks, multiple chronic conditions, and high

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cost-of-care diseases,[10] the emergence of more integrated environmental, health promotion, disease prevention, care management, decision-making, and productivity-focused models became predominant[11–13].

118.3 WELLNESS, HEALTH PROMOTION, AND DISEASE MANAGEMENT "ROI" AND "VOI"

The ROI ("return on investment") of wellness and health promotion programs to reduce health care costs (particularly in the near term) has intermittently moved from promising[14–16] to pessimistic.[17] Edington's three-decades-long studies indicated that the healthiest and lower-risk individuals had the lowest near- and long-term costs and that moving moderate- and highest-risk groups to lower-risk levels showed a reduction in medical costs generally within 18–36 months after risk level reduction.[14,16] However, program costs were rarely considered in most ROI calculations or captured using any standard methodology. While the lack of standardization in methods also hampered analyses of disease management programs (optimizing self-care for common, expensive chronic diseases such as hypertension, hyperlipidemia, asthma, coronary artery disease, back pain, and diabetes), due to the higher prescription and medical care utilization and costs, program interventions were more likely to demonstrate near-term medical cost savings ("positive ROI"). The RAND Health Quarterly Workplace Wellness Programs Study,[17] one of the largest systematic reviews of health promotion programs, demonstrated that while some health measures did improve, over a five-year period, there was no statistically significant reduction in total monthly medical costs comparing companies with and without workplace wellness programs. Health promotion programs are increasingly being measured by a more comprehensive framework: the "value" of investment. "VOI" was more broadly defined as loyalty to the company; lower turnover, reduction in absenteeism; improvement in job performance ("presenteeism"); reduction in work-related illnesses, injuries, and safety incidents; earlier return-to-work, improved business performance, and lower workers' compensation claims and cost.

118.4 FROM WELLNESS TO WELL-BEING, HEALTH, AND PRODUCTIVITY

As health promotion and disease prevention programs evolved, more emphasis was placed on understanding and aligning environment, culture, policy, programs, and incentives to be more integrated and emphasize comprehensive health, well-being, personal performance, and productivity. The federal government had already created the clinical- and patient-oriented US Preventive Services Task Force[18] and the population-focused US Community Preventive Services Task Force,[19] respectively, to review and rank evidence and make recommendations regarding interventions that improved health on either an individual or group level. The National Institute of Occupational Safety and Health (NIOSH), building on the Integrated Employee Health NASA IOM Report,[11] similarly recognized the need for an integrated model of intervention that aligned health promotion with more traditional "health protection" (occupational safety and health) to create the Total Worker Health™ initiative.[20]

This initiative provides new tools, frameworks, and integrated metrics to assess and improve the "environment", which can promote or detract from improving health and business performance.[12,21–27]

118.5 EMERGING TRENDS AND TECHNOLOGIES

New scientific and economic evidence is emerging and being applied to systems and technologies to initiate and sustain healthy behaviors for both individuals and populations.

The clinical practice of *lifestyle medicine*, rooted in the rapidly evolving understanding of *epigenetics*, *microbiome, and neuroplasticity* represents a major new front in the prevention, treatment, and reversal of common disease.[28,29] Basic science research has demonstrated that inflammation is the common etiologic pathway for the majority of chronic diseases. Growing evidence demonstrates that plant-based eating, physical activity, stress reduction, restorative sleep, addiction reduction/cessation, and meaningful social connection are clinically effective and create new opportunities for linkages and synergies with environmental and population-based strategies[29]

A better understanding of the *mind–body continuum*, including the neuro-humoral science of "happiness" and the production of dopamine/endorphins by multiple stimuli, has led to an augmented appreciation of the chemistry and pathways to enhanced well-being.[29] The power of *social connection*, which underlies the phenomena of connection and contagion,[30] and intrinsic motivators, which can be very personal and strong (purpose, passion, mission), are also being described and deployed.[21]

Built environments that design healthy architectural and human support systems that naturally promote productivity as well as the deployment of *choice architecture*, which makes the "right thing to do the easy thing to do", are becoming more mainstream in creating and sustaining a culture of health. Re-connecting individuals and home, school, worksite, and healthcare settings to the *natural outdoor environment*[30–32] has been shown to improve both public health and human functioning.

Behavioral economics[33,34] and thoughtful alignment and application of incentives have increasingly informed the design and deployment of comprehensive health management programs.

Personal biomeasurement with real- or near-time feedback using wearable technologies tethered to social media support for ongoing behavior change and optimal self-care

is promising and appeals to an increasingly "wired" generation. *Physicians prescribing coaching* using electronic medical records (EMRs) and the trusted "power of the white coat" to produce better outcomes, increase patient engagement, and improve provider satisfaction are being implemented[35, 36].

Healthcare financing and delivery innovations occurring through the Affordable Care Act (ACA) and employer purchasing coalitions and broader use of *value-based incentivized health reimbursement arrangements and health savings accounts* have further accelerated the adoption and impact of wellness strategies. The "volume to value transformation" has led to the emergence of *accountable population healthcare models* designed to meet the "Triple Aim"[37] of improving health, enhancing patient experience, and reducing the per capita cost of care. *Growing consumerism and transparency* in healthcare appropriateness, quality, and costs can further accelerate the prevention, treatment, and even reversal of disease versus "usual care" models characterized by ineffective, inefficient, overutilized, and costly care. *Consumer and patient activation* to improve health and medical care can be measured using validated tools and deployed on a population basis.[38] And *shared decision-making* is increasingly accepted as foundational to producing better outcomes at lower cost using evidence-based decision aids.[39] *Moving care and caring "forward"* to on-site, near-site, homes, schools, and worksites for both coaching and medical care delivery where it is more accessible, engaging, integrated, and lower cost is rapidly accelerating, particularly among large, self-insured employers.

CLINICAL APPLICATIONS

Physicians, as the most trusted agent in healthcare, will be expected by employers initially and other purchasers over time to become competent in lifestyle medicine to prevent, treat, and reverse common chronic diseases.

- Clinicians increasingly will be expected not only to understand epigenetics in causing common, chronic inflammatory-mediated diseases but also to apply brief motivational interviewing techniques to better engage patients in lifestyle interventions.
- Clinical practice workflows, EMRs, and telehealth utilization accelerated by the COVID-19 pandemic will increasingly be linked to consumer-, employer-, and community-centric health behavior coaching programs, online tools, monitoring/feedback technologies, and support groups delivered outside the traditional office setting.

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Part XX

Exercise Psychology



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119 Mind/Body Interactions in the Exercise Domain

Stressing the Body to Improve Psychophysiological Functioning

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KEY POINTS

- Examining important psychological constructs (e.g., stress, behavioral motivation) across multiple levels (e.g., psychological, biological) will yield much more meaningful answers to mind–body problems than single-level analysis.
- There is a need to focus on the multifaceted nature of the stress response, including the influence of psychological determinants, as the complete stress response and the underlying mechanisms have yet to be fully unraveled in humans.
- Promising evidence indicates the stress response can be "trained" through regular exercise behavior, but there is a need for understanding how individual differences mediate the "toughening" effect of exercise.

119.1 MONISM VERSUS DUALISM

In the previous editions of this chapter,[1–3] we discussed at length what "mind/body" means, how it could be studied, and how it has been studied in the exercise domain through a biological psychology perspective. Biological psychology is "the study of the physiological, evolutionary, and developmental mechanisms of behavior and experience … and emphasizes the goal to relate biology to issues of psychology" (p. 5).[4] Biological psychology assumes mental activity and brain activity are inseparable, a single unit (i.e., monism), and progress in this field has been exponential. This monistic assumption is a departure from the dualistic approach wherein mind and body are treated as separate entities. As Cacioppo, Tassinary, and Berntson[5] noted:

> Monism has replaced any lingering notions of dualism, as psychological states are more likely to be conceived as represented in and acting through cortical, limbic, and brain stem regions, with influences on autonomic, neuroendocrine, and immune activity, which in turn serve to modulate crucial cellular and molecular processes. Afferent information, in turn, travels from the peripheral to the central nervous system to influence the brain and behavior in social contexts. (p. 2)

However, dualistic thinking continues to dominate the field of exercise science. This is likely because much of the research conducted within the exercise domain focuses purely on physiological adaptations (e.g., musculoskeletal, cardiorespiratory, metabolism), psychological outcomes (e.g., self-reported anxiety, depression, well-being), or behavior promotion, intentionally or unintentionally separating the mind and body. However, the emergence of cross-level analysis (i.e., examination across biological and psychological levels), what we referred to in the previous work as "seedlings of change", continues in exercise research, providing foundational evidence of the mind/body phenomena prior to, during, and following acute and long-term exercise. The present chapter aims to give the reader an updated sampling of work utilizing a mind/body approach in the exercise domain since the previous edition of *Lifestyle Medicine*,[3] while focusing on the stress response, exercise as a stressor, promotion of exercise as a health behavior, and the psychophysiological benefits of regular exercise.

119.2 OUR BODIES UNDER STRESS

"Stress" is a feature of daily life, but what is "stress"? Hans Selye,[6] credited with coining the term "stress" as we know it today, defined stress as a "non-specific response of the body to a demand". Selye adopted the term "stress" from the field of physics, which generally defined stress as total force per unit area. In physics, stress can take different names—tensile, compressive, bulk—all of which refer to disruption of the structure of a material. Thus, it is conceivable for human stress to be psychological, physiological, environmental, and so on, as long as it disrupts bodily equilibrium or "homeostasis". Homeostasis, coined by Walter Cannon,[7] refers to the relatively narrow limits within which our internal bodily systems (e.g., nervous, cardiovascular, respiratory, endocrine) automatically coordinate to maintain a relatively steady, functional internal

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state. With developments in research, stress has been more recently defined as a "state in which homeostasis is actually threatened or perceived to be so" by adverse forces (p. 374).[8] These adverse forces, more commonly referred to as *stressors*, may be internal or external, real, or perceived. It is when these stressors are of great enough intensity, duration, or frequency (i.e., temporality) to exceed one's regulatory capacity that the organism's stress system is activated, resulting in a cascade of internal system changes with the singular goal of re-establishing homeostasis.[9,10] For example, temporality refers to a stressor that could occur for 20 seconds every minute or a two-second interval that occurs ten times in a minute. There is consensus that the stress response is natural, protective, and necessary to function, but an overactive or dysfunctional stress response, especially when prolonged, results in major negative health consequences.

While stress can be both positive (i.e., eustress) or negative (i.e., distress), how an individual appraises a stimulus (i.e., potential stressor) will influence their regulatory control.[11] Only a stressor that is perceived to exceed an organism's natural regulatory capacity (e.g., an unpredictable and/or uncontrollable stimulus) has the potential to induce a stress response.[12] Moreover, emerging evidence within animal studies suggests the stress response is "demand specific", signifying specific conditions or environmental signals that elicit a patterned array of hormonal and neural responses to ready the organism for the specific behavioral demand (e.g., fighting, fleeing, defending, submitting, or hunting).[13] However, this demand specificity has yet to be unraveled in humans, leaving a great deal of room for individual variability in stress appraisal, reactivity, and recovery. We know the human stress response is psychophysiological, involving patterned physiological alterations to aid in preparing the organism to neutralize a perceived threat (e.g., the appraised demands of the stressor outweigh available resources). Outlined below is a summary of a physiological response to non-specific stressors.

The stress response begins when a threat, real or perceived, activates the cerebral cortex in areas such as the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and somatosensory cortex. The information is processed and directed to subcortical structures, including the amygdala, ventral basal ganglia, and thalamus, all of which "communicate" with the hypothalamus. A signal conveying sensory information (e.g., pain, danger) can also be sent directly to the amygdala prior to it being processed in the cortex, allowing for a faster response to life-threatening stimuli. The hypothalamus is then responsible for evoking the stress response by "directing" signals through two neuroendocrine pathways: the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenocortical (HPA) axis. The SAM axis is considered a fast response and is most directly related to the "fight, flight, or freeze" behavioral response. Activation of the SAM-axis pathway begins with hypothalamic stimulation following a "stressor", where the preganglionic sympathetic neuron is activated to directly stimulate the adrenal medulla (of the adrenal glands; an endocrine organ structured atop the kidneys) to release catecholamines (norepinephrine, epinephrine) into the bloodstream toward target organs. The release of nor/epinephrine is responsible for increasing heart rate (and cardiac contractility), metabolic rate, blood pressure, muscle tension, and respiration, for pupil and bronchial dilation, and for blood to be shunted from the gut to the muscles; all of which facilitate the coordination of internal systems for an appropriate behavioral response to a stressor. It is generally believed the activation of the SAM axis optimizes functioning. Indeed, evidence suggests a fast, large increase in nor/epinephrine response from baseline to stressor is positively related to task performance. In addition, when this large increase of nor/epinephrine following stressor onset was coupled with a relatively fast (within minutes) decline of nor/epinephrine following stressor cessation, less anxious feelings were reported, and the individual tended to have greater trait emotional stability.[14]

In contrast, activation of the HPA axis is a slower, more prolonged stress response, which can lead to undesirable health conditions, often associated with stress, if left unchecked. The HPA axis response begins with stimulation of the hypothalamus, the integrative center of the autonomic nervous system (ANS), following a "stressor". However, instead of ganglionic activation, this pathway begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus into hypothalamic-pituitary circulation. CRH targets corticotropic cells within the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH, in turn, stimulates the adrenal cortex, resulting in the synthesis and release of glucocorticoids (e.g., cortisol) and mineralocorticoids (e.g., aldosterone). Cortisol, considered the primary stress hormone, mobilizes fuels (glucose) for energy use. Acutely, cortisol acts to benefit the organism, but prolonged or overexposure to cortisol can disrupt almost all internal body systems, resulting in pathogenesis.[15,16] Thus, the stress response system is natural and ultimately helpful to mobilize an organism to effectively deal with a stressor. However, even while most individuals in modern Western civilization are not regularly exposed to life-threatening stressors, perceived stress and the associated negative health consequences resulting from overexposure to stress (and cortisol) are on the rise. There is an apparent need to focus attention on the stress response. Is it possible to train individuals to appraise stressors differently in an era of increasing, yet non-life threatening, distress? Better yet, can the internal, collaborative physiological systems be trained to react and recover more efficiently to stressors?

119.3 EXERCISE AS A CONTROLLED STRESSOR

The consequences of an inappropriate stress response (e.g., prolonged stress response or delayed recovery) have been

related to increases in physiological (e.g., cardiovascular, metabolic, immune, digestive) and psychological (e.g., anxiety, depression, fatigue) diseases and disorders.[17] Because exercise has been shown to positively impact all of these outcomes, exercise scientists have examined how exercise can alter an individual's response to stress and found compelling evidence that exercise can diminish exaggerated stress reactivity and combat stress-related health effects.[18,19] Indeed, Dienstbier[14] proposed exercise as a self-regulatory method to promote "active toughening" (i.e., effective adaptation) of the stress response systems. He suggested an introduction of controllable, intermittent stressors (such as regular exercise behavior) as a way to "physiologically toughen" an individual's stress response and increase stress tolerance.

Recall that a cascade of internal physiological alterations occurs when an organism is stressed, and Selye believed this cascade of events was a "non-specific" response to a given demand. With this foundation, research has been dedicated to examining how a stressor can induce adaptations of the stress response systems and improve the stress response given a similar stressor. With evidence of an acute bout of exercise eliciting a physiological stress response (e.g., increase in plasma catecholamines, cortisol), exercise was confirmed a stressor. Exercise scientists furthered this exploration by testing whether an exercise stressor could evoke not only physiological adaptations to similar exercise stressors but also to psychosocial stressors like public speaking and memory tasks.

The cross-stressor adaptation hypothesis (CSAH) posits that continued or repeated exposure to a specific stressor (e.g., exercise) will induce an adaptation of the stress response system(s), and thus decrease stress reactivity to a similar stressor and reduce sensitivity to dissimilar stressors, highlighting the importance of habituation. Sothmann and colleagues[20] posed that an exercise stressor of sufficient intensity and/or duration (i.e., exercise that exceeds the regulatory capacity of the organism) shares a similar physiological stress response to a psychological/mental stressor (e.g., public speaking, timed mathematic equations). This led to research aimed at understanding whether exercise adaptations are homotypic (i.e., exercise stressor produces habituation and sensitization only to exercise stressors of similar duration and/or intensity) or heterotypic (i.e., exercise stressors provide adaptations across differing psychosocial stressors). Researchers have found that an exercise stressor can induce adaptations to similar exercise stressors, and, while findings are inconsistent, there is some evidence exercise stressors also improve stress responses to psychosocial stressors.

119.3.1 Stressing the Endocrine System through Exercise

Research has primarily focused on the stress-buffering effects of regular aerobic exercise. A systematic review by Mücke et al.[21] reviewed research examining the influence of regular physical activity and fitness on various indices of stress reactivity, including cortisol. As they argue, previous research has used a wide variety of stressor tasks, ranging from physical to cognitive, to socioevaluative, each of which might elicit varying physiological responses. As such, reviewing studies that have used a fairly standardized stressor, namely the Trier Social Stress Test (TSST),[22] Mücke et al. found that ten of the 12 studies included found either full or at least partial support for reduced HPA reactivity (i.e., smaller cortisol response) to the TSST in those who were either more active or more fit. Another way of examining the exercise-stress relationship is to determine to what extent an acute bout of exercise might impact stress reactivity. For example, Zschucke and colleagues[23] examined stress reactivity (via cortisol and α-amylase) following a mental stressor task in young (~24.5 years) sedentary or trained males after they completed a 30-minute aerobic activity of the same relative intensity (60–70% VO_{2max}). All participants, regardless of fitness level, had a blunted cortisol response to the mental stressor task following the bout of exercise compared with a light stretching condition. Zschucke et al. also found that cardiorespiratory fitness was inversely related to cortisol response to the mental stressor ($r = -0.39$). using a slightly different approach, Caplin et al.[24] randomly assigned healthy male participants to one of three different exercise intensity conditions (light, moderate, vigorous) and examined cortisol responses to a subsequent mental stressor (the TSST). There was a dose-dependent cortisol response to the TSST, with the vigorous intensity group showing a slower rise and lower peak in cortisol response along with a more rapid return to pre-stressor levels. These findings[21, 23] suggest an acute bout of exercise reduces or blunts the stress response to a follow-up mental task, perhaps through a negative feedback loop.[23,24]

Taking a different perspective, Gerber, Ludyga, Mücke, Colledge, Brand, and Pühse[25] proposed that general perceptions of stress (i.e., low vs. high) may interact with physical activity levels to impact the neuroendocrine response following a stressor. They studied cortisol activity following a brief psychosocial stressor (10 minutes TSST) between groups of individuals engaging in low (<20 minutes at least 3·week^{-1}) versus high levels of vigorous exercise (≥20 minutes at least 3·week^{-1}) and found more cortisol reactivity for those engaging in less vigorous exercise in response to the TSST. They also observed that this cortisol reactivity was mediated by the individual's perception of stress, where those who perceived greater levels of general stress had greater cortisol reactivity, but much more so in those who did not engage in sufficient levels of vigorous physical activity. This suggests psychological interpretation or "appraisal" of a stressor impacts the physiological stress response but engaging in regular vigorous physical activity can work to offset this reactivity. Indeed, Lazarus and his colleagues have theorized and tested the stressor-appraisal-response chain dynamics and found these "intra-individual differences" in cognitive appraisal, such as perceiving a stressor as a challenge versus a threat, are associated with differing psychophysical outcomes following a stressor.[26,27]

119.3.2 Stressing the Cardiovascular System through Exercise

It has been known for some time that cardiovascular reactivity to psychosocial stressors increases risk for cardiovascular disease. There is also evidence of greater cardiovascular reactivity negatively impacting hippocampal gray matter and amygdala volume, brain structures important for controlling cardiovascular responses during stress, a year after the cardiovascular reactivity measures were taken.[28] Evidence suggests those who are more aerobically fit have less cardiovascular reactivity to a given stressor.[18] Heart rate (HR) and blood pressure (BP) responses have been extensively examined, with the consensus being those with greater aerobic fitness levels have attenuated stress reactivity (as indexed by smaller HR and BP responses to a stressor).[29,30] It has also been postulated that, rather than directly influencing reactivity, aerobic fitness leads to faster cardiorespiratory system recovery following a stressor.[31] Additionally, the individual's perception of the stressor (e.g., as a challenge vs. threat) can elicit differing cardiovascular system responses (challenge is associated with increased vasodilation while threat is associated with vasoconstriction).[11] This led to considering how the nervous and cardiovascular systems interacted. Heart rate variability (HRV) is one method used to better understand whether autonomic nervous system (ANS) adaptations were indeed occurring alongside cardiovascular adaptations. Briefly, the heart is innervated by both parasympathetic (vagus nerve) and sympathetic fibers. When an organism is within parasympathetic dominance, the more activated vagus nerve results in greater vagal tone. Vagal tone is associated with less psychophysiological arousal and is indicative of an individual at rest. However, even at rest, an individual's parasympathetic and sympathetic nervous systems are working simultaneously, and a stressor, real or imagined, can lead to parasympathetic withdrawal (reduction in vagal tone) or activation of sympathetic fibers, resulting in increased psychophysiological arousal, HR, BP, and so on.

Ultimately, HRV is simply a measure of the time intervals between subsequent heartbeats (the intervals between R-spikes, or interbeat intervals [IBIs] found within an electrocardiogram). Greater variability in IBIs while at rest is associated with greater vagal tone (i.e., parasympathetic dominance), while less variability (i.e., more consistent heartbeats) is associated with less vagal tone (i.e., parasympathetic withdrawal). As such, HRV can be viewed as a physiological marker of stress directly associated with PNS activity.[32,33] Indeed, HRV has been used as an index of morbidity and mortality, with research demonstrating that more consistent IBIs (i.e., less HRV) are predictive of dysfunction in the cardiovascular and immune systems as well as mental health challenges like anxiety, depression, and stress regulation.[34]

This evidence led to the question of whether and how exercise alters HRV, as an increase in HRV would provide some evidence of beneficial nervous system adaptations. A few studies have examined the impact of varying exercise modalities on HRV, with mixed findings on the effects of aerobic, resistance, and mindfulness exercises (e.g., yoga) on HRV improvements.[31,35,36].In a more real-life setting, von Haaren and colleagues[37] randomly assigned 61 college-aged male engineering students to either a 20-week aerobic exercise intervention (two sessions·week^{-1} for ~30 minutes per session) or a control group. Participants in the exercise training group had greater HRV compared with the control group during a real-life stressor (i.e., academic exams). There is a consistent association between fitness and greater HRV, but isolating exercise behavior as the reason for HRV improvements remains relatively elusive. In part, this is because HRV has primarily been used to reflect training load and overreaching in athletes. However, it seems HRV research is fostering attention in other aspects of the exercise domain. Research in this area may soon result in a better understanding of HRV as an indicator of psychophysiological reactivity and recovery following exercise and psychosocial stressors.

119.3.3 Stressing the Immune System through Exercise

As for immune system reactivity, circulating inflammatory markers are of interest.[38–40] A review of the literature by Slavish and colleagues[38] differentiated salivary inflammatory markers according to varying stressors (e.g., exercise, psychosocial). Their findings indicated that fluctuations in interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are fairly consistent across exercise and psychosocial stressors (refer to reference [38] for inflammatory marker characteristics). They did note that a lack of consistent methodology across studies requires caution in broad-stroke interpretations. Moreover, Pedersen and Hoffman-Goetz[41] iterate in detail the acute, immunosuppressant effect of an exercise stressor, while also discussing observed immunological adaptations that can occur over time for regular exercisers. Consistent evidence illuminates the potential for acute immunosuppression following exercise, especially if the exercise stressor is intense and prolonged. However, regular bouts of moderate-intensity exercise have been shown to be "immuno-protective", where proper recovery between intermittent exercise stressors is essential to gain such immunoprotective effects.[42] This exercise-inducing immune-protective effect is thought to be a result of, in part, reductions in inflammation, thymic mass maintenance, and enhanced immunosurveillance.

119.3.4 Stressing the Mind through Exercise

Beyond the focus on physiological stress, it is also important to consider a few additional points, namely mental resistance and resilience (see reference [43]). Mental resistance refers to how effectively an individual regulates stress before the deleterious effects of the stressor would have a negative impact. An increase in mental resistance would

allow greater levels of a stressor to be experienced (i.e., in either intensity, duration, or temporality) without detrimental effects. Mental resilience is the ability to recover from a stressor once experienced. As Levinsohn and Ross[44] put it, the notion of resilience has been used to describe the "mental elasticity of rebounding from adversity" (p. 89). Future work examining the ability of regular exercise to develop greater mental resistance is needed, as is the examination of whether exercise can enhance mental resilience to life's adversities (see reference [45]). Building mental resistance and resilience can aid in "toughening" an individual[14] such that an individual is more likely to: (1) perceive a stressor as a challenge rather than a threat; and (2) develop and employ effective coping mechanisms to recover more quickly from a stressor. As stated previously, one's cognitive appraisal of a stressor as well as one's ability to "bounce back" following a stressor influences the intensity and duration of the stress response.

Cognitive appraisal refers to both primary and secondary appraisals.[26] Primary appraisal indicates an individual's evaluation of the "encounter" (i.e., stressor) and determines whether there is potential for harm or benefit to life, a loved one, self-esteem, values, goals, and so on. Meanwhile, secondary appraisal refers to the evaluation of "control" or whether the individual can do anything to prevent harm or increase benefit, such as employment of coping strategies like acceptance, information seeking, social engagement, and behavior/social inhibition. If an individual perceives a benefit in some way, and the individual believes they have control or strategies that can increase the benefit, then the stressor is perceived as a "challenge"; this is ideal for an appropriate, healthy stress response. However, if an individual perceives a stressor as harmful or aversive, they will consider strategies and potentially begin coping, defined as "the person's constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the person's resources" (p. 993)[26] to reduce harm. An individual's cognitive appraisal of a stressor and its accompanying arousal can mediate their cardiovascular output to that stressor. Jamieson, Nock, and Mendes showed that individuals who were instructed to reappraise a stressor as adaptive and aiding in performance (i.e., viewing the stressor and its arousal as a challenge) had increased cardiac efficiency (i.e., greater cardiac output, decreased vascular resistance) when compared with those who received no reappraisal instruction (i.e., viewed the stressor and its arousal as more threatening).[11] This is where Dienstbier's[14] proposal of "active toughening" could impact not only the physiological systems but the psyche (or mind) as well. Regular exercise behavior, when considered from a macro behavior perspective, could build general mental resistance across stressor types; individuals are more likely to appraise a given stressor as a challenge versus a threat. There is a sound basis for such reframing or reappraisal of stressors and the arousal it brings.[46] Exercise behavior could also build mental resilience such that beneficial coping strategies are more readily used to recover from uncontrollable stressors. However, even with cross-sectional studies providing initial insight into the positive relationship between physical fitness and mental resilience, the empirical evidence supporting this view is limited and is worth further exploration.

In conclusion, previous work in the exercise domain has shown that: (a) physical stress, like exercise, can lead to activation of the HPA axis;[47] (b) those who exercise regularly show reductions of adrenocortical system activity at the same absolute exercise workload compared with inactive or untrained individuals;[48] and (c) HPA axis adaptations occurring as a result of regular exercise can translate (i.e., cross-over) to psychosocial stressors.[49] These adaptations may be reflected in either a smaller response magnitude (i.e., habituation) to submaximal load or an enhanced response to maximal demands (i.e., sensitization).

119.4 EXERCISE PROMOTION FROM A MIND/BODY PERSPECTIVE

The vast majority of exercise psychology literature, especially that related to behavior promotion, emphasizes theoretical frameworks that are strictly cognitive (i.e., "mind" only) based, all but ignoring "body"-based influences. The temporal self-regulation theory (TST), a framework that incorporates neurobiological factors to explain exercise behavior, incorporates higher-order cognitive functioning as an important psychophysiological factor for behavior engagement.[50,51] The set of higher-order cognitive processes is often referred to as "executive functioning". This includes cognitive flexibility (i.e., ability to switch from one concept to another), planning, attentional inhibition (i.e., suppression of stimuli that are irrelevant to the task at hand), working memory (i.e., storing and managing information to complete learning, reasoning, and decision-making behavior), and scheduling. As noted by Hall and Fong, substantial existing evidence[52–57] has shown that exercise results in improvements in executive function (e.g., cognitive control, mental flexibility, working memory). Moreover, higher levels of executive functioning can increase engagement in behaviors that require consistent, controlled effort, like that needed for exercise. Thus, Hall and Fong[50,51] propose that a positive feedback loop exists such that individuals with stronger executive functioning can more consistently engage in an exercise routine, which serves to further strengthen executive functioning and the neural circuitry (e.g., prefrontal cortex, anterior cingulate cortex) subserving it. Recall that the stress response begins in brain areas such as the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). These structures are where executive functioning and other cognitive processing occur. Thus, the TST's emphasis on executive functioning and neural circuits provides a neurobiological mechanism responsible for one's "self-regulation capacity", and this self-regulation capacity is thought to be a major determinant of stress reactivity and recovery as well as

future behavior. While a relatively novel theory with a need for more empirical investigation, there is some additional psychophysiological evidence to support the TST for exercise behavior promotion.

Recall the cortex of the brain is structurally divided by the longitudinal fissure into symmetrical left and right hemispheres. Thus, a typical cortex contains two dorsolateral prefrontal cortices (dlPFC); one in the left hemisphere and the other in the right hemisphere. This is important because, with advances in the field of neuroscience, there is evidence that a relatively more active right dlPFC is associated with emotional dysregulation, while a relatively more active left dlPFC is associated with emotion regulation. The valence-motivation model[58,59] postulates that resting, frontal cortical activity reflects a biological disposition to respond with more positive affect in the presence of relatively greater left frontal hemispheric activation or more negative affect with relatively greater right frontal hemispheric activation. Further, such frontal cortical hemispheric asymmetries in activation reflect a disposition to approach versus withdraw from given stressors that exceed the individual's self-regulatory threshold. In sum, aligning with the evidence of the left versus right dlPFC, a relatively more activated left frontal cortex predicts positive affective states, approach motivation, and appetitive behavior, but a relatively more activated right frontal cortex predicts negative affective states, withdraw motivation, and aversive behavior.

Taken together, the TST provides a psychophysiological theory proposing deliberate, consistent behavior as a consequence of an individual's self-regulation capacity, which is formed by the individual's neural circuity (e.g., dlPFC, ACC) and associated executive functioning. This neural circuitry and associated executive functioning can be developed through a positive feedback loop, so that better executive functioning leads to more exercise engagement, and regular engagement in exercise leads to better executive functioning. There also appears to be a dispositional (or trait) attribute for self-regulation capacity, in which greater relative activation of the left anterior hemisphere is predictive of a positive, approach orientation to engage in exercise behaviors. According to the TST, this should be trainable given sufficient engagement in exercise stressors of sufficient intensity and/or duration.

119.5 EXERCISE FOR PSYCHOPHYSIOLOGICAL FUNCTIONING

The study of cognitive and affective (feeling) states has grown exponentially over the past 30 years, especially in the exercise domain. However, affective and cognitive responses to exercise have almost exclusively been examined separately, leaving the interplay of these two processes less understood. Although core affect has been defined as a general affective state that occurs without the need for cognitive processing, emotions and moods are defined by the need for some type of cognitive appraisal.[60] Meanwhile, cognitive function is an umbrella term associated with a variety of things including, but not limited to, concentration, attention, learning and memory, planning, and problem-solving. Within exercise psychology, executive functioning has been extensively studied to better understand the influence of exercise on cognitive functioning. Executive functioning, as mentioned previously, has been linked to brain areas in the frontal lobe, specifically within the prefrontal cortex, as well as subcortical structures linked to memory (e.g., hippocampus). While there is a recent emergence of literature in biological psychology addressing affective-cognitive processing (i.e., how affective states interact with cognitive processing), there is a gap in the literature addressing the affective-cognitive dysregulation that can occur under prolonged distress. For example, traumatic or prolonged stress can increase one's risk of physical health disorders (e.g., hypertension, headaches) as well as mental health disorders (e.g., anxiety, depression). There is evidence that emotional reactivity as well as cognitive processing is hindered for those diagnosed with physical and mental health disorders. However, there is a relatively sparse literature addressing how affective and cognitive processing interact to influence dysregulation. Examining cognition independently from affect and vice versa is limiting and provides an incomplete picture. Given the relative lack of theoretical and mechanistic approaches regarding the reciprocal interplay between cognition and affect as it relates to exercise behavior, the scarce research that is attempting to assess the affective-cognitive mind, especially while in dysregulation (e.g., anxiety, depression) deserves to be examined.

A reasonable question is whether an affective disorder results in deficits in executive function or do deficits in executive function result in undesirable affective states. For example, a common symptom of depression (a mood disorder) is the inability to think clearly, concentrate, or make decisions.[61] These symptoms suggest a deficit in cognitive function, including executive function. As noted earlier, the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC) are primary brain structures involved in executive functioning. However, in depressed individuals, the connections between these brain structures are altered, resulting in reductions in certain executive functioning tasks.[62] Whether increases or decreases in neural activity are observed, it has become generally established that depressed individuals differ in their cognitive processing abilities.[63] Similarly, evidence suggests that greater anxiety results in variations in cognitive control processing.[64] Anxiety is considered an aversive emotional state occurring in the presence, or perception, of a threatening stressor that typically evokes a psychophysiological and behavioral response.[65] For individuals with higher levels of anxiety, increased neural activation occurs in the inferior frontal cortex in response to negative affective stimuli (e.g., fear); individuals with lower levels of anxiety have greater neural activation in response to more positive affective stimuli (e.g., happy)[66] In sum, both depression and anxiety are accompanied by alterations in

cortical activity and functioning: depression negatively impacts cognitive processing; anxiety increases attention to threat-related stimuli, reducing cognitive processing efficiency (i.e., attentional control).[65]

Some research has been done to compare changes in attention, a component of executive function, and depressive symptoms (e.g., rumination) between individuals clinically diagnosed with major depressive disorder (MDD) and "healthy" controls following exercise (e.g., focused meditation, aerobic training). In this limited work, depressive symptoms have been shown to decrease, while at the same time, cognitive control improves, but more so for those with MDD.[67–69] Additionally, Olson et al.[68] suggest that exercise may offer a neurobehavioral treatment for enhancing cognitive control and attenuating depressive symptoms. Although this is an intriguing initial foray into the affective-cognitive interplay within the exercise domain, this needs to become a focus of future research. There is a lack of exercise literature examining changes in anxiety, depression, and other affective functioning in conjunction with cognitive functioning, and vice versa. Such work is needed to understand the reciprocal roles of affective and cognitive function as it relates to exercise behavior and individual health.

119.6 SUMMARY

As we had stated earlier, it is difficult to argue that "mind" and "body" are not inextricably linked. The simultaneous examination of mind/body from multiple levels (e.g., psychological, biological, sociological) will result in a far greater informational yield than will persisting in the examination of mind or body separately and/or from single levels of analysis.[5] The most important point, as always, is to begin with specific, testable research questions. These will lead to innovative research designs and careful and proper selection of the best tools to use in answering these questions. Such an approach will increase the likelihood of uncovering the patterns and meaning in mind/body relationships (i.e., strong inference) rather than just adding more bricks to the brickyard.[70]

As chronic stress has been directly linked to a broad range of diseases and disorders,[17,71] it is imperative to understand the mechanisms underlying the stress response, and further, to determine preventive and treatment practices that can slow the disease process, as well as provide an avenue for improved health. As such, understanding the mechanistic changes following an exercise stressor is an avenue of important focus, as exercise has consistently been shown to improve the systematic functioning of all body systems. However, methodological approaches are inconsistent and differ widely when examining both exercise and psychosocial stressors. A need for consistency in methodology and conceptual sophistication has been deemed necessary to better understand the impact of stress, as well as the role exercise plays in (a) preventing and/or mediating stress reactivity and (b) leading to greater stress tolerance, resilience, and stress recovery.

In conclusion, stress reactivity and recovery are important areas of research, as overwhelming levels of stress are more likely today than ever. There is an accumulation of evidence suggesting exercise, as long as the exercise bout is appraised as a challenge and sufficient recovery is implemented, can "toughen" the individual, increase self-regulation capacity, and ultimately increase future exercise behavior. However, the potential for individual differences in appraisal, demand specificity, and biological mechanisms remain unanswered questions.

CLINICAL APPLICATION

Psychophysiology offers great promise for providing a better understanding of the prominent clinical issues in exercise psychology. The techniques, tools, and methodologies allow for the examination of clinically important questions (e.g., how does exercise improve psychophysiological stress reactivity and recovery). As research continues to produce relevant findings, these can be used to optimize individual treatment plans.

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120 Genetic Influences on Regular Exercise Behavior

Eco J.C. de Geus, PhD and Matthijs D. van der Zee, MSc

KEY POINTS

- Despite broad knowledge that regular moderate to vigorous physical activity decreases the risk for morbidity and mortality, a large proportion of the population in industrialized societies does not engage in regular leisure-time exercise activities.
- A growing body of twin and family studies show that genetic factors explain around 45% of the individual differences in the adoption and maintenance of regular exercise, with clear changes in the heritability estimates across the lifespan.
- In childhood, genetic factors (♀25%–♂36%) and the shared family environment (♂52%–♀63%) are the main causes of the observed variance in regular exercise behavior.
- In adolescence, genetic factors (♀♂49%) and the shared family environment (♂23%–♀31%) are the main causes of the observed variance in regular exercise behavior.
- In adulthood, genetic factors (♂48%–♀50%) and environmental factors (♀♂44%) unique to the individual are the main causes of the observed variance in regular exercise behavior.
- Ongoing large-scale gene-finding efforts are rendering important clues on the biological pathways underlying regular exercise to improve the success of interventions on this crucial health behavior.

120.1 INTRODUCTION

Regular engagement in physical activity lowers the risk for morbidity and mortality through cardiovascular disease (CVD), type 2 diabetes, and cancer.[1–4] Despite these well-documented benefits of physical activity, a large proportion of adults worldwide do not engage in such activities regularly.[5,6] Consequently, a physically inactive lifestyle remains a major threat to health in modern-day society, with substantial economic costs.[7] This is reflected in public health recommendations worldwide, which unanimously include an encouragement to a more active lifestyle.[8–11]

Correlates and determinants of a physically active lifestyle have been studied intensively over the past three decades to define optimal targets for intervention. Over 30 years ago, Dishman and colleagues stated that "one barrier to developing effective methods to encourage physical activity (…) is the lack of knowledge of the determinants of regular physical activity".[12] Since then, researchers have identified numerous potential determinants in cross-sectional or longitudinal studies that contribute to the adoption and maintenance of physical activity. Physical activity encompasses a broad domain of activities at work, at home, during transportation, and in leisure time. In this chapter, the emphasis is on voluntary exercise activities in leisure time such as jogging, swimming, exercising at fitness clubs, and participation in recreational or competitive team and individual sports. Such voluntary exercise activities are often specifically aimed at improving skills, fitness, and health and are rapidly becoming the major source of physical activity of moderate to vigorous intensity in many industrialized countries. Furthermore, whereas many aspects of physical activity, such as activity at work or physically active transportation, may be very situational and hard to modify, the readily modifiable nature of voluntary exercise activities makes it a prime target for behavioral intervention.

The bulk of studies devoted to the determinants of voluntary exercise behavior have attempted to explain low exercise prevalence in terms of social and environmental barriers. These include, among others, poor access to facilities,[13] low socioeconomic status,[14,15] non-Caucasian race,[16] high job strain,[17] subjective "lack of time",[18] low belief in health benefits,[14] and low social support by family, peers, or colleagues.[18,19] Although these social factors are important, they explain only a small part of the individual differences in voluntary exercise behavior. In this chapter, we review the evidence from twin and family studies that genetic factors play an important role too.

120.2 DEFINITIONS OF VOLUNTARY EXERCISE BEHAVIOR

Heritability estimates of behavioral phenotypes are sensitive to the exact definition of the phenotype. We will therefore first give an overview of how voluntary exercise behavior has been defined in the studies used in this review. The four important characteristics of the studies presented in Table 120.1 and Figures 120.1–120.4 are that the reported exercise activities were performed regularly, voluntarily, in leisure time, and in the context of fitness or sports. We stress

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TABLE 120.1

Prevalence of Voluntary Exercise Behavior in a Large Population-Based Sample from the Netherlands

		Males					Females				
		Weekly METhours					Weekly METhours				
		Mean	SD	IQR	%Sedentary	%Vigorous	Mean	SD	IQR	%Sedentary	%Vigorous
<9*	N = 8157	14.0	12.0	16.9	24.5%	4.8%	8.9	8.7	8.8	27.2%	1.6%
	Twins (99.95%)	14.0	12.0	16.9	24.5%	4.8%	8.9	8.7	8.8	27.2%	1.6%
10–12	N = 7803	24.3	18.2	23.1	12.6%	23.8%	14.6	13.3	16.7	15.5%	7.8%
	Twins (98.89%)	24.2	18.0	23.1	12.5%	23.8%	14.6	13.3	16.8	15.4%	7.9%
	Singletons (1.11%)	26.7	28.6	27.8	23.4%	21.3%	12.3	10.6	16.4	22.5%	2.5%
12–15	N = 17,523	25.5	20.0	27.4	16.5%	29.4%	16.9	16.1	21.0	19.0%	13.4%
	Twins (95.62%)	25.5	19.9	27.2	16.3%	29.3%	16.9	16.1	21.0	19.0%	13.4%
	Singletons (4.37%)	25.2	22.9	31.1	21.0%	30.7%	16.5	15.8	22.4	19.5%	13.4%
15–18	N = 13,851	26.9	25.0	35.6	24.7%	36.3%	17.2	19.1	26.6	29.3%	16.4%
	Twins (88.32%)	27.0	25.0	35.6	24.6%	36.3%	17.2	19.3	26.7	29.3%	16.5%
	Singletons (11.33%)	26.9	25.1	38.6	25.4%	37.2%	16.9	18.0	26.2	29.1%	15.3%
18–21	N = 9622	23.7	24.8	36.0	29.5%	29.4%	15.0	18.2	22.9	34.1%	12.7%
	Twins (78.75%)	23.1	23.9	36.0	29.4%	28.7%	15.1	18.3	22.9	33.4%	13.1%
	Singletons (19.75%)	25.6	27.1	37.5	30.4%	31.4%	14.7	18.0	23.3	37.0%	11.4%
	Parents/spouses (1.51%)	34.2	36.2	31.0	21.1%	39.5%	15.2	19.2	21.9	31.8%	12.1%
21–25	N = 7061	21.3	22.7	35.0	30.5%	24.9%	14.9	17.8	21.9	30.9%	11.1%
	Twins (71.70%)	21.6	22.3	35.4	29.5%	25.3%	15.4	18.2	22.0	30.2%	12.2%
	Singletons (23.03%)	21.0	23.6	33.3	32.0%	24.0%	14.2	17.4	20.0	31.5%	8.6%
	Parents/spouses (5.27%)	19.2	23.4	32.2	36.6%	24.4%	11.0	12.8	16.8	38.6%	5.5%
25–35	N = 9104	17.0	20.7	25.5	35.3%	16.1%	11.0	14.6	16.2	39.2%	6.5%
	Twins (59.20%)	17.9	21.3	26.7	32.6%	16.6%	11.9	15.4	17.0	37.0%	7.4%
	Singletons (17.90%)	17.3	20.4	26.5	35.2%	17.3%	11.3	14.0	16.4	35.9%	6.9%
	Parents/spouses (22.89%)	15.0	19.3	24.0	41.0%	14.3%	8.1	12.1	12.0	48.6%	3.6%
35–45	N = 18,971	11.7	17.2	17.5	46.6%	8.5%	8.8	11.8	13.4	43.3%	3.5%
	Twins (17.33%)	15.1	18.8	21.8	33.1%	10.5%	11.0	13.5	16.0	35.4%	5.2%
	Singletons (4.94%)	15.1	20.5	23.5	38.2%	11.8%	10.5	13.5	15.3	36.4%	4.7%
	Parents/spouses (77.70%)	11.0	16.6	16.2	49.3%	8.0%	8.1	11.1	12.3	45.8%	2.9%
45–55	N = 16,658	11.3	17.8	16.4	49.8%	8.4%	9.1	13.0	13.4	46.3%	4.5%
	Twins (9.58%)	13.3	17.9	18.2	40.4%	10.9%	10.8	14.6	16.4	41.4%	6.0%
	Singletons (3.27%)	11.5	15.3	17.3	44.7%	7.3%	10.4	13.9	14.6	41.2%	5.8%
	Parents/spouses (87.14%)	11.1	17.9	16.0	50.5%	8.2%	8.7	12.7	12.8	47.3%	4.2%
>55	N = 7989	11.3	19.7	16.0	53.6%	9.2%	8.2	13.3	11.3	51.7%	4.1%
	Twins (16.87%)	11.1	18.6	14.7	52.7%	9.3%	8.5	13.6	11.0	52.1%	5.2%
	Singletons (5.19%)	10.8	18.1	16.0	50.7%	6.7%	9.1	15.5	12.0	52.1%	5.9%
	Parents/spouses (77.92%)	11.4	19.9	16.0	53.8%	9.3%	8.0	13.0	11.2	51.5%	3.6%

This table was constructed using 78,525 unique individuals. For over half of these individuals, multiple data points were available, some of which could fall into the same age-bin. Data from these participants were weighted per age-bin such that the total weight per participant was 1 within each age-bin. N, number of unique participants (i.e., sum of weights) with valid data; SD, weighted standard deviation; IQR, weighted inter-quantile range; vigorous exercisers are defined as subjects with a METhours score over 35 (i.e., at least five hours per week vigorous [MET=7] activity).

that this definition of voluntary exercise behavior is different from total physical activity, even when a restriction is made to leisure-time physical activity (LTPA), or more narrowly to LTPA that is of moderate to vigorous intensity. Such LTPA measures will encompass almost all voluntary exercise behavior but may additionally include gardening, dancing, or active transportation by walking or bicycling to school/work, none of which are considered to fall under voluntary exercise behavior in our definition. We further exclude obligatory exercise activities like physical education classes or job-related sports and exercise (military boot camps; firefighter training) and activities that are done infrequently like sailing, surfing, or skiing during a limited number of days per year. We note that our definition of voluntary exercise behavior also *excludes* accelerometer/step counter-based physical activity. Without additional self-reporting, these activity counts cannot distinguish between voluntary exercise activities or other forms of moderate to

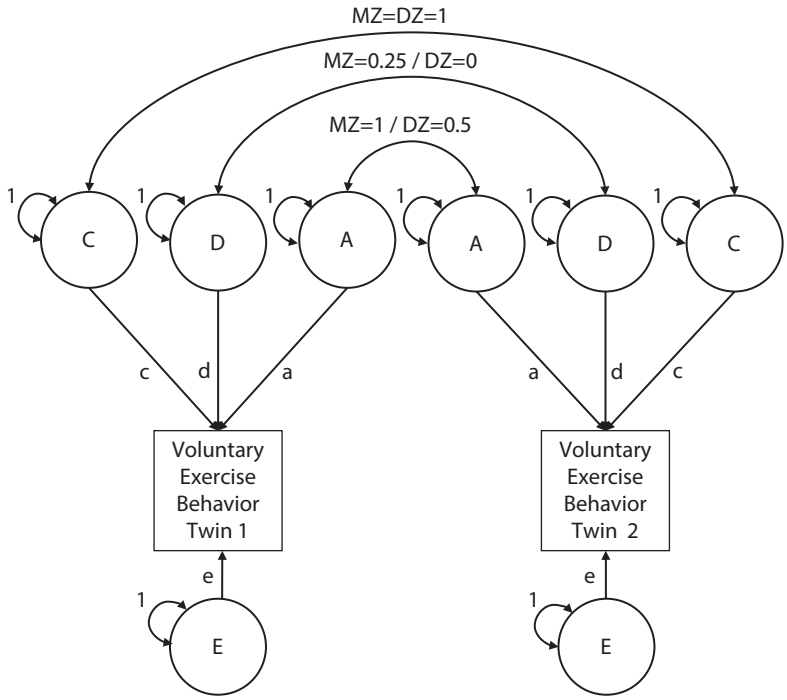


FIGURE 120.1 Path diagram depicting the correlated latent factors that can cause twin resemblance in voluntary exercise behavior. Note: These are the additive (A) and non-additive (D) genetic factors and shared environmental (C) factors. Based on biometrical theory we can set the correlation of the latent additive genetic factors for MZ twins to 1, and for DZ twins to 0.5. The non-additive genetic factors are correlated 1 in MZ twins and 0.25 in DZ twins or lower if there is much epistasis.[68] The correlation of shared environmental factors is set to 1 for both types of twins. The latent unique environmental factors are (per definition) uncorrelated in both DZ and MZ twins. Unobserved latent variables have no scale: their variance is arbitrarily set to 1 (the double arrows that start and end in the latent factors). Path coefficients a, c, d, and e represent the factor loadings of voluntary exercise behavior on the latent factors. In a classical twin study, only three of the four a, c, d, and e path coefficients can be estimated simultaneously. As a rule of thumb, a, c, and e are estimated, unless the MZ correlation is much larger than twice the DZ correlation, pointing to genetic non-additivity.

vigorous activity (e.g., vacuum cleaning, bicycling, stair climbing).

Studies on regular voluntary leisure-time sports and exercise activities all used self-reporting, but the exact methods have greatly differed across studies. Some studies used surveys, whereas others used interviews. Exercise behavior was assessed with only a single "YES/NO participation" question[20] or by presenting subjects with a list of specific exercise activities,[21,22] whereas still others allowed all exercise activities to be reported in a free response format.[23] The quantitative metrics for exercise behavior have differed accordingly. Some studies use a categorical scale classifying participants in a dichotomy of "regular exercisers and non-exercisers", sometimes adding an additional level of moderate exercisers, but using different thresholds for the minimum frequency and the minimum intensity of the exercise activities to separate regular exercisers from moderate or non-exercisers. Ideally, the volume of voluntary exercise behavior is expressed as the energy expenditure in exercise activities across a fixed time interval (e.g., METhours per week). This can be done by multiplying frequency per week, duration in hours, and the estimated intensity for each activity and then summing across all reported exercise activities. Unfortunately, the type, duration, frequency, and intensity of multiple possible exercise activities have not always been assessed or reported in detail in all studies.

120.3 PREVALENCE OF VOLUNTARY EXERCISE BEHAVIOR

In the Netherlands Twin Register, data on exercise behavior has been collected by virtually the same methods through surveys of large numbers of twins, their parents, siblings, spouses, and the children of twins and siblings.[24] To assess the volume of voluntary exercise behavior, we ask whether the participant exercised regularly in their leisure time ("Yes" or "No"). If the participants (or their parental informant) responded affirmative, they were asked to indicate all the exercise activities done regularly. For each exercise activity reported, they noted the number of months per year, weekly frequency, and average duration in minutes of the activity. Depending on the age of the participants (≤16 vs >16 years), Ainsworth's Compendium of Physical Activity[25] or the adaptation for children by Ridley[26] was used to assign a metabolic equivalent of task (MET) value to each exercise activity. This reflects its energy expenditure as a multiple of the basal energy

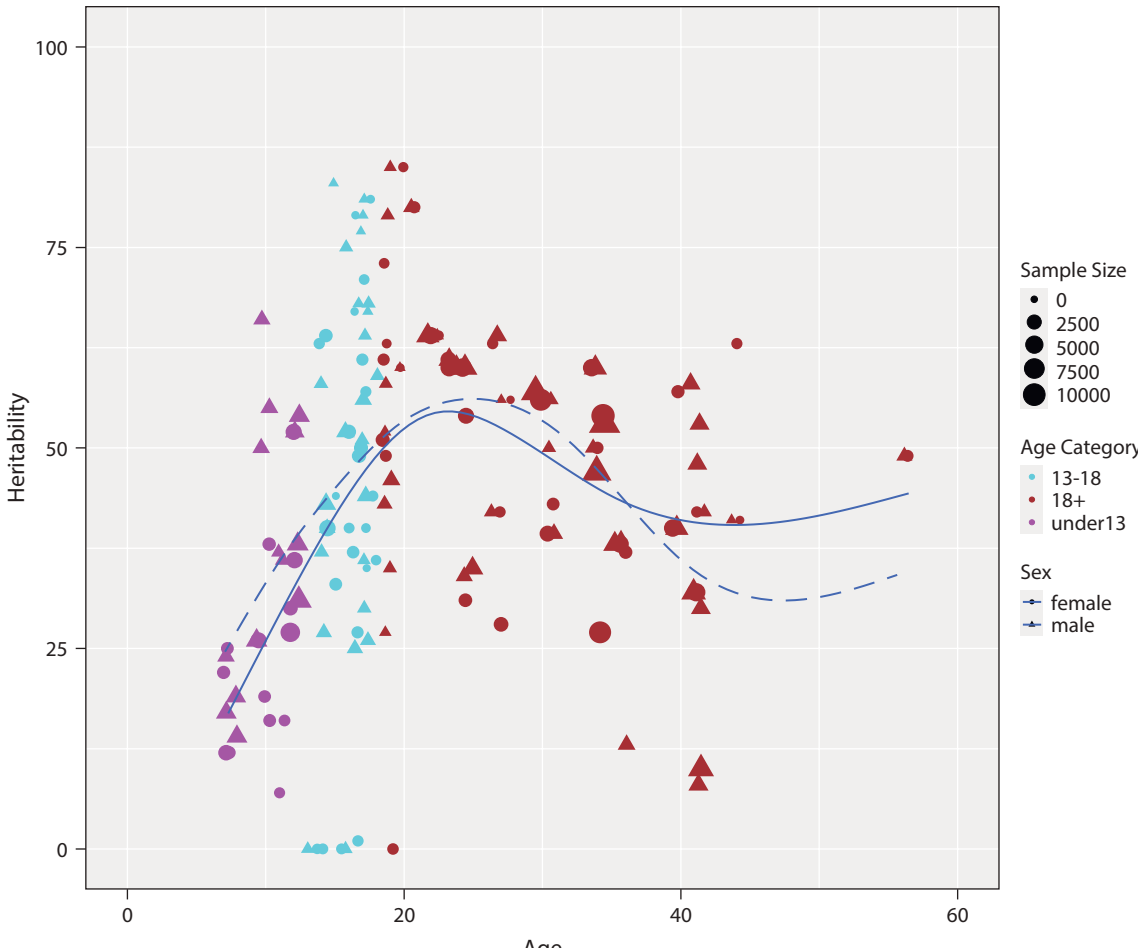


FIGURE 120.2 Heritability estimates for voluntary exercise behavior as a function of age. Note: The scatterplot depicts 168 heritability estimates (on a 0% to 100% scale) from 28 twin studies. Coding indicates whether the estimate derives from samples with mean twin age under 13 (light), between 13 and 18 (medium), and over 18 (dark). Different shapes indicate males (triangle) and females (circle). The size of the circle/triangle is weighted by the square root of the sample size. The two fit lines are the GAM functions around the male (dashed line) and female (solid line) estimates, which also take the study weight into account.

expenditure (approximately 1 kcal/kg/hour) in an average person engaged in that activity. For each participant, a total weekly METhours value was computed across all exercise activities by summing the products of the number of hours spent weekly on each exercise activity and its MET value. Activities were only scored if that participant had engaged in them for at least three months during the past year. For children and adolescents, exercise during obligatory physical education classes at school was not included in the weekly METhours value for voluntary exercise behavior. The six-month test–retest reliability of the weekly METhours value was found to be 0.91[27] and we also found substantial tracking over time using follow-up periods of up to 20 years.[28]

Amassing data across a 30-year period of research in the Netherlands Twin Register results in 162,286 observations from 78,525 unique participants (54.4% females) from 23,681 nuclear families (see Table 120.1). The mean age of the sample was 29.7 (SD = 17.6). A total of 67.3% of these participants engaged in regular voluntary exercise activities, whereas 32.7% were classified as non-exercisers. When considering the frequency and intensity of the exercise activities in METs, little over half of the population (62.4%) engaged in moderate to vigorous exercise activities (4 MET or more) for at least 60 minutes per week, and only 12% could be considered vigorous exercisers (i.e., engaging in vigorous exercise activities [7 MET or more] for at least 300 minutes per week).

In Table 120.1, we illustrate the effects of two of the best-known determinants, age and sex, on the prevalence of voluntary exercise behavior. We furthermore report exercise behavior separately for the twins, their singleton siblings, and, in the older age groups, for the parents and spouses. As many participants took our surveys multiple times, even in a single age-bin, the data were weighted such that the sum of weights per unique participant is one (e.g., if three observations are available for a participant in the age-bin 45–55, the weight of each would be one-third). This means that sample overlap between age bins is possible in

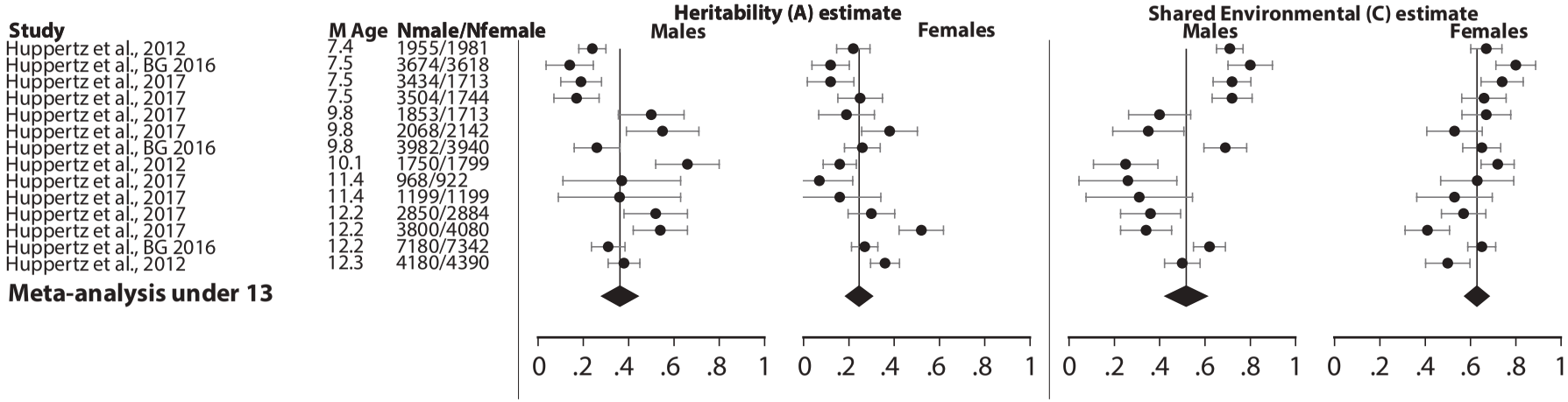


FIGURE 120.3 Forest plot and meta-analytic estimate of the contribution of additive genetic (A) and common environmental (C) factors to the variance in voluntary exercise behavior in childhood.

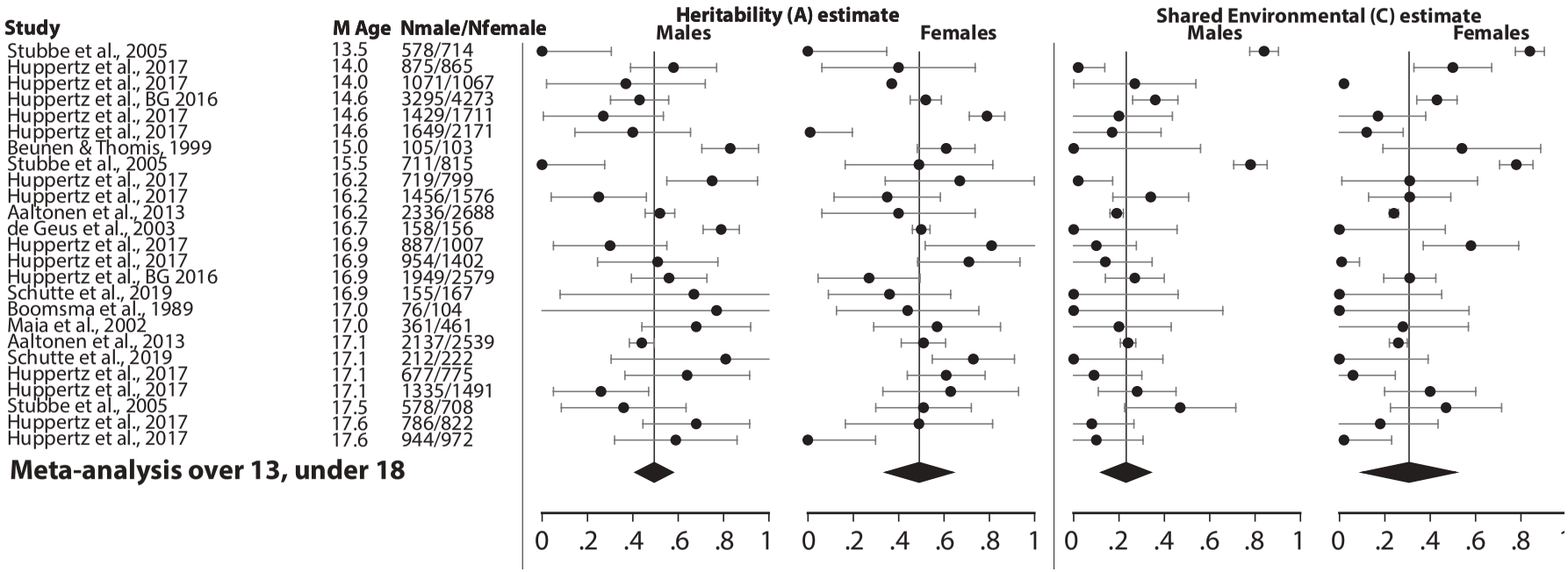


FIGURE 120.4 Forest plot and meta-analytic estimate of the contribution of additive genetic (A) and common environmental (C) factors to the variance in voluntary exercise behavior in adolescence.

Table 120.1, but after weighting there is no sample overlap within age-bin.

We found a lower volume of exercise behavior in young children (<9) compared with older children and adolescents. This contrasts with findings for total physical activity, which is known to decrease from the highest level in early childhood to lower levels in late childhood and adolescence.[29] We interpret this to reflect the predominance of play in determining the total physical activity of young children.[30] In keeping with previous reports, the volume of voluntary exercise behavior in leisure time is lower in females than in males and shows a general decline after adolescence in both sexes. For example, 75.3% of the male youngsters between 15 and 18 years old engage in some form of regular exercise and 37.3% engage in regular vigorous exercise, whereas in adults over 55 years, these numbers have dropped to 46.3% and 9.2%. Formal testing of the linear and quadratic effects of age (in years) and sex (females coded 1) and their interaction on weekly METhours in weighted general equation estimation (GEE) models, accounting for the nested (family) structure of the data, revealed an effect of sex, with males showing higher levels of exercise ($\beta = -0.47$, SE = 0.01, $p < 10^{-99}$). There was also a linear decrease in exercise with age ($\beta = -0.01$, SE = 0.001, $p = 1.8\times10^{-16}$) as well as an additional quadratic age effect ($\beta = -1.19\times10^{-4}$, SE = 1.88×10^{-5}, $p = 2.09\times10^{-10}$). A significant interaction between age and sex ($\beta = 0.004$, SE = 0.0004, $p = 2.31\times10^{-14}$) shows that the decrease in exercise after adolescence is less pronounced in females, compared with males, which is in line with previous findings.[23]

To reconfirm that exercise behaviors do not differ between twins and non-twins,[23] we selected families with same-sex twins where at least one non-twin sibling of the same sex had also participated. We then compared the voluntary exercise behavior of twins with their non-twin siblings, by rerunning the weighted regression mentioned previously with the addition of variables for monozygotic (MZ) and dizygotic (DZ) status separately or a combined twin-status variable. These regressions revealed no significant differences with non-twin siblings for either MZ twins ($\beta = 0.01$, SE =0.02, $p = 0.35$) or DZ twins ($\beta = 0.02$, SE = 0.02, SE = 0.02, $p = 0.15$).

Overall, a clear picture arises from Table 120.1 for the Dutch population. Despite its well-documented benefits, a large group of people do not engage in voluntary exercise on a regular basis, particularly in adulthood. These findings are very much in line with those from other European countries.[21] Furthermore, worldwide, the prevalence of a complete lack of regular voluntary exercise behavior in adults varies between 21% and 53%, depending on the exact age group and the assessment methods used.[6,31] What factors cause exercisers to exercise and, more importantly, what keeps non-exercisers from doing the same? The remainder of this chapter will review evidence from twin and family studies for a significant genetic contribution to voluntary exercise behavior.

120.4 TWIN STUDIES ON VOLUNTARY EXERCISE BEHAVIOR

As with many other traits, exercise behavior appears to run in the family. The familial resemblance observed for exercise can represent genetic influences ("nature") or they can represent environmental influences that are shared within a family ("nurture"). Twin studies can separate these two mechanisms by comparing the resemblance in MZ or identical twins to the resemblance in dizygotic DZ or fraternal twins. MZ twins are the result of the division of a single fertilized egg during an early stage in embryonic development, whereas DZ twins result from two separate fertilized eggs. When twins are reared together, they share part of their environment, and this sharing of the family environment is the same for MZ and DZ twins. The important difference between MZ and DZ twins is that the former share (very close to) all of their genetic variants, whereas the latter share on average only half of the genetic variation segregating in the family.[32,33]

If the resemblance in exercise behavior within MZ pairs is about twice as large as in DZ pairs, which can be tested by comparing the MZ (rMZ) and DZ (rDZ) twin correlations, this suggests that additive genetic factors (A) influence exercise behavior. Additive genetic factors represent the sum of all linear effects of the genetic loci that influence the trait of interest. The contribution of additive genetic variance to the total variance is known as the narrow sense heritability. If the MZ resemblance is more than twice as large as the DZ resemblance, this suggests the additional influence of non-additive genetic factors (D), due to allelic interactions within (dominance) and across genes (epistasis). The contribution of all genetic variance, additive and non-additive, to the total variance is called broad sense heritability. If the MZ twin correlation is less than twice the DZ correlation, this points to the additional influence of common environmental (C) factors contributing to the twin resemblance. Common environmental factors are defined as those environmental factors that are shared within a family, such as parenting behaviors, family functioning, neighborhood, or socioeconomic status. The extent to which even genetically identical MZ twins raised in the same family do not resemble each other is ascribed to the unique (or non-shared) environmental factors (E). These include all unique experiences for each twin separately, like differential jobs or lifestyles, accidents, or other life events, and in childhood, differential treatment by the parents, going to different schools, and having non-shared friends and peers, but also somatic mutations and the stochastic part of epigenetic changes. Measurement error will also be subsumed by the unique environmental factor.

The effect of genetic and environmental factors on exercise behavior in a sample of MZ and DZ pairs can be graphically depicted in a path diagram (Figure 120.5). However, because the additive and non-additive genetic factors cannot be estimated simultaneously with shared environmental factors, at least not using only data from twins, a model

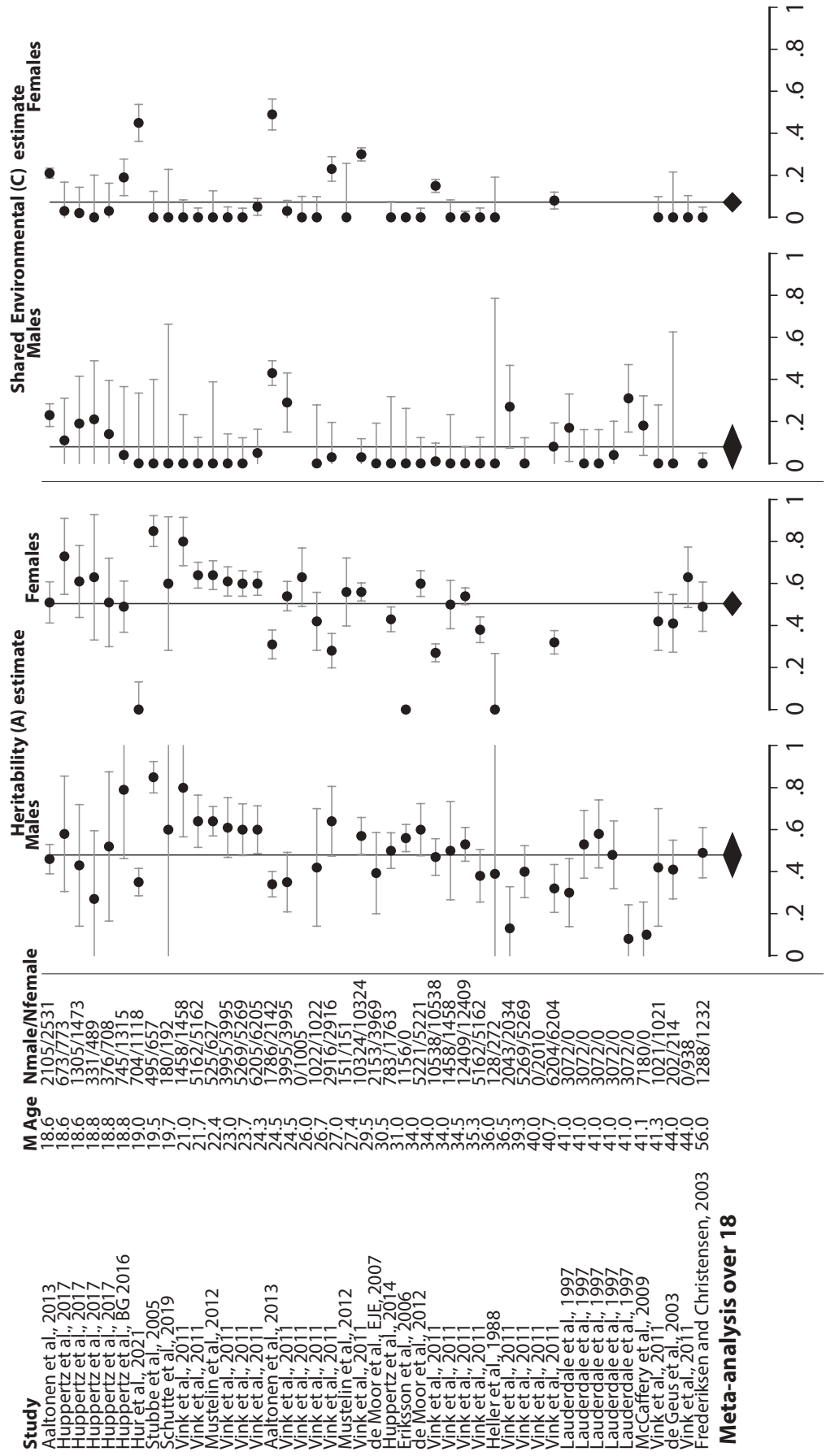


FIGURE 120.5 Forest plot and meta-analytic estimate of the contribution of additive genetic (A) and common environmental (C) factors to the variance in voluntary exercise behavior in adulthood.

estimating A, C, and E for exercise behavior is usually preferred over an ADE model. Non-additivity is left unmodeled because the MZ correlation for exercise behavior is rarely larger than twice the DZ correlation. In terms of the parameter estimates obtained from fitting the twin model to the data, the heritability can be expressed as $a^2/(a^2 + c^2 + e^2)$. This heritability can also be represented as a percentage by multiplying this ratio by 100. The proportions of variance ascribed to shared environmental and unique environmental factors can be computed in a similar manner and are given by, respectively, $c^2/(a^2 + c^2 + e^2)$ and $e^2/(a^2 + c^2 + e^2)$.

An overview of heritability estimates from twin studies conducted on voluntary exercise behavior is given in Figure 120.1. These studies converge on the finding that exercise behavior is heritable across the lifespan, despite substantial heterogeneity in the measures used within and across studies, comprising of: a dichotomy of yes/no sports or regular exercise participation;[20,34–43] time spent weekly on sports;[44,45] the Sports Index from the Baecke questionnaire;[46–49] daily energy expenditure on exercise activities;[50] weekly METhours/minutes spent on sports and exercise activities with intensity higher than 3 or 4 MET;[45,51–54] or categories (e.g., sedentary, moderate, vigorous) based on weekly METhours/minutes[55] or weekly exercise frequency.[56, 57] Figure 120.1 shows remarkable age-related changes in the relative contribution of genetic factors to the total population variance in exercise behavior, which are very similar for males and females. To capture this age dependence and arrive at more stable estimates across multiple studies and multiple measures within single studies, we conducted an inverse variance-weighted meta-analysis on the reported estimates for A and C separately across childhood (mean sample age between seven and 13), adolescence (mean sample age between 13 and 18), and adulthood (ages 18 and over). Results are depicted in Figures 120.2 to 120.4, with the column labeled "M" denoting the mean age of the sample.

Meta-analysis of samples with mean age under 13 estimates male heritability at 36% and female heritability at 25%. In parallel, the estimated variance explained by shared environmental factors was 52% for males and 63% for females. Large changes in genetic and environmental contributions to regular exercise behavior occur in the transition from childhood to adolescence. For example, Huppertz et al.[55] used a combination of univariate modeling on a very large cross-sectional set of Dutch twins (birth year ranged between 1986 and 2004) and a genetic simplex model on the subset of twins that had longitudinal data across multiple ages. Heritability was found to be low in seven-year-olds (14% in males and 12% in females), but gradually increased up to age 18 (79% in males and 49% in females). In contrast, the initially very high relative contribution of the common environment to the variance in childhood exercise behavior rapidly waned when children grew into adolescence and young adulthood (from 80% to 4% in males and from 80% to 19% in females). This pattern of findings was confirmed in studies using slightly different exercise measures and taking into account possible interactions of genetic factors with parental education.[45,58]

That common environmental factors shared by (twin) siblings play a large role in childhood is likely explained by the important role of the parents at this age. Parental modeling has been invoked to explain the correlation between the exercise behaviors of parents and offspring,[59,60] meaning that children copy the behavioral example of their parents. However, actual modeling of the parental phenotype as a common environment shared by twins showed such parental modeling to be absent or small at best.[41] Other effects of sharing the family environment are needed to explain the strong common environmental effects in childhood. These influences include encouragement by parents and siblings to be active, giving exercise activities priority over other leisure time activities, praising the child's activity and/or performance, watching the child be active, telling the child that exercise is beneficial, and enrolling the child in exercise programs or sports clubs, providing transportation to sports venues and supplying the child with equipment and financial support.[61] Such parental support is more strongly correlated to children's exercise behavior than the exercise behavior of the parents themselves.[59,62]

Meta-analysis of samples with a mean age between 12 and 18 estimates both female and male heritability at 49%. The estimated variance explained by common environmental factors in adolescence is about halved from childhood to 23% for males and 31% for females. Twin studies in the Netherlands, Finland, Sweden, and Belgium all show this age-moderation of the genetic and common environmental effects on exercise behaviors[44,56,63] and, independent of country, common environmental factors are a bit more important in early adolescence for girls than for boys. These results suggest that the influence of the family environment and parents becomes less prominent, giving way to increased influence from peers and coaches[64] while simultaneously the influence of genetic factors becomes more important, possibly related to enjoyment and ability. A large body of literature has confirmed self-efficacy, the belief that one can perform a given activity at an adequate level of performance, is a powerful determinant of whether someone engages in and adheres to an exercise program.[65,66] Self-efficacy may be an especially strong factor in adolescence, when the sensitivity to one's own relative ranking among peers may be the largest.

Meta-analysis of samples with mean age above 18 estimates male and female heritability at 48% and 50%, respectively. The remaining variation in adult exercise behavior is influenced by environmental factors unique to a single twin, whereas the common environment that the twins shared early in life, including a shared womb, no longer plays a role of importance. Results from the largest study on voluntary exercise behavior using an extended twin pedigree design[54] suggested that the common environment shared by siblings explains 4% of the variance in adult exercise behavior and the common environment shared by twins

explains 8%. During adulthood, genetic factors influencing performance level and intrinsic enjoyment of exercise will remain important, but extrinsic motivation derived from esthetic and health benefits may also become important. Interestingly we found that sharing a household with a spouse, which should be considered part of the unique environment of a person, yielded high (20–24%) contributions to the variance in exercise behavior. Because an extended family study encompasses partner/spouse relationships of different durations, this effect could be attributed to the increasing resemblance in partners' exercise behavior that occurs over time through marital interaction. Other unique environmental factors that come into play in adulthood and can impact on exercising are increasing job demands and child caretaking obligations, or lower exercise capability due to increasing health problems.

The results from the twin studies in Figures 120.1 to 120.4 demonstrate convincingly that heritable factors are present at all ages. The heritability of voluntary exercise behavior peaks during late adolescence and young adulthood but remains substantial throughout adulthood. Taken together, these results imply that family-based interventions are useful to increase this health behavior in children, whereas individually based interventions, taking into account innate differences in exercise capability and enjoyment, might be better suited for adolescents. Furthermore, as identified in our extended twin-family study, there is a growing influence of spouses on each other's exercise behaviors over time, which suggests that simultaneously targeting the spouses in partner programs is a useful strategy.

120.5 FAMILY STUDIES ON VOLUNTARY EXERCISE BEHAVIOR

The estimation of A, C, and E from the crucial comparison of MZ and DZ resemblance in the twin design makes various, often untested, assumptions. These include the equal environment assumption,[67] random mating assumption,[68] and absence of gene-by-environment correlation.[69] The equal environment assumption states that the MZ twins do not share a larger amount of common environment than DZ twins, based on people's change in treatment purely from the perceived zygosity. This would make MZ twins more alike through reasons other than the shared genome. The random mating assumption assumes that parents do not seek each other out as partners based on their exercise behaviors. If assortative mating on exercise behavior is present, the correlation between genetic factors influencing exercise behavior is higher than the theoretical 50% in DZ twins and full siblings, which can cause underestimation of heritability and overestimation of the shared environmental effects. The assumption that there is absence of gene-by-environment correlation (rGC) would be violated if children modeled their exercise behavior after the exercise behaviors of the parents. This would lead to a scenario where parents not only pass on their "genes for exercise behavior" but also create the strongest exercise behavior-shaping environment for their offspring. Such rGC would inflate the C estimation.[70]

Only one twin study has explicitly tested the equal environment assumption for a set of relevant traits, including total physical activity and physical activity at work or in leisure time separately.[47] No evidence for violation of the equal environment assumption was found for any of the physical activity traits. The presence of assortative mating and cultural transmission and how they impact heritability estimates has been actively tested by adding data from more types of relatives to the twin design, such as data from parents, grandparents, spouses, and siblings. Ten studies have employed extended family designs to report on the familial resemblance of voluntary exercise behavior among adolescent offspring (age range 13 to 20 years) and their parents.[41,54,71–78]

Spouse correlations inform on the presence of assortative mating, whereas parent-offspring correlations enable a test for the effects of direct cultural transmission. The spouse correlation for exercise behavior was significant in all these studies and the sample-size weighted mean was $r_{spouses} = 0.28$. However, extended twin-family studies that took assortative mating into account led to nearly the same heritability estimates as the twin-only model.[41] Mean parent-offspring correlations across 51,201 parent-offspring pairs was $r_{par\text{-}off} = 0.19$, which is substantially lower than the mean correlation between 21,900 full sibling pairs ($r_{sibs} = 0.30$). The stronger intragenerational than intergenerational resemblance cannot be attributed to genetic effects as both types of pairings share on average 50% of their genetic variation. It is largely because of a common environment shared by the offspring to which peers and siblings appear to contribute much stronger than parents. This aligns well with findings by de Moor et al.[41] that explicitly modeled environmental effects common to twins and siblings only and those also shared with the parents. In a sample of 3525 adolescent twins and their non-twin siblings (13 to 18 years) and 3138 parents from 1736 families, 42% of the variation in adolescent exercise behavior in boys could be explained by genetic factors and 52% could be explained by common environmental factors shared with co-twins and siblings but not with the parents. In girls, 36% of the variance in exercise was explained by genetic factors and 41% by generation-specific common environmental effects, with little evidence for cultural transmission.

Taken together, the results of extended twin-family studies suggest that heritability estimates for exercise behavior obtained from studies using only twins are not overly biased by assortment or cultural transmission. However, a final source of bias in the classical twin study design comes from the ubiquitous choice to set the non-additive genetic component to zero. As indicated before, a twin study cannot simultaneously model the A, C, D, and E parameters from just two pieces of relevant information (the MZ and DZ correlations). To circumvent this under-identification problem, D is often assumed to be zero. If this assumption is violated,

estimates of A tend to be biased upward and estimates of D and C tend to be biased downward.[79] This issue can also be partly overcome by including multiple different family members. For example, van der Zee et al.[54] constructed 19,543 extended pedigrees in the Netherlands Twin Register that specified all family relations among participants older than 16 years (N = 50,690 individuals). These pedigrees included twins with their non-twin siblings, spouses, children, and parents. Results confirmed the influence of genetic factors on METhours weekly spent on exercise in adulthood, but in contrast to most twin studies, a significant non-additive (D) genetic component (15%) in exercise behavior was found in this extended pedigree study. Progress in the identification of the actual genetic variants underlying the heritability of exercise behavior will help to resolve the exact contribution of additive and non-additive genetic effects.

120.6 GENE-FINDING STUDIES

The heritability of exercise behavior has been well established, but less is known about the actual genetic variants that are associated with this trait. Candidate gene studies in single small-sized cohort studies are now widely distrusted as a reliable source of replicable association because most complex behavioral traits are highly polygenic with only a very low percentage of the variance in the trait explained by a single genetic variant.[80] Instead, the ubiquitous method of choice to identify genetic variants influencing complex traits like exercise behavior is a genome-wide association study (GWAS), simultaneously testing the association of millions of variants across the entire genome.

The first GWAS on exercise that we conducted in 2009[81] tested for an association with leisure-time exercise behavior in two independent samples comprising 1644 Dutch and 978 American subjects. In retrospect unsurprising, neither sample yielded results that withstood the scrutiny of the multiple testing correction that needs to be applied due to the millions of tests performed simultaneously (p-value below 5×10^{-8}). Two more studies in Korea and the US increased the sample size to 8842 and 22,219, but again failed to detect significant associations with leisure-time exercise after the required stringent correction for the multiple testing burden.[82,83] In a follow-up study using the same leisure-time exercise behavior definition as de Moor et al.[81] but now in a ten-fold larger sample of 14,626 Dutch participants, van der Zee et al.[84] still came up empty-handed. A study of 16,016 Japanese adults did report one genome-wide significance for leisure-time exercise behavior.[85]

The number of genome-wide variants detected only went up once GWAS were scaled up to hundreds of thousands of participants by using the unique resource of the UK Biobank (UKB). Klimentidis et al.[86] performed a GWAS in the UKB (N_{max} = 377,234) assessing various physical activity measures with touchscreen-based surveys, among which were included vigorous physical activity (VPA) and strenuous sports or other exercises (SSOE). After applying corrections for work-related physical activity and an indicator of socioeconomic status, a dichotomy of zero versus three days of 25+ minutes of VPA yielded six loci that were associated with variation in this VPA measure. For SSOE, a dichotomy of participants spending no versus at least two days of sports or other exercises for 15+ minutes added another five genome-wide significant loci, with the most strongly associated variant in the *CADM2* gene. The above demonstrates the main truism in the GWAS field. Samples at a scale of 100,000 participants are needed to identify genetic variants in highly polygenetic phenotypes.

Detection of the genetic variants underlying the heritability of voluntary exercise behavior is clearly still in its infancy. It is nonetheless a sure route to increased future understanding of the actual biological pathways underlying the individual differences in the choice for regular exercise behavior, that is, the biology that makes exercisers exercise but keeps non-exercisers from doing the same. Knowledge of these pathways may further help resolve causality in the well-known association of exercise with other lifestyle behaviors such as overeating and smoking, or with physical health problems like cardiovascular and metabolic disease[87] and mental health problems including depression.[88] Finally, large-scale meta-analytic GWAS of regular exercise or other physical activity traits can be used to compute polygenetic risk scores for these traits.[89] These can be exploited in stratified or personalized interventions that take innate biological differences into account and therefore increase the success of an intervention. Following existing models of the use of genetic information in healthcare, polygenetic risk scores for regular exercise behavior could be used to focus our resources for intervention on those who are likely to need the intervention the most,[90] give feedback on where they fall on the genetic risk scale to increase their motivation to engage in the intervention to avert an unwanted (disease) outcome,[91,92] or tailor our interventions to better fit the person's genetic risk profile with regard to injury sensitivity,[93] and whether the focus should be on enjoyment, competitive performance, or what the predicted health benefits are (e.g., with regard to weight loss).

CLINICAL APPLICATIONS

In keeping with the acknowledged importance of the interplay of nature and nurture in many other behavioral traits, future interventions to increase regular exercise behavior should prominently include knowledge of its genetic/biological determinants instead of sole reliance on social/environmental determinants. Although research on the specific genetic/biological determinants is in its early phase, and the use of polygenetic scores is still only a future promise, some recommendations can already be extracted from the twin and family studies reviewed here to increase the success of interventions on regular exercise behavior:

- In childhood, shared environmental influences additionally explain family resemblance in exercise behavior, implying that family-based interventions

provide a meaningful route to increase this health behavior in children.

- In adolescence, shared environmental influences appear to be largely generation-specific and innate factors become a dominant influence. This implies that interventions in adolescence should be tailored to the individual and their relationship with peer groups. A large emphasis on athletic competence, for instance, might be counterproductive for those adolescents at the low end of innate exercise abilities.
- Adulthood sees a substantial decrease in the prevalence of regular exercise behavior, with the increased competition for time by work-related and social roles. Given the increasing resemblance in the exercise behavior of spouses over time, partner programs can be an effective strategy. Despite the increased importance of unique environmental factors, genetic factors remain important in determining who will become/remain an adult exerciser. Enforcing preset levels on the frequency, duration, and intensity of exercise activities in guidelines may not be compatible with variation in the innate ability to enjoy and "feel good" after intense or prolonged exercise.

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121 Influence of Physical Activity on Brain Aging and Cognition

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KEY POINTS

- Physical activity plays an important role in brain health throughout the lifespan.
- Numerous studies have shown that physical activity enhances cognition throughout the lifespan.
- Physical activity improves biomarkers of brain health.
- Physical activity decreases the likelihood of various dementias including Alzheimer's disease.
- Physical activity plays an important role in improving affect and decreasing anxiety and tension.
- Physical activity plays an important role in multiple aspects of healthy sleep.

121.1 INTRODUCTION

There are strong associations between physical activity and cognition and brain health, in general.[1–16] These associations are particularly relevant as the worldwide population continues to age.

Issues related to brain health and cognition have become increasingly important, particularly in the older population, and across the lifespan. A robust scientific literature has emerged in this area. The concepts in this chapter utilize the same definition of brain health that was adopted by the Physical Activity Guidelines for Americans Advisory Committee 2018 Report (PAGA, 1), which stated that brain health is a concept that involves "optimal or maximal functioning of behavioral and biological measures of the brain and its subjective experiences arising from brain function".[1] This is a very similar definition that has been adopted in the Presidential Advisory Statement from the American Heart Association and American Stroke Association entitled "Optimal Brain Health".[17]

Research in neurobiology has advanced significantly in the last decade. There are multiple aspects of brain health including cognition, reduction of the risk of dementia,[18] perception of quality of life,[19] and sleep.[20] Advances in technology have also allowed the measurement of a variety of biological markers of brain structure and function. Numerous studies have now shown a strong and positive relationship between physical activity and brain health. These studies provide the underpinnings both for the recent focus on this topic from the PAGA 2018[1] and AHA/ASA Presidential Advisory[17] on "Optimizing Brain Health".

Issues of physical activity, brain health, and cognition are critically important to practitioners of lifestyle medicine since physical activity is one of the cornerstones and pillars of lifestyle medicine. The linkages between physical activity and brain health are an important and emerging area of interest in lifestyle medicine. With all of these factors in mind, it is a propitious time to consider issues related to brain health both from an individual and a public health standpoint.

121.2 BACKGROUND ON PHYSICAL ACTIVITY IN BRAIN HEALTH

Important research in the area of physical activity and cognition began to appear in the 1970s, both with animal and human investigations.[21] These studies examined physical activity and its impact on dopamine and reaction time in older and younger subjects. Several researchers reported faster reactivity (shortened reaction times) in older men and women who engaged in regular physical activity.[22–24] These findings contributed to the notion that reaction time was an index of the general integrity of the neurologic system and thus a proxy for cognitive function. Experiments in animal models supported these findings and further advanced this field.[25,26]

The next major breakthrough in human research involved the assessment of physical activity-induced effects on decision-making abilities. Studies showed that both intelligence and reasoning were enhanced by physical activity. Electroencephalography (EEG) technologies, which evolved in the 1990s, allowed more specific evidence concerning how the brain functioned in younger and older men who had high levels of physical activity. These findings led to important studies demonstrating that cognition was enhanced in physically active individuals.

Contributions in this area were buttressed by research utilizing newly available technology, namely magnetic resonance imaging (MRI), which demonstrated positive relationships between brain tissue density and the integrity of white matter and cardiovascular fitness in both men and women.[27] These MRI studies also led to findings that individuals with higher levels of cardiovascular fitness demonstrated resistance to atrophy of the brain with aging.

This line of research ultimately led to additional studies utilizing advances in genetics which showed strong

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cognitive benefits of physical activity for carriers of the APOE ε4 genotype. The APOE gene has been strongly associated with a higher risk of Alzheimer's disease (AD).[28] As a result, physical activity has now entered the area of Alzheimer's research and contains enormous potential.

In addition, studies have increasingly been published in the area of aging that explore the potential of reducing cognitive decline through physical activity in middle-aged and older adults. Such studies have led to the concept of "cognitive reserve", which denotes the idea that physical activity and other healthy lifestyle factors throughout the lifespan may, indeed, promote resilience against cognitive decline in old age.[29,30]

121.3 PHYSICAL ACTIVITY AND AGING

The positive role of physical activity on cognition has been most strongly demonstrated in men and women over the age of 60 years.[31] Individuals in this age range are likely to incur age-related decline in central nervous system (CNS) function, potentially due to inflammation or oxidative stress. The research examining physical activity in older adults has shown strong benefits suggestive of protective effects, slowing the cognitive decline typically associated with aging and dementia-related pathology.

It has been well described that as individuals age, changes in multiple organ systems occur. In particular, the effect of aging on the brain includes significant structural changes. These changes include loss of neurons and synaptic plasticity, particularly in the prefrontal cortex, which can result in a less efficient brain as well as decreases in memory and difficulties in "executive function",[32] an aspect of cognitive functioning that includes cognitive control, mental flexibility, and working memory, all of which are largely dependent on the prefrontal cortex. In contrast, knowledge and expertise tend to be well maintained in normal aging. These processes are largely independent of frontal lobe activity.[33]

In addition, decreases in brain volume are seen with normal aging by the seventh decade. Older individuals tend to compensate for reduced brain activity by instituting various aspects of the brain to accomplish tasks.[34] The change in the frontal lobe, and prefrontal cortex, in particular, is demonstrated functionally by a loss of such executive functions as working memory.

One physical change in the brain associated with pathologic aging is the development of amyloid plaque and neurofibrillary tangles (NFTs).[35] These structural changes in the brain may be responsible for initiating the disease process of dementia and ultimately lead to AD.

121.4 BENEFITS OF PHYSICAL ACTIVITY ON BRAIN AND COGNITION

Several biological processes may underlie the benefits of physical activity on cognition. Effects of physical activity on various biological aspects of the brain underscore the ability of physical activity to enhance cognitive reserve.[36] These biological aspects include neurotransmitters and neurotrophic factors THAT allow for increased growth and survival of neurons. In addition, physical activity enhances connections between neurons, classified as synaptogenesis, as well as the growth of new neurons (neurogenesis) and increased cerebral blood flow (angiogenesis).

Research has demonstrated that regular physical activity results in a reduction of age-related brain atrophy, and in some instances, a reversal of neural decline (i.e., neurogenesis, synaptogenesis). Several studies have shown increases in brain volume in both grey and white matter after a six-month aerobic exercise intervention.[37] Various executive functions such as inhibitory control, mental flexibility, and memory decoding have all shown benefits from physical activity.

Physical activity may also delay the symptoms associated with dementia and the normal aging process. The emerging literature on individuals with advanced Alzheimer's disease has shown mixed results in the area of physical activity.[17] However, individuals who have mild cognitive impairment (MCI) demonstrated significant improvement in executive function with increased physical activity. This is important since MCI is thought to be a stage often leading to AD. These studies in MCI patients suggest that physical activity reversed some of the neuropathological properties.[17] The mixed results in Alzheimer's patients suggest that the benefits of physical activity are more likely after long-term interventions. As such, changes in physical activity earlier in life are very important for lowering the risk of AD.

121.5 DEFINING OPTIMAL BRAIN HEALTH

The role of cognitive function and other aspects of brain health provided the underlying rationale for the American Heart Association (AHA) and American Stroke Association (ASA) to issue a joint Presidential Advisory to define "optimal" brain health in adults.[17] This Advisory underscores the concept that cardiovascular risks are also closely associated with brain health for the prevention of dementia in later life. A healthy brain is essential for living a long and full life. Sustaining brain health over the course of a lifetime is essential to maximize one's overall quality of life, functional ability, and independence.

As the AHA-ASA Presidential Advisory notes, most definitions of brain health emphasize the absence of overt vascular or neurogenetic injuries such as from strokes or AD. However, "optimal" brain health extends this concept to include the capacity to function and adapt to the environment. This underscores the important role of cognition.

The recommendations from the AHA-ASA Presidential Advisory emphasize seven metrics to contribute to optimal brain health, including increased physical activity. This is the same framework initially defined by the AHA as "Life's Simple 7".[38] These metrics include not smoking, consuming

a healthy diet, weight management (BMI less than 25 kg/m^2), and a strong emphasis on physical activity. The metrics in "Life's Simple 7" closely mirror the pillars of lifestyle medicine. An added benefit of following these metrics involves the important role they also play in minimizing risk factors for heart disease and stroke, including high blood pressure. The Presidential Advisory notes that physically active individuals have a 35% lower risk of cognitive decline compared with those who are physically inactive. These findings are very similar to those published in the PAGA 2018.

The role of physical activity in lowering the risk of heart disease and also in maintaining brain health is important for both individuals and public health. Multiple studies have shown that physical activity improves cognitive function throughout the lifespan. It is particularly important for older individuals. It is estimated by the year 2050, the population of adults over age 65 in the United States will reach 83.7 million individuals, which is double the 2012 level of 43.1 million.[1] Physical activity may be both an efficacious and cost-effective approach to improving multiple aspects of health, including cognitive function, in this population.

In the area of dementia and AD, the Alzheimer's Disease Foundation estimates that the annual cost of AD in the United States is approximately $250 billion per year. It has been estimated that in the last five years of life, the cost of dementia per person was $287,000.[39] These costs associated with AD and other dementias may increase to $785 billion per year by 2050. Increased physical activity may be a highly effective approach for lowering both the risk of developing AD as well as mitigating its cost. It has been estimated that 21% of AD cases in the United States are attributed to physical inactivity. If a 25% increase in physical activity could be achieved, it could potentially prevent 230,000 cases of AD.

In addition to its other benefits, increased physical activity improves quality of life (QOL).[40] Low levels of QOL have been linked to higher mortality risk in older individuals as well as greater use of healthcare facilities.

Regular physical activity has also been demonstrated to improve mental health, including reducing risk of depression and anxiety. Both depression and anxiety are common in the adult population in the United States. Increased physical activity has been shown to be as or more effective than pharmaceutical therapy for both of these conditions.

121.6 PHYSICAL ACTIVITY IN COGNITIVE RESERVE

The strong research base on the multiple benefits of physical activity on the brain throughout the lifespan has led a number of investigators to propose the concept of "cognitive reserve". Cognitive reserve refers to the capacity of the mature adult brain to sustain function and resist the effects of disease or injuries sufficient to cause a decline in cognition or the development of clinical dementia. It has been postulated that individuals who experience these declines have less cognitive reserve than individuals who do not and that physical activity helps build and maintain cognitive reserve.[36]

Cognitive reserve may be classified either as active or passive reserve. Active reserve relates to the adaptability of neurocircuits to respond to cognitive challenges. This can be exemplified by compensation and the use of other parts of the brain when confronted with challenges. Passive reserve, in contrast, refers to the structural properties of the brain. This involves brain tissue density, white matter integrity, and vascularity. Research has demonstrated that cognitive reserve is correlated with neurotransmitters and neurotrophic factors as well as an increase in synaptogenesis (generation of new brain synapses) and neurogenesis (generation of new neurons).[41,42] All of these factors appear to be related to increased physical activity.

It should be noted that cerebral blood flow decreases with age and dementia. Physical activity has also been shown to improve blood volume and vasculature in the brain through a process called angiogenesis. This process involves the development of new blood vessels through sprouting of the existing vessels and epithelial cells.

All the above processes are components of cognitive reserve and are positively influenced by physical activity. Thus, physical activity has enormous potential to help delay the onset of deterioration of cognitive function.

121.7 THE ROLE OF PHYSICAL ACTIVITY IN BRAIN HEALTH AND COGNITION

The PAGA 2018 Scientific Report devoted a whole section to the interface between physical activity and brain health, in general, and cognition, in particular.[1] In the area of cognition, improvements from physical activity were demonstrated for academic achievement and processing speed as well as memory, executive function, and decreased risk of dementia. Most of the evidence for these benefits comes from aerobic activity (e.g., brisk walking), although other forms of exercise (e.g., muscle strengthening, sports participation, yoga) may also contribute to these benefits.

Strong evidence also exists that physical activity has transient benefits for various domains of cognition such as working memory and processing speed. These findings have been demonstrated, particularly in children and older adults.[43]

Chronic effects of moderate or vigorous physical activity have been demonstrated, particularly in individuals over the age of 50. These benefits extend to individuals who have evidence of mild impaired cognition and may also be of benefit in conditions such as attention deficit hyperactivity disorder and Parkinson's disease.

The most dramatic improvements in cognitive function based on physical activity have been shown to involve executive function, which relates to impulse control and the ability to plan activities.

121.8 PHYSICAL ACTIVITY AND IMPAIRED COGNITIVE FUNCTION

Cognitive function is vitally important for the ability to plan actions and maintain neural connections which, in turn, are essential to optimize QOL and independence.[17] In essence, a healthy brain is essential for both living a longer and fuller life. Poor brain health may be associated with such underlying disorders as AD, stroke, and other causes of vascular cognitive impairments including brain trauma and neurodegenerative disorders.

The United States has the second largest number of people living with AD (3.9 million people), exceeded only by China (5.4 million people with AD).[44] Worldwide, over seven million new cases of dementia are diagnosed annually, and by 2050, the prevalence of dementia is expected to increase by over 100% in high-income countries and over 250% in low-income countries. It has been estimated that more than 10% of adults over the age of 60 have some component of memory loss and 35% report at least some level of functional difficulty.[45] The PAGA 2018 Scientific Report documents that greater amounts of physical activity are associated with reduced risk of cognitive decline and risk of dementia including AD. Some evidence indicates that physical activity can improve cognitive function, particularly with those who have mild cognitive impairment and perhaps even those who have mild degrees of dementia.

121.9 PHYSICAL ACTIVITY AND QUALITY OF LIFE

The concept of quality of life is based on the way individuals perceive and react to their health status or non-medical aspects of their lives. QOL is typically divided into health-related QOL and non-health-related QOL. The relationship between physical activity and perceived positive QOL is strong and is particularly evident in older adults (over the age of 50) and particularly over the age of 65. Even younger individuals between the ages of 18 and 65 improve health-related QOL based on physical activity compared with treatment control. As such, physical activity is an important contribution to leading productive and happy lives with improved QOL.

121.10 PHYSICAL ACTIVITY AND AFFECT

Affect may be defined as the subjective experience of feeling states including pleasure, displeasure, and arousal.[46] The PAGA 2018 Scientific Report documents that there is strong evidence that there seems to be a relationship between the level of exercise intensity and affect. For example, high levels of intensity of exercise may actually lead to negative affect. There is increasing evidence that the way people feel during physical activity is an important determinant of their continued participation. Physical activity has been demonstrated to reduce acute ("state") anxiety and longer participation in physical activities can reduce "trait" anxiety in both middle-aged and older individuals.[47–51] (See Section 121.11.) Physical activity can also reduce symptoms of depression. (See Section 121.12.)

121.11 PHYSICAL ACTIVITY AND ANXIETY

Anxiety has been defined as a "noticeable psychological, physical, emotional state most characterized by feelings of apprehension, fear or expectation of fear, worry, nervousness and physical expectations arising from activation of the autonomic nervous system". The annual prevalence of significant anxiety disorders is estimated to be approximately 18% in the United States. Females are more likely to experience anxiety than males. Anxiety is considered pathological when it emerges in situations that are not objectively dangerous, are excessively strong, or significantly constrain the life of the individual affected with anxiety. Symptoms of anxiety may also be reflective of high levels of stress in the modern world.

The relationship between physical activity and anxiety and anxiety disorders has been studied in numerous research trials.[47–51] Physically active people are found to have decreased emotional stress. Regular physical activity has been shown to lower anxiety in healthy individuals. Most of the literature is based on aerobic activity, although there is some evidence that decreased anxiety may be found in response to resistance strength training.[52] Physical activity may deflect negative thoughts or emotions. Physical activity carried out in a group may contribute to social interactions, which may contribute to relieving anxiety. There is some evidence that regular physical activity may increase endorphins, which may contribute to its anxiety-reducing benefits. This has been largely speculative in the past, but recent evidence from PET scans has suggested that decreased levels of anxiety correlate with opioid-like binding in several brain areas. These findings, however, are preliminary and need to be confirmed with further studies.

121.12 PHYSICAL ACTIVITY AND DEPRESSION

Major depressive disorders (MDD) annually affect approximately 10% of the population in the United States.[53] The lifetime prevalence of MDD is 10% in men and 15% in women. Even if individuals do not meet diagnostic criteria for MDD, symptoms of even mild depression can have a negative impact on health.

Physical activity has been shown in multiple studies to lower the risk of depressive disorders.[54,55] There is evidence of an inversive relationship between symptoms of depression and physical activity, although the complexity of this relationship suggests that these relationships be treated with caution. Physical activity (particularly aerobic activity) has also been associated with a reduced risk of developing depression. This appears to exhibit a dose-response relationship. One study showed that engaging in more than 30

minutes/day of physical activity reduced the odds of experiencing depression by 48%.[54] Most studies in this area have been based on a model of 12 weeks of physical activity and examining its effects on depression.[56–62]

Studies have shown significant decreases in depressive symptoms throughout the adult lifespan. Physical activity has been shown to be equally effective for lowering symptoms of depression as cognitive behavioral therapy and anti-depressant pharmaceutical therapy.

121.13 PHYSICAL ACTIVITY AND SLEEP

The PAGA 2018 Scientific Report reports strong evidence that both acute and regular bouts of physical activity improve sleep outcomes in adults.[1] There is also evidence that physical activity improves sleep outcomes across age and sex.

Sleep is a pillar of lifestyle medicine and it is important to health and well-being across the lifespan.[63] Sleep plays a critical role in biological functions and it is important in neural development, learning, memory, emotional regulation, cardiovascular health, and metabolic health. Numerous studies have shown that sleep latency (length of time between going to bed and falling asleep), total sleep time, sleep efficiency, sleep quality, daytime sleepiness, insomnia, and obstructive sleep apnea are all improved with regular physical activity.[64–69] These benefits have been shown in a variety of different age groups including young, middle age, and older men and women.

Improvements in sleep carry significant public health benefits. For example, approximately 10% of adults have clinically diagnosed insomnia[70] and 26% of adults between the ages of 30 and 70 suffer from obstructive sleep apnea (OSA).[71] In addition, 25% of the population reports getting insufficient sleep for at least 15 hours every 30 days, and between 25% and 48% of the population report a sleep problem of some kind.[72] Thus, physical activity can play a major role in a variety of conditions. It should also be noted that sleep problems are associated with increased risks of accidents, cardiovascular risk factors, obesity, stroke, and all-cause mortality. It has been estimated that the United States suffers economic costs in excess of $400 billion/year as a result of insufficient sleep.[73]

121.14 SUMMARY

The linkages between physical activity and brain health are wide-ranging and profound. This includes not only cognition but also risk of a variety of chronic diseases and overall quality of life. For this reason, both the PAGA 2018 Scientific Report and Presidential Advisory on "optimal brain health" from the AHA and ASA focus on physical activity and improved brain function and cognition. For all of these reasons, it is incumbent upon lifestyle medicine practitioners to inquire about both physical activity and various aspects of brain function in every clinical encounter.

CLINICAL APPLICATIONS

- Increased physical activity is essential for multiple benefits in virtually every patient.
- The relationship between physical activity and cognition is particularly important and often underemphasized in clinical medicine.
- Emerging evidence has accumulated that regular physical activity is important for many aspects of brain health including cognition.
- Physical activity also positively interacts with several other factors related to brain health including improved mental health, lower risks for anxiety and depression, and improved sleep.
- Physical activity is important not only to brain health maintenance and appropriate cognition but also in decreasing the likelihood of age-related cognitive decline and other forms of dementia.

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122 Physical Activity and Anxiety

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KEY POINTS

- Anxiety disorders are the most common mental disorder, with global estimates calculating a prevalence of up to 25%.
- Anxiety disorders can be treated with psychotherapy, medication, and complementary methods (e.g., exercise), however, demand for more effective treatment remains high.
- Regular physical activity is linked to less anxiety, but more research is needed to show a definitive preventative effect.
- One-time exercise seems to have an acute anxiolytic effect in individuals with and without anxiety disorders.
- The literature is sparse concerning specific disorders, but findings suggest a therapeutic effect in patients with agoraphobia/panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, and social anxiety disorder, but not in specific phobia.
- Both aerobic exercise and resistance exercise show anxiolytic effects.
- Psychological and biological mechanisms seem to mediate the beneficial effects of physical activity on anxiety.

122.1 ANXIETY: DEFINITIONS AND DIAGNOSES

Anxiety, in general, is a normal and even essential human emotion, as it secures survival. In preparing for a fight or flight reaction, it signals (assumed) danger and may so protect the organism from harm. It activates physiological changes (e.g., sweating, faster heartbeat, and breathing), and, consequently, also has cognitive (e.g., dashing thoughts) and behavioral (e.g., leaving the situation) correlates. Panic is differentiated from anxiety by having even faster changes and very quick onset. So, a panic reaction is a fast, defensive reaction, which allows the organism to leave a possibly dangerous situation as quickly as possible.

Anxiety is considered pathological if it emerges in situations not objectively dangerous, if it is excessively strong, and if anticipatory anxiety constrains the life of the affected.[1,2] In this regard, anxiety disorders can be differentiated from "normal" and subclinical anxiety. According to the International Classification of Diseases 11 (ICD-11) of the World Health Organization (WHO), anxiety disorders are grouped within anxiety and fear-related disorders (6B).

We will focus here on diagnoses relevant to the chapter, that is, anxiety disorders and other related disorders that have been studied in association with physical activity. For any other detailed diagnostic criteria, we recommit to the ICD-11.[2]

Generally, the specific diagnoses can be classified by the nature of anxiety. In phobic anxiety disorders, anxiety is evoked only, or predominantly, by well-defined situations, which are not dangerous. As a result, these situations are avoided whenever possible or endured with dread. Furthermore, contemplating entering the phobic situation generates anticipatory anxiety.

Agoraphobia:

- Anxiety in at least two of the following situations: public places, crowds, traveling far away from home, or traveling alone. Agoraphobia is further specified by the existence of a history of panic disorder.

Social anxiety disorders (SAD):

- Anxiety centered around the fear of scrutiny by other people.

Specific (isolated) phobias:

- Anxiety is restricted to highly specific situations such as proximity to particular animals, heights, thunder, and dental treatment, and the phobic stimulus is avoided whenever possible.

In contrast, in the so-called "other anxiety disorders", the manifestation of anxiety is the major symptom and is not restricted to any particular situation or object.

Panic disorder (PD):

- Core features are recurrent attacks of severe anxiety (panic). These are discrete periods of intense fear accompanied by somatic or cognitive symptoms like sweating, trembling, breathlessness, dizziness, fear of losing control, or even mortal fear. Panic attacks are unpredictable as they are

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not restricted to any particular situation or circumstance. Although anticipatory anxiety (fear of further panic attacks) is common, people experience intervals without anxiety in between the attacks.

Generalized anxiety disorder (GAD):

- The essential feature is anxiety, which is free-floating, that is generalized and persistent but, again, not restricted to any particular situations or circumstances.
- Furthermore, patients present with worries (e.g., that they or a relative will become ill or have problems), muscular tensions, vegetative hyper-irritability, and other physical symptoms.

Obsessive-compulsive disorder (OCD):

- Essential features are recurrent obsessional thoughts and/or compulsive acts, which are distressing, and the patient often tries to resist them.
- The acts are done to prevent objectively unlikely events, which the patient fears might otherwise occur. Anxiety is almost invariably present and gets worse if compulsive acts are resisted.

Post-traumatic stress disorder (PTSD)

- Differs as to the existence of causative influences. It occurs as a response to a stressful event or situation of an exceptionally threatening or catastrophic nature, which is likely to cause distress in almost anyone.
- Typical features include episodes of reliving the trauma and feelings of emotional "numbness", feeling detached from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities or situations resembling the trauma. Usually, autonomic arousal with hypervigilance, an enhanced startle reaction, and insomnia are also present.

122.1.1 Anxiety Disorders: Incidence and Impact

Among all mental disorders, anxiety disorders are the most common, and their prevalence and course are reasonably well described. The overall prevalence of anxiety disorders is shown to be high. Global estimates assume a prevalence ranging between 3.8 and 25%[3] Data from the United States suggests considerable variations between the most (specific phobias, 15.6%) to the least prevalent (OCD, 2.3%) disorders. The age of onset is typically in childhood or adolescence, the course is often chronic-recurrent, and anxiety disorders are highly comorbid with each other and with other mental disorders.[4] Furthermore, except for OCD, women are at a significantly higher risk of suffering from anxiety disorders.[5]

The individual and social impact of anxiety disorders has been pointed out repeatedly. Anxiety disorders constitute a major health economic challenge, and their costs might even have been underestimated in the past.[6] The economic costs include psychiatric and non-psychiatric care, emergency care, hospitalization, drug prescription, reduced productivity, absenteeism from work, and suicide.[7] On a more individual level, anxiety disorders predict numerous unfavorable sociodemographic, clinical, and functional outcomes and are especially associated with unfavorable interpersonal outcomes.[8]

122.2 TREATMENT: HOW CAN ANXIETY DISORDERS BE TREATED?

122.2.1 Psychotherapeutic Treatment of Anxiety Disorders

Cognitive behavioral therapy (CBT) is long known to be the gold standard in psychotherapy for anxiety disorders. Its positive effect is one of the best-assured results in psychotherapy research in general. Numerous clinical trials have supported the efficacy of CBT for anxiety disorders. Several meta-analytic results of treatment outcome studies have supported this finding, showing strong effects of CBT for panic disorder and agoraphobia, social phobia, OCD, GAD, and PTSD.[9] Cognitive therapy and exposure therapy alone, in combination, or combined with relaxation training have been shown to be effective across different anxiety disorders, with no differential efficacy for any treatment components for any specific diagnoses.[9] Superior effects for CBT in GAD and PTSD but not for SAD were the only difference in the diagnostic level reported here. In line with these earlier findings is a more recent review of meta-analytic findings on the efficacy of CBT for the treatment of anxiety disorders by Olatunji et al.[10] The authors reviewed contemporary meta-analytic studies and support the finding that CBT procedures, and particularly exposure-based treatment approaches, are highly efficacious.

Self-help efforts have been evaluated, playing a role as an initial basic treatment in stepped-care models of treatment or as a strategy to prevent a disorder from developing. Furthermore, they are promising in meeting the lack of professionals providing evidence-based psychotherapy and the demand for treatment with minimal cost to health services. For a review of the outcomes of self-help efforts, see Morgan and Jorm.[11] Researchers also explored the possibility of using the Internet to deliver CBT (Internet-assisted CBT, ICBT). Recent reviews and meta-analyses report that therapist-supported ICBT appears to be efficacious in treating anxiety in adults and that therapist-supported ICBT may even not be significantly different from face-to-face CBT in reducing anxiety.[12, 13] Newer meta-analyses analyzing the evidence for specific anxiety disorders also show positive results, underlining the potential of ICBT.[14–16]

122.2.2 Pharmacological Treatment of Anxiety Disorders

The pharmacological treatment of anxiety disorders has been studied intensively and clinical trials showing its effectiveness have been well replicated. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) are recommended as first-line drugs due to their positive benefit/risk balance.[17] Other options include the calcium modulator pregabalin, tricyclic antidepressants (like imipramine and clomipramine), buspirone, moclobemide (selective and reversible inhibitor of monoamine oxidase), the antidepressant agomelatine, and the atypical antipsychotic quetiapine.[17] Benzodiazepines are very effective due to their rapid onset of action and ability to be used on an on-demand basis, although their long-term use is not recommended because of their potential for abuse and dependence and their lack of antidepressant properties.[17] The most recent development in the field of pharmacotherapy for the treatment of anxiety disorders is the antidepressant vortioxetine, which was investigated in controlled studies involving patients with GAD. However, no significant improvement compared to placebo could be demonstrated meta-analytically.[18]

122.2.3 Is a Combination of Pharmaco- and Psychotherapy Even Better?

To increase the efficacy of either psychotherapy or pharmacological treatment, the combination of both has been discussed as an option for faster and more sustained treatment. Although this approach may seem obvious, confirming empirical findings are not.

Pull[19] found little benefit for a combination of psychotherapy and pharmacotherapy for the treatment of anxiety disorders versus monotherapies when taking randomized controlled trials (RCTs), meta-analyses, and reviews into account. Zwanzger et al.[20] found that there might be evidence for the superiority of combination therapy under some conditions, although the authors did not see evidence for the beneficial effects of combined treatment for long-term outcomes. Consistently, Hofmann et al.[21] report in their meta-analysis that pharmacotherapy may be a useful strategy for enhancing acute-phase CBT outcomes, while they do not support the benefit of combination therapy for long-term CBT outcomes. Interestingly, the authors report a significant publication bias in terms of smaller effects in more recent studies, which might be due to more rigorous assessment methods.

The most recent meta-analysis in the field shows that combinations of psychotherapy and pharmacotherapy have a large effect size.[22] However, only a few combination studies were seen as suitable for the comparison due to methodological reasons and some of these had not been conducted with the most powerful drugs.[23] Current treatment recommendations generally list CBT and pharmacotherapy as equally beneficial for panic disorder, agoraphobia, GAD, and social phobia,[24] while the preference of the informed patient is emphasized to be decisive. A combination of both is recommended if monotherapy is not sufficient.[22] For specific phobias, OCD, and PTSD, psychotherapy is seen as superior and recommended as first-line treatment.[23–26]

122.2.4 Complementary Treatment Methods and Add-Ons

Complementary and alternative interventions to treat anxiety are highly popular, and evidence in the past was sparse.[26] There is a growing body of literature, though official guidelines have oftentimes not yet included these treatments.[27] Hypnosis and biofeedback as well as methods of complementary medicine such as acupuncture, osteopathy, or homeopathy are often recommended by healthcare practitioners, however, controlled studies fulfilling basic methodological standards are lacking.[17]

On the side of phytotherapy, inconsistent results have been shown, with lavender oil, kava-kava, *Withania somnifera*, and *Gingko biloba* being among the most promising candidates.[28] However, further research is needed due to methodological shortcomings and to confirm preliminary findings.[28] Meditation, relaxation training, and yoga are shown to be somewhat effective in numerous disorders, even though the potential risk of bias has been pointed out repeatedly.[29,30] Mindfulness-based interventions (MBIs), as an increasingly popular therapeutic approach, have been taken into the scope of research. They seem to be effective in the treatment of anxiety and have been shown to increase the effectiveness of CBT, though further research is warranted.[29, 30]

Exercise has been considered a promising therapeutic option for anxiety disorders, as in a wide range of research it has been shown to have positive effects on major depression.[31] However, recent meta-analyses emphasize that the positive effect of exercise in the treatment of depression might have been overestimated, when taking a closer look into the methodology of confirming studies[32] or when closely compared with psychological treatment or antidepressant medication.[33]

A detailed illustration of evidence-based results for the link between anxiety disorders and physical activity will be given in the following passages.

122.3 WHAT LINKS ANXIETY (DISORDERS) AND PHYSICAL ACTIVITY?

Physical activity has been defined as bodily movements produced by skeletal muscles that result in energy expenditure.[34] It, therefore, includes either leisure activity (jogging, cycling, etc.) which increases fitness, as well as gardening, housework, or walking. Exercise is seen as a subset of physical activity, as it is defined as planned, structured, and repetitive physical activity that has improvement or maintenance of physical fitness as a final or intermediate

goal.[34] Earlier research had focused on the effect of exercise explicitly,[35] while more recent research has also focused on everyday physical activity, which is seen as beneficial for health.[36] In the literature, though, both terms are not always differentiated. In the following, we will review studies on physical activity, exercise (training), and sports.

122.3.1 Physical Activity and the Prevalence and Incidence of Anxiety Disorders

Physical activity is long known to be associated with a range of health benefits and the absence (i.e., inactivity) can have harmful effects on health and well-being as it increases the risk for medical disorders like coronary heart disease, diabetes, certain cancers, obesity, and hypertension, as well as all-cause mortality.[37]

Compared with a wide range of research on the positive effects of physical activity on depression, anxiety disorders have been less frequently studied. Additionally, the diversity of anxiety disorders makes it difficult to generalize from studies on one specific anxiety disorder to others. Furthermore, changes in the diagnostic criteria complicate the interpretation of early studies.

Cross-sectionally, the link between physical activity and anxiety has been intensively studied, and high self-reported levels of physical activity have generally been found to be associated with better mental health, including lower emotional distress and fewer symptoms of anxiety.[38–44]

Concerning different diagnoses in the field of anxiety disorders, Goodwin[45] analyzed the data of the US National Comorbidity Survey and found significant associations between regular physical activity and a lower prevalence of specific phobia, social phobia, panic disorder, and agoraphobia in a representative sample of adults in the United States. A representative, cross-sectional study in Japan[46] including 4000 people showed a positive relation between dislike of physical activity and higher odds ratios for panic attacks and panic disorder, which was found to be especially true for women. A Dutch study reported lower rates of anxiety disorders in individuals who exercised at least one hour per week, without evidence for a linear dose-response relationship.[47] On the other hand, studies can also be found that do not support the association between physical inactivity and symptoms of anxiety.[48–51]

Problems occur when trying to compare these studies as the measurements of anxiety and physical activity are inconsistent. Furthermore, in most studies, fitness was not directly assessed, and measuring exercise habits and anxiety disorders in cross-sectional surveys generally is ambiguous about cause and effect. Prospective longitudinal studies are needed to prove the hypothesis that physical activity has a preventative effect on anxiety but are rare when it comes to anxiety disorders.

McDowell et al.[52] suggest a small preventative effect in their recent review and meta-analysis of prospective cohort studies, although study quality was low-moderate. In line, Teychenne et al. reviewed the literature and found sedentary time to be inversely associated with symptoms of anxiety.[53] In contrast, a newer meta-analysis[54] examining the effectiveness of physical activity in the primary prevention of anxiety found no preventative effect, with study quality being low. Despite results suggesting an association between physical activity and fewer symptoms of anxiety, more high-quality, consistently designed prospective studies and meta-analyses are still needed. Furthermore, it is not yet clear whether there is a causal relationship between physical activity and (less) anxiety, as often is implicitly assumed in population-based studies. It is also conceivable that common genetic factors both influence exercise behavior and anxious symptoms, a possibility supported by evidence from a Dutch study.[55]

122.3.2 Evidence of the Therapeutic Impact of Physical Activity on Anxiety

122.3.2.1 Anxiolytic Effect in Healthy Individuals

The anxiolytic effect of aerobic exercise in healthy individuals has been investigated in numerous studies and several older meta-analyses suggest a fear-reducing effect in healthy people.[56,57] More recent reviews and meta-analyses confirm evidence of an anxiolytic effect of exercise on anxiety symptoms in people without established anxiety disorders.[58] For the anxiolytic effect on trait anxiety, a training period of at least ten weeks and a workout in the aerobic power range seem to be critical,[56] while reductions in state anxiety immediately after performing single bouts of exercise have also been reported.[59,60] Recently, a study examining the anxiolytic effects of resistance exercise also showed promising results, meaning that patients could potentially have more options when it comes to choosing exercise intervention.[61]

122.3.2.2 One-Time Physical Activity and Anxiety

The anxiolytic effect of a one-time physical activity was first described by Orwin.[62] Other early case reports also described the anxiolytic effect of one-time physical activity in patients with specific phobias.[63,64] Symptoms of anxiety in healthy people, in whom panic attacks were experimentally induced by caffeine intake, cholecystokinin tetrapeptide (CCK-4), or CO_2 inhalation, decreased after a single session of physical exercise on the bicycle ergometer or a treadmill.[65–67] Before a CO_2 challenge, 18 panic disorder patients practiced either moderate exercise or very light exercise. Panic reactions were smaller in patients who performed moderate exercise compared with patients in the control condition (very light exercise)[68] In a cross-over design, healthy individuals and patients with panic disorder were studied by Ströhle and colleagues.[69] The effects of rest and 30 minutes of aerobic treadmill exercise were compared with each other after CCK-4-induced panic attacks. It was shown that panic attacks were less frequent in the exercise condition and that 30 minutes of physical

activity caused an acute anti-panic and anxiolytic effect. Similarly, Lindenberger et al.[70] showed an effect of moderate-intense acute aerobic exercise on clinical symptoms in patients with dental phobia. Recent studies suggest that acute exercise is especially helpful in individuals with high baseline anxiety,[71,72] however, not all of them show significant effects.[73] Ensari et al.[59] provide meta-analytic findings driven by high-quality studies over the last 25 years and show that acute exercise can yield small reductions in state anxiety. However, research in this field is still plagued by floor effects associated with missing studies with patients experiencing high baseline anxiety.[59]

122.3.2.3 Long-Term Physical Activity and Anxiety

The effect of physical training in patients with manifest anxiety disorders has received more attention in the last couple of years and the number of eligible studies is growing rapidly. Hence, the evidence that exercise is an effective treatment for patients with anxiety disorders is becoming clearer:

- *Panic disorder.* Early findings of a case series revealed the anxiolytic effect of aerobic endurance training in the treatment of patients with panic disorder.[74] The effectiveness of exercise in reducing symptoms was confirmed by other studies, which, however, also showed the superiority of pharmacotherapy[75,76] and psychotherapy.[77] However, one must not forget the side effects of pharmacotherapy, which are not found in psychotherapy and exercise therapy.[75] One study showed that exercise might have similar effects to relaxation techniques.[76] Gaudlitz et al.[78] showed that the effectiveness of psychotherapy can be augmented with an adjunctive exercise regimen. Newer studies also show similar trends: Plag et al.[79] demonstrated the effectiveness of high-intensity interval training in comparison with a low-intensity exercise regimen in reducing symptoms of panic disorder, with higher intensity leading to stronger effects. Lattari et al.[80] further underline these findings, showing a significant decrease in baseline anxiety following 12 sessions of aerobic exercise. Additionally, Bischoff et al.[81] found that exercise could enhance exposure therapy outcomes. Most recently, Machado et al.[82] reviewed the existing literature and concluded that exercise has positive effects on symptoms of panic disorder. However, the amount of evidence and methodological issues prevent them from recommending exercise as monotherapy for panic disorder.
- *PTSD.* There is growing evidence that patients with PTSD benefit from exercise training, although definitive statements about PTSD cannot be made yet. Rosenbaum et al.[83] conducted a review and meta-analysis of the evidence in 2015 and found that physical activity reduced PTSD symptoms more effectively than control. However, trials with yoga were included, which reduces the significance of this topic, since yoga is considered different from other types of exercise. Conversely, Nordbrandt et al.[84] could not find significant differences between the treatment-as-usual group and the exercise plus treatment-as-usual group in a relatively large RCT with traumatized refugees. However, this also may be because traumatized refugees tend to have smaller treatment effects than other populations.[84] Nevertheless, the overwhelming evidence suggests a positive effect of exercise on PTSD,[85–91] with lower baseline cardiorespiratory fitness potentially predicting a greater symptom reduction through regular exercise.[90]
- *OCD.* Promising effects of exercise for symptom reduction have been reported[92–94] and the potential clinical utility of regular aerobic exercise in conjunction with CBT for these patients has also been confirmed.[95] However, taking these and other studies together, Freedman et al.[96] could only find mixed results in their narrative review, with the only RCT reviewed having negative findings.
- *GAD.* Sparse studies show the anxiolytic effects of exercise,[97–100] with higher-intensity exercise seeming to be more effective than lower-intensity exercise.[99]
- *SAD.* Two studies show that both mindfulness-based stress reduction (MBSR) and exercise have anxiolytic effects,[101,102] with exercise being potentially more effective in individuals with more severe baseline symptoms and MBSR more effective with lower baseline symptoms.[102]
- *Specific phobias.* Patients with specific phobias were examined in studies looking at the effects of exercise on varied anxiety disorders, and the literature suggests a positive effect.[103,104] However, this disorder has not received a lot of attention regarding exercise interventions. Weisman and Rodebaugh[105] found no difference from control when examining the effects of exercise on exposure therapy outcomes in patients with specific phobia, undermining the aforementioned findings.

Most studies have focused on aerobic exercise as an intervention, with resistance exercise receiving less attention. However, this is changing, with newer studies showing comparable effects between both exercise regimens.[104] Exercise also seems to augment cognitive behavioral therapy outcomes in patients with anxiety,[106–108] which could have a significant impact on response rates.

122.3.2.4 Recent Meta-Analytical Findings

Meta-analyses by both Bartley et al.[109] and Pearsall et al.[110] do not support the claim that exercise is effective in treating anxiety symptoms and specific anxiety disorders. However, the overwhelming evidence of other systematic reviews

and meta-analyses shows a different picture. Earlier findings[58,111,112] can now be supported by more recent studies, all of which show evidence of the anxiolytic effect of exercise.[113–117] These effects are seen not only in adults but also in children and young people.[118,119] Wegner et al.[112] as well as Stubbs et al.,[58] suggest that exercise seems to be more effective in improving anxiety symptoms in people with a current diagnosis of an anxiety disorder compared with participants with a non-clinical range of anxiety. Other meta-analyses reviewing patients without anxiety disorders also find anxiolytic results,[116,120] with effect sizes similar to those of pharmacotherapy.[116] All authors agree that the database, although growing, is still sparse and that further well-conducted and methodologically sound RCTs, as well as high-quality meta-analyses, are needed to draw definitive conclusions.

In summary, physical exercise appears to have an "acute" anxiety-dissolving effect and longer-term anxiety-reducing effects when used for appropriate clinical pictures as a therapeutic add-on. Particularly suitable sports cannot be named yet, although both endurance training and resistance exercise seem to have positive effects.[119] To what extent exercise can also be used as the main intervention for anxiety disorders is still an unsettled question, although the growing evidence suggests this possibility. It is, however, certain that athletes are consistently less anxious and depressed than physically inactive people.[121] On the other hand, it is not clear whether sport sustains mental health or whether mental health and engagement in sports have a common basis.

122.3.3 Mechanisms of the Anxiolytic Activity of Exercise

122.3.3.1 Psychological Mechanisms

From a psychological point of view, there is some empirical evidence that the effect of exercise is based on the improvement of perceived coping skills and increased self-efficacy.[122] Anxiety disorders often go hand in hand with the most stressful experience of being trapped, seeing no solution, and helplessly being at the mercy of the symptoms. The possibility to gain relief through exercise opens a way out. Once a person sees a way out of a seemingly hopeless situation, and feels able to exercise control over the events, stress level decreases and the associated symptoms improve. The awareness to have the means to self-regulate improves self-confidence and thereby promotes health.[123]

Other authors believe that the effect of physical activity lies in the deflection of negative thought content.[124] If physical exercise is carried out in a group, social interaction and reinforcement could also contribute to relieving anxiety.

The anxiolytic effect of endurance training in patients with panic disorder can also be regarded as an exposure strategy toward interoceptive cues. Patients often experience normal bodily sensations such as increased heart rate or a fast pulse as dangerous or even life-threatening. If these sensations occur during a panic attack, they are inexplicable and uncontrollable for the patient. However, if these sensations occur repeatedly during exercise, the patient can get used to them, perceive them as natural and not life-threatening, and therefore alter their cognitive and affective reaction to them.[125] In this sense, exercise can be considered a form of interoceptive exposure.[126] Furthermore, exercise seems to contribute positively to the reduction of anxiety sensitivity,[125,127] which is conceptualized as a permanent fear of anxiety and anxiety-related sensations and which is a risk factor as well as a maintaining factor for anxiety-related psychopathology.

For a more detailed overview of psychological mechanisms underlying the effect of exercise on anxiety disorders, see Gaudlitz et al.[128].

122.3.3.2 Biological Mechanisms

Concerning biological mechanisms of action underlying the beneficial effect of exercise for the treatment of anxiety disorders, different mechanisms on neurochemical and physiological levels have been discussed.

It was shown that endurance training leads to a normalization of serotonin receptors[129,130] and increased levels of the neurotransmitter serotonin. This effect has been observed when serotonergic agents are administered via psychopharmacotherapy (SSRIs). Furthermore, exercise-induced changes in endorphins, endogenous peptides that act as opioid receptor agonists and are also related to mood, have long been explored. While for a certain time, these observations had been based entirely on findings of enhanced endorphin levels in the peripheral blood, Boecker and co-workers[131] were able to disclose the central mechanism and identify a relationship between exercise and perceived euphoria during exercise by using PET (positron emission tomography). The level of euphoria was significantly increased after running and was inversely correlated with opioid binding in several brain areas.[131] However, the hypothesis that endorphins mediate exercise-induced anxiety reduction has also been challenged as evidence is mixed.[132]

Exercise also has positive effects on stress reactivity (e.g., the hypothalamus-pituitary-adrenal [HPA] axis). In patients with anxiety disorders, over-activity of the HPA system might be present[133] and lead to a permanently increased release of the stress hormone cortisol into the body. This can have many adverse consequences such as the loss of nerve cells in the hippocampus or the weakening of immune reactions.[134,135] Physical activity seems to be able to reduce cortisol levels in the body or prevent increases in cortisol.[136] This finding is supported by different research results on the effects of endurance training,[137–140] but also on the effects of an acute bout of exercise on patients with specific phobia.[70] Furthermore, atrial natriuretic peptide (ANP) appears to play a role in the modulation of fear and panic and could be responsible for psychological adaptation processes during exercise. Moreover, ANP may be involved in the process of anxiolytic effects of chronic physical activity.[141]

Exercise has also been found to normalize reduced levels of brain-derived neurotrophic factor (BDNF) and therefore has neuroprotective or even neurotrophic effects. BDNF can cause nerve regeneration, particularly in the hippocampus, which is reduced in stress-affected patients. Since antidepressants produce the same effect, it is hypothesized that the antidepressant and anxiolytic effects of physical activity might be mediated by an increased release of BDNF.[132,142–144] Reduced BDNF levels have been associated with both increased general anxiety and anxiety disorders.[132] Meta-analytically driven effect size analysis generally supports the role of exercise as a strategy for enhancing BDNF levels in humans[142] and this could especially be shown for aerobic compared with resistance training interventions.[143] When using exercise therapeutically in patients with anxiety disorders, research on BDNF has been very sparse so far, so more evidence must be generated to draw definitive conclusions. Ströhle et al.[144] showed that moderate-intense exercise significantly increased BDNF concentrations in patients with panic disorder (but not in healthy controls) who had significantly reduced concentrations compared with healthy controls at baseline.

It seems that aerobic exercise modulates hormones, neurotrophic factors, and neurotransmitter levels in humans, but the individual response probably depends on factors such as genes, age, and hormonal status.[145] The latter factors would need to be integrated into future studies considering individual differences and more systematically also in patients with anxiety disorders. For a more detailed overview of biological mechanisms, see DeBoer et al.[132] and Gaudlitz et al.[128]

122.4 CONCLUSION AND RECOMMENDATIONS

Although there are many studies underlining the association between (more) physical activity and (less) anxiety, many questions remain. Also, clinicians are still waiting for answers to questions as to type, frequency, duration, and intensity of exercise to "prescribe" to whom.[146] However, the literature suggests that exercise might be more efficacious in treating anxiety in less-active people[90] and people with a clinical range of anxiety.[58,112] Furthermore, LeBouthillier and Asmundson tested aerobic exercise versus resistance training as transdiagnostic interventions and found both exercise modalities to be efficacious in improving disorder status, while aerobic exercise improved general stress and anxiety and resistance training improved disorder-specific symptoms.[104] Until this and the above-mentioned questions are further clarified, the guidelines of the WHO should be followed: Adults should at least do 150 minutes of moderate-intensity aerobic activity (e.g., brisk walking, household chores), 75 minutes of vigorous-intensity aerobic activity (e.g., running), *or* an equivalent mix of moderate- and vigorous-intensity aerobic activity each week, all performed in bouts of at least ten minutes.[147] Additionally, strengthening exercises of all major muscle groups should be performed at least two days a week.[147] Despite those widely accepted guidelines, which have been in use for almost a decade now, the challenge of implementation, especially for people with mental disorders, must be faced and input is needed from randomized controlled clinical trials. Most recently, Stevens et al.[148] suggest focusing on social identity and self-categorization theories (rather than on individual-level factors like cognition or attitudes) as a new approach that still has to be proven useful in supporting patients in engaging in physical activity.

CLINICAL APPLICATION

Population	Recommendation
Healthy individuals or individuals with a subclinical range of anxiety Individuals with anxiety disorders	Guidelines of the WHO[147]: • At least 150 minutes of moderate-intensity aerobic activity (e.g., brisk walking, household chores) • *or* 75 minutes of vigorous-intensity aerobic activity (e.g., running) • *or* an equivalent mix of moderate- and vigorous-intensity aerobic activity each week, all performed in bouts of at least ten minutes • *and* strengthening exercises of all major muscle groups at least two days per week

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123 Physical Activity and Depression

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KEY POINTS

- Evidence indicates physical activity can be utilized in the treatment and prevention of depression.
- This may be particularly relevant in diseased populations where the depression comorbidity results in significantly poorer outcomes.
- Several potential biological mechanisms underlie the antidepressant effects of exercise. Understanding these mechanisms may facilitate matching patients to effective treatment of depression.
- Future research must continue to evaluate strategies for implementing exercise as a treatment in real-world clinical settings.

123.1 PREVALENCE AND BURDEN OF DEPRESSION

Depressive disorders annually affect approximately 10% of the population in the United States with a lifetime prevalence of 10% in men and 15% in women. Costs associated with depressive disorders have grown, as the annual economic burden of depressive disorders is estimated at $210 billion.[1] Even in individuals who do not meet the diagnostic criteria for major depressive disorder (MDD), depressive symptoms have negative influences on health. Elevated depressive symptoms are associated with an increased risk of MDD,[2] reduced physical and job functioning,[3–5] higher rates of disability,[6] and increased social dysfunction.[4,7]

Further increasing the burden of depressive disorders is the limited accessibility and effectiveness of treatments. Only 55% of people with a depressive disorder receive treatment and only 32% of those receiving treatment experience alleviation of symptoms.[8] Randomized controlled trials (RCTs) have shown the efficacy of three classes of treatment in reducing depressive symptoms: antidepressants, psychotherapy, and neurostimulation.[9] Despite the empirical evidence demonstrating the efficacy of these treatments, the remission rate for initial treatment is approximately 30% and approximately one-third of patients fail to achieve remission even after multiple treatment attempts.[10–14] These data highlight the need for more cost-effective, accessible, and alternative treatments for depressive disorders. Exercise is one potential treatment that has been supported through research.

123.2 CROSS-SECTIONAL AND LONGITUDINAL STUDIES OF EXERCISE

The relationship between physical activity and depressive disorders was first identified in epidemiological work. Higher levels of physical activity and cardiorespiratory fitness have consistently been associated with lower depressive symptoms and risk of depression onset.[15–18] In a recently published meta-analysis of longitudinal associations across 111 studies, the odds of incident cases or an increase in subclinical depressive symptoms were reduced by 21% for individuals meeting WHO physical activity guidelines.[19] While the majority of epidemiological research has focused on aerobic activity, recent cross-sectional studies report lower depressive symptoms among individuals engaging in resistance training.[20–22]

Although there is strong evidence that there is an inverse relationship between symptoms of depression and physical activity, the complex and multi-faceted nature of the relationship requires that researchers gain a better understanding of how other factors may moderate or influence this relationship. Recent studies have identified that this inverse relationship exists in low- to middle-income countries,[23] exists as we age,[24] and may even exist with as little as one hour of physical activity per week.[25] However, there is no consensus on how much physical activity (PA) is protective for depression; the WHO Guideline Development Group revealed that knowledge on dose response, especially optimal dose, from adequately powered studies, is understudied.[26] Though findings have supported stronger depression odds reductions after moderate and vigorous PA which met WHO guidelines[19] the impact of meeting PA guidelines has not been the focus of the majority of available investigations. Research from The Irish Longitudinal Study on Ageing (TILDA) Waves 1 and 2, which is one of only three studies evaluating the association between meeting PA guidelines and depression, showed that meeting PA guidelines was cross-sectionally associated with 40% lower odds of depression, and conferred small-to-moderate protective effects against developing depression (23%).[27]

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123.3 RANDOMIZED CONTROLLED TRIALS OF EXERCISE

123.3.1 Efficacy of Aerobic Exercise in Reducing Depressive Symptoms

Building on the findings from epidemiological studies, a number of RCTs have examined the treatment effects of aerobic exercise on depressive symptoms in individuals with MDD. Dunn et al.[28] randomized 80 adults, aged 20–45, to either high-dose aerobic exercise (17.5 kilocalories per kilogram of weight [KKW] at a self-selected intensity), low-dose aerobic exercise (7 KKW at a self-selected intensity), or an exercise placebo group (i.e., stretching). Following 12 weeks, the mean Hamilton Rating Scale for Depression (HRSD) score was reduced by 47% in the high-dose exercise group, which was significantly greater than the reductions in HRSD score observed in the low-dose exercise (30%) and placebo groups (29%).

Blumenthal et al.[29] randomized adults, age 40 and older, with MDD to one of four treatment groups: home-based aerobic exercise, supervised aerobic exercise, antidepressant medication (sertraline), or a placebo pill. Following 16 weeks of treatment, greater remission rates were observed in the home-based (45%) and supervised exercise (40%) compared with a pill placebo (31%).

The Regassa study[30] randomized 946 patients with depression into one of three treatment groups for 12 weeks: exercise, internet-based cognitive behavioral therapy, and 12 weeks of treatment as usual that was delivered by their primary care physician. Among the exercise group, participants were further randomized into one of three types of exercise: light exercise (stretching, yoga, etc.), moderate exercise (moderate-intensity aerobics class), and vigorous exercise (high-intensity aerobics and strength training). Participants in all exercise groups attended hour-long classes three times a week for 12 weeks. At the conclusion of the trial, patients who participated in the exercise classes had significantly reduced Montgomery–Asberg Depression Rating scores than those in the treatment-as-usual group. Building on previous reports of positive long-term effects of exercise as a treatment for depression,[31–33] long-term follow-up data from the Regassa study reported that light and vigorous exercise groups had experienced reduced Montgomery–Asberg scores compared with treatment as usual and moderate exercise, though all groups experienced either stable or reduced depressive symptoms.[34]

123.3.2 Efficacy of Resistance Training Exercise in Reducing Depressive Symptoms

Another group of studies has examined the effect of resistance training exercises on depressive symptoms.

At least five studies of clinically depressed adults have suggested that resistance exercise training may be as or more efficacious for reducing symptom severity compared with aerobic exercise training.[35–40] However, this literature has also been characterized by consistent weaknesses, including small sample sizes, limited post-intervention follow-up, and lack of investigation of putative mechanisms.

A ten-week study found resistance training significantly reduced depressive symptoms compared with an attentional-control group. Furthermore, 59% of the resistance training group had achieved a clinically meaningful response compared with only 26% in the control group.[37] After the ten-week assessments, participants in the resistance training group were instructed to continue engaging in twice-weekly, unsupervised resistance training sessions for another ten weeks. Depressive symptoms remained significantly lower in the resistance training group after this phase and the percentage of participants classified as "non-depressed" was 73% compared with 36% in the control group. The significant difference in depressive symptoms between the groups remained at a 26-month follow-up.[36]

In another trial, older adults were randomized to one of three conditions: high-dose resistance training, low-dose resistance training, or standard care. At the end of eight weeks, the high-dose group had significantly greater reductions in depressive symptoms compared with the other two groups and there was no significant difference between the low-dose and standard care groups. Participants in the high-dose group were also more likely to achieve a clinical response, defined as a 50% reduction in depressive symptoms, as 61% of the high-dose participants achieved a clinical response compared with 29% of the low-dose group and 21% of the standard care group.[35]

123.3.3 Meta-Analyses Examining the Efficacy of Exercise in Reducing Depressive Symptoms

In addition to the studies referenced above, several other trials have examined the effect of exercise interventions in patients with depressive disorders. The results of these studies have been summarized in a number of meta-analyses.[41–44] These meta-analyses report significant effect sizes for the reduction of depressive symptoms following an exercise intervention. The effect sizes reported in these meta-analyses range from 0.83 to 1.39, indicating a large treatment effect. The latest Cochrane Review reported a smaller effect size and recommended further research to clearly illustrate a clear relationship between exercise as a treatment for depression.[45] However, an additional meta-analysis[46] and a critical appraisal highlighted methodological limitations of the Cochrane review and made arguments for including additional studies in the report.[47] Both the critical appraisal and the meta-analysis reported larger effect sizes for exercise as a treatment for major depressive disorder.

Recent meta-analytic evidence supported the efficacy of resistance exercise training for depressive symptoms (d = 0.66), including a large, near one-standard deviation improvement among samples with mild-to-moderate depressive symptoms (d = 0.90) that approximates a 50%

symptom reduction classified as a clinically meaningful treatment response.[48] Even when only the most rigorously designed trials were included, the average reduction in depressive symptoms remained nearly a half-standard deviation in magnitude.

In addition to evaluating depression symptoms, meta-analyses have also explored other secondary outcomes associated with depression, such as quality of life and other psychosocial indicators. One meta-analysis explored the impact that exercise has on quality of life indicators among depressed patients and found that exercise improved overall quality of life, physical quality of life, and psychosocial quality of life.[49]

123.3.4 Exercise versus Established Treatments

The studies described above compare exercise to some version of a control group. Further studies have compared exercise with established treatments for MDD. Results of two studies conducted by Blumenthal et al.[29,50] indicated no significant difference in treatment response to exercise versus SSRI in older adults. However, evaluation of long-term outcomes in these studies suggests a benefit to exercise compared with SSRI.[31–33] Klein et al.[51] found no significant difference in changes in depressive symptoms between exercise and group psychotherapy, while Hallgren et al.[30] found no difference between three exercise intensity groups and internet-based cognitive–behavioral therapy. These findings are further supported by the Rethorst et al.[41] meta-analysis, which also included the results of unpublished studies and reported no difference in effect size in studies comparing exercise with SSRI or psychotherapy.

123.3.5 Exercise as an Adjunctive/Augmentative Therapy

As previously mentioned, Blumenthal et al.[50] examined exercise as an adjunctive treatment by including a group that received both SSRI and aerobic exercise. While this group demonstrated significant reductions in depressive symptoms, this reduction was not significantly different from those who received only SSRIs or aerobic exercise. Two RCTs to date have examined exercise as an augmentative treatment for non-remitted MDD. Mather et al.[52] randomized older adults, who had received at least six weeks of antidepressant medications without a sustained response, to either aerobic exercise or health education classes. Following a ten-week intervention, the exercise group had a significantly higher response rate compared with the health education group. Trivedi et al.[53] compared the efficacy of two doses of aerobic exercise as augmentation for non-remitted MDD. Following the 12-week intervention, both groups had significant increases in remission rates and there was a trend toward higher remission rates in the high-dose exercise group, although the difference between the two groups was not significant.

123.4 EXERCISE PRESCRIPTION

While there is substantial evidence supporting the use of exercise in the treatment of MDD, research has not provided a clear indication of the proper dose of exercise needed to elicit an antidepressant effect. Complicating the matter is the fact that several aspects of the exercise intervention could potentially influence the efficacy of the intervention, including session frequency, session duration, exercise intensity, intervention duration, and exercise modality.[54]

123.4.1 Session Frequency and Duration

Exercise intervention trials in participants with MDD have varied in the frequency of exercise sessions (i.e., the number of sessions per week). Dunn et al.[28] found no difference in effect between groups exercising three times per week versus five times per week. This finding is supported by meta-analytic results demonstrating no difference in effect sizes across trials with different session frequency.[41]

Typically, exercise has been prescribed in terms of session duration, in which participants exercise for a set amount during each session. The session duration used in trials for MDD has usually ranged between 30 and 60 minutes. To date, no trial has directly compared interventions of differing session duration. However, examination of moderating variables in the Rethorst et al.[41] meta-analysis suggests that sessions lasting 45–59 minutes are most effective.

Another approach to prescribing exercise has been through the calculation of caloric expenditure. Dunn et al.[28] compared low dose (7 KKW) with high dose (17.5 KKW). In this trial, 17.5 KKW resulted in greater reductions in depressive symptoms, suggesting that there is a minimum dose of exercise needed to elicit an antidepressant response and that the total amount of exercise dose completed may be more important in determining the optimal exercise dose than the session frequency or session duration.

123.4.2 Exercise Intensity

One shortcoming in previous research in this area is the lack of adequate monitoring of exercise intensity. Some trials have not monitored exercise intensity or have allowed participants to "self-select" exercise intensity. Exercise intensity has ranged from 50% to 85% of HRmax among trials that did monitor intensity. No trial has compared exercise intensities in reducing depressive symptoms, though the Rethorst et al. meta-analysis found no difference in effect size across trials based on exercise intensity.

For resistance training, both trials conducted by Singh et al.[35,37] prescribed resistance training at 80% of 1-RM, though Singh et al.[35] compared this intensity of resistance training with a group given lower-intensity resistance training at 20% of 1-RM. The results of this trial suggest a dose-response relationship between resistance training intensity and changes in depressive symptoms as the high-dose group

had significantly greater reductions in depressive symptoms compared with the low-dose group.

A recent randomized control trial evaluated the effect of exercise intensity on depression symptoms.[30] Helgadóttir, Hallgren, Ekblom, and Forsell[55] randomized adults between the ages of 18 and 67 into one of four groups for a 12-week intervention that targeted depression symptoms: light exercise (yoga), moderate exercise, vigorous exercise, and treatment as usual. There were no significant differences between the exercise groups; however, each of the three exercise groups had significantly lower post-treatment scores when compared with treatment as usual.

123.4.3 Intervention Duration

Previous trials have reported significant reductions in depressive symptoms in as little as four weeks, though most trials have treatment periods of several months. Meta-analytical results suggest that longer intervention durations may be more efficacious in reducing depressive symptoms in patients with MDD. Rethorst et al.[41] report larger effect sizes in trials of ten weeks or longer compared with those trials with intervention durations of four to nine weeks.

123.4.4 Exercise Modality

The majority of trials examining the antidepressant effects of exercise have used aerobic exercise activities. However, as previously noted, other trials have shown the efficacy of resistance training in reducing depressive symptoms.[35,37] A recent meta-analysis confirmed the efficacy of resistance training in reducing depressive symptoms; however, training volume and improvement in strength were not associated with improved depressive symptoms in the included trials.[48] Currently, there is no evidence to indicate that one modality of exercise is more efficacious in treating MDD. One trial has directly compared differing modalities, finding no difference between an aerobic exercise group and a resistance training group,[56] while meta-analytic results have revealed no difference in effect size between the two modalities.[41, 48]

123.4.5 Adherence to Exercise Interventions

Ultimately, the aim of the prescription of exercise as a treatment for MDD is to individualize treatments to optimize patient outcomes. This requires the identification of factors that may influence response to treatment. One of the largest influences on treatment efficacy is treatment adherence. It has been postulated that exercise may be unsuccessful as a treatment for MDD due to the belief that patients with MDD will not adhere to an exercise program. However, in studies that have compared exercise interventions to SSRIs, there are no statistical differences in treatment adherence between the two treatments.[29,50] Furthermore, the Rethorst et al.[41] meta-analysis calculated the adherence rates of trials included and found a dropout rate of 14.6%. This rate is comparable to dropout rates observed in groups receiving SSRIs and psychotherapy.[57,58]

Additional strategies can be used in conjunction with an exercise intervention to improve adherence. First, the intervention itself can be modified to improve adherence. For example, Blumenthal et al.[29] found better adherence to a home-based exercise compared with laboratory-based exercise. In another study, Dunn et al.[28] found altering session frequency (three weeks vs. five weeks) resulted in no difference in adherence. A meta-analysis conducted by Stubbs et al.[59] reported that both patients who are recruited to supervised exercise sessions and recruited out of an inpatient setting are less likely to drop out.

123.5 IMPROVING DEPRESSIVE SYMPTOMS AMONG PERSONS WITH CHRONIC HEALTH CONDITIONS

In addition to trials examining the effect of exercise in individuals with MDD, another group of trials has examined the effect of exercise on depressive symptoms in diseased populations. Comorbid depressive disorders are commonly observed among individuals with chronic diseases. In addition to the burden associated with MDD, the comorbidity of MDD is often associated with poorer disease outcomes due to a reduction in treatment adherence associated with the presence of a depressive disorder.

Across available RCTs among a myriad of chronic illnesses, exercise training resulted in a small but significant mean improvement in depressive symptoms (0.29) across illnesses.[60] Moderator analyses showed stronger improvements among patients with mild-to-moderate depressive symptoms, among those who met recommended levels of physical activity, and among those for whom exercise training also significantly improved functional outcomes.

123.5.1 Cardiovascular Disease

Given the role of exercise in the prevention and treatment of cardiovascular disease, there have been several trials that have examined the effects of an exercise program on depressive symptoms in cardiovascular disease patients. A randomized control trial that was conducted in 82 medical centers in the United States, France, and Canada concluded that heart failure patients randomized to receive supervised aerobic exercise sessions and follow-up home exercise sessions experienced a statistically significant decrease in their Beck Depression Inventory Score (BDI II). Blumenthal et al.[61] found that participants with ischemic heart disease randomized to a 16-week aerobic exercise intervention had significantly lower BDI scores compared with participants receiving usual care. In another trial, participants with chronic heart failure randomized to an aerobic exercise intervention had significantly lower BDI scores compared with the treatment-as-usual (TAU) group.[62] Similarly, Kulcu et al.[63] found a significant decrease in BDI scores

following eight weeks of aerobic exercise in patients with congestive heart failure compared with TAU.

123.5.2 Type 2 Diabetes

Individuals with type 2 diabetes are at increased risk for developing depression. Given their increased risk of reporting depression symptoms,[64] this population can benefit from both the physical and mental health benefits associated with physical activity. A cross-sectional study by Craike et al.[65] not only found that physical activity explained 22% of the variance in depression symptoms among people with type 2 diabetes, but also found differences in the effect of exercise intensity when stratifying the sample by weight status. Normal weight and overweight individuals with type 2 diabetes experienced a negative association between symptoms of depression and vigorous physical activity; however, people classified as obese experienced a negative association for both moderate and vigorous physical activity.

123.5.3 Cancer

In patients with cancer, trials have examined the effects of exercise both during and following treatment. The outcomes of these trials are not always focused on depressive symptoms and the results of those trials that did assess depressive symptoms are equivocal.[66] However, there are clear psychological benefits from exercise in cancer patients including decreased fatigue, increases in positive mood, and improved quality of life.[67]

A few studies have explored the effect of exercise on depression in patients undergoing treatment for cancer or cancer survivors. A meta-analysis that explored the relationship between cancer-related fatigue and exercise measured depression as a secondary outcome and reported that exercise had a moderate effect on depression symptoms.[68] Another study randomized breast cancer patients into either high-dose aerobic exercise, standard aerobic exercise, or a combination of aerobic exercise and resistance training.[69] This trial reported among all patients, higher doses and a combination of aerobic and resistance training were not superior to standard aerobic exercise. However, patients who reported symptoms of depression at baseline were more responsive when randomized into the combination group. Although patients who reported baseline depression and were assigned to the high-dose group did not have statistically significant reductions in depression symptoms compared with those assigned to the standard group, the authors did report meaningful effect sizes for those in the high-dose group.[69]

123.5.4 Neurologic Disorders

In a meta-analysis of 26 trials of individuals with neurologic disorders (Alzheimer's disease, migraine, multiple sclerosis, Parkinson's disease, spinal cord injury, stroke, and traumatic brain injury), exercise was found to reduce depressive symptoms.[70] The majority of work done in this area has focused on individuals with multiple sclerosis. A more recent meta-analysis of 14 trials found exercise reduces depressive symptoms among individuals with multiple sclerosis. Furthermore, this effect was moderated by improvement in fatigue; studies in which exercise improved fatigue demonstrated significantly larger decreases in depressive symptoms.[71]

123.5.5 Other Diseases

While the number of trials in other diseased populations is not as large as in cardiovascular disease, research has examined the effects of exercise on depressive symptoms in patient populations.[72] As an example, patients with fibromyalgia display lower levels of depressive symptoms following exercise interventions.[73,74] Similarly, patients with COPD have reductions in depressive symptoms following an exercise intervention.[75,76]

123.6 MECHANISMS OF THE ANTIDEPRESSANT ACTION OF EXERCISE

Several mechanisms have been proposed to explain the antidepressant action of exercise. These mechanisms typically fall into one of two categories: neurobiological markers and psychosocial factors.

123.6.1 Serotonin

Serotonin is the neurobiological marker most commonly associated with MDD. Low levels of plasma serotonin (5-HT) have been widely observed in patients with MDD,[77] while SSRIs are the most commonly prescribed medication for the treatment of MDD. SSRIs inhibit 5-HT transport,[78] ultimately reducing plasma, serum, and whole-blood serotonin levels.[79,80] Results of animal studies indicate that exercise increases the neural discharge of serotonin,[77,81] tryptophan levels in the raphe nucleus[82–84] and hippocampus,[81] and serotonin metabolism.[85–87]

In animal models, exercise-induced alterations have been linked to reductions in depression-like behavior. Kim et al.[88] induced a depressive state through a series of foot shocks, which also reduced the expression of serotonin in the dorsal raphe and reduced the expression of 5-HT1A receptors. Subsequent treadmill exercise increased 5-HT and 5-HT1A expression. These increases were associated with reduced depressive symptoms. Exercise prior to stress exposure also protects against a detrimental reduction in serotonergic functioning. Ten weeks of swimming exercise prior to foot shock increased 5-HT in the hippocampus and reduced behavioral consequences of stress exposure.

A study by Otsuka et al.[89] suggests intensity alters the effects of exercise on serotonergic functioning.

Treadmill running at a low speed (15/m/min) increased c-Fos expression in 5-HT dorsal raphe nucleus neurons and reduced depression and anxiety behaviors. However, running at a faster speed (25 m/min) did not significantly alter serotonergic functioning or depression/anxiety behaviors.

Less evidence exists regarding the effects of exercise on serotonergic functioning in humans. Acute exercise increases plasma tryptophan, while exercise training increases plasma prolactin, 5-HTT, and 5-HT2A receptors,[90] but decreases serum serotonin levels.[91]

123.6.2 Inflammation

Additionally, inflammatory processes may directly and indirectly affect the pathophysiology of depression by influencing neurotransmitter systems.[92] Inflammatory factors are thought to negatively interact with other pathways to induce monoamine dysfunction, which is characteristic of the etiology of depression. Inflammation may contribute to reduced serotonin synthesis through reductions in circulating tryptophan, the precursor of serotonin, and increased neurotoxic byproducts (i.e., kynurenine) known to induce depression.[93] Immune activation by cytokines induces indoleamine 2,3-dioxygenase, an alternative metabolic pathway for tryptophan, leading to a relative depletion of tryptophan and serotonin.[92] Further, kynurenine is metabolized to kynurenic acid, which activates α7 nicotinic receptors, reducing dopamine release, and quinolinic acid, which activates glutamate NMDA receptors.[92]

Importantly, the repetitive skeletal muscle action involved in exercise alters serotonin release and metabolism in the brain through increased free fatty acid levels and the use of branched-chain amino acids during exercise that stimulate the potential for enhanced serotonin synthesis.[94] Additionally, elevated peroxisome proliferator-activated receptor-gamma coactivator-1α increases skeletal muscle expression of kynurenine aminotransferase enzymes to ultimately decrease kynurenine levels in the brain.[95] Exercise also alters the number and function of inflammatory factors.[96] For example, the largest RCT of exercise training for depression conducted to date showed that, among 116 of 945 depressed Swedish adults who completed the trial, higher baseline serum IL-6 was significantly associated with reduced depression severity after exercise and reduced IL-6 following exercise was significantly associated with parallel reductions in depression severity.[97] Similarly, in the TREAD study, higher baseline levels of TNF-α were associated with greater improvement in depressive symptoms, while changes in depressive symptoms were positively correlated with changes in IL-1β.[98] However, this innovative and integrative hypothesis remains understudied as a psychobiological mechanism of the protective effects of exercise for depression and warrants further examination at both the population level and in experimental trials.

123.6.3 Brain-Derived Neurotrophic Factor

Research indicates that brain-derived neurotrophic factor (BDNF) is thought to play a role in the development and treatment of MDD. Compared with healthy adults, serum BDNF is lower in untreated MDD patients, and serum BDNF levels are inversely correlated with symptom severity and increase following treatment.[99]

Exercise appears to increase peripheral BDNF level. Two meta-analyses report moderate increases in BDNF following an acute bout of exercise.[100,101] Both analyses found this effect to be moderated by sex, as the post-exercise increase in BDNF was larger in males than females, and Dinoff et al.[100] report greater increases in BDNF following exercise sessions of longer duration. These meta-analyses summarized studies of primarily healthy adults, but similar effects have been observed in studies of patients with MDD.[102,103]

BDNF levels also increase in response to exercise training.[101,104] Only one study included in these analyses was conducted in a sample of patients with MDD. In this study, no significant effect of exercise training on serum levels of BDNF was observed. It is worth noting that in this study, participants had been treated with an SSRI of adequate dose and duration prior to enrollment, which may confound the observed effects on BDNF as SSRI treatment increases peripheral BDNF.[105]

123.6.4 Hypothalamic-Pituitary-Adrenal Axis

Patients with MDD demonstrate elevated levels of cortisol in plasma and urine,[106–108] increased corticotropin-releasing factor (CRF) in cerebral spinal fluid,[109,110] and increased size and activity of the pituitary and adrenal glands.[111] Patients with MDD also demonstrate increased hypothalamic-pituitary-adrenal (HPA) axis reactivity to psychological stress.[112] HPA-axis function normalizes in response to MDD treatment.[113,114]

Evidence also suggests alterations in the HPA axis in response to exercise. Bouts of acute aerobic exercise result in increased cortisol excretion, while chronic aerobic exercise is associated with reduced cortisol excretion.[115] Acute aerobic exercise also reduced cortisol response to the Montreal Imaging Stress Test.[116] Furthermore, physical fitness is associated with reduced cortisol response to stress in the form of exercise[117] and psychological stress.[118] These findings are supported by a wealth of animal research demonstrating altered HPA-axis response to stressors following chronic exercise training.[119–122]

There is also evidence that these exercise-induced alterations in HPA-axis response to stress lead to improvement in depression. Liu et al.[123] induced depression-like behavior in rats through chronic uncontrolled foot shock. Physiologically, this stress increased serum corticosterone. Four weeks of swimming exercise reduced serum corticosterone, which was associated with reductions in depression-like behavior.

123.6.5 Endocannabinoids

Research has implicated endocannabinoids in the etiology and treatment of MDD.[124] Patients with MDD demonstrate lower levels of endocannabinoid ligands serum 2-arachidonylglycerol (2-AG) and anandamide,[125,126] while the level of 2-AG is negatively correlated with the duration of the current depressive episode.[126] Studies in rats indicate that endocannabinoid receptor CB_1 antagonists produce antidepressant effects,[127,128] while administration of fluoxetine results in a decrease in CB_1 gene expression.[129]

A single bout of aerobic exercise in humans increases anandamide, suggesting that exercise activates the endocannabinoid system.[130] Increased AEA following an acute bout of exercise is negatively correlated with depression, tension, and total mood disturbance factors on the Profile of Mood States and positively correlated with vigor.[131] The acute increase of endocannabinoids may be dependent on the intensity of the exercise. Raichlen et al.[132] observed increases in endocannabinoids following moderate-intensity exercise but no change following high- or low-intensity exercise.

Evidence of chronic effects of exercise on endocannabinoids is limited to animal models. CB_1 gene expression is reduced with chronic aerobic exercise,[133] mirroring the effect of fluoxetine of CB_1 gene expression. Exercise also alters CB_1 receptor sensitivity, which provides a protective effect against exposure to stress.[134]

123.6.6 Psychosocial Factors

In addition to the neurobiological mechanisms described above, psychosocial factors may also play a role in the antidepressant effects of exercise. Low self-efficacy is often associated with depressive symptoms.[135] It has been proposed that self-efficacy can be improved through physical activity.[136,137] Trials in patients with MDD consistently report an increase in self-efficacy following chronic exercise[138–140] and these increases in self-efficacy are associated with a decrease in depressive symptoms.[138] Another construct proposed as a mechanism for the antidepressant action of exercise is distraction. It has been postulated that exercise can serve as a distraction from stress and therefore reduce depressive symptoms.[141,142] However, Craft[138] found no significant difference in distraction following an aerobic exercise intervention in women with MDD.

123.7 PREDICTORS OF THE ANTIDEPRESSANT ACTION OF EXERCISE

Ultimately, the study of the antidepressant effects of exercise will inform how exercise can most effectively be used as a treatment. As described previously, the heterogeneity in treatment response indicates the need to tailor treatments to individual patients. One approach to tailor treatments is to attempt to predict treatment response based on pre-treatment patient characteristics. Recent studies have aimed to identify predictors of treatment response to antidepressant medications and psychotherapy.[143–145] A similar approach could inform which patients are most likely to benefit from exercise as a treatment.

A review by Schuch et al.[146] summarized the previous research efforts to identify predictors of treatment response to exercise. In the TREAD study,[53] biological factors associated with better treatment response to exercise included higher baseline levels of BDNF[147] and TNF-α.[98] Lavebratt et al.[97] also report elevated baseline inflammation, specifically IL-6, predicted better treatment response to exercise. Pre-treatment clinical characteristics associated with better response to exercise treatment include better physical health,[148] lower anxiety,[148] and the presence of hypersomnia,[149] and atypical depressive symptoms.[150]

The eventual utility of these predictors will be to differentiate exercise as a treatment among the variety of treatment options available. For example, exercise appears to be most effective as a treatment for individuals with elevated inflammation.[97,98] In contrast, higher levels of inflammation have typically been associated with poorer treatment response to SSRIs.[151,152] This suggests it may be possible for clinicians to choose between different treatments based on patient characteristics. However, it should be noted that the effects of these individual predictors may not be large enough to inform clinical decision-making. As a result, more recent research has attempted to combine multiple factors to predict MDD treatment response.[153]

123.8 FUTURE DIRECTIONS

Several areas for research will further clarify and define the role of exercise in the treatment of MDD. First, while there is evidence for a dose-response relationship, the combination of time, frequency, and intensity of exercise required for the optimal reduction of depressive symptoms has not been identified. Not only will this maximize the treatment effect, but identifying the appropriate dose of exercise is also important to allow physicians to provide a clear exercise prescription to patients.

Current exercise prescription recommendations are based on summaries of previous studies.[54] It should also be noted that there is likely individual variation in response to exercise. Therefore, there is not likely to be a "one size fits all" exercise prescription. Few studies have directly compared multiple exercise doses or intensities, though the results of those studies do suggest different patients respond differently to different exercise programs. This evidence corresponds with studies of physiological mechanisms of differential neurobiological response to varying exercise stimuli. For example, Otsuka et al.[89] reported increases in c-Fos expression in 5-HT neurons following low-speed treadmill running but not high-speed running. Conversely, c-Fos increased in CRF neurons following high-speed treadmill running but not low-speed running.

Researchers should continue to explore the role of exercise as an adjunctive or augmentation treatment. Integrating

exercise with established treatments has the potential to maximize treatment in a population that typically has a modest response to treatment. Results from previous trials suggest that exercise may be especially effective in maintaining treatment effects[31,33,154] and as a treatment for individuals who do not fully respond to initial SSRI treatment.[52,155] Finally, despite epidemiological evidence suggesting the protective effect of physical activity on future MDD, no trial has prospectively examined the preventive effects of exercise.

The role of exercise in the treatment of MDD will ultimately depend on treatment professionals being willing and properly educated to prescribe exercise to their patients. Recent data indicate that only 5% of general practitioners include exercise as one of their most recommended treatments for MDD, compared with 92% for antidepressant medications. This disparity is likely because only 41% of general practitioners believe exercise to be "very effective" or "quite effective" in treating MDD.[156]

Based on the existing evidence, several professional organizations, including the American Psychiatric Association,[157] the Canadian Network for Mood and Anxiety Treatments,[158] the National Institute for Health and Clinic Excellence,[159] and the Royal Australian and New Zealand College of Psychiatrists,[160] now recommend exercise as a treatment for MDD. However, significant shortcomings remain in the recommendation of exercise as a treatment for MDD.[161] Strengthening the evidence supporting exercise as a viable treatment option for depression will require demonstration of effectiveness in real-world settings. As such, researchers have called for a shift from well-controlled randomized controlled trials to pragmatic trials conducted in clinical settings.[162]

CLINICAL APPLICATIONS

Exercise is efficacious in the treatment of depressive disorders as either a monotherapy or as an augmentation to another antidepressant treatment. For patients interested in exercise as part of their treatment, evidence indicates achieving a weekly goal of approximately 150 minutes of moderate-intensity physical activity per week. Aerobic activities and resistance training have both been shown to be effective in reducing depressive symptoms.

Beyond the reduction of depressive symptoms, exercise has the potential to significantly improve the physical health of persons with depression. Compared with general populations, persons with depression are at an increased risk for cardiovascular disease, type 2 diabetes, and certain cancers.[163–166] Overall, meta-analyses have estimated the relative risk of all-cause mortality is increased by 64–81% in persons with depression compared with non-depressed individuals. Conversely, engagement in exercise is associated with a decreased risk of chronic health conditions and reduced mortality risk.[167–169] As such, engagement in exercise has the potential to significantly reduce the burden of depression, not only by reducing depressive symptoms but also by improving the physical health of those with depression.

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Part XXI

Injury Prevention



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124 Injuries and Lifestyle Medicine

David A. Sleet, PhD, Michael F. Ballesteros, PhD, and Judith R. Qualters, PhD

KEY POINTS

- Injuries are an enormous public health problem, placing a huge burden on individuals, families, communities, and the health care system.
- Injuries are the leading cause of death for ages 1–44 in the United States, with unintentional injuries as the main cause.
- Injuries are not "accidents"; most injuries are predictable and preventable.
- Acute exposure to energy at levels beyond human tolerance, or the absence of essentials such as oxygen, are the root causes of injury.
- Injury rates vary by geography and socio-demographics such as age, sex, race, and income.
- Injuries are costly to society and such costs can be averted through the use of devices such as seat belts, life jackets, smoke alarms, helmets, product safety devices, environmental safeguards, and behavioral health services for those at risk of suicide.
- Lifestyle medicine practitioners can play an important role in injury prevention by working with patients and communities to improve behaviors, laws, enforcement, environments, and products.
- Many evidence-based strategies for reducing unintentional injuries are available but are infrequently used.
- Lifestyle practitioners have an important role in injury prevention by implementing evidence-based strategies that will save lives.

124.1 INTRODUCTION

Injuries, which include unintentional injuries, violence, and suicide, are a major public health problem affecting patients, families, and the communities in which they live.[1] This chapter will focus primarily on unintentional injuries, which account for two-thirds of the public health injury burden, and will include some information on suicide (see Chapter 129).

Public health shares a common goal with lifestyle medicine to increase awareness of lifestyle-based causes of disease and injury.[2] In addition to the many preventable diseases that are seen in the practice of lifestyle medicine, there is one health threat that the public still accepts as a *fait accompli*—injuries. We have not yet fully integrated injury prevention into lifestyle medicine, and patients are not as educated on how to lower their risks of injury as they are on how to lower their risks of cancer or heart disease. Perhaps this is in part due to the belief by the public that injuries are accidental, acts of fate or bad luck, random events, or acts of God.

124.2 INJURIES OR ACCIDENTS?

An injury is distinct from an accident. Accidents are not generally considered predictable or preventable. Injuries are the medical consequences of an "accident". The Oxford English Dictionary defines the term *accident* as "an unusual event, which proceeds from some unknown cause … unexpected … happening by chance or fortune".[3] The word *injury,* on the other hand, has its root in the Latin term *injuris,* which literally means "not right". The dictionary defines injury as "hurt, damage or loss sustained"—in short, harm of any kind, done or sustained.[4] Public health and medical science favor using the term "crash", "incident", "collision", or "event" instead of "accident" to describe the circumstances that give rise to an injury[5]. The *British Medical Journal* banned the word "accident" from its lexicon in 2001[6] because it fails to distinguish between the event (fall or crash) and the outcome (tissue damage).

Injury in public health is defined as unintentional or intentional damage to the body resulting from acute exposure to thermal, mechanical, electrical, or chemical energy or from the absence of such essentials as heat or oxygen.[7] Most injuries can be prevented through changes to products, behaviors, and environments.[8] Using terms such as *injury prevention* rather than *accident prevention* helps make clear the potential for preventing such events. Lifestyle medicine can be an important source to dispel the myth of "accidents" and help patients and the public recognize that injuries are preventable if only certain steps are taken to reduce the risks at home, on the road, at work, and in the community.[9]

124.3 INJURY AS A PUBLIC HEALTH PROBLEM

The National Academy of Sciences in 1985 pronounced that "injury is the most under-recognized public health problem facing the nation today".[10] The science of injury control demonstrates that using public health and health promotion approaches can be effective in preventing injuries.[11,12]

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Injuries, like diseases, result from interactions between persons (host factors), agents or vectors (e.g., energy exchange), and the environment (physical and social environmental factors). This approach is the foundation for understanding injury prevention.[13,14]

Despite the injury burden, injury prevention has received relatively little attention from legislators, teaching institutions, journal editors, and, most strikingly, the healthcare system when compared with other public health issues. While there have been some notable exceptions to this tendency recently (e.g., pediatric traumatic brain injury guidelines, opioid prescribing guidelines, clinical training, and electronic health records (EHRs) decision support tools for injury), more needs to be done to elevate injury prevention in preventive medicine and public health. In addition to focusing on traditional areas in lifestyle medicine (e.g., physical activity, nutrition, tobacco, hypertension), lifestyle medicine practitioners can add preventing injury as part of a comprehensive public health approach to lifestyle change by supporting evidence-based policies, providing community education, and linking clinical care with injury prevention.[9,15,16]

124.4 BURDEN OF INJURIES

In the United States, unintentional injuries are the fourth leading cause of death for people of all ages and the leading cause of years of potential life lost (YPLL) before age 65 years—2.2 times that of malignant neoplasm and 2.4 times that of heart disease.[17]

Figure 124.1 compares the ten leading causes of death in 2020 by rank and age grouping. In the United States, unintentional injuries are among the top ten causes of death in each age group throughout the lifespan and the *leading* cause of death for people ages 1–44 years. Injuries represent the first, second, and third leading causes of death among ages 15–24 and 25–34 and accounted for more deaths than the other seven causes combined. For children and youth ages 1–24, injuries dominate all other causes of death.[18] Motor vehicle injuries predominate as a cause of death among ages 5–34. Suicide is a leading cause of death for those 10–44 years of age.

Table 124.1 presents CDC data on the number, percent, and rate per 100,000 population for unintentional injury deaths and suicide. The top three causes of unintentional injury death are poisonings (drug and non-drug), falls, and traffic injury deaths.[17]

Deaths are only a small part of the problem. Non-fatal unintentional injuries place a heavy burden on the healthcare system and expend valuable pre-hospital, hospital, and rehabilitation resources. In fact, an estimated 2.9 million people were hospitalized, and 22.9 million people were treated in emergency departments (EDs) in 2020.[17] Approximately one-third of all emergency department visits[19] and 6% of all hospital stays[20] are due to injuries.

Table 124.2 shows the estimated number of non-fatal unintentional and self-harm injuries treated in hospital US EDs among all ages, races/ethnicities, and sexes in 2020. The highest numbers and rates were for falls, transportation, and struck by and against injuries, with over 30% of the ED visits due to injuries resulting from falls. Over 480,000 individuals were treated for self-harm injuries, which include suicide attempts.[17]

124.4.1 Costs

The costs of injuries are staggering.[21] In 2019, the total lifetime medical and work-loss costs of injuries in the United States was $4.2 trillion in 2019, including the costs of fatal injuries ($2.2 trillion) and non-fatal injuries ($2 trillion).[22] Over $1.4 trillion of the fatal injury costs were attributed to unintentional injuries, followed by suicide $463 billion, and homicide $209 billion. Among unintentional injury costs, drug poisonings, including prescription drug overdoses, accounted for 45% of fatal injury costs; transportation-related fatal injuries, 28%; falls, 11%; and suffocation, 4%.[17]

124.4.2 Health Disparities

Injuries are not distributed evenly throughout the population. Children, adolescents, males, the elderly, the poor, certain racial/ethnic groups, and those of low SES are at elevated risk.[23] A recent analysis of National Institute of Health-funded research projects addressing unintentional injuries in children found that among 34 grants (between 2011 and 2018), only eight focused on racial and ethnic minority children.[24] Injury epidemiology can be an important tool to help explain these variations, identify groups at higher risk for injury, and target specific interventions to reduce the burden. For example:

- *Age*: Unintentional injury death rates vary by age with the lowest rates among those 5–14 years old (3.8 per 100,000 population in 2020), and the highest rate among those 75 years of age and older (191.2 per 100,000 population).[17]
- *Sex*: Males are 2.3 times more likely to die from an unintentional injury than females (age-adjusted death rates: 80.4 vs. 35.6, respectively)[17]
- *Race and ethnicity*: Unintentional injury death rates also vary by race and ethnicity. The highest death rates are among Non-Hispanic (NH) American Indian and Alaska Natives (99.8) and NH Blacks (66.9). While NH Asians and Hispanic-all races have the lowest rates (18.2 and 41.2, respectively).[17]
- *Suicide*: Suicide death rates are highest among Non-Hispanic American Indian and Alaska Natives (23.9) and Non-Hispanic Whites (16.8).[17]
- *Urbanization level*: Death rates for unintentional injuries in non-metro areas are 1.2 times higher than rates in metro areas (68.8 vs. 55.7, respectively).[17]
- *Poverty*: Unintentional injury death rates for counties with >20% poverty are 79% higher compared

Ten leading causes of death, by age group, all race/ethnicities, both sexes, United States, 2020

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	All Ages
1	Congenital Anomalies 4,043	Unintentional Injury 1,153	Unintentional Injury 685	Unintentional Injury 881	Unintentional Injury 15,117	Unintentional Injury 31,315	Unintentional Injury 31,057	Malignant Neoplasms 34,589	Malignant Neoplasms 110,243	Heart Disease 556,665	Heart Disease 696,962
2	Short Gestation 3,141	Congenital Anomalies 382	Malignant Neoplasms 382	Suicide 581	Homicide 6,466	Suicide 8,454	Heart Disease 12,177	Heart Disease 34,169	Heart Disease 88,551	Malignant Neoplasms 440,753	Malignant Neoplasms 602,350
3	SIDS 1,389	Homicide 311	Congenital Anomalies 171	Malignant Neoplasms 410	Suicide 6,062	Homicide 7,125	Malignant Neoplasms 10,730	Unintentional Injury 27,819	COVID-19 42,090	COVID-19 282,836	COVID-19 350,831
4	Unintentional Injury 1,194	Malignant Neoplasms 307	Homicide 169	Homicide 285	Malignant Neoplasms 1,306	Heart Disease 3,984	Suicide 7,314	COVID-19 16,964	Unintentional Injury 28,915	Cerebro-vascular 137,392	Unintentional Injury 200,955
5	Maternal Pregnancy Comp. 1,116	Heart Disease 112	Heart Disease 56	Congenital Anomalies 150	Heart Disease 870	Malignant Neoplasms 3,573	COVID-19 6,079	Liver Disease 9,503	Chronic Low-Respiratory Disease 18,816	Alzheimer's Disease 132,741	Cerebro-vascular 160,264
6	Placenta Cord Membranes 700	Influenza & Pneumonia 84	Influenza & Pneumonia 55	Heart Disease 111	COVID-19 501	COVID-19 2,254	Liver Disease 4,938	Diabetes Mellitus 7,546	Diabetes Mellitus 18,002	Chronic Low-. Respiratory Disease 128,712	Chronic Low-Respiratory Disease 152,657
7	Bacterial Sepsis 542	Cerebro-vascular 55	Chronic Low-Respiratory Disease 54	Chronic Low-Respiratory Disease 93	Congenital Anomalies 384	Liver Disease 1,631	Homicide 4,482	Suicide 7,249	Liver Disease 16,151	Diabetes Mellitus 72,194	Alzheimer's Disease 134,242
8	Respiratory Distress 388	Perinatal Period 54	Cerebro-vascular 32	Diabetes Mellitus 50	Diabetes Mellitus 312	Diabetes Mellitus 1,168	Diabetes Mellitus 2,904	Cerebro-vascular 5,686	Cerebro-vascular 14,153	Unintentional Injury 62,796	Diabetes Mellitus 102,188
9	Circulatory System Disease 386	Septicemia 43	Benign Neoplasms 28	Influenza & Pneumonia 50	Chronic Low-Respiratory Disease 220	Cerebro-vascular 600	Cerebro-vascular 2,008	Chronic Low-Respiratory Disease 3,538	Suicide 7,160	Nephritis 42,675	Influenza & Pneumonia 53,544
10	Neonatal Hemorrhage 317	Benign Neoplasms 35	Suicide 20	Cerebro-vascular 44	Complicated Pregnancy 191	Complicated Pregnancy 594	Influenza & Pneumonia 1,148	Homicide 2,542	Influenza & Pneumonia 6,295	Influenza & Pneumonia 42,511	Nephritis 52,547

FIGURE 124.1 Ten leading causes of death, by age group, all race/ethnicities, both sexes, United States, 2020.

TABLE 124.1

Unintentional Injury and Suicide Deaths, All Ages, All Race/Ethnicities, and Sexes, United States, 2020

Cause of Death	No.	%	Rate*
Unintentional			
Poisoning	87,404	43.5	27.05
Fall	42,114	21.0	10.27
Motor vehicle traffic	40,698	20.3	11.99
Suffocation	6768	3.4	1.83
Drownings†	4589	2.3	1.37
Fire and burns	3036	1.5	0.79
Natural disasters, animals, and environmental exposures	2118	1.1	0.56
Struck by or against a person or object	906	0.5	0.25
Pedestrian	899	0.4	0.27
Firearms	535	0.3	0.17
Machinery	530	0.3	0.14
Pedal cyclist	454	0.2	0.12
Cut or pierced by a sharp object	166	0.1	0.04
Overexertion	20	0.0	0.01
Other transportation‡	1929	1.0	0.56
Other and unspecified causes§	8789	1.0	0.52
Total unintentional deaths	**200,955**	**100.0**	**57.53**
Suicide	**45,979**	**100.0**	**13.48**

Source: CDC. Web-Based Injury Statistics Query and Reporting System. National Center for Injury Prevention and Control (NCIPC). Centers for Disease Control and Prevention, Atlanta, GA.[17]

*Age-adjusted rates per 100,000 population.

† The number and percentage include water transport.

‡ The number and percentage of other transportation deaths includes other land transport and other transport, and excludes drowning by water transport.

§ The number and percentage of other and unspecified causes of death includes the following subcategories combined: unspecified; other specified, classifiable; and other specified, not elsewhere classifiable.

TABLE 124.2

Estimated Number of Non-Fatal Unintentional and Self-Harm Injuries Treated in Hospital Emergency Departments, All Ages, All Race/Ethnicities, and Sexes, United States, 2020

Cause of Non-Fatal Injury	No.	%	Rate*
Unintentional Injuries			
Falls	6,841,044	32.7	1,918.20
Transportation†	2,867,414	13.7	880.41
Struck by or against a person or object	2,252,101	10.8	709.46
Poisoning	1,796,671	8.6	550.21
Cut or pierced by a sharp object	1,542,027	7.4	479.15
Overexertion	1,512,124	7.2	466.64
Bite or sting other than a dog bite	552,495	2.6	169.56
Foreign body	447,969	2.1	142.86
Dog bites	316,421	1.5	99.99
Fires and burns	276,092	1.3	86.51
Machinery	132,361	0.6	38.71
Inhalation/suffocation	54,226	0.3	16.44
Natural/environmental	53,746	0.3	15.87
Firearm	29,317	0.1	9.19
Drowning/submersion	7121	0.0	2.43
BB/pellet gun	7073	0.0	2.33
Other, unknown, and unspecified causes	2,213,226	12.1	782.7
Total Unintentional injuries	**20,902,133**	**100.0**	**6,268.40**
Self-harm	**483,084**	**100.0**	**155.77**

Source: CDC. Web-Based Injury Statistics Query and Reporting System. National Center for Injury Prevention and Control (NCIPC). Centers for Disease Control and Prevention, Atlanta, GA.[17]

*Age-adjusted per 100,000 population.

†The number, percentage, and rate of transportation-related injuries include the following subcategories combined: motor vehicle occupant, motorcyclist, pedal cyclist, pedestrian, and other transportation.

with counties with <5% poverty, and this gap has been widening over time.[25]

- *Disability*: Risk of unintentional injury is two to three times higher among youth with a disability.[26]

More research is needed to better understand the key drivers of these disparities and how policy and tailored prevention strategies can be used to achieve injury-related health equity.[27]

124.5 INJURY PREVENTION AND CONTROL

Lifestyle interventions for injury can, and do, work to lower risks.[28–31] In recognition of this, the US Department of Health and Human Services *Healthy People 2030* initiative includes strategies for the prevention and control of injuries in their data-driven national objectives to improve health (https://health.gov/healthypeople). Specific goals and objectives include reducing fatal injuries from traumatic brain injury (TBI), overdose deaths, motor vehicle crashes, self-harm, and falls, and reducing ED visits for non-fatal unintentional injuries. Most, if not all these risks are influenced by lifestyle choices.

Three categories of interventions that can effectively reduce unintentional injuries include education/behavior change, legislation/enforcement, and technology/engineering.[32] Each strategy can enhance the effects of the other. Specific interventions that support prevention include using individual protective devices such as helmets and seat belts; reducing risky driving behaviors such as texting and driving; installing smoke alarms; requiring alcohol interlock devices in the vehicles of offenders; supporting enhanced enforcement such as roadside breath testing for alcohol; and improving practices of physicians, providers, and other healthcare workers such as screening and brief interventions, counseling, and motivational interviewing.[33]

Individual and community actions are required for these strategies to succeed, and they are fostered by education, stimulated by social and organizational change, and encouraged through public policy, legislation, and enforcement activities.[34]

Through the elimination of injury as a cause of death, estimates reveal that the average US life expectancy at birth could be increased by approximately 1.5 years (with notable variations by sex, ethnicity, and race). Under this assumption, an estimated 48,400 injury deaths and $61 billion in medical and work-loss costs could be averted annually.[35]

124.6 HOW LIFESTYLE MEDICINE PRACTITIONERS CAN HELP PREVENT INJURIES

There is an urgent need for lifestyle medicine practitioners (and providers) to effectively link injury prevention approaches and tools to the clinical care of patients. Injury prevention counseling, for instance, can be an effective intervention with patients and families.[36,37] To date, however, office-based counseling has not been universally applied. In the 2016 DocStyles survey, healthcare providers were asked about the use of clinical fall risk assessments in older adults. Overall, only about half of primary care providers reportedly screened for fall risk at wellness visits.[38] A 2021 study asked healthcare providers about their diagnosis and management practices related to driving after a mild TBI, and 52% reported they talked with patients on how to safely return to driving more than 75% of the time. However, they did not consistently screen for risk factors and did not provide patients with written instructions for self-care.[39]

Lifestyle medicine physicians often see patients and their families for treatment after an injury has occurred, but they have the opportunity to go "up-stream" to uncover the root causes, collect injury surveillance data on specific causes, and design preventive interventions for specific populations in the clinical environment. There are also opportunities in patient care to implement interventions such as screening and brief interventions for alcohol or opioid misuse and screening and counseling older patients on fall prevention.[40]

Physicians can also inform decision-makers about the need to strengthen legislation or set healthcare and reimbursement policies that promote and incentivize prevention. Healthcare professionals who serve on medical school or nursing faculty can offer to teach courses on trauma prevention and can also help prepare medical and allied health students with material related to injury prevention.

Reducing injuries will also require a shift in how society thinks about hazards, the environment they live in, their personal risk behaviors, and the value of prevention. Lifestyle medicine can contribute to this shift by engaging in a variety of actions in the community to protect the public, such as:

- Supporting efforts to strengthen policies in your state that prevent injuries such as primary seat belt laws, strong teen driving policies, smoke alarm installation policies, adherence to evidence-based opioid prescribing guidelines, and motorcycle and bicycle safety measures such as helmet use.
- Supporting community drowning prevention strategies such as the use of four-sided fences around residential swimming pools and the use of life jackets while boating.
- Collecting data on the clinical and healthcare costs and consequences of injuries treated in the ED or in private practice settings.
- Strengthening collaboration with local coalitions, such as Safe Kids, Injury Free Coalition for Kids, local drowning prevention coalitions, the National Safety Council, or State Public Health Departments and State Offices of Highway Safety.
- Supporting efforts to build injury prevention into healthcare reform
- Testifying at hearings and town meetings about evidence-based injury prevention strategies.
- Supporting or conducting research on risk and protective factors and interventions to reduce all forms of injury and trauma, including those on and off the job.
- Strengthening pre-hospital care, comprehensive trauma care systems, and trauma registries
- Integrating injury prevention into existing health delivery systems, such as pediatric and rural health clinics, and adding injury assessments and screenings into electronic health records (EHRs).
- Assuring age-appropriate injury prevention information is added to all periodic health examinations and risk assessment systems.

124.7 FUTURE DIRECTIONS

The National Academy of Sciences/Institute of Medicine report *Reducing the Burden of Injury*[41] emphasized the importance of using a scientific approach to injury prevention and called on public health agencies and others to work with medical care organizations, healthcare providers, states and communities, businesses, and other federal agencies to pursue alliances that would help reduce injuries. Injury epidemiologists, behavioral scientists, and lifestyle medicine practitioners can work side-by-side to identify, prevent, and control injuries, and to explore ways to better integrate our public health and healthcare delivery system, strengthen data systems and advance the use of digital technologies to better support health outcomes across the life span, identify risk and protective factors, test culturally appropriate interventions, and conduct evaluations of existing injury prevention efforts.

Injury prevention has evidenced significant progress in the United States in the past 30 years. Fatal and non-fatal injuries have been reduced and funding for injury prevention

and control research and infrastructure support for state programs have all increased.[15] But more work needs to be done. The challenge now is to engage lifestyle medicine and primary care physicians in becoming more active in fostering lifestyle behaviors to prevent injuries.[2,9,42] Rapid advances in clinical decision support systems embedded in electronic health records, use of telehealth services for broader service delivery as was seen during the COVID-19 pandemic, and resources such as CDC's Stopping Elderly Accidents, Deaths, and Injuries (STEADI) toolkit, which supports healthcare providers in fall risk assessment and treatment, provide some ways of addressing this challenge.[43]

Lifestyle medicine practitioners and the Lifestyle Medicine Association are important partners in fostering strategies to prevent injuries. Primary care professionals and other gatekeepers can help make injury-free choices the easiest choices for patients and the public, thus reducing injuries from all causes.[44] And, as integral members of their communities, lifestyle medicine practitioners can play a pivotal role in advancing a culture of safety throughout the life course of patients and families.[45]

124.8 CONCLUSIONS

Although injuries have plagued societies since the beginning of time, injury science has taught us that injuries are both predictable and preventable. Using theory and a combination of environmental, product engineering, and behavioral approaches that target the host, agent, and environment stand the best chance of succeeding.[8,46,47] Approaches will need to be adapted to different populations, lifestyles, and life stages with a particular sensitivity to social determinants of injury. Because there are so many different injuries with varied causes, tailored strategies are necessary. Lifestyle medicine and primary care family practitioners are important allies in encouraging lifestyle choices that reduce injuries.

As the editors of the *American Journal of Lifestyle Medicine* wrote in the introduction to their inaugural issue:[48]

> We need to focus our patients' attention on the important daily practices and habits that can either promote good health or, if these practices are not positive, lead to adverse health consequences. This is one of the great challenges for health care practitioners in the 21st century. (p.9)

Injury prevention can now be added to the list of daily practices and habits that will promote good health.

CLINICAL APPLICATIONS

- Include injury prevention in all your health promotion and disease prevention activities with patients.
- Expand your record-keeping to collect and monitor patient risk factors for injuries (e.g., chart reminders for teens about texting and driving or about opioid-related overdose risk among middle-aged adults).
- Assess the safety practices of patients and their families (e.g., consistent use of seat belts, helmets, and life jackets, avoidance of drinking and driving, and preventive measures to prevent falls in older adults).
- Assess for depression and risk factors for suicide in patients experiencing stress or traumatic life events.
- Set goals for your patients to change risky lifestyles that predispose them to injuries.
- Encourage patients to use protective gear in play and sports.
- Assess the risks of unintentional injury and suicide among racial and ethnic minority groups who are disadvantaged.
- Promote the collection and dissemination of local injury-specific data to help develop effective interventions at the community level.
- Have information available on how patients can access resources in the community for injury and suicide prevention (e.g., CDC, local safety council, state health departments, mental health clinics, suicide helpline, SafeKids chapters, poison control centers, and local prevention coalitions).
- Screen for alcohol misuse and poly-drug use using tools such as brief intervention and motivational interviewing (www.cdc.gov/opioids/providers/training/index.html).
- Advise parents on the correct use of age-appropriate child safety seats and booster seats with their children.
- Support improvements in pre-hospital and hospital care for injured victims and support comprehensive trauma care systems in your community.
- Maximize the use of EHRs for injury data and use prescription drug monitoring programs to improve prescribing practices.

Disclaimer: The findings and conclusions in this manuscript are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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125 Motor Vehicle Crashes, Injuries, and Deaths: Epidemiology and Prevention

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KEY POINTS

- Motor vehicle crashes (MVCs) are a leading cause of death and a major cause of morbidity in the United States.
- MVC deaths and injuries are costly to society and the healthcare system.
- MVC deaths and injuries to drivers, passengers, motorcyclists, pedestrians, and bicyclists are preventable.
- Effective evidence-based strategies are widely available, but most are not universally implemented.
- Primary prevention holds the most promise for reducing the MVC death/injury burden (e.g., sobriety checkpoints and ignition interlocks).
- Healthcare providers can play an important role in primary prevention by conducting screening and patient education in clinical settings and supporting effective public policies.

125.1 MOTOR VEHICLE CRASH DEATH/INJURY AND LIFESTYLE MEDICINE

Motor vehicle crash (MVC) injury and lifestyle choices are inextricably linked.[1] For many, a healthy lifestyle entails independence that comes with the ability and freedom to drive.[2] Motor vehicle travel continues to be a popular mode of travel in the United States. In the span of 100+ years, the number of registered vehicles in the United States has grown from about 1.3 million in 1913 to about 276 million in 2020.[3] In 2020, about 92% of households had at least one vehicle available to drive.[4] There were about 228 million licensed drivers in the United States in 2020, and each licensed driver drove an average of 12,724 miles on over four million miles of public roads.[5] However, motorization has consequences for crashes, injuries, medical care, and deaths.

MVCs are a leading cause of death for people aged 1–75 years in the United States, and they are the number one cause of death for children, youth, and young adults combined across the age range of 5–24 years.[6] MVCs accounted for approximately 40,000 deaths and more than 2.1 million emergency department visits for non-fatal MVC injuries in 2020.[6] In comparison, 349 people died in non-military airplane crashes in the United States in 2020.[7]

MVCs also result in substantial monetary costs. In 2020, MVC deaths resulted in approximately $430.7 billion in total costs (in 2020 US dollars), including about $537 million in medical costs and about $430.2 billion in cost estimates for lives lost.[6] Additionally, non-fatal transportation injuries resulted in approximately $331.5 billion in total costs (in 2020 US dollars), which included $51.1 billion in medical costs, $15.7 billion in lost productivity costs, and $264.7 billion in quality-of-life loss costs.[6]

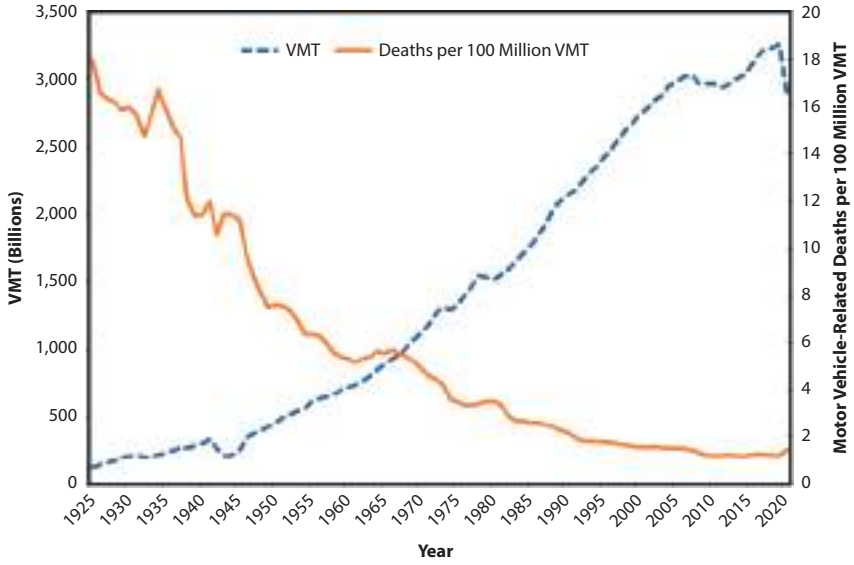
Nevertheless, substantial progress has been made. While road environment exposure has increased (as measured by vehicle miles traveled), there has also been a 92% decline in MVC deaths per 100 million vehicle miles traveled between 1925 and 2020[3] (Figure 125.1). Improvements in motor vehicle safety are considered one of the ten greatest public health achievements over the past 100 years. These improvements have been possible primarily due to advances in vehicle safety, road improvements, and driver behavior change,[8–10] which have mitigated many of the negative effects of increased motorization. This achievement is an example of how injury prevention science has played a critical role in reducing MVC deaths without taking cars off the road. Despite these remarkable declines, MVCs remain a leading cause of death among most age groups in the United States.[6]

125.2 HEALTH EQUITY CONSIDERATIONS

Some populations are disproportionately affected by MVCs.

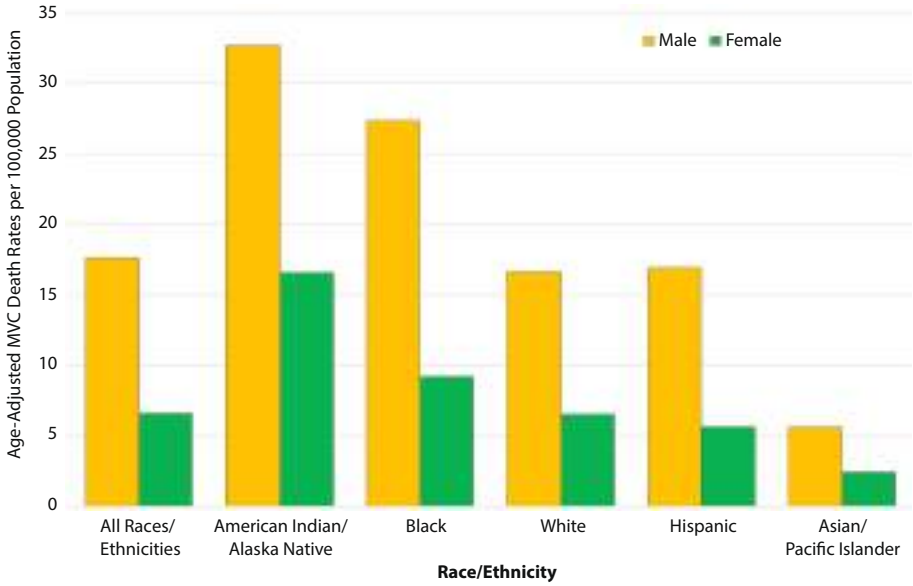
- *Disparities by sex*. Males consistently have higher MVC death rates than females. In 2020, the age-adjusted MVC death rate among males (17.6 per 100,000 males) was about 2.7 times higher than that of females (6.5 deaths per 100,000 females)[6] (Figure 125.2).
- *Disparities by age*. MVC death rates are typically higher among young adults and older adults than among other age groups. In 2020, the highest MVC death rates by age group were among young adults aged 20–24 years (19.4 deaths per 100,000 population), young adults aged 25–29 years (17.9 deaths per 100,000 population), and older adults aged ≥85 years (16.7 deaths per 100,000 population).[6]

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Abbreviation: VMT = vehicle miles traveled.
Data Source: https://injuryfacts.nsc.org/motor-vehicle/historical-fatality-trends/deaths-and-rates/.
Note: The National Safety Council (NSC) did not directly provide VMT. VMT were calculated based on the number of motor-vehicle related deaths and the death rates per 100 million VMT provided by NSC. Therefore, VMT estimates in this figure may differ slightly from VMT estimates provided by the Federal Highway Administration (FHWA) due to rounding.

FIGURE 125.1 Annual vehicle miles traveled and motor vehicle-related deaths per vehicle miles traveled—United States, 1925–2020.



Abbreviation: MVC = motor vehicle crash.
Data Source: CDC WISQARS, available at: https://www.cdc.gov/injury/wisqars/.
ICD-10 Codes: V02–V04 (.1,.9), V09.2, V12–V14 (.3–.9), V19 (.4–.6), V20–V28 (.3–.9), V29 (.4–.9), V30–V39 (.4–.9), V40–V49 (.4–.9), V50–V59 (.4–.9), V60–V69 (.4–.9), V70–V79 (.4–.9), V80 (.3–.5), V81.1, V82.1, V83–V86 (.0–.3), V87 (.0–.8), V89.2.
Notes: Data for White, Black, American Indian/Alaska Native, and Asian/Pacific Islander only include Non-Hispanic ethnicity. Data for Hispanic ethnicity include all races. Rates are standardized to the 2000 US population. The race/ethnicity categories are displayed in descending order (from left to right) by overall (not sex-specific) age-adjusted motor vehicle crash death rates in 2020.

FIGURE 125.2 Age-adjusted motor vehicle crash death rates by race/ethnicity and sex—United States, 2020.

- *Disparities by race/ethnicity.* MVC death rates are typically highest among non-Hispanic American Indian and Alaska Native people (AIAN) and are also disproportionately high among non-Hispanic Black people. In 2020, the age-adjusted MVC death rate among AIAN people was 24.4 per 100,000 population, which was 1.4–6.2 times higher than the rates of other racial/ethnic groups. Age-adjusted MVC death rates among Black people (17.7 per 100,000 population) were the second highest when compared with other racial/ethnic groups. Similar disparities exist when examining

MVC deaths among racial/ethnic groups by sex[6] (Figure 125.2).

- *Disparities by urban/rural status.* Within the United States, disparities persist by rurality, with higher MVC death rates and less restraint use in rural compared with urban areas.[11–13]
- *Disparities by US state.* MVC death rates vary widely by state. In 2020, age-adjusted MVC death rates ranged from a low of 5.1 per 100,000 population in Massachusetts to a high of 27.7 per 100,000 population in Mississippi. Many states with the highest death rates were located in the South, and many states with the lowest death rates were located in the Northeast[6] (Figure 125.3).
- *Disparities among high-income countries.* In 2019, the United States had the highest population-based MVC death rate out of 29 high-income countries. The 2019 US death rate (11.1 per 100,000 population) was 2.3 times higher than the average rate (4.8 per 100,000 population) among 28 other high-income countries. Additionally, the US population-based death rate increased nominally (by 0.1%) from 2015 to 2019, whereas the average percent change among 27 other high-income countries was −10.4%.[14]

While the public health burden of MVCs is large, effective strategies to prevent deaths and injuries exist. Healthcare providers (HCPs) have an opportunity to address motor vehicle safety and discuss what works to keep patients safe on the road. The rest of this chapter will briefly summarize the epidemiology of MVC deaths and injuries by topic and discuss evidence-based strategies to reduce the personal, societal, and healthcare burden they present. At the end of each motor vehicle safety topic section, there is a brief summary with suggestions about what HCPs can do.

125.3 MOTOR VEHICLE INJURY PREVENTION STRATEGIES

125.3.1 Alcohol-Impaired Driving

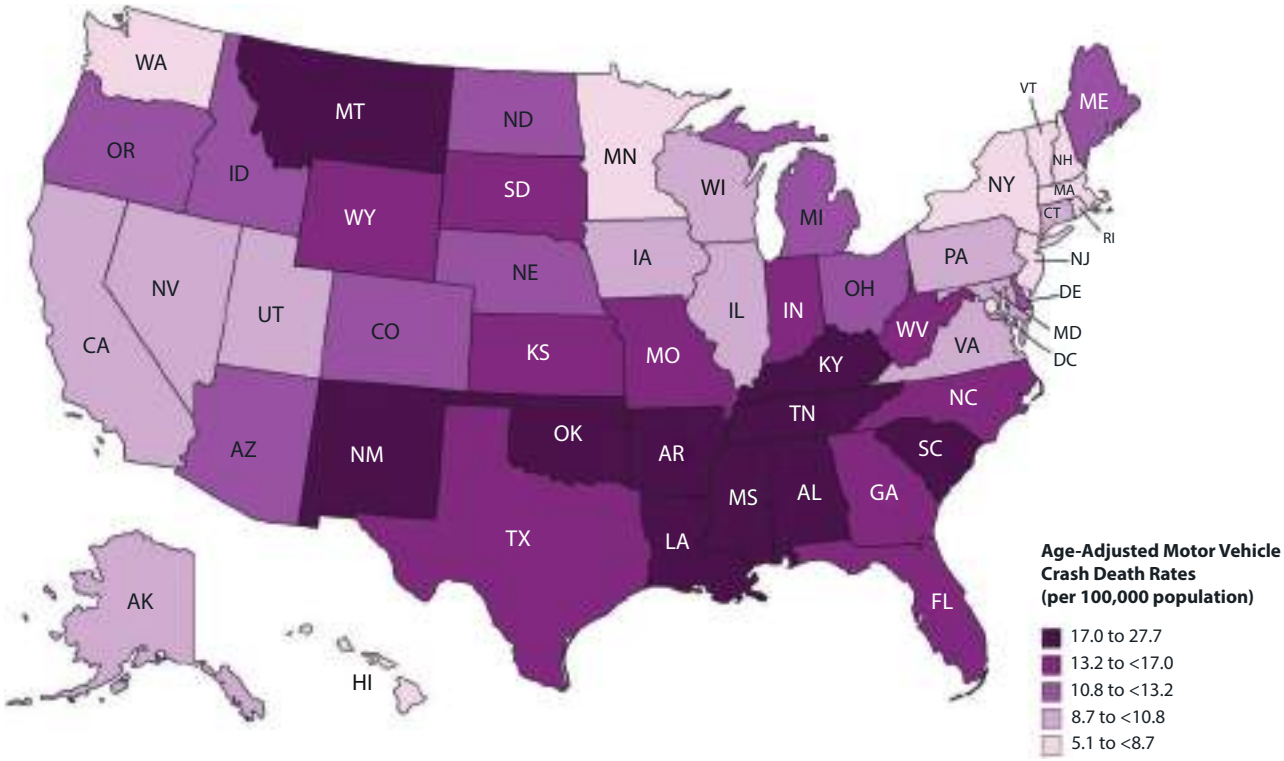
Alcohol-impaired driving has been a persistent motor vehicle safety problem in the United States. Since the mid-1990s, approximately 30% of MVC deaths each year have involved at least one alcohol-impaired driver.[15,16] The Centers for Disease Control and Prevention's (CDC) Transportation Safety website offers additional information about alcohol-impaired driving.

Screening, interventions, and assessment/treatment programs typically focus primarily on reducing alcohol consumption; however, they can be beneficial for reducing many alcohol-related harms, including alcohol-impaired driving.[17–19] Examples include the following:

- *Screening, brief intervention, and referral to treatment (SBIRT).* These interventions typically focus on identifying people who drink alcohol excessively (but do not have alcohol use disorder) before they commit an alcohol-impaired driving offense. Brief interventions often involve assessing readiness to change as well as motivators and barriers for behavior change. SBIRT has been implemented in hospitals, emergency departments, other clinical settings, and non-clinical settings (e.g., colleges and high schools).[17–19]
- *Electronic screening and brief intervention (e-SBI).* These interventions take advantage of technology (i.e., electronic devices such as computers, cell phones, and tablets) to facilitate the delivery of key elements of face-to-face SBI. At a minimum, e-SBI involves screening individuals for excessive drinking and delivering a brief intervention with personalized feedback about the risks and consequences of excessive drinking.[20] CDC's Alcohol Screening Tool can be used by adults to assess their drinking and create a personal change plan.
- *Alcohol use disorder (AUD) assessment and treatment.* People who have AUD can benefit from referrals to specialized treatment. Long-term programs including close monitoring for alcohol use and tailored treatment are typically most effective.[17] See Chapter 98 in this textbook for more information.
- *Programs for people who are convicted of alcohol-impaired driving offenses.* When people are convicted of alcohol-impaired driving, this is an opportunity to assess drinking patterns and refer them for brief interventions or specialized treatment, as appropriate. These assessment and treatment programs should be implemented in combination with other strategies (e.g., ignition interlocks) and should not be used as a replacement for other sanctions.

Other effective strategies for reducing alcohol-impaired driving include:

- *Publicized sobriety checkpoints and high-visibility saturation patrols.* These law enforcement strategies entail police patrolling locations to find impaired drivers and either randomly or selectively checking drivers for impairment. Times and locations are usually selected based on when and where alcohol-impaired driving and related crashes are more common. These strategies are most effective when well-publicized (e.g., through mass media campaigns) and when conducted regularly.[17,21]
- *Alcohol ignition interlocks for all people convicted of alcohol-impaired driving, including first-time offenders.* Ignition interlocks are devices that can be installed in cars and measure alcohol on the driver's breath. Interlocks prevent the car from starting if the driver has a blood alcohol concentration (BAC)



Data Source: CDC WISQARS, available at: https://www.cdc.gov/injury/wisqars/.
ICD-10 Codes: V02–V04 (.1,.9), V09.2, V12–V14 (.3–.9), V19 (.4–.6), V20–V28 (.3–.9), V29 (.4–.9), V30–V39 (.4–.9), V40–V49 (.4–.9), V50–V59 (.4–.9), V60–V69 (.4–.9), V70–V79 (.4–.9), V80 (.3–.5), V81.1, V82.1, V83–V86 (.0–.3), V87 (.0–.8), V89.2.
Note: Rates are per 100,000 population and are standardized to the 2000 US population.

FIGURE 125.3 Age-adjusted motor vehicle crash death rates by US state—United States, 2020.

above a certain level (usually 0.02 grams/deciliter). These devices are effective for preventing repeat alcohol-impaired driving offenses while they are installed but are less effective for reducing recidivism once they are removed. However, coupling AUD assessment and treatment programs with ignition interlocks has shown benefits for reducing alcohol-impaired driving recidivism even after interlocks are removed.[22] States with all-offender ignition interlock laws have experienced the largest reductions in the number of alcohol-impaired drivers involved in fatal crashes, as compared with states requiring interlocks only for some offenders or no offenders.[23]

- *Lower blood alcohol concentration (BAC) limits.* Forty-nine US states and the District of Columbia (DC) have a BAC limit of 0.08 grams/deciliter (g/dL) for drivers, which means drivers with a BAC ≥0.08 g/dL are considered impaired by the legal definition. However, driver impairment begins at even lower BAC levels.[24] In 2018, Utah implemented a 0.05 g/dL BAC law, resulting in substantial reductions in MVCs, alcohol-involved crashes, and deaths per mile driven.[25] Globally, most high-income countries have BAC laws set at 0.05 g/dL or lower,[14,26] which can reduce alcohol-impaired driving.[24]
- *Other laws that can reduce alcohol-impaired driving.* All US states and DC have zero tolerance laws, which prohibit people aged <21 years from driving with any measurable amount of alcohol in their systems. All states and DC also have minimum legal drinking age laws, which require people to be aged ≥21 years to purchase alcohol. Both laws have been effective in reducing alcohol-impaired driving crashes and related injuries/deaths.[17,24,27,28] Other policies/strategies intended to reduce drinking to impairment by decreasing the availability, accessibility, and affordability of alcohol (e.g., increasing alcohol taxes and regulating alcohol outlet density) can also be beneficial for reducing alcohol-impaired driving.[24]

What HCPs can do:

- Screen patients for excessive alcohol use and AUD. Patients who drink alcohol excessively can benefit from brief behavioral counseling interventions,[29] and patients who have AUD can be referred to more extensive alcohol treatment programs.
- Support effective alcohol-impaired driving prevention strategies, such as lower BAC limits for drivers and ignition interlocks for all people convicted of alcohol-impaired driving.

125.3.2 Drug- and Polysubstance-Impaired Driving

Drug-impaired driving is driving while impaired by any illicit or legal substance (including prescription or over-the-counter medications). Polysubstance-impaired driving is driving while impaired by two or more substances (e.g., alcohol and cannabis). Drug- and polysubstance-impaired driving have become an increasing public health concern in the United States, particularly because of increased state-level legalization of cannabis (medical and/or non-medical) and because of the ongoing opioid overdose epidemic.

After alcohol, cannabis is the most common substance associated with impaired driving.[30,31] Cannabis has negative effects on many skills that are important for safe driving, such as motor coordination, decision-making, judgment, and reaction time.[30,32] Also, acute cannabis intoxication has been associated with MVCs.[32,33] The most common polysubstance-impaired driving combination is alcohol and cannabis, and this combination can impair driving skills even more than either substance alone.[34] Cannabis use is illegal at the federal level; however, as of July 2022, 19 states and DC allow for non-medical adult use and medical use, and 18 additional states allow for medical use.[35]

Many substances (e.g., cannabis) are processed differently in the body than alcohol. Thus, there is typically poor correlation between blood concentrations of non-alcohol substances and impairment. Also, non-alcohol substances often remain in the body much longer than alcohol.[30,32] Polysubstance use is common, and determining each substance's individual as well as combined effects on driving can be difficult.[30] Less is known about the involvement of non-alcohol substances in MVCs since standardized toxicological testing[36] for drivers involved in MVCs is not universally implemented across the United States. CDC's Transportation Safety website offers additional information about drug- and polysubstance-impaired driving.

While less is known about how to reduce drug- and polysubstance-impaired driving, some strategies include:

- *SBIRT.* Screening can be beneficial for identifying people who use substances in a harmful way.[37] Brief interventions could be implemented in some situations for people who use other substances with similar techniques to those used for people who drink excessively.
- *Substance use disorder assessment and treatment.* People with substance use disorders can be linked to specialized treatment. For example, people with opioid use disorder may benefit from treatment with medication such as buprenorphine or methadone.[38]
    - The Substance Abuse and Mental Health Services Administration (SAMHSA) offers a Behavioral Health Treatment Services Locator and an Evidence-Based Practices Resource Center.
    - CDC offers an Addiction Medicine Toolkit where HCPs can learn more about diagnosis and treatment of substance use disorders, linkage to care, stigma reduction, and patient communication strategies.

  SBIRT and assessment/treatment of substance use disorders may help reduce harmful substance use; however, more research is needed to determine if these interventions can reduce drug-impaired driving.
- *Publicized sobriety checkpoints and high-visibility saturation patrols* may have the potential to reduce drug- and polysubstance-impaired driving. There is minimal research to assess their effectiveness specifically for drug-impaired driving.[39] If conducted, they should include *drug recognition experts*—police officers with specialized training who can recognize impairment by substances other than (or in addition to) alcohol.

What HCPs can do:

- Consider screening patients for excessive alcohol use[29] and other substance use[37] simultaneously to maximize time and resources, as well as opportunities for brief interventions or linkage to treatment, as appropriate.
- Counsel patients about the effects of any substances (illicit, prescription, or over-the-counter) they use and how these substances can affect the ability to drive safely.

125.3.3 Child Passenger Safety

In 2020, 607 child passengers aged <13 years died in MVCs[40] and more than 63,000 child passengers were injured.[6] Correct and consistent use of age- and size-appropriate car seats and booster seats is essential to keep children safe when traveling in motor vehicles.[41] Car seats and booster seats are effective in reducing injuries and deaths among children.[41–45] However, many children travel completely unrestrained, are restrained incorrectly, or graduate to the next stage of child passenger safety too early.

CDC's current child passenger safety guidelines are as follows:

- *Stage 1.* From birth until age 2–4, children should be buckled in a *rear-facing car seat with a harness* until they reach the maximum weight or height limit of their car seat. Never place a rear-facing car seat in the front seat of a vehicle. Front passenger airbags are especially dangerous for young children in rear-facing car seats.[41]
- *Stage 2.* After outgrowing their rear-facing car seat and until at least age 5, children should be buckled in a *forward-facing car seat with a harness* until they reach the maximum weight or height limit of their car seat.

- *Stage 3.* After outgrowing their forward-facing car seat, children should use a *belt-positioning booster seat* until the seat belt fits properly without a booster seat, which typically does not occur until children are aged 9–12 years.
- *Stage 4.* Children no longer need to use a booster seat when the *seat belt* fits them properly. A seat belt fits properly when the lap belt is across the upper thighs (not the stomach) and the shoulder belt is across the center of the shoulder and chest (not on the neck/face or off the shoulder). Children aged <13 years should sit in the back seat of the vehicle so that they are not near frontal airbags.[41,46] Airbags are designed to be used in combination with seat belts for adults and can cause serious injuries or death to children.

Effective strategies to increase restraint use among children include the following:

- *Child restraint laws* requiring children to use approved car seats, booster seats, or seat belts appropriate for their weight, height, and age when traveling in motor vehicles increase restraint use.[17,47,48]
  - *Short-term, high-visibility enforcement* of child restraint laws coupled with widespread media advertisements can enhance the effectiveness of child restraint laws.[17,47]
  - *Strengthening/extending current child restraint laws* can also be beneficial for increasing age- and size-appropriate restraint use.
    - *Booster seat provisions.* Child restraint laws requiring children who have outgrown car seats to use booster seats until at least age nine can help reduce injuries and deaths.[13,49–52] As of July 2022, only five US states require children to use booster seats until at least age nine. CDC's Booster Seat Planning Guide can assist with assessing, planning, and implementing improved booster seat laws.[49]
    - *Provisions requiring children to remain rear-facing until at least age two.* Current guidance from CDC and the American Academy of Pediatrics (AAP) recommends that children remain in rear-facing car seats for as long as possible and until they reach the maximum weight and height limits of their car seat.[41,46,53] Most children should be able to ride rear-facing in convertible car seats until they are aged 2–4 years. As of July 2022, 17 US states and DC require children to be rear-facing until age two.
- *Distribution plus education programs* help parents/caregivers obtain new, unused car seats and learn how to properly use and install them. These programs often include hands-on demonstrations. *Incentive and education programs* are similar and reward parents/caregivers for correctly using car seats. Both types of programs typically offer instructional aids such as print materials and videos for parents/caregivers.[17,47,54]

What HCPs can do:

- Reinforce the importance of properly using car seats, booster seats, and seat belts correctly and on every trip. Children aged <13 years should sit in the back seat of the vehicle.
- Share child passenger safety resources with parents/caregivers whose children are aged <13 years, such as CDC's Transportation Safety website and CDC's infographics about the four stages of child passenger safety.
- Suggest that parents/caregivers consider seeking assistance with education and installation of car seats and booster seats from certified Child Passenger Safety Technicians. Parents/caregivers can also attend local car seat inspection stations.[55] These services are usually free.
- Determine if there are local distribution/education programs for families who cannot afford car seats and provide those resources to families.
- Support strengthening/extending current child restraint laws when laws are not on par with best practice.

125.3.4 Restraint Use among Teens and Adults

The use of seat belts is the most effective way to save lives and reduce injuries in crashes[56]—yet millions of teens and adults do not use seat belts on every trip. Seat belts reduce death and serious injury by about half.[56] Nonetheless, about half of occupants aged ≥13 years who are killed in crashes are unrestrained.[57] CDC's Transportation Safety website offers additional information about seat belt use.

Restraint use varies significantly by age, race/ethnicity, location, and other factors.[11,58–61] Compared with other age groups, teens and young adults aged 16–24 years have the lowest seat belt use rates.[58] Additionally, seat belt use in the back seat is substantially lower than in the front seat.[58,62]

Effective strategies for increasing seat belt use include the following:

- *Primary enforcement seat belt laws.* These laws allow police officers to stop and ticket someone just for not using a seat belt. Primary seat belt laws result in higher rates of seat belt use and fewer MVC deaths than secondary seat belt laws,[17,63] which only allow officers to give tickets if a driver is stopped for another reason. Seat belt laws are most effective when they cover occupants in the

front seat and the back seat.[58] As of July 2022, 20 US states and DC have primary enforcement seat belt laws covering all seating positions.

- *Increased penalties.* Increased penalties for violating seat belt laws can increase seat belt use.[17,64] Penalties may include higher fines or negative points on a driver's license.
- *Short-term, high-visibility enforcement.* Efforts such as "Click-It-or-Ticket" involve a short period of increased and highly publicized police efforts. Combining law enforcement and media coverage can be particularly effective for reaching people who typically have lower seat belt use rates (e.g., men, teens, and young adults).[17] Conducting these enforcement efforts at night may have added benefits since seat belt use is lower and other transportation risk behaviors are typically higher at night.[17]

What HCPs can do:

- Remind patients about the effectiveness of seat belts and that it is important to use them on every trip, even for short distances.
- Emphasize the importance of being good role models by using a seat belt, especially for parents/caregivers who want to set a good example for their children.
- Support primary enforcement seat belt laws for all seating positions and other effective strategies for increasing seat belt use.

125.3.5 Teen Driver Safety

MVCs are a leading cause of death for teenagers. In 2020, about 2,700 teenagers (aged 14–19 years) were killed and about 216,000 were non-fatally injured in MVCs.[6] Per mile driven, teen drivers (aged 16–19 years) are approximately three times as likely as drivers aged ≥20 years to be involved in a fatal MVC.[65] Teen drivers are particularly susceptible to being involved in MVCs due to their age and their inexperience behind the wheel.[66] Engaging in risky behaviors such as speeding, impaired driving, non-use of seat belts, and distracted driving puts them at additional risk.

Effective strategies include the following:

Graduated Driver Licensing (GDL) systems help new drivers progressively gain skills and driving experience under lower-risk conditions. The three stages of GDL include 1) learner's permit; 2) intermediate/provisional license; and 3) full licensure.[67] GDL systems exist in all US states and DC, although the strength of laws in each state varies. GDL laws have been repeatedly shown to be effective in reducing teen crashes and deaths.[17,68] Best practice GDL systems include a minimum age of 16 for obtaining a learner's permit, a mandatory learner's permit holding period of 12 months, at least 70 supervised practice hours, no teen/young adult passengers, restrictions against nighttime driving between 10:00 pm and 5:00 am (or longer), and a minimum age of 18 for full licensure.[69–71] CDC's Graduated Driver Licensing System Planning Guide can help states develop plans to strengthen GDL practices. Please see CDC's Transportation Safety website for more information about GDL.

Parental/guardian monitoring, supervision, and involvement have shown some benefits for reducing transportation risk behaviors and increasing safe driving among teen drivers.[72,73] Parents/guardians can restrict driving under high-risk conditions, such as prohibiting nighttime driving and not allowing their teen to drive with any young passengers—even if their state's GDL laws do not have these restrictions. Parents/guardians can also set clear rules and expectations with their teen driver for them to follow GDL practices and not engage in transportation risk behaviors (e.g., impaired driving or distracted driving). They can also formalize a commitment to safe driving practices with their teen through a signed Parent-Teen Driving Agreement, which can be found on CDC's Transportation Safety website. Moreover, parents/guardians can practice with their teen to ensure their teen gets many hours of supervised driving experience under varied conditions.

What HCPs can do:

- Counsel parents/guardians about their responsibility to keep their teens safe on the road, and counsel teens about their responsibility to become safe, responsible drivers.[55,73,74]
- Remind parents/guardians and teens about the importance of GDL systems, and ensure they are familiar with their state's GDL laws. Encourage parents to set additional restrictions if state GDL does not align with best practice.
- Stress the need for parents to practice driving with their teen under varied conditions, monitor their teen's driver behaviors, establish a Parent-Teen Driving Agreement with their teens, and set a good example for their teens by using seat belts and not driving while impaired or distracted.[55]
- Encourage parents/guardians and teens to purchase the safest cars possible within their budget. Parents/guardians can consult a list of safe and affordable vehicles for teens and can read research about the benefits of newer vehicle safety technologies for teen drivers on the Insurance Institute for Highway Safety's website.

125.3.6 Older Adults

The older adult population (aged ≥65 years) in the United States is growing rapidly. The older adult population grew from 41.4 million in 2011 to 55.7 million in 2020, representing a 34.6% increase.[75] During the same period, there was only a 1.3% increase among people aged <65 years.[75] About 86% of older adults (47.7 million) have driver's licenses.[5,75]

Frailty increases with age; therefore, older adults are more likely to be killed or seriously injured if they are involved in MVCs.[76] About 7,500 older adults were killed in MVCs and about 196,000 older adults were treated in emergency departments for non-fatal MVC injuries in 2020.[6]

What HCPs can do:

- Encourage older adult patients to download and use CDC's MyMobility Plan and related resources. The plan and its resources can help older adults plan to stay safe, mobile, and independent as they age, as well as help them reduce injury risks that often come with age.
- Review each patient's prescription and over-the-counter medications to reduce side effects and interactions. CDC's Medicines Risk Fact Sheet contains information about medications that might have side effects associated with MVCs and falls.
- Motivate patients to follow a regular physical activity program to increase strength, balance, and flexibility.
- Recommend that patients have their eyes checked annually and that they wear glasses/corrective lenses as required, which can benefit them as drivers, pedestrians, or bicyclists.
- Encourage older adults to consider potential alternatives to driving, such as riding with a friend/family member, using a ride share service, or using public transportation.

125.3.7 Pedestrians

Pedestrian deaths have increased by almost 50% in the last decade.[6,77] In 2020, about 7,000 pedestrians were killed in MVCs, and approximately 104,000 pedestrians were treated for non-fatal MVC injuries.[6] Risk factors for pedestrian deaths and injuries include walking in urban areas, walking at non-intersections, walking at nighttime, and vehicle speed.[77,78]

Effective interventions to reduce pedestrian deaths and injuries include the following:

- *Reducing vehicle speeds.* An adult pedestrian's risk of dying if struck by a car traveling about 30 miles per hour is <20%, but that same pedestrian would have almost a 60% risk of dying if they were struck at about 50 miles an hour.[79] Therefore, reducing vehicle speeds through roadway design interventions or lower speed limits can be particularly beneficial for pedestrians, especially in urban areas.
- *Roadway countermeasures that enhance the visibility of pedestrians and/or physically separate them from motor vehicles.* Examples include sidewalks, crosswalks (particularly with visibility enhancements), specific types of flashing pedestrian warning signs, medians/pedestrian refuge islands, and leading pedestrian intervals.[80]
- *Increasing visibility, especially at night.* Wearing retroreflective materials (particularly on extremities) or flashing lights can dramatically increase the distance from which a pedestrian can be seen and thus can help to prevent pedestrian deaths and injuries.[17,81]

What HCPs can do:

- Encourage patients to be aware of the risks that pedestrians face and to protect themselves by:
  - Increasing their visibility at night by carrying a flashlight and wearing reflective clothing.
  - Walking on sidewalks or other paths instead of the road. If no sidewalks or paths are available, walk on the shoulder facing traffic.
  - Crossing streets at a crosswalk or intersection.
  - Avoiding the use of electronic devices when walking—especially when crossing the street.
  - Avoiding walking if they have been drinking alcohol and/or using other substances, which can impair judgment and coordination.
- Support implementation of speed reduction countermeasures (e.g., roadway design features and lower speed limits).

125.3.8 Motorcyclists

Almost 5,600 motorcyclists were killed in the United States in 2020,[82,83] and about 181,000 motorcyclists were treated in emergency departments for non-fatal MVC injuries.[6] Riding on motorcycles is inherently more dangerous than riding in motor vehicles, since motorcycles are less stable and lack the protection of a vehicle shell.[82] In 2020, the death rate per vehicle mile traveled among motorcyclists was about 28 times higher than the death rate per vehicle mile traveled for passenger car occupants.[83]

Effective interventions to reduce motorcyclist deaths and injuries include the following:

- *Motorcycle helmet use* reduces the risk of head injury in an MVC by about 69%,[84] and it reduces the risk of death by about 40%.[85] Although motorcycle helmets sold in the United States are required to meet the federal safety standard (as indicated by the "DOT certification" label), noncompliant helmets can be found and are used by some motorcyclists.
- *Universal helmet laws* are the most effective way to increase helmet use. These laws require all motorcyclists (drivers and passengers of all ages) to use helmets.[86–88] Motorcycle helmet use is substantially higher in states with universal helmet laws compared with states that have partial or no motorcycle helmet laws.[89] Also, universal helmet

laws are associated with reductions in motorcyclist crash death rates.[90] As of July 2022, only 18 US states and DC have universal helmet laws.
- *Motorcycle rider training* may be beneficial on the individual level, but effectiveness studies on a population level have had mixed results.[17] Compulsory training programs show some promise,[88] particularly if they incorporate on-the-road skills-building methods.
- *Anti-lock brakes* are required in all new cars but are not required for motorcycles. The use of motorcycles with anti-lock brakes is recommended.[82,91] Fatal crash rates for motorcyclists using motorcycles with anti-lock brakes are 22% lower than fatal crash rates for motorcyclists using motorcycles without anti-lock brakes.[82,91]
- *Use of protective and highly visible clothing* can also have safety benefits.[17,88,92,93]

What HCPs can do:
- Counsel patients on the importance of using federally certified helmets and making sure they are fitted properly.
- Suggest that patients who ride motorcycles take motorcycle rider training, use motorcycles with anti-lock brakes, and use clothing that is protective and highly visible.

125.3.9 Bicyclists

In 2020, 932 bicyclists were killed in MVCs in the United States,[94] and about 131,000 bicyclists were treated in emergency departments for non-fatal MVC injuries.[6] Risk factors for bicyclist deaths and injuries include riding without helmets, riding in urban areas, riding on major roads (other than interstates and freeways) and not at intersections, and using alcohol and/or other impairing substances.[94]

Effective interventions to reduce bicyclist deaths and injuries include the following:

- *Bicycle helmet use* substantially reduces the risk of head and brain injury in a crash.[95–98]
- *Bicycle helmet laws* are effective for increasing helmet use.[17,98,99]
- *Roadway design interventions* that physically separate bicyclists from motor vehicles are also effective. Examples include segregated bike lanes and well-designed and illuminated intersections.[98]

What HCPs can do:
- Reinforce the importance of bicycle helmet use. Encourage patients to make sure that their helmets fit properly.
- Encourage patients to increase their visibility at night by wearing fluorescent and/or retroreflective clothing and adding lighting to bicycles.[17,98,99]

125.3.10 Speed

Speed affects both the likelihood and severity of MVCs. In 2020, 29% of fatal MVCs involved speeding.[100] MVC injuries that occur at high speeds are more severe, particularly for pedestrians and bicyclists. Traffic calming and roadway design measures that compel drivers to slow down can help reduce speeds, including narrowing streets, road diets, curb extensions, speed bumps, roundabouts, and rumble strips.[79,80,101] These measures are often backed up by low speed limits (about 20 miles per hour) in urban areas and/or areas with high pedestrian traffic.[79] Other effective speed-reducing strategies include automated speed enforcement, red light cameras, and variable speed limits.[17,80]

What HCPs can do:
- Remind patients about the importance of not speeding—particularly in areas where there are pedestrians and bicyclists.
- Support efforts to implement automated speed enforcement, red light cameras, lower speed limits, and roadway design features that reduce speeds.

125.3.11 Distracted Driving

Every day, about nine people in the United States are killed in MVCs reported to involve a distracted driver.[102] Distracted driving is any activity that takes the driver's attention away from driving, such as cell phone use, eating, or adjusting radio or climate controls. Any of these distractions can increase the chance of an MVC.

Many US states have enacted laws prohibiting handheld cell phone use or texting while driving bans. In isolation, these laws have had limited effectiveness; however, high-visibility enforcement of these laws has shown promise in helping to address distracted driving. High-visibility enforcement involves increased numbers of police officers patrolling a specific area along with paid and earned media, thereby increasing drivers' perceived risk of getting a ticket.[17]

What HCPs can do:
- Remind patients about the dangers of all types of distractions while driving.
- Remind patients of the distracted driving laws in their state, which can be found on the Insurance Institute for Highway Safety's website.

125.3.12 Technology and Motor Vehicle Safety

New technologies are being implemented every day in vehicles and on roads to improve road safety. The 2020 United Nations General Assembly (UNGA) resolution 74/299 ("Improving global road safety") highlights the role of innovative automotive and digital technology for motor vehicle safety. Vehicle and infrastructure technology are also central components of the Safe System approach.[103]

In the future, fully autonomous vehicles or self-driving cars have vast potential safety benefits; however, they are not currently commercially available. Nonetheless, there are many vehicle safety technologies currently available in modern vehicles that can help reduce transportation risk behaviors, crashes, injuries, and deaths. Examples include the following:

- *Front and rear crash prevention*. Forward collision warning, automatic emergency braking, backup cameras, and rear cross traffic alerts.
- *Lane departure prevention*. Lane departure warning, lane keeping assist, blind spot warning, and side view cameras.
- *Transportation risk behavior reduction*. Passive alcohol detection systems, high speed alerts, and drowsiness alerts.
- *Protection of vulnerable road users*. Bicycle/pedestrian detection and braking systems.
- *Other*: Adaptive cruise control, tire pressure monitoring system, and electronic stability control.

What HCPs can do:

- Advise patients to learn more about vehicle safety technologies and driver assistance technologies at the National Safety Council's My Car Does What website, the National Highway Traffic Safety Administration's Driver Assistance Technologies website, and the Insurance Institute for Highway Safety's Advanced Driver Assistance website.
- Encourage patients to purchase cars with as many vehicle safety technologies as their budget allows and encourage them to prioritize safety technologies over convenience technologies.
- Remind patients that some vehicle technologies (e.g., complex navigation systems) can decrease safety by contributing to driver distraction.

125.3.13 The Safe System Approach, Global Road Safety, and Prevention Efforts

MVCs cause substantial morbidity and mortality worldwide.[26] Globally, approximately 1.35 million people are killed in MVCs every year, and about 93% of those deaths occur in low- and middle-income countries.[26] Additionally, MVCs are the leading cause of death for people aged 5–29 years.[26]

Many current global and domestic efforts to reduce MVC deaths and injuries emphasize widespread adoption of the Safe System approach—which accommodates for human error, accounts for human vulnerability, and works to protect all road users. Its core elements include safe roads, safe vehicles, safe road users, safe speeds, and post-crash care. Multiple high-income countries (such as Australia, the Netherlands, New Zealand, Spain, and Sweden) that have embraced the Safe System approach have had success reducing MVC deaths and injuries.[103]

In the United States, multiple cross-sectoral efforts and initiatives to improve motor vehicle safety are also ongoing. The Road to Zero Coalition's primary goal is to eliminate all US MVC deaths by 2050 and seeks to do this through three approaches: 1) doubling down on what works through proven, evidence-based strategies; 2) advancing life-saving technology in vehicles and infrastructure; and 3) prioritizing safety by adopting the Safe System approach and creating a positive safety culture. Healthy People 2030 has four motor vehicle safety goals and three other transportation-related goals including reducing deaths from MVCs, reducing drunk driving, reducing drowsy driving, and increasing restraint use. The 2021 US Government Bipartisan Infrastructure Law (i.e., the Infrastructure Investment and Jobs Act) authorizes major investments in the US transportation sector, including opportunities to improve motor vehicle safety. The National Roadway Safety Strategy, issued by the US Department of Transportation in 2022, establishes a comprehensive plan that outlines critical actions needed to improve motor vehicle safety.

Globally, the World Health Organization (WHO) established global road safety goals through the initiation of the first Decade of Action for Road Safety (2011–2020). WHO subsequently initiated a second Decade of Action for Road Safety (2021–2030), and the accompanying resolution re-commits to halving MVC deaths and injuries. The first-ever high-level UNGA meeting on improving global road safety was held in mid-2022 and resulted in the adoption of a political declaration detailing actions to accelerate road safety improvements. Additionally, the United Nations Sustainable Development Goals (SDGs) (adopted in 2015) established two road safety-related goals:

- SDG 3.6 called for a 50% reduction in MVC deaths/injuries by 2020.
- SDG 11.2 calls for accessible, safe, affordable, and sustainable transportation systems for all, with an emphasis on meeting the needs of women, children, people with disabilities, and older adults.

What HCPs can do:

- Be aware of and support global and domestic efforts to reduce motor vehicle crash deaths and injuries.
- Support implementation of the Safe System approach.

CLINICAL APPLICATIONS

Each motor vehicle injury prevention strategies section in this chapter has recommendations for healthcare providers specific to each topic. In addition to those recommendations, here are several overarching and cross-cutting clinical applications that apply more broadly to motor vehicle safety.

- Include motor vehicle injury prevention in all your health promotion and disease prevention activities with patients.
  - Encourage lifestyle behaviors that decrease the likelihood of MVCs, injuries, and deaths.
  - Set goals with patients to reduce crash risk by changing behaviors (e.g., using a seat belt on every trip; using helmets when riding on motorcycles or bicycles; not driving after drinking alcohol and/or using other substances).
- Assess and record MVC risk and protective factors regularly when counseling patients and their families and include these risk factor assessments in electronic health records and chart reviews.
- Conduct annual patient medication reviews to assess polypharmacy and drug interactions that might affect driving. This is important for all patients but particularly important for older adults, who commonly take multiple medications.
- Support efforts to strengthen comprehensive trauma systems in your state and improve prehospital care.

Disclaimer: The findings and conclusions in this book chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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126 Drowning Prevention

Tessa Clemens, PhD and Briana Moreland, MPH

KEY POINTS

- Drowning is a leading cause of death among children. From 2011 to 2020 over 4000 people in the United States died from drowning each year and over 8000 people were treated in the emergency department each year for non-fatal drowning.
- Non-Hispanic Black or African American persons and non-Hispanic American Indian or Alaska Native persons have the highest rates of fatal drowning.
- The most common locations of fatal drowning differ by age group. The majority of infant drownings occur in bathtubs, the majority of drownings among children aged one to four years occur in swimming pools, and among persons aged ≥15 years, the majority occur in natural water (Figure 126.1).
- Drowning is preventable. Effective drowning prevention strategies include installing fences that fully enclose swimming pools, learning basic swimming and water safety skills, wearing life jackets while boating, close and constant supervision of children in or near water, and knowing and administering cardiopulmonary resuscitation if drowning does occur. When participating in aquatic activities, avoiding alcohol and staying in lifeguard-supervised settings can help prevent drowning.

126.1 DEFINITION OF DROWNING

The definition of drowning has evolved over time; a previous review identified over 20 definitions for fatal drowning and 13 for non-fatal drowning.[1] In 2002, existing definitions were deemed unsuitable for surveillance and epidemiological research because they included characteristics of the drowning event, pathophysiological changes, as well as the outcome.[2] Using separate definitions for fatal and non-fatal drowning was also identified as a potential contributor to underestimation of the burden of drowning.[2] The following definition was adopted by consensus of the World Congress on Drowning in 2002: "Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid".[2] Drowning outcomes include death (fatal drowning) and morbidity or no-morbidity (non-fatal drowning).[2] Consistent use of drowning terminology across sectors and disciplines is important to enable adequate comparisons and clear and consistent drowning prevention messaging and advocacy.[3] The term "near-drowning" should be avoided as it implies that a drowning did not occur and that drowning is necessarily fatal. Non-fatal drowning can result in serious long-term morbidity, and correct terminology should be used to describe non-fatal drowning cases so that they can be better studied and prevented.

126.2 EPIDEMIOLOGY OF DROWNING

From 2011 to 2020, on average, over 4000 people in the United States died from drowning each year and there were an additional 8000 estimated emergency department visits for non-fatal drowning annually.[4] Rates of fatal and non-fatal drowning vary by demographic characteristics such as age, sex, and race/ethnicity.[4] Rates of drowning deaths have decreased overall in the past two decades.[5] However, this decrease has been more pronounced in some groups than others. Drowning deaths disproportionately affect Black or African American and American Indian or Alaska Native children and young adults.[5] Persons with certain medical conditions may also have a higher risk of drowning.[6,7] The most frequent locations where drowning deaths occur differ by age, race, and ethnicity.[5]

126.2.1 Age

Children aged one to four years have the highest rates of fatal drowning, and from 2011 to 2020 more children aged one to four years died from drowning than from any other cause except birth defects.[4] From 2011 to 2020, 2.6 per 100,000 children aged one to four years died from drowning.[4] Children aged one to four years also have the highest rates of drowning-related emergency department visits (21.1 per 100,000 children from 2011 to 2020). Drowning was the second leading cause of unintentional injury death among children aged 5–14 years and the third leading cause of unintentional injury deaths among persons aged 15–29 years from 2011 to 2020.[4] Drowning death rates are lower throughout the rest of adulthood and increase among older adults aged ≥65 years (1.5 per 100,000 older adults from 2011 to 2020). Older adults aged ≥65 years have higher drowning death rates than all other age groups except children aged one to four years.[4]

126.2.2 Sex

From 2011 to 2020, males had higher fatal (2.0 per 100,000) and non-fatal (3.1 per 100,000) drowning rates compared

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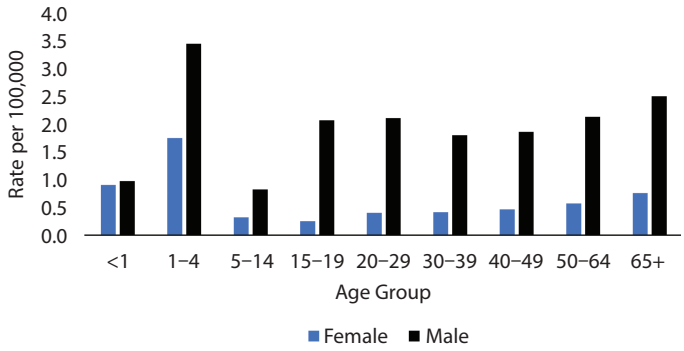


FIGURE 126.1 Fatal drowning rates by age group and sex, National Vital Statistics System, United States 2011–2020. International Classification of Disease 10th revision drowning death codes: W65-W74, V90, V92.

with females (fatal: 0.6 per 100,000; non-fatal: 2.0 per 100,000).[4] Males have higher fatal drowning rates across all age groups except infants aged <1 year where drowning death rates do not differ by sex.[4] Possible reasons for the higher drowning rate among males compared with females include increased exposure, risk-taking behavior, overestimation of swim skills, decreased use of life jackets, and alcohol use.[8–10]

126.2.3 Racial and Ethnic Disparities

There are persistent racial and ethnic disparities present in drowning death rates.[5] Non-Hispanic Black or African American persons aged ≤29 years have fatal drowning rates 1.5 times higher than non-Hispanic White persons of the same age.[5] Non-Hispanic American Indian or Alaska Native persons aged ≤29 years have fatal drowning rates 2.0 times higher than non-Hispanic White persons of the same age.[5] Despite an overall decrease in the rate of fatal drowning over the past 20 years, these disparities persist and may be increasing in some groups.[5] From 2005 to 2019, the drowning death rate ratio between non-Hispanic Black or African American persons aged ≤29 years and non-Hispanic White persons aged ≤29 years significantly increased.[5]

The reasons for racial and ethnic disparities in drowning deaths are not well understood. Some possible explanations for these disparities are lower reported swimming ability among African American youth[11] and increased fear of drowning among Black youth and their parents, leading to potential hesitancy in swim lesson participation.[12] More research is needed to explain the higher rates of drowning deaths among non-Hispanic American Indian or Alaska Native youth and non-Hispanic Black or African American youth.

126.2.4 Medical Conditions

Medical conditions including seizure disorders, autism, and some heart conditions are associated with increased drowning risk.[7,13] Seizure disorders, such as epilepsy, have been associated with increased drowning deaths in children[14] and adults.[15] Persons with epilepsy have 15 to 19 times the risk of drowning deaths as the general population.[16] Drowning is also a leading cause of unintentional injury death among children with autism spectrum disorders.[13,17] Deaths among persons diagnosed with autism were nearly 40 times as likely to be caused by drowning than deaths among the general population.[17] Heart conditions may also be associated with an increased risk of drowning.[7,13] Ischemic heart disease has been associated with an increased risk of drowning[7] and although rare, long QT syndrome, a cardiac condition that causes arrhythmias, can increase the risk of drowning.[18]

126.2.5 Location of Drowning

Overall, most drowning deaths occur in natural water such as lakes, rivers, and oceans (45%) and swimming pools (18%).[19] Children aged one to four years account for over one-third of all fatal drownings in swimming pools;[19] 1.5 per 100,000 children aged one to four years drowned in swimming pools on average from 2011 to 2020.[19] The location of drowning differs by age, race, and ethnicity. Non-Hispanic Black or African American persons have the highest fatal drowning rates in swimming pools.[5] This disparity is most pronounced in youth aged 10–14 years.[5] Non-Hispanic Black or African American youth aged 10–14 years have drowning death rates 7.6 times higher than non-Hispanic White youth aged 10–14 years in swimming pools.[5] Non-Hispanic Black or African American children and young adults aged ≤29 years have drowning rates 1.8 times higher in swimming pools than non-Hispanic White children and young adults.[5]

Fatal drowning in natural water is most common among persons aged ≥15 years.[19] Non-Hispanic American Indian or Alaska Native persons have the highest fatal drowning rates in natural water.[19] Among persons aged ≤29 years, non-Hispanic American Indian or Alaska Native persons had fatal drowning rates 2.7 times higher than non-Hispanic White persons in natural water.[5] This disparity was most pronounced in persons aged 25–29 years.[5] Non-Hispanic American Indian or Alaska Native persons aged 25–29 years had drowning rates 4.0 times higher than non-Hispanic White young adults in natural water[5] (Figure 126.2).

Rates of fatal drowning in bathtubs are highest among infants aged <1 year, accounting for approximately 68% of drowning deaths among infants from 2011 to 2020.[19] Boating-related drowning death rates are highest among adults aged ≥20 years.[19] Although drowning in natural water accounted for the highest percentage of drowning deaths among older adults (aged ≥65 years), older adults had higher percentages of drowning deaths in swimming pools and bathtubs compared with persons aged ≥15 years[4] (Figure 126.3).

Overall, persons living in rural areas have higher rates of fatal drowning compared with those living in urban areas.[19] However, drowning death rates in rural compared with urban areas differ by location of drowning; rates of fatal drowning in natural water and on boats are higher among persons living in rural areas compared with those living in urban areas, while rates of fatal drowning in pools are higher among persons living in urban areas compared to those living in rural areas.[19]

126.3 DROWNING PREVENTION STRATEGIES

Drowning happens quickly and quietly; without immediate intervention, drowning is often fatal or results in serious outcomes with long-term morbidity. Therefore, primary prevention strategies that stop drowning from occurring are most effective. Proven primary prevention strategies for drowning include installing barriers controlling access to water, basic swimming and water safety skills training programs, and wearing life jackets. Close supervision and avoiding alcohol during water-related activities can also reduce drowning risk.[20] If primary prevention strategies fail and the drowning process is started, knowing how to administer cardiopulmonary resuscitation can make a

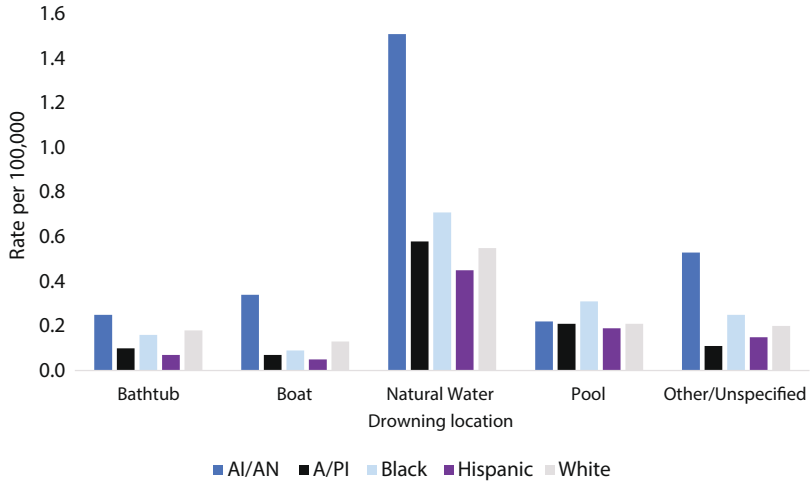


FIGURE 126.2 Fatal drowning rates by location and race/ethnicity, National Vital Statistics System, United States 2011–2020.

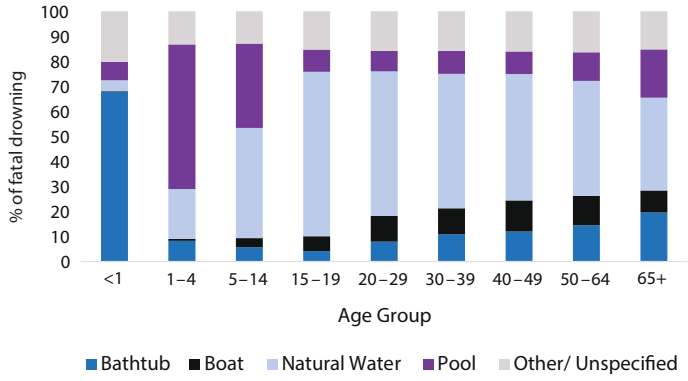


FIGURE 126.3 Percentage of drowning deaths in each location by age group, National Vital Statistics System, United States 2011–2020.

Non-Hispanic American Indian or Alaska Native (AI/AN), non-Hispanic Asian or Pacific Islander (A/PI), non-Hispanic Black or African American (Black), non-Hispanic White (White), Hispanic persons could be of any race International Classification of Disease 10th revision drowning death codes: bathtub: W65, W66; boat: V90, V92; natural water: W69, W70; pool W67, W68; other/unspecified: W73, W74

critical difference during the time it takes emergency medical services to arrive.

126.3.1 Barriers Controlling Access to Water

Barriers that control access to swimming pools can prevent drowning in the event of a lapse in caregiver supervision. Such barriers include pool fencing, pool covers, pool alarms, and door alarms. Pool fencing is the most effective of these measures; a meta-analysis of available studies found the odds ratio (OR) for drowning in a fenced versus unfenced pool to be 0.27 (95% CI: 0.16–0.55), and the OR for four-sided, isolation fencing that completely encloses the pool versus three-sided, perimeter fencing where the house acts as the fourth side of the enclosure to be 0.17 (95% CI: 0.07–0.44).[21] The World Health Organization recommends fully enclosing pools with four-sided isolation fencing with self-closing and self-latching gates and legislating and enforcing such barriers as one of ten actions to reduce drowning.[22] In 2009, Queensland, Australia, introduced new legislation requiring that pools be enclosed with four-sided isolation fencing.[23] Six years after the legislation was introduced, drowning rates among children aged <5 years significantly decreased.[23] To prevent children from climbing over, under, or through them, pool fences should meet the following specifications outlined by the Consumer Product Safety Commission:[24]

- Fence height should be a minimum of four feet (at least five feet is preferable) with less than a four-inch gap under the fence (less than two inches if the fence is on grass or pebbles).
- Vertical bars or slats should not have gaps more than four inches between them.
- Fence construction should limit hand holds that could be used to aid climbing (e.g., horizontal bars should be at least 45 inches apart and should be on the inside of the fence, closest to the pool).
- Fences should have self-closing, self-latching gates. Latches should be at least 54 inches above the bottom of the gate, or the latch release mechanism should be on the swimming pool side of the gate at least three inches below the top of the gate, and the gate and fence should have no opening greater than half an inch within 18 inches of the latch.
- Objects that could be used to climb over the fence should not be placed nearby (e.g., storage boxes, patio furniture).

Pool covers and pool nets that can hold the weight of a child are less likely to be effective because they need to be removed and replaced each time the pool is used, increasing the likelihood that the pool will be unintentionally left unsecured between uses.[13] Pool alarms, designed to sense disturbances of pool water, and wristbands that alarm when exposed to water, have been demonstrated to function properly when tested, but no study has established whether they prevent drowning.[25] The effectiveness of door alarms, intended to alert caregivers that a child has gained access to the pool area by leaving the home, has also not been studied.[13] Pool covers, pool alarms, and door alarms should not be relied on exclusively as barriers but can function as additional layers of protection when used in conjunction with proven barriers such as four-sided isolation fencing that completely encloses the pool.[13]

126.3.2 Basic Swimming and Water Safety Skills Training

Implementation of basic swimming and water safety skills training programs can reduce the risk of drowning.[27] Such programs are recommended by the World Health Organization for children six years of age and older[27] and by the American Academy of Pediatrics for children as young as one year of age and older.[6,13] There is currently no evidence to support a recommendation for infant (<1 year) swim lessons.[13] Introducing swimming training in this age group should be carefully considered by the caregiver and pediatrician as it may increase the risk of gastrointestinal tract infections, dermatitis, acute respiratory illness, hyponatremia, and hypothermia.[13]

The goal of basic swimming and water safety skills training programs is to move participants toward water competency. Water competency is the ability to anticipate, avoid, and survive common drowning situations, as well as the ability to recognize and safely assist a person who is in distress in the water. There are three main components of water competency:[1] water safety skills,[2] basic swimming skills,[3] and helping others.[27]

1. *Water safety skills* include knowing your limitations, avoiding unsafe behaviors (e.g., never swimming alone, only swimming in safe areas, not diving in shallow or unsafe water, always wearing a life jacket while boating, not using alcohol or drugs during aquatic activities), understanding how different physical and environmental conditions (e.g., physical fitness, medical conditions, currents in water) affect swimming in open water, and knowing how to call for help.
2. *Basic swimming skills* include the ability to safely enter and exit water, turn around and orient to safety as well as turnover in the water, float and/or tread water, swim to safety (at least 25 yards), and the ability to perform these skills while clothed.
3. *Helping others* includes always providing close and constant supervision around water, knowing how to recognize a drowning person, knowing safe ways to rescue a drowning person without putting yourself at risk, and knowing CPR.

Despite evidence of the benefits of participating in basic swimming and water safety skills training, inequities in the

adoption and uptake of programs by race, ethnicity, and socioeconomic status exist.[26] For example, Black or African American people have lower self-reported swimming skills than people from other racial and ethnic groups.[11,28,29] Studies have identified structural barriers (i.e., financial constraints, lack of time, and lack of facilities)[30] and attitude and behavioral barriers (e.g., fear of being in and around water)[12,30] for Black or African American people in developing swimming skills. More research is needed to determine how to improve access to basic swimming and water safety skills training programs for communities at increased risk of drowning. Engaging these populations to understand and address barriers to accessing and participating in prevention programs will be critical to developing effective and inclusive drowning prevention strategies.[5]

126.3.3 Personal Floatation Device (Life Jacket) Use

Personal floatation devices (life jackets) reduce the risk of fatal drowning during recreational boating for people of all ages and swimming abilities.[30] US Coast Guard-approved life jackets should be worn properly by boaters at all times and can also be worn by children playing near water and by inexperienced swimmers during other aquatic activities such as swimming or wading.[32] Despite evidence supporting the efficacy of wearing life jackets to reduce drowning and recommendations by national organizations, life jacket use remains low when unmandated. Life jacket use ranges by boat type and age, with the lowest observed rates among recreational motorboat users and adults. A 21-year study from 1999–2019 in the United States reported life jacket wear rates among recreational boaters ranged from 21–25% for all recreational boaters combined (all ages and types of boats). The lowest wear rates were among adults (18 years and older) on open motorboats ranging from 5–7%, and the highest were among youth (less than 18 years) on non-powered paddle craft ranging from 64–93%.[33] Legislation has been shown to increase life jacket wearing. An Australian study indicated that the probability of life jacket use in Victoria increased from 22% to 63% on small-powered vessels after legislation was introduced.[34] Mandatory wear regulations in four lakes in the state of Mississippi resulted in an increase in life jacket use from 13% to 68% three years after the regulations had been introduced.[35]

The safest option is for all boat users, regardless of age, boat type, or activity, to wear a life jacket at all times while boating. The most effective lifejackets are US Coast Guard-approved and have the following specifications:[36]

- Fit snuggly with all clips, zippers, and ties fastened and with loose strap ends tucked in.
- Materials in good condition and do not have holes, rips, or tears.
- Properly fitted for the person wearing it, and when fastened, the life jacket should not be able to ride up over the individual's chin and ears.

126.3.4 Active Supervision of Children

Absent or inadequate supervision has been identified as a contributing factor in pediatric drowning.[37] Although passive interventions that are always in effect (e.g., pool fencing) are more likely to be effective than active interventions that require an action (e.g., caregiver supervision), designating a responsible adult to supervise children closely and constantly when in or near the water provides an important layer of protection; adult supervision should work in conjunction with barriers to reduce the risk of drowning among children.[13] Three commonly described dimensions of supervision are proximity, attention, and continuity:[38]

- Proximity: proximity may be most important for young children and beginner swimmers. Touch supervision, where the adult is within arm's reach and can quickly assist the beginner swimmer, should be used in these cases.[13]
- Attention: adults supervising children during aquatic activities should maintain visual and auditory attention and avoid distracting activities like reading, using the phone, and consuming alcohol or drugs.[13]
- Continuity: drowning happens quickly and quietly, therefore, children and beginner swimmers should be supervised constantly when in and near water.[13]

126.3.5 Alcohol

Alcohol is an important risk factor associated with drowning; 30–70% of individuals who drowned while engaging in recreational aquatic activities had alcohol in their bloodstream.[39] The consumption of alcohol during aquatic activities can result in poor judgment and poor performance, which increases the risk of the drowning process starting in the first place. Additionally, alcohol can have physiological effects that contribute to more severe drowning outcomes such as poor balance and orientation, and increased risk of hypothermia.[40]

Several studies have examined alcohol involvement in recreational boating fatalities. A California study estimated a relative risk of death of 10.7 for boat operators with a blood alcohol concentration (BAC) of about 0.10 g/100mL.[41] A case-control study conducted in Maryland and North Carolina estimated that the odds of death for recreational boat passengers and operators increased at even low levels of BAC; a BAC of 0.01 g/100ml resulted in an OR of 1.3 (95% CI 1.2–1.4). A high BAC of 0.25 g/100ml resulted in an OR of 52.4 (95% CI 25.9–106.1).[40] A case-control study that compared fatal with non-fatal recreational boating injuries in Washington found that fatalities were 70% more likely to have alcohol involved (95% CI 1.1–2.8).[42] Despite evidence that alcohol is a risk factor for recreational boating injury, studies suggested that recreational boaters do not fully perceive this risk. The results of two independent survey studies indicated that recreational boaters believe

that passengers can safely drink more alcohol than operators,[43,44] and that individuals on stopped boats can safely drink more than those on moving boats.[43]

Avoiding alcohol when swimming, boating (for both operators and passengers), or supervising children can reduce the risk of drowning.

126.3.6 Lifeguard Supervision

Lifeguards can serve an important role in both primary and secondary drowning prevention. Lifeguards prevent drowning by enforcing safety rules to prevent injuries, educating swimmers, and monitoring aquatic conditions. In fact, a study demonstrated that rescues only represent 1.9% of lifeguard activity, whereas prevention actions, that prevent the need for a rescue in the first place, comprise the majority of a lifeguard's activities during their time on duty (54.8%).[45] Lifeguards are also trained to identify and rescue persons who get into trouble in the water and/or begin drowning. Lifeguard supervision can reduce drowning in multiple ways:[46]

- The presence of lifeguards may decrease risk-taking behavior near or in the water.
- Lifeguards monitor aquatic environments and alert swimmers to hazards. For example, they may notice dangerous conditions developing (e.g., rip tides, strong waves) that could increase drowning risk and can make swimmers aware of these conditions.
- Lifeguards are trained in safe water rescue techniques and resuscitation and can rescue a person and provide effective treatment prior to the arrival of emergency medical services.

While actively guarding, lifeguards are most effective when focused on the water and not asked to take on other activities, such as selling concessions.[46] Lifeguards are not a substitute for caregiver supervision. Even when a lifeguard is present, close and constant supervision by caregivers can prevent child drownings. Lifeguard-supervised settings are the safest option for all persons, especially those with an increased risk of drowning due to medical conditions or other risk factors.

126.3.7 Cardiopulmonary Resuscitation

The likelihood of surviving a drowning event is improved when immediate rescue and resuscitation are initiated. Bystander cardiopulmonary resuscitation (CPR) has been associated with improved neurologically favorable outcomes in drowning persons.[47] In the event that lifeguards or other trained rescuers are not on site, caregivers and/or witnesses of drowning events play a pivotal role that may determine the outcome of the person who drowned. Without the immediate basic resuscitation (i.e., CPR) that can only be initiated by on-scene bystanders, subsequent advanced resuscitation techniques, such as administering defibrillation and medications, may be of little value.[48] Although compression-only CPR has been recommended as an approach to bystander CPR in some settings,[49] both compression and ventilation are recommended for effective CPR with drowning patients.[13] However, compression-only CPR is still better than not attempting any form of CPR.[50] Being trained in basic CPR is useful for all persons, especially caregivers. Many organizations such as the American Red Cross[51] and the American Heart Association[52] offer CPR training courses, both online and in-person.

CLINICAL APPLICATIONS

- Include drowning prevention and water safety in your health promotion and disease prevention activities with patients.
- Provide age-specific education about drowning prevention for patients and families (e.g., remind caregivers of infants about the importance of supervising closely and constantly in the bathtub, remind caregivers of toddlers that drowning happens quickly and quietly, and provide examples of effective barriers).
- Provide patients who have medical conditions that place them at increased risk of drowning (e.g., seizure disorders, autism, cardiovascular disease) and their families with water safety tips. Encourage people with seizure disorders to shower instead of taking a bath and encourage people with medical conditions to participate in aquatic activities in supervised settings.
- Encourage families to fully enclose home pools, including above-ground pools of either temporary or fixed installation, with four-sided isolation fencing with self-closing, self-latching gates.
- Talk with caregivers about enrolling their children in basic swimming and water safety skills training. Have information available on how families can access these programs in your communities (e.g., YMCA Safety Around Water Program,[53] American Red Cross swim programs[54]).
- Reinforce that wearing properly fitting US Coast Guard-approved life jackets at all times during boating activities can prevent drowning. Remind caregivers that life jackets can also be worn by children and beginner swimmers when in or near water during non-boating-related activities. Discourage the use of foam toys and water wings as floatation devices.
- Screen for alcohol and substance misuse using existing tools such as brief intervention and motivational interviewing to identify the potential for impaired boating. Reinforce that using alcohol and other drugs while participating in aquatic recreation and while supervising children in or near the water are risk factors for drowning.

- Encourage caregivers to take basic cardiopulmonary resuscitation training and have information on hand about how families can access this training in your community or online (e.g., through the American Red Cross[51] or the American Heart Association[52]).
- Identify whether legislation related to drowning prevention measures such as isolation pool fencing and mandatory life jacket wear exists in your state.

Disclaimer: The findings and conclusions in this manuscript are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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127 Improving the Care of Children with Mild Traumatic Brain Injury: CDC's Evidence-Based Pediatric mTBI Guideline

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KEY POINTS

- Mild traumatic brain injury (mTBI) is caused by a blunt force applied to the head or body that leads the brain to accelerate and decelerate with translational, rotational, and/or angular forces.
- mTBI presents differently among children, relative to adults, due to anatomical, physiological, and cognitive differences.
- Several validated symptom scales are available to healthcare professionals to aid in the diagnosis of mTBI among children.
- Most children with mTBI have a good recovery and no longer experience symptoms one to three months post-injury.
- Certain premorbid conditions and risk factors may suggest a delayed recovery among children with mTBI and should be assessed as part of prognostic counseling.
- Access to social supports and referral to mental healthcare may help reduce mental health sequelae after an mTBI.
- mTBI treatment may include cognitive and vestibular rehabilitation, sleep hygiene, and/or non-narcotic analgesia.

127.1 INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), approximately 223,000 traumatic brain injury (TBI)-related hospitalizations in 2019 and more than 64,000 TBI-related deaths in 2020 occurred in the United States.[1] These estimates do not include people seen in primary care offices, specialty clinics, federal, military, or US Department of Veterans Affairs settings, or those who do not seek medical care.[2] Developing a national system that standardizes the measurement of TBI to comprehensively capture its incidence, prevalence, and outcomes is needed to better understand the full burden of this injury.[2]

A greater focus on reducing health disparities is critical to preventing TBI among those at greatest risk and minimizing adverse outcomes following this injury. Prior studies have found high levels of lifetime TBI among people who are experiencing homelessness,[3] those who reside in correctional and detention facilities,[4] and women in domestic violence shelters.[5] American Indian/Alaska Native children and adults have higher rates of TBI-related hospitalizations and deaths than other racial or ethnic groups,[6,7] and people living in rural areas have a higher rate of TBI-related death compared with those living in non-rural areas.[8] Research on health disparities and TBI by race and ethnicity also demonstrate inequities in patient evaluation and outcomes based on the intent of injury, namely violence-related TBI.[7,9]

127.2 MILD TRAUMATIC BRAIN INJURY

A TBI is caused by a blunt force applied to the head or body that leads the brain to accelerate and decelerate with translational, rotational, and/or angular forces. These direct or indirect forces lead to a wave of energy that passes through brain tissue, injures it, and triggers neuronal dysfunction that involves a complex cascade of ionic, metabolic, and physiologic events (Figure 127.1).[10,11] This cascade, and microscopic axonal dysfunction, results in clinical signs and symptoms of TBI.[10]

At least 75% of patients with TBI who seek medical care are initially classified as having a mild TBI (mTBI).[12] There are several, somewhat varying definitions of mTBI in the published literature. Moreover, debate exists regarding whether the term "concussion" is synonymous with mTBI or is a subset of it. In a systematic review containing research on mTBI over a 25-year period, CDC defined mTBI to include patients with "GCS [Glasgow Coma Scale] scores of 13 to 15 with or without the complication of intracranial injury (ICI) on neuroimaging, and regardless of potentially requiring a hospital admission and/or neurosurgical intervention".[13] For the sake of consistency, this chapter will use the CDC Systematic Review definition of

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FIGURE 127.1 The mechanism of mTBI.

mTBI, and the term concussion is utilized when referencing studies that used the term.

127.2.1 mTBI among Children

Children are at particular risk for an mTBI in part due to participating in contact sports[14] and their still-developing gross motor skills (e.g., learning to walk), which can make them more susceptible to a fall. Unique anatomic and physiologic factors, such as larger head-to-body size ratio, weaker neck muscles, and differences in cerebral blood flow and metabolism may also increase their vulnerability to an mTBI and a potentially prolonged recovery.[15,16]

During the acute period, children with mTBI commonly present with one or more non-specific signs or symptoms that fall into broad categories (Table 127.1).[17] These categories or subtypes are not mutually exclusive and may include:[17]

- Somatic symptoms (e.g., headache, balance disruption)
- Cognitive symptoms (e.g., amnesia, disorientation)
- Mood/affective symptoms (e.g., irritability, fatigue)
- Sleep-related symptoms (e.g., trouble falling asleep)

127.2.2 Indications of Deteriorating Neurological Function

Children should be carefully observed by reliable caregivers during the first 24–48 hours following a potential mTBI. Healthcare professionals should advise parents that any severe or worsening signs and symptoms warrant immediate medical attention. These may include:

- Decreasing levels or any loss of consciousness.
- Focal neurologic deficit (e.g., weakness or numbness in any extremity).
- Repeated vomiting or increasing severity of symptoms.
- Seizures, slurred speech, increasing confusion, unusual behavioral change, or irritability.
- Significant cervical pain with tenderness and/or loss of range of motion, paresthesias, or weakness.
- Blood or fluid drainage from the nose or ears.
- Bruising under the eyes or behind the ears.

127.3 EVIDENCE-BASED PRACTICES FOR CARING FOR CHILDREN WITH AN mTBI

CDC published the Pediatric mTBI Guideline in September 2018 to provide evidence-based guidance for healthcare professionals on the care of pediatric patients with mTBI seen in primary care, outpatient specialty, inpatient, and emergency care settings.[18] The CDC Guideline contains 19 sets of clinical recommendations on diagnosis, prognosis, and management and treatment (Tables 127.2–127.4) developed based on best practices outlined in a report by the National Academies of Sciences, Engineering, and Medicine.[19] Details on the literature research, systematic review, and overall methodology used to develop the CDC Guideline are available at www.cdc.gov/TraumaticBrainInjury.

127.3.1 mTBI Diagnosis

CDC Guideline recommendations for diagnosing mTBI among children are provided in Table 127.2. Diagnosing an mTBI may be challenging as some symptoms are common to other conditions, such as headache syndromes, and may be present without any injury at all (e.g., feeling fatigued, being forgetful).[20–22] Further, children with disabilities and younger children may not be able to recognize or verbalize their symptoms. Thus, assessing each patient completely and systematically is essential. Components of an initial evaluation for mTBI generally should consist of a physical exam to identify: 1) indications of ICI and deteriorating neurological function (e.g., hemotympanum, pupillary asymmetry); 2) factors that impact mTBI management (e.g., concurrent injuries or baseline deficits, vestibular and/or oculomotor dysfunction); and 3) characteristics and circumstances of the injury, and symptom type and severity level.[23] Evaluating common conditions (e.g., early signs of viral infection, poor sleep) is useful to help rule out other contributing factors (e.g., cervical tenderness, scalp hematoma).

A primary objective of an initial clinical evaluation for a pediatric patient with an mTBI is to identify the risk for ICI.

TABLE 127.1
Clinical Presentation of mTBI in Children

Somatic	Cognitive	Mood/Affective	Sleep
• Headache • Dizziness • Balance disruption • Nausea/vomiting • Visual disturbances (photophobia, blurry/double vision) • Phonophobia	• Confusion • Anterograde amnesia • Retrograde amnesia • Loss of consciousness • Disorientation • Feeling mentally "foggy" • Vacant stare • Inability to focus • Delayed verbal and motor responses • Slurred/incoherent speech • Excessive drowsiness	• Emotional lability • Irritability • Fatigue • Anxiety • Sadness	• Trouble falling asleep • Sleeping more than usual • Sleeping less than usual

TABLE 127.2
Recommendations for Diagnosing mTBI among Children

Neuroimaging

Clinical evaluation of a child with a possible mTBI includes balancing potentially devastating complications of a more severe injury against the risks associated with head computed tomography (CT).

- Healthcare professionals *should not* routinely obtain head CT for diagnostic purposes among children with mTBI.
- Healthcare professionals *should* use validated clinical decision rules to identify children at low risk for ICI, among whom head CT is not indicated, and identify children who may be at higher risk for significant ICI and, therefore, may need head CT. Existing decision rules combine a variety of factors that might indicate higher risk, including the following:
  - Age <2 years old
  - Vomiting
  - Loss of consciousness
  - Severe injury
  - Severe or worsening headache
  - Amnesia
  - Non-frontal scalp hematoma
  - Glasgow Coma Score <15
  - Clinical suspicion of skull fracture

Neuropsychological Tools

Several validated tools can be applied quickly and inexpensively. Evidence to determine whether baseline testing among children better identifies mTBI as compared with post-injury scores alone is insufficient.

- Healthcare professionals *should* use an age-appropriate, validated symptom rating scale as a component of the diagnostic evaluation for children presenting with acute mTBI.
- Healthcare professionals *may* use validated, age-appropriate computerized cognitive testing in the acute period of injury as a component of an mTBI diagnosis.

Serum Biomarkers

Current evidence for recommending any of the studied biomarkers for an mTBI diagnosis among children is insufficient.

- Healthcare professionals *should not* perform these tests outside of a research setting, at this time, for the diagnosis of children with mTBI.

Patients at elevated risk for ICI should undergo neuroimaging and may need immediate neurosurgical intervention. The CDC Guideline recommends that healthcare professionals use validated clinical decision rules to identify patients at risk for ICI.[18] The goal of decision rules is to help healthcare professionals avoid exposing patients to unnecessary radiation resulting from a head CT, while also ensuring that children with increased risk for ICI receive needed imaging and interventions. The Pediatric Emergency Care Applied Research Network (PECARN) decision rules is a tool validated for use with pediatric patients.[24] Several studies support the effectiveness of the PECARN rules in identifying pediatric patients with head injury at risk for ICI.[25–28]

The CDC Guideline does not recommend that healthcare professionals routinely image a pediatric patient with suspected mTBI for diagnostic purposes.[18] This includes the use of CT, MRI, SPECT, and skull X-ray. Instead, healthcare professionals should use age-appropriate, validated symptom-rating scales to assess for mTBI.[18] These

scales are designed to assess symptom type and severity level during the acute period and should not be used in isolation.[29] Examples of validated scales include the Post-Concussion Symptom Inventory (embedded within the Acute Concussion Evaluation tool),[30,31] Health and Behavior Inventory (HBI) (embedded in the Child-Sport Concussion Assessment Tool),[32,33] Sport Concussion Assessment Tool (SCAT),[33,34] and the Post-Concussion Symptom Scale.[32] Importantly, most scales are not validated for use among children ages ten years and under and some symptoms commonly reported by young children (e.g., changes in appetite, increased dependence on parents) may not be represented.[35,36] When using these scales, healthcare professionals may consider factors such as the testing venue (e.g., noise, distractions) and fatigue (e.g., sleep disturbance, time of day), which may affect a patient's performance.[35,36]

127.3.2 mTBI Prognosis

CDC Guideline recommendations on the prognosis of mTBI among children are provided in Table 127.3. The length of recovery following an mTBI is unique to the characteristics of the injury and the child. Most longitudinal studies show some children will have persistent symptoms one-month post-injury, but most symptoms resolve within three months to one-year post-injury.[37,38] Few children with mTBI (2%)[37] experience symptoms one-year post-injury. The length of recovery for a child may vary based on factors such as previous history of mTBI,[39] sex,[40] more severe initial presentation of an mTBI,[37,41] and the presence of pre-existing comorbid conditions (e.g., mood and learning disorders, migraine headaches).[13,16,42] Other risk factors for delayed recovery described in the CDC Guideline include Hispanic ethnicity, lower socioeconomic status, current neurological or psychiatric disorder, and family and social stressors.[18] Children who are at higher risk for delayed recovery are more likely to need additional interventions and referral to a specialist.

Healthcare professionals should conduct a clinical history and screen for identifiable risk factors for poor prognosis using validated prediction rules.[18] No single assessment tool can predict outcomes. Instead, healthcare professionals should use a combination of tools to assess recovery among children with mTBI. These tools may include both cognitive and balance tests and validated symptom scales. The CDC Guideline states that comprehensive neuropsychological evaluations (e.g., cognitive, social, and behavioral assessments) can assist in determining the etiology of cognitive impairment and can direct treatment for such impairment based on the patient's symptoms.[18] Further, healthcare professionals may assess and monitor for mental health sequelae. Ledoux and colleagues found that children with mTBI are more likely to experience mental health issues (e.g., psychiatric hospitalization and self-harm) compared with children who receive care for an orthopedic injury.[43] Improved access to social supports (e.g., emotional support,

TABLE 127.3
Recommendations for Prognosis of mTBI among Children

General Healthcare Professional Counseling for Prognosis

Evidence shows that education and clear communication from healthcare professionals can optimize outcomes.

- Healthcare professionals *should* counsel patients and families that most children with mTBI do not show significant difficulties that last more than one to three months post-injury.

Prognosis Related to Premorbid Conditions

Increased risk of delayed recovery or prolonged symptoms are associated with certain premorbid conditions among children with mTBI.

- Healthcare professionals *should* assess the premorbid history of children to assist in determining the prognosis for mTBI. This assessment should occur either prior to injury as part of pre-participation athletic examinations or as soon as possible post-injury.

Assessment of Cumulative Risk Factors and Prognosis

Evidence shows that various demographic and injury-related factors predict outcomes for children with mTBI.

- Healthcare professionals *should* screen for various known risk factors for persistent symptoms among children with mTBI.

No single risk factor is strongly predictive of outcome. However, evidence suggests symptoms may last longer for:

- Older children/adolescents
- Children of Hispanic ethnicity
- Children from lower socioeconomic status
- Children with more severe presentations of mTBI (including those associated with intracranial injury)
- Children who report higher levels of acute post-concussion symptoms

Assessment Tools and Prognosis

Healthcare professionals can more effectively counsel patients with mTBI when they have assessed risk factors for outcome and recovery. However, no single assessment tool can predict outcomes.

- Healthcare professionals *should* use a combination of tools to assess recovery among children with mTBI.

Interventions for mTBI with Poor Prognosis

While most mTBI symptoms resolve within one to three months, some children are at risk for persistent symptoms or delayed recovery which may require further interventions.

- Healthcare professionals *should* monitor children with mTBI at high risk for persistent symptoms based on premorbid history, demographics, and/or injury characteristics.

problem-solving advice) and referral to mental healthcare—a key element of recovery that warrants attention from healthcare professionals—may help reduce mental health sequelae after an mTBI.[44,45]

127.3.2 mTBI Management and Treatment

CDC Guideline recommendations on managing and treating mTBI among children are provided in Table 127.4. To promote a good recovery, they recommend that healthcare professionals provide assurance and information to families about the warning signs for more severe injury, symptom-monitoring tips, the return to activity process (such as return to school and sports), and when to follow up for additional care.[18] Further, children and their families should be made aware that mTBI symptoms may not appear right away and may evolve (e.g., "wax and wane") during recovery, but these changes are part of the normal recovery process.[20] Previous studies show that nearly 25% of pediatric patients with mTBI experience psychological distress after concussion.[46] Patient education, reassurance about the likelihood of a good recovery, and understanding among families regarding the importance of post-injury care and what to expect may ease patient and family concerns and improve outcomes.[47]

Following two to three days of rest post-mTBI, the CDC Guideline recommends a gradual return to cognitive and non-strenuous physical activities that do not substantially exacerbate symptoms (Figure 127.2).[18] This includes returning to school. Too much rest and social isolation during a child's initial recovery period may worsen symptoms, lead to emotional sequelae, and prolong recovery.[48] Healthcare professionals may provide discharge instructions customized to a patient's symptoms that include when to return to activity and should advise children to avoid activities that put them at risk for another injury to the head and brain throughout the course of recovery.[18,42,49]

Some students will not need any adjustments to their schedule or academic workload when they return to school. However, others may struggle with symptom exacerbation when they begin to increase cognitive activities at school.[20] To support a child's return to school, healthcare professionals may provide written communication to school staff regarding the child's type and severity of symptoms and recommended accommodations.[18] This may include a return-to-school letter that outlines breaks and recommended adjustments.[18] Example adjustments include environmental modifications (e.g., using headphones to reduce noise distractions), curriculum changes (e.g., reduced workload), activity limits (e.g., short rest breaks), and presentation strategies (e.g., paper materials versus a smartboard for light-sensitive students).[44] These adjustments may be kept in place until the child can engage in regular school activities without significant exacerbation of symptoms (i.e., has returned to their pre-injury symptom baseline).

Complete recovery is when a child participates in their regular non-sports-related daily activities and remains free

TABLE 127.4
Recommendations for Managing and Treating mTBI among Children

General Areas of Treatment for Patients and Families

Health outcomes are generally optimized through patient health literacy and the resulting behavior modification. In addition, evidence shows that rest or reducing cognitive and physical activity is beneficial immediately following an mTBI.

- In providing education and reassurance to the family, the healthcare professional *should* include the following information:
  - Warning signs indicating more serious injury
  - Expected course of symptoms and recovery
  - Instructions on monitoring post-concussive symptoms
  - Prevention of further injury
  - Management of cognitive and physical activity/rest
  - Instructions regarding return to school and return to play/recreation
  - Clear follow-up instructions
- Healthcare professionals *should* counsel patients and families on how to gradually increase scheduled activity after the first several days of rest that does not exacerbate symptoms and closely monitor symptom expression (number, severity).
- To assist children returning to school following an mTBI, medical and school-based teams *should* counsel the student and family on how to gradually increase the duration and intensity of academic activities as tolerated to expand participation without significantly exacerbating symptoms.

Symptom and Problem-Specific Treatment and Management

Painful headache, dizziness, sleep problems, and cognitive dysfunction are common symptoms among children after mTBI and intervention may be necessary.

- Healthcare professionals and caregivers *should* offer non-narcotic analgesia to children with painful headache following acute mTBI, but also provide counseling to the family regarding the risks of analgesic overuse, including rebound headache.
- Healthcare professionals *may* refer children with subjective or objective evidence of persistent vestibulo-ocular motor dysfunction, following an mTBI, to vestibular rehabilitation.
- Healthcare professionals *should* provide guidance on proper sleep hygiene methods to facilitate recovery from pediatric mTBI.
- Healthcare professionals *should* recommend treatment for cognitive dysfunction that reflects its presumed etiology.



FIGURE 127.2 Steps for return to activity plan for children following an mTBI.

of symptoms. The return to sports should only be initiated once the child has complete recovery, and per requirements in most state laws, has obtained approval from a healthcare professional to return to sports.[49] The CDC Guideline and the Consensus Statement on Concussion in Sport describe a gradual, stepwise progression that should be followed to safely return an athlete to sports participation.[49] The return to sports process is best achieved using a team approach that includes coaches, parents, and athletic trainers (when available).[42,49]

Painful headache, dizziness, sleep problems, and cognitive dysfunction are common symptoms among children after an mTBI, and intervention may be necessary.[18] The CDC Guideline recommends that healthcare professionals use non-narcotic analgesia for children with painful headache following mTBI along with counseling regarding the risks of analgesic overuse, including rebound headache.[18] Other treatments for mTBI may include cognitive and vestibular rehabilitation and guidance on sleep hygiene, as needed.[18] Children with mTBI whose symptoms do not resolve as expected with standard care within four to six weeks should be referred to an appropriate specialist for further assessments or interventions.[18]

FUTURE DIRECTIONS

Equally important to the development of an evidence-based guideline is a comprehensive approach to integrating the guideline into clinical practice. CDC created implementation tools and strategies to not only build awareness of the CDC Pediatric mTBI Guideline, but also to encourage its use, and ultimately, achieve integration of the recommendations into standard medical practice. This included customizing educational tools for audiences that play a role in supporting implementation of the recommendations such as the following: healthcare providers; parents; school professionals; sports coaches; and medical organizations. CDC implementation tools are available at www.cdc.gov/HEADSUP. Evaluating the uptake, application, and impact of the CDC Pediatric mTBI Guideline and implementation tools will be critical to understanding their utility in improving the diagnosis and management of mTBI among children. Periodically revisiting and revising the CDC Guideline and implementation tools to incorporate new evidence and a focus on health equity will also be critical.

CLINICAL APPLICATIONS

- Educate and reassure patients and families about the high likelihood of a good recovery.
- Emphasize mental health and social support as key elements of recovery.
- Do not routinely image patients (i.e., CT, MRI, SPECT, and skull X-ray) with suspected mTBI for diagnostic purposes.
- Discuss the risks of head CT in the context of risk factors for ICI with patients and families.

- Assess recovery using a combination of tools (e.g., cognitive and balance tests, symptom-rating scales).
- Use validated clinical decision rules to identify patients at risk for ICI and validated symptom rating scales to diagnose mTBI.
- Advise patients to return to cognitive and nonstrenuous physical activities that do not increase symptoms following two to three days of rest, at most.
- Monitor return to school and academic progress in school to determine if and what adjustments are needed.
- Oversee patients' return to play progression, along with sports coaches, parents, and athletic trainers.
- Refer children with mTBI to an appropriate specialist if their symptoms do not resolve as expected with standard care within four to six weeks.

Disclaimer: The findings and conclusions in this manuscript are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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128 Older Adult Falls: Epidemiology and Effective Injury Prevention Strategies

Robin Lee, PhD, Ramakrishna Kakara, MPH, and Gwen Bergen, PhD

KEY POINTS

- Falls among older adults are a major public health burden in the United States. Each year more than one in four (27.3%) adults aged 65 and older sustain a fall, resulting in 9,000,000 injuries requiring medical treatment or restricted activity.
- In 2015, the estimated medical costs attributable to fatal and nonfatal falls was approximately $50.0 billion.
- Common modifiable risk factors include gait and/or mobility disorders, muscle weakness, balance impairments, impaired cognition, medications (anti-psychotics, tricyclic anti-depressants, selective serotonin reuptake inhibitors, benzodiazepines, etc.), orthostatic hypotension, foot and ankle problems, vision impairment, and environmental or home hazards.
- Many effective interventions can reduce fall risk factors and prevent falls (e.g., strength and balance programs, medication management, cataract surgery).
- Fall prevention activities can be incorporated in multiple clinical settings such as outpatient facilities, inpatient settings, pharmacy services, and rehabilitation centers.
- Lifestyle medicine practitioners can play a unique role in the prevention of older adult falls by identifying patients at high risk, screening them for fall risk, assessing their modifiable fall risk factors, and intervening to reduce identified risk using effective interventions.

128.1 EPIDEMIOLOGY

Each year, in the United States, more than one in four (i.e., 14 million in 2020) older adults (adults ≥ 65 years) report a fall.[1] Around one in ten older adults (i.e., 5 million in 2020) report a fall injury requiring medical treatment or restricted activity for at least one day.[1] As some older adults have multiple falls in a year, in 2020, there were an estimated 36.7 million falls and 8.9 million fall injuries. The older adult population in the United States is projected to increase from 56 million in 2020 to about 98 million in 2060.[2] In 2060, nearly one in four Americans will be at least 65 years of age.[2] If the proportion of older adults who fall each year remains the same, there will be about twice as many older adults experiencing falls or fall injuries in 2060. The number of falls may increase to 70 million and fall injuries to 17 million.

Incidence alone gives an important but incomplete assessment of the problem. Figure 128.1 shows that since the year 2001, the age-adjusted fall death rate has more than doubled. In 2020, more than 36,000 older adults died due to falls, i.e., averaging around 100 deaths every day.[3] Living longer with more chronic conditions may explain some of the observed increase.[4]

These numbers translate into significant costs. In 2015, estimated medical costs attributable to fatal and non-fatal falls were approximately $50 billion.[5] The portion attributed to Medicare for the treatment of non-fatal falls was $28.9 billion.[5] The overall spending for fatal falls was estimated to be $754 million.[5] In a recent study of 2016 healthcare spending, falls ranked among the top 20 most expensive health conditions among older adults, just behind ischemic heart disease.[6]

Fatal and non-fatal fall burden differs by demographics. Figure 128.2 illustrates that although death rates increased consistently for both men and women between 2001 and 2020, men have higher death rates than women. However, a larger number of women die because of a fall compared with men each year.[7] This is due in part to the gender imbalance in the older age groups—older women (31.2 million in 2020) outnumber older men (25.2 million in 2020)[8]—and to the increased susceptibility of women to injury, such as hip fracture, when they fall.[9] Deprey et al. found that hip fractures and head injury were the most common types of fall injury that led to death among older adults.[10]

In addition to fall deaths, non-fatal fall injuries that require medical attention are a growing problem among older adults. In 2020, there were about three million fall-related emergency department (ED) visits and more than 997,000 fall-related hospitalizations.[3] Figure 128.3 illustrates that, like fall-related deaths, fall-related ED visits have been increasing over time for both men and women, with women accounting for a larger proportion of injuries.[3] Fall-related injury among older adults differs from fall-related deaths in that women have a higher injury rate than men.

The rate of falls and fall injuries vary by race and ethnicity. American Indian/Alaska Natives and Non-Hispanic

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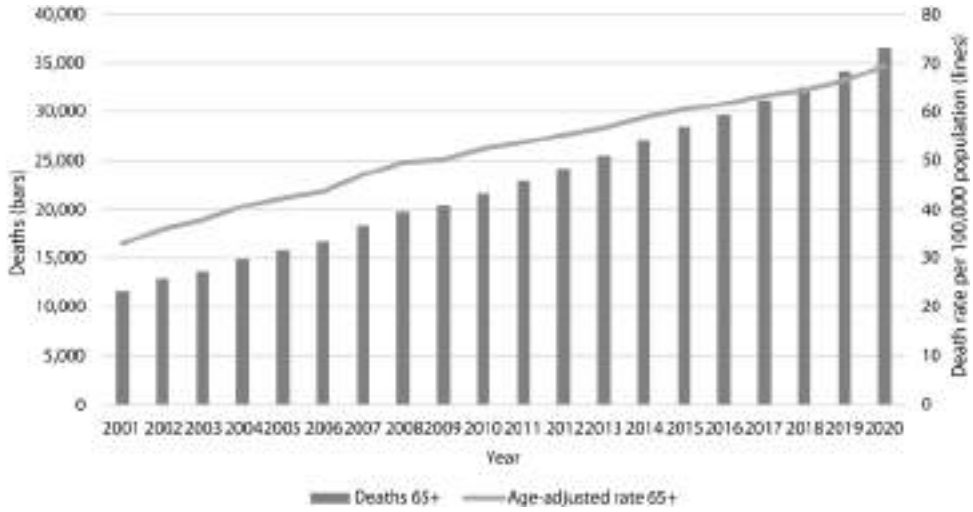


FIGURE 128.1 Number of fall deaths and fall death rates, ages 65 and older, United States, 2001–2020.

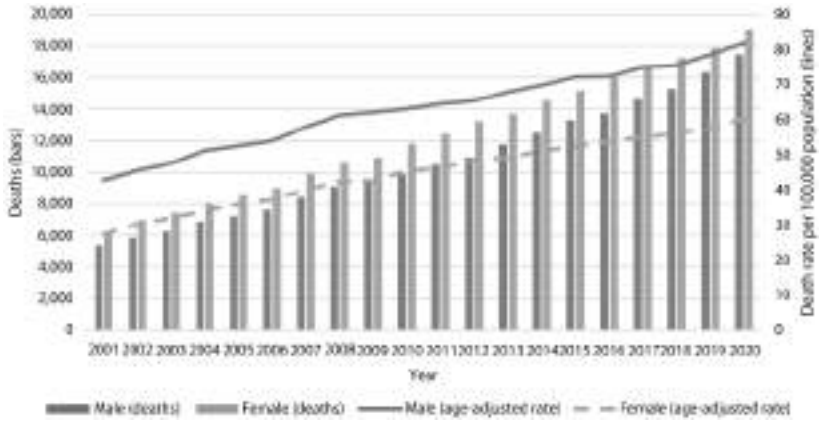


FIGURE 128.2 Number of fall deaths and fall death rates by gender, ages 65 and older, United States, 2001–2020.

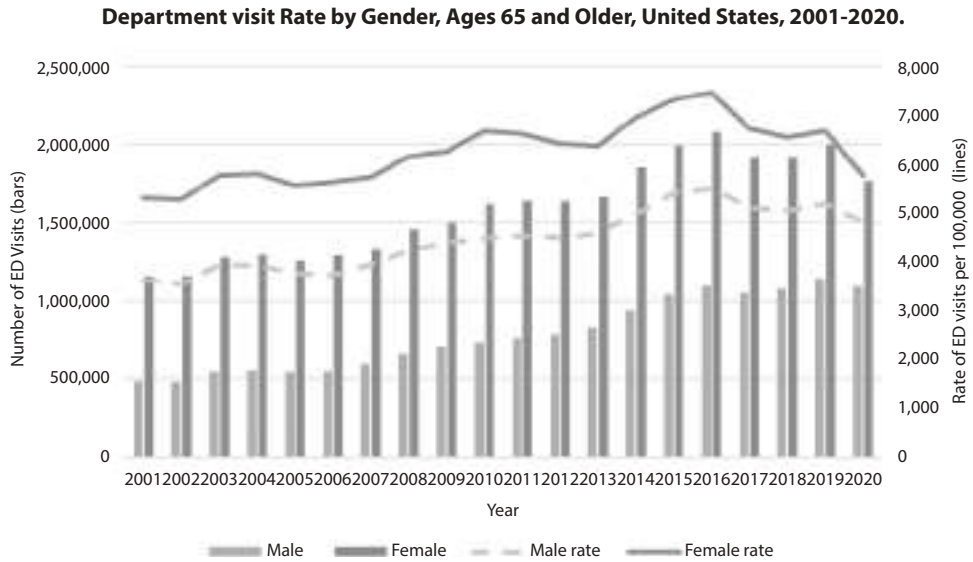


FIGURE 128.3 Number of fall-related ED Visits and fall-related ED visit rate by gender, ages 65 and older, United States, 2001–2020.

White people have disproportionately higher rates of falls and fall injuries compared with Non-Hispanic Blacks and Asian/Pacific Islanders.[11] By geography, older adults in rural counties also report a larger rate of falls when compared with their urban counterparts.[11]

Fear of falling and subsequent loss of independence are common concerns among older adults.[12] Falls are the most common cause of traumatic brain injuries (TBI) and around 90% of hip fractures among older adults occur due to falls.[13] Hip fracture-related hospitalizations are associated with lasting disability outcomes and considerably increase the likelihood of a long-term nursing home admission[14] thus creating either a temporary or permanent loss of independence.

A firm understanding of the risk factors for falls is required to reduce risk and prevent these outcomes.

128.2 RISK FACTORS

Falls and fall deaths increase with age. However, age-related physical and physiologic changes are only partially responsible for older adult falls. Chronic conditions, when in the presence of age-related changes, put an older adult at a higher risk.[15] Chronic conditions affect multiple systems in the body which can impair sensory and locomotor functions.[15] With age, the number of chronic conditions in an older adult increases,[16] and with every additional comorbidity, an older adult is more prone to a fall.[17] The following are some chronic conditions associated with older adult falls: stroke,[18] depression,[19] diabetes mellitus,[20] Parkinson's disease,[21] osteoarthritis in the knee,[22] and osteosarcopenia (defined as a combination of osteopenia/osteoporosis and sarcopenia).[15,23]

Multiple reviews have identified comorbidity and age-related changes as factors that increase fall risk.[13,15,17,24] For example, abnormal gait,[25,26] low muscle mass and strength,[27,28] impaired balance,[29] impaired cognition,[30] poor vision,[17,24] fear of falling,[17] and history of falls[17] are among the most common fall risk factors. Recent systematic reviews and meta-analyses have identified other risk factors such as orthostatic hypotension,[31] foot problems,[32] hearing loss,[33] chronic pain (e.g., in feet, knees, and back),[34] and acute or chronic multisite pain.[35]

Seppala et al. in a series of systematic reviews and meta-analyses identified specific medications including psychotropic drugs (e.g., anti-psychotics, tricyclic anti-depressants, selective serotonin reuptake inhibitors, benzodiazepines)[36] some cardiovascular drugs (e.g., loop diuretics),[37] and other drugs such as anti-epileptics and opioids[38] as increasing fall risk in an older adult. Polypharmacy, or the use of multiple medications is another risk factor.[38] Multiple medications could be associated with falls due to increased likelihood of using fall-risk-increasing drugs, or increased probability of drug-drug interactions.[38] In Seppala et al.'s review, most studies defined polypharmacy as using four or more medications concurrently.[38]

While falls can occur in any location, older adult falls occur more often indoors,[11,39] and in and around a person's home compared with public places.[10,11] Poor lighting, loose/frayed rugs, trailing electrical cords, unstable furniture, stray objects around the home, and snow/ice cover are common environmental hazards.[13,40,41] Common circumstances leading to a fall are tripping over objects (e.g., furniture, clutter),[13,42] using poorly designed stairs (e.g., those with high step height, low tread length, or absent handrails),[42,43] transferring (e.g., from a bed to chair),[44] getting in/out of something (e.g., bathtub),[45] and doing household chores (e.g., reaching for items in storage areas).[45,46]

Although many of the risk factors are independent predictors of falls, it is important to note that they often are interrelated (e.g., gait and cognition)[47] and interact with each other (e.g., mobility and environmental hazards).[46] And, as the number of risk factors increases so does an individual's risk for a fall.[13]

128.3 EVIDENCED-BASED STRATEGIES

Among older adults, there are many effective fall prevention interventions.[48,49] Some interventions focus on one specific risk factor and multifactorial interventions address multiple modifiable risk factors.[49,50] Implementation of these interventions, at the population level, is estimated to have the potential to prevent thousands of falls and avert millions in healthcare costs.[51]

128.3.1 Strength and Balance Programs

Exercise, particularly exercise that targets strength, gait, and balance, has been found to reduce fall risk, falls, injurious falls, and death, although the effect differs by duration, intensity, type, time for follow-up, and other factors.[50,52–55] A pooled analysis of 88 trials found that exercise reduced the rate of falls by 21% in community-dwelling older adults, with greater effects seen from exercise programs that challenged balance and involved more than three hours/week of exercise.[56] A systematic review by the US Preventive Services Task Force (USPSTF) found that exercise interventions reduced the number of older adults experiencing a fall by 11% and the number of fall injuries by 19%.[53] The most common exercise component in the trials reviewed by USPSTF was gait, balance, and functional training.[53] A review of 59 systematic reviews found exercise was consistently effective for community-dwelling older adults but not for those in care facilities.[55]

Multifactorial interventions that include exercise along with other intervention strategies (e.g., vision improvement, removal of home hazards) tend to be the most effective at reducing fall and fall injuries.[57,58] A 2017 systematic review and meta-analysis by Tricco et al. found that exercise plus vision assessment and treatment were among the most effective interventions to reduce injurious falls[58]. The American Geriatric Society/British Geriatric Society (AGS/BGS) Guideline recommends an exercise program that targets strength, gait, and balance with the highest-grade A recommendation (i.e., a strong recommendation

that physicians provide the intervention to eligible patients), and that exercise be included as a component of multifactorial interventions.[52]

There are a variety of effective fall prevention strategies to which providers can refer their patients. Burns et al. produced a compendium of effective randomized controlled trials that reduce the rate of falls or falling.[49] Included are 17 single and 16 multifactorial exercise interventions[49] The compendium also includes information on randomized controlled trials that have been translated into community-based programs.[49] In addition, two of these programs delivered in community settings have also been found to be cost-effective[59]—Stepping On: Moving for Better Balance[60] and tai chi.[61,62]

128.3.2 Home Modification

Hazards in the home are common and can be reduced by conducting home modifications. Home modifications led by an occupational therapist have been shown to reduce both the fall rate and number of older adults who fell.[50,52,55,63,64] In the critical review of two systematic reviews, Pighills et al. found that environmental assessment and modification reduced falls by 21% and the number of older adults who fell by 12%[64] Environmental assessment and modification were effective only with high-risk older adults and when delivered by occupational therapists[64] The AGS/BGS Guideline gives a grade A recommendation (i.e., a strong recommendation that physicians provide the intervention to eligible patients) for home environmentt assessment and intervention for older persons who have fallen or who have risk factors for falling, and for mitigation of identified home hazards, with evaluation and intervention to promote safe behavior.[52]

128.3.3 Medication Management

A recent systematic review and meta-analysis of 14 trials found that medication review (defined as a structured evaluation of a patient's medicines to optimize medicine use and improve health outcomes) was effective in preventing fall-related injuries, specifically fractures, in community-dwelling older adults.[65] Both a Cochrane systematic review and the review for the updated AGS/BGS Guidelines found that withdrawal or tapering of certain medications, including psychoactive medications, was an effective strategy as a single intervention or as a component of a multifactorial intervention.[50,52] The updated AGS/BGS Guideline recommends withdrawal or minimization of psychoactive medications with a B grade (i.e., a recommendation that clinicians provide this intervention to eligible patients).[52] Beyond the AGS/BGS Guideline, medications that cause dizziness, sedation, confusion, blurred vision, or orthostatic hypotension represent a modifiable risk factor for falls. Stopping these medications when possible, switching to safer alternatives, or reducing medications to their lowest effective dose may help prevent falls (www.cdc.gov/steadi).

128.3.4 Vision Improvement

Although vision impairment is an independent risk factor for falls among older adults, it is an underrepresented area of research.[66] A network meta-analysis of seven trials found that vision improvement in conjunction with strength and balance exercise, medication management, and home modification is most effective in reducing falls, followed by vision improvement and exercise.[67] Vision improvement included ophthalmologic examination, prescription glasses, and performing cataract surgery.[67] Harwood et al. found that first eye cataract surgery reduced fall rate and fracture risk among older women.[68] While additional research is needed to determine whether men would also benefit from cataract surgery, the AGS/BGS Guideline currently recommends expedited first eye cataract surgery with a B grade (i.e., clinicians provide this intervention to eligible patients) for older women in whom cataract surgery is indicated.[52]

128.3.5 Podiatric Care

Foot problems and footwear have been identified as risk factors for falls, but there are few studies that document the effectiveness of addressing these issues as a fall prevention strategy.[50,52,69] In a recent systematic review and meta-analysis of nine podiatry interventions, multifaceted podiatry interventions and multifactorial interventions that included a podiatry component were found to be effective over single component podiatry interventions.[69] While single component interventions included routine podiatry care and the use of balance-enhancing insoles or off-the-shelf footwear, multifaceted interventions had an additional component of foot and ankle exercises.[69] Multifactorial interventions assessed for and addressed other fall risk factors in addition to podiatry risk assessment and referral.[69] Multifaceted podiatry interventions reduced the rate of falls by 23% and multifactorial interventions by 27%.[69] With the effects of the two interventions being similar, Wylie et al. suggest that foot and ankle exercises might have a protective effect against falls.[69] Although the evidence is not strong enough for an AGS/BGS Guideline recommendation, footwear can affect balance, gait, and posture. Therefore, wearing shoes with a low heel height and shoes with slip-resistant soles is logical.[70]

128.3.6 Multifactorial Interventions

In a multifactorial intervention, an older adult's fall risk is assessed and interventions (such as exercise, home modification, and medication management) are administered based on the risk factor profile of the individual.[71] The 2018 USPSTF and 2018 Cochrane reviews found that multifactorial interventions reduced the rate of falls by 21% and 23%, respectively.[53,71] The most common types of interventions used in the reviewed trials were exercise and home modification, followed by medication management and psychological intervention (e.g., cognitive behavioral interventions,

referral to mental health services).[71] Although the USPSTF and Cochrane reviews did not find reductions in other fall-related outcomes, a more recent systematic review and meta-analysis found a 23% reduction in the number of older adults experiencing a fall, in addition to the reduction in fall rates in both high-risk and healthy individuals.[72] In the 2017 systematic review and meta-analysis of 283 trials designed to address older adult fall prevention, Tricco et al. found that exercise plus vision assessment and treatment; exercise plus vision assessment and treatment plus environmental assessment and modification (e.g., home modification); and clinic level quality improvement strategies (e.g., case management) plus multifactorial assessment and treatment, plus calcium supplementation, plus vitamin D supplementation were all associated with a reduced risk of injurious falls compared with usual care.[58] In addition, reductions in the number of fractures and the number of hip fractures were associated with a combined use of osteoporosis treatment plus calcium supplementation plus vitamin D supplementation.[58]

128.4 INTEGRATING EFFECTIVE FALL PREVENTION WITH CLINICAL CARE

Given many of the fall risk factors are clinical in nature (e.g., medication use, vision impairment), it is important for healthcare providers to implement a comprehensive fall prevention program that includes screening their older patients for fall risk, assessing their patient's modifiable risk factors, and intervening to reduce the identified risk using effective interventions. Such programs require a team-based approach in which all members of the team (e.g., physicians, nurses, medical assistants, administrative staff) play an integral role. The Center for Disease Control and Prevention's (CDC) STEADI initiative offers guidance to outpatient clinics on how to integrate a fall prevention program within the practice's existing workflow and electronic health records. Included is a step-by-step guide on how to assess practice readiness, obtain support, adapt electronic health records, train staff, and identify reimbursement and quality improvement opportunities. STEADI-based fall prevention programs have successfully been implemented in various health systems. After adopting a STEADI-based program, the Oregon Health and Science University was able to screen two-thirds of their older patients for fall risk, intervene, and treat 85% of older patients with gait impairment, 97% with orthostatic hypotension, 82% with vision impairment, 90% consuming inadequate vitamin D, 75% with foot issues, and 22% on high-risk medications. At United Health Services in New York, patients screened at risk for a fall who were given a STEADI-based fall prevention care plan to reduce their risk had fewer fall-related hospitalizations compared with older adults who were at risk but who did not receive a fall prevention care plan.[73]

Emory Healthcare in Atlanta, Georgia, implemented a telemedicine version of STEADI-based fall prevention. The healthcare system had incorporated STEADI-based fall prevention into their clinical workflow, modified their electronic health record, and trained providers to initiate telemedicine fall prevention in their outpatient clinics when the SARS-CoV-2 (COVID-19) pandemic started.[74] Nurses screened and assessed patients for fall risk factors via phone or video conference, and communicated findings and recommendations to providers to intervene based on identified risk factors. This adapation eliminated the need to travel to the appointment and showed promise for providing fall prevention to older adults who live in more rural areas with limited resources. The main disadvantage was that many older adults lacked either the technology needed or the ability to use it. Between 2011 and 2021, in the United States, the percentage of people aged 65 and older who reported using the Internet increased from 46% to 75%.[75] As more older adults obtain access to the internet and become more comfortable using the technology, this disadvantage will be lessened.

While most older adults seek medical care from outpatient practices, it is also important to consider other clinical settings. The risk of a fall among recently hospitalized older adults is substantially increased in the first 30 days after discharge.[76] Therefore, it is also important to reduce the risk of falls in hospitalized older adults during and after their hospital stay. The CDC STEADI: Best Practices for Developing an Inpatient Program to Prevent Older Adult Falls after Discharge, offers inpatient teams and healthcare systems a framework for promoting safe mobility and managing older patients' post-discharge fall risk.[77]

Pharmacists also play an integral role in fall prevention. As medication experts, pharmacists can identify older adults who may be at risk based on the type of medications filled (e.g., anti-depressants and opioids can increase fall risk) or the number of prescription medications filled.[78–80] They can then screen these older patients for fall risk, review their medications, and make suggestions to the patient and their health providers on ways to optimize their medications to improve health and reduce fall risk.[81]

Many older adults perceive falls as an inevitable part of aging. Therefore, successful fall prevention requires both buy-in from healthcare providers and older adults. The CDC's Still Going Strong awareness campaign (www.cdc.gov/stillgoingstrong) offers information for older adults and caregivers on how common injuries, like falls, can be prevented as we age. The campaign uses positive messaging to encourage older adults to remain healthy and independent by taking simple steps today to prevent future injuries from occurring.

128.5 CONCLUSIONS

In the United States, on average, an older adult falls every second of every day. With the number of older adults and fall death rates rising, the situation will worsen without active participation from all health sectors. Unlike other public health problems, we have considerable information on the burden, risk factors, and effective prevention

strategies to prevent falls and reduce their impact. Using this information, we can help older patients maintain their health and independence by screening them for fall risk, assessing their modifiable fall risk factors, and recommending effective interventions based on their identified risk.

CLINICAL APPLICATIONS

- Utilize annual Medicare Wellness visits or other clinical appointments to screen older patients for fall risk, or any time a patient presents with an acute fall.
- If not at risk, prevent future risk by recommending effective prevention strategies (e.g., refer to a community exercise program to maintain strength and balance, assess vitamin D intake).
- If at risk, assess the patient's modifiable risk factors (e.g., gait, strength, and balance, medications used, orthostatic blood pressure) and fall history.
- Intervene to reduce identified risk factors using effective strategies. This includes discussing patient and provider health goals and developing an individualized patient care plan.
- Query patients during regularly scheduled visits about any recent falls, near falls, or fall injuries.
- Maintain information on falls and fall risks in the electronic health record.
- Follow up with the patient in 30–90 days to discuss ways to improve patient receptiveness to the care plan and address barriers.
- Use available resources such as CDC's STEADI materials to implement a comprehensive fall prevention program into your existing clinical practice. Tools and resources are available for inpatient, outpatient, and pharmacy settings at www.cdc.gov/steadi.

Disclaimer: The findings and conclusions in this manuscript are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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129 Suicide Prevention: CDC's Approach to Prevention

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KEY POINTS

- In 2020, suicide was in the top ten leading causes of death among age groups 5–9 through 55–64 and was the 12th leading cause of death overall.
- Suicide is just the tip of the iceberg. In 2020, there were 483,084 visits for self-harm to US hospital emergency departments with more than 180,000 hospitalizations.
- Suicide rates vary by race and ethnicity, with non-Hispanic American Indian/Alaska Natives (AI/AN) and non-Hispanic Whites having the highest rates.
- Veterans, people who live in rural areas, middle-aged adults, and older adult males are also disproportionately affected by suicide.
- A range of risk and protective factors for suicide exist at the individual, relationship, community, and societal levels.
- The Centers for Disease Control and Prevention (CDC) developed the "Suicide Prevention Resource for Action" that contains strategies and approaches with the best available evidence to prevent and respond to suicide risk, including those for healthcare providers.

129.1 INTRODUCTION

Suicide is a serious public health issue that affects people across the lifespan. Suicidal behavior can be fatal or non-fatal (planning or attempts). Suicide is death caused by injuring oneself with the intent to die. An attempt is when someone harms themselves with any intent to end their life but does not die due to their actions.[1] Suicide and suicide attempts cause serious physical, emotional, and economic impacts. People who attempt suicide and survive may experience serious physical and psychological injuries that can have long-term health effects. They may also experience depression and other mental health concerns.[2,3] More than 90% of people who attempt suicide and survive never go on to die by suicide.[4]

Suicide affects the health and well-being of surviving friends, loved ones, co-workers, and the community. These survivors of suicide loss may experience shock, anger, guilt, depression, or anxiety, and they may even experience thoughts of suicide themselves.[2, 3] Suicide also includes tremendous financial costs. Suicides and suicide attempts cost the nation an estimated $490 billion per year in medical, work loss, quality, and value of life.[5]

CDC's National Center for Injury Prevention and Control (NCIPC) uses the public health approach to systematically address suicide.[6] Data are used to define and describe the nature of the problem, study the factors that increase or decrease risk, and evaluate strategies and approaches with the best available evidence. This is followed by wide implementation and dissemination of what works.[7]

129.2 THE EPIDEMIOLOGY OF SUICIDE

Suicide rates increased 35% between 1999 and 2018 and then declined 5% between 2018 and 2020, yet nearly 46,000 lives were lost to suicide in 2020.[8,9] Suicide dropped below the top ten leading causes of death (LCD) in 2020 for the first time since 2008 due to the emergence of COVID-19 and increases in liver disease deaths.[9] However, suicide is still a major concern. While deaths in young children are not often classified as suicide due to the difficulty in ascertaining intent,[10] for the first time, in 2020, suicide was the tenth LCD among children five to nine years old (20 suicides). Suicide was the second LCD among people aged 10–14 and 25–34 years, third for those 15–24, fourth among people 35–44, seventh for those 45–54, and the ninth LCD among adults aged 55–64. By age and sex, suicide rates are greatest for males aged 85+ years (52/100,000 person-years). Rates are highest among females aged 50–54 (8.6/100,000). The most suicides (47.2%) occur among middle-aged adults 35 to 64 years.[8]

Suicides reflect only part of the problem. Among adults in 2020, 12.2 million seriously thought about suicide, 3.2 million made a plan, and 1.2 million attempted suicide.[11] Among high school youth during the COVID-19 pandemic, 20% thought about suicide, and 9% attempted suicide.[12] Further, 483,084 people visited hospital emergency departments (EDs) for self-harm in 2020, which included more than 182,000 hospitalizations.[8] Other research indicates that over half of persons with serious thoughts of suicide never seek health services.[13] Consequently, health records alone underestimate the true prevalence of suicidal behavior.

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It was feared that the social isolation, economic decline, family stressors, new and worsening mental health symptoms, and disruptions to work and school related to public health mitigation measures for COVID-19 would lead to increases in suicides, but this did not occur. Suicide rates declined in 2019 and 2020, the first decline since 2005. However, rates increased among three subgroups, Hispanic males, non-Hispanic multiracial females, and persons aged 25–34 years. These groups may have been particularly hard hit during the pandemic.[14]

Some hypotheses for the overall decline include that people in close quarters at home may have noticed family member distress, leading to intervention, or people availed themselves of increased virtual resources during the pandemic, such as telehealth and digital tools.[15,16] Precedent for declines does exist, as rates declined during some past disasters only to increase after the disaster passed. For example, US suicide rates dropped 26% during the influenza pandemic of 1918 compared with the pre-pandemic period (1910–1917) and increased 10% in the post-pandemic period (1921–1928).[17] Finally, the famed sociologist, Emile Durkheim, theorized that major crises were associated with a decline in suicides because upheavals in society, such as wars, sharpen collective feelings and enhance connectedness by concentrating activities toward a single end, achieving greater societal integration, at least temporarily.[18] These potential explanations signal that suicide rates could increase once again as the pandemic begins to slow and its effects linger as people go back to their usual routines. Remaining vigilant to signs of suicide is critical.

Unlike suicides, ED visits for suspected suicide attempts increased early in the COVID-19 pandemic. Specifically, during February 21, 2021–March 20, 2021, ED visits for suspected suicide attempts were 50.6% higher among girls aged 12–17 years than in the same period in 2019; among boys, ED visits for suspected suicide attempts increased by 3.7%.[19] Among adults, 21% (2.5 million people) who had serious thoughts of suicide and 8.5% who made a plan in the past year, related these thoughts and actions to the COVID-19 pandemic.[11]

Suicide, non-fatal attempts, and/or ideation disproportionately affect certain populations. Suicide rates are higher among males (Figure 129.1), while suicidal thoughts and suicide attempts are greater among females[20] (Figure 129.2). Overall, suicide rates are highest among persons aged ≥85 years, followed by those aged 75–84 and 25–34 years.[14] However, rates of non-fatal self-harm are highest among adolescents and young adults.[8] Certain US populations such as non-Hispanic American Indian/Alaska Native (AI/AN), Asian/Pacific Islander (A/PI), Black, and Hispanic populations have their highest suicide rates among young adults (20–29 years), whereas non-Hispanic White populations have their highest rates among those 45–54 and ≥80 years old[8] (Figure 129.3).

Veterans, people who live in rural areas, and tribal populations are disproportionately affected by suicide.[21] Veterans have an adjusted suicide rate that is 52.3% greater than the non-veteran US adult population, and people who have previously served in the military account for 13.7% of suicides among adults.[22]

Groups at increased risk for non-fatal self-harm include sexual and gender minorities, youth, and females. Almost a quarter (23.4%) of high school students identifying as lesbian, gay, or bisexual reported attempting suicide in the prior 12 months versus 6.4% for heterosexual peers.[3,20]

Use of a firearm is the leading method of suicide in the United States followed by suffocation and drug poisoning. Poisoning is the means most used in non-fatal self-harm cases.[14]

129.3 RISK AND PROTECTIVE FACTORS

129.3.1 Risk Factors

No single cause for suicide exists. It is influenced by many factors acting at multiple levels—individual, relationship,

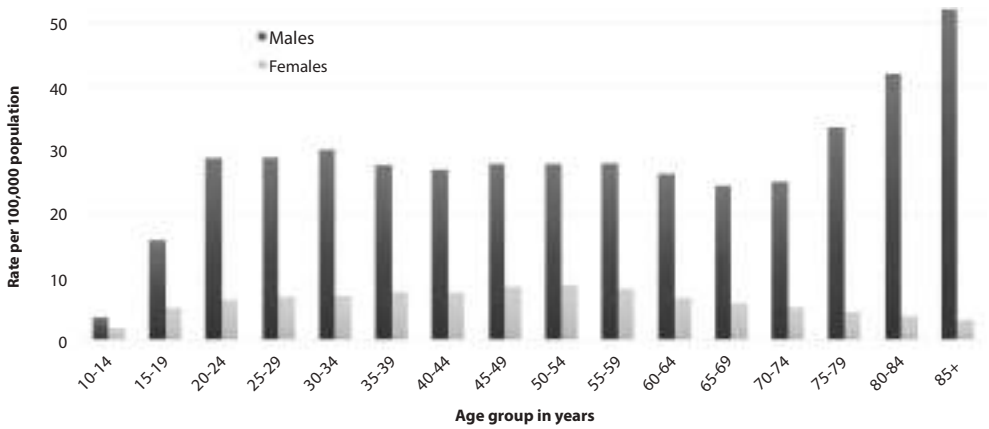


FIGURE 129.1 Suicide rates among all persons by age and sex—United States, 2020; *suicide was defined by ICD-10 codes X60–X84, Y87.0, U03. (source: CDC's National Vital Statistics System Citation: Centers for Disease Control and Prevention [CDC]. WISQARS—Web-based Injury Statistics Query and Reporting System. CDC, National Center for Injury Prevention and Control; 2022. Available at: www.cdc.gov/injury/wisqars. Accessed 17 March 2022).

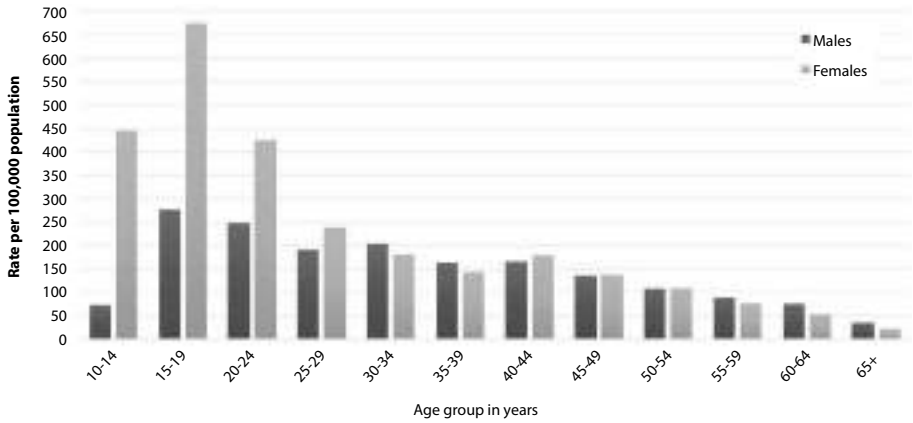


FIGURE 129.2 Non-fatal self-inflicted injury among all persons by age and sex—United States, 2020 ; *non-fatal self-inflicted injury was defined by ICD-10-CM codes, https://www.cdc.gov/nchs/data/nhsr/nhsr108.pdf (source: CDC's National Electronic Injury Surveillance System-All Injury Program Citation: Centers for Disease Control and Prevention [CDC]. WISQARS—Web-based Injury Statistics Query and Reporting System. CDC, National Center for Injury Prevention and Control; 2022. Available at: www.cdc.gov/injury/wisqars. Accessed 17 March 2022).

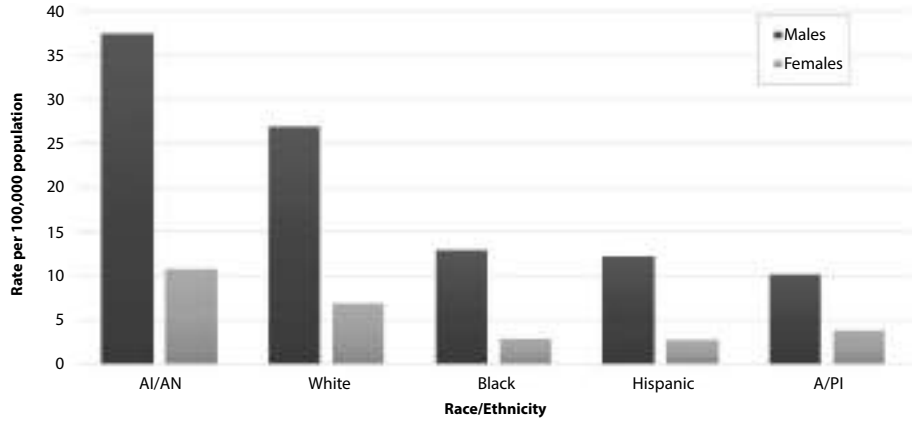


FIGURE 129.3 Age-adjusted suicide rates among males and females by race/ethnicity—United States, 2020 ; *suicide was defined by ICD-10 codes, X60–X84, Y87.0, U03. AI/AN, American Indian/Alaskan Native; A/PI, Asian/Pacific Islander (source: CDC's National Vital Statistics System Citation: Centers for Disease Control and Prevention [CDC]. WISQARS—Web-based Injury Statistics Query and Reporting System. CDC, National Center for Injury Prevention and Control; 2022. Available at: www.cdc.gov/injury/wisqars. Accessed 17 March 2022}.

community, and societal—over time.[21] Individual-level risk factors include previous suicide attempts; mental illness (such as depression); social isolation; criminal, legal, and/or financial problems; job problems or loss; impulsive or aggressive tendencies; serious physical illness; and substance use disorder.[23] Risk factors at the relationship level include adverse childhood experiences, such as child abuse and neglect; bullying; family history of suicide; relationship problems such as a break-up, violence, or other loss; and victimization from sexual violence. Community-level risk factors are barriers or lack of access to health or mental health care; cultural and religious beliefs that suicide is acceptable (e.g., suicide is a noble resolution of a personal problem); and a suicide cluster in the community. Societal-level risk factors include stigma associated with mental illness or help-seeking; easy access to lethal means among people at risk (e.g., firearms, medications); and unsafe media portrayals of suicide. Some risk factors vary by age, gender, and culture, while others are universal.[23]

129.3.2 Risk Factors among Children/Pre-Adolescents

Suicide among children, particularly prior to puberty, is a rare event. This may be due to the two most common risk factors—depression and exposure to drugs and alcohol—which do not typically occur until adolescence.[24] In addition, determining suicidal intent in young children is difficult.[10] However, some young children die by suicide and may understand the implications of the behavior.[25] Some research suggests that a lack of fear of physical pain and death may enable the behavior.[24]

129.3.3 Risk Factors among Adolescents and Young Adults

Adolescence is a time of transition and growth characterized by biological, psychological, and social changes. It often includes risk-taking and pushing boundaries to

achieve greater independence. Successfully navigating adolescence impacts the transition into young adulthood when new job and family responsibilities take precedence.[26] Risk factors for suicide during adolescence and young adulthood may include the onset of mental illness/substance use, prior suicide attempts, hopelessness, family history of suicidal behavior, parental divorce, child maltreatment, school problems, bullying, a peer's suicide, poor problem-solving, easy access to lethal means among young people at risk, conduct disorder among males, troubled relationships with parents and peers, and peer victimization.[26,27]

129.3.4 Risk Factors among Middle-Aged Adults

Middle adulthood challenges may include changes in marriage, job, health status (onset of chronic illness, disability), children leaving home, and caring for an aging parent.[28] Less is known about the unique suicide-related risk factors in this age group because much of the research on suicidal behavior has focused on youth and older adults.[29] However, some risk factors include mental health conditions, alcohol and/or substance use, relationship problems (e.g., lack of connectedness, divorce, adverse childhood experiences, criminal/legal difficulties, and job/financial problems.[30] On a population level, research finds, for example, that suicide rates among working-age adults 25–64 years tend to increase during recessions and fall during times of economic expansion.[31]

129.3.5 Risk Factors among Older Adults

Older adulthood may be characterized as a time of more predictable and stable emotions, but both social roles and networks change, as does physical functioning.[32] Based on post-mortem psychological autopsy studies, research shows that between 71% and 95% of older adult suicides involved a mental health condition, most notably, depression.[33] More recent research, based on medical examiner/coroner and law enforcement reports and death certificates in 41 states/jurisdictions, indicates 33% of older adult suicides in 2019 had *known* mental health conditions, as reported by next of kin.[30] While certain physical conditions have been associated with suicide, including cancer and heart disease, a more important factor may be the presence of multiple conditions and not the specific illnesses themselves.[34] Still, other studies indicate that it is not the physical health condition that matters but rather one's activity limitation.[35] Additionally, a study in one health system found that 67% of older adults who died by suicide had visited a healthcare provider in the month prior to death,[36] offering an opportunity for prevention. Other risk factors in older age include, loss of a spouse, a lack of social connectedness to family, friends, and community, access to lethal means among people at risk, and a greater intent to die.[37]

Finally, looking across age groups, research has shown that suicide and violence (e.g., intimate partner and sexual violence, child maltreatment, and elder abuse and neglect) are interconnected and share many underlying factors.[38] Understanding the overlapping causes of suicide and violence and what can protect people and communities is important. For example, suicide and violence are shaped by structural factors, such as racism and sexism, resulting in inequities in outcomes.[21]

129.3.6 Protective Factors

Protective factors buffer or reduce suicide risk. Like risk factors, they occur across the individual, relationship, community, and societal levels. Protective factors at the individual-level include coping and problem-solving skills to build resilience; reasons for living (family, friends, pets, etc.); cultural and religious beliefs that discourage suicide; and sense of self-worth.[23] At the relationship level, they include connections to individuals, family, community, societal institutions, and supportive relationships with healthcare providers. Research shows that connectedness to family, in particular, is effective at reducing suicide risk among youth.[39] Community-level protective factors are safe and supportive school, work, and community environments, and sources of continued care after psychiatric hospitalization. Protective factors at the societal-level include the availability and accessibility of physical and mental healthcare and reduced access to lethal means (e.g., firearms, pesticides, medications) among people at risk. Unfortunately, less research is conducted on protective factors in comparison with risk factors.

129.3.7 Prevention Strategies

In 2017, CDC released "Preventing Suicide: A Technical Package of Policy, Programs, and Practices", which was updated to the "Suicide Prevention Resource for Action" in 2022 (Prevention Resource)[3,40] This report documents a collection of strategies that represent the best available evidence. Communities and states can use the Prevention Resource to sharpen their focus on strategies and approaches with the greatest potential to prevent suicide. A strategy is defined as the preventive direction or action to achieve the goal of preventing suicide. Approaches are specific ways to advance the strategy, such as through policies, programs, or practices. Communities and states can use the resource for selecting prevention strategies and approaches based on the local suicide problem, existing patterns in the data (e.g., populations disproportionately impacted by suicide), and available resources for responding. Adopting multiple strategies and approaches can lead to a substantial and potentially synergistic effect and improve outcomes. This resource targets suicide risk and protective factors at the individual, relationship, community, and societal levels. The seven strategies and their corresponding approaches shown below start with those that will most likely impact the population as a whole, followed by those focused more narrowly on individuals.

Suicide Prevention Resource for Action

Strategy	Approach
1) Strengthen economic supports	• Improve household financial security • Stabilize housing
2) Create protective environments	• Reduce access to lethal means among persons at risk of suicide • Create healthy organizational policies and culture • Reduce substance use through community-based policies and practices
3) Improve access and delivery of suicide care	• Cover mental health conditions in health insurance policies • Increase provider availability in underserved areas • Provide rapid and remote access to help • Create safer suicide care through systems change
4) Promote healthy connections	• Promote healthy peer norms • Engage community members in shared activities
5) Teach coping and problem-solving skills	• Support social-emotional learning programs • Teach parenting skills to improve family relationships • Support resilience through education programs
6) Identify and support people at risk	• Train gatekeepers • Respond to crises • Plan for safety and follow-up after an attempt • Provide therapeutic approaches
7) Lessen harms and prevent future risk	• Intervene after a suicide (postvention) • Report and message about suicide safely

Brief information about each strategy and the rationale for its inclusion in CDC's Prevention Resource is provided below. Consult www.cdc.gov/suicide/prevention/index.html for additional details.

- Strengthen economic supports:
  Research indicates that suicides increase during economic downturns (and decrease during expansions).[31] The financial strain associated with job loss, long periods of unemployment, eviction/foreclosure, and other consequences of unanticipated financial stress can exacerbate suicide rates, both directly and indirectly, through worsening physical and mental health concerns. Expanding unemployment benefits, providing temporary financial assistance, and implementing housing policies that allow people to stay in their homes can help buffer the negative effects of financial strain, and thereby promote suicide prevention.
- Create protective environments:

  Creating environments that address risk and protective factors where people live, work, and play can help prevent suicide.[41] For example, the burden of suicide is highest among middle-aged adults,[8] certain occupational groups,[42] and people in detention facilities,[43] such as jail or prison. Therefore, implementing programs, practices, and policies in these settings can buffer against suicide risk. This may involve reducing access to lethal means (e.g., safe storage practices);[44] creating healthy organizational policies and culture in the workplace;[45] and developing community-based policies and practices to reduce substance misuse.[46, 47]
- Improve access and delivery of suicide care:

  Research suggests that services are improved when health and behavioral healthcare systems are integrated and set up to effectively and efficiently deliver care.[48] Identifying ways to improve access to care that is timely, affordable, and high quality is critical. Such approaches include implementing mental health parity laws;[49] implementing policies and practices to increase provider availability, especially in underserved areas;[50] and creating safer suicide care through systems change.[51,52]
- Promote healthy connections:

  Connectedness is the degree to which an individual or group is socially close, interrelated, or shares resources with each other. It typically refers to connectedness to family, friends, or others. However, it may also convey connectedness to school, church, or other organizations. Connectedness may protect against suicide by decreasing isolation, encouraging adaptive coping behaviors, and increasing access to helping services, belongingness, self-worth, and resilience.[53] Two evidence-based approaches for enhancing connectedness include programs that 1) normalize help-seeking and 2) community engagement activities that may buffer against suicide risk by

decreasing isolation and increasing knowledge of mental and physical health services.[26]

- Teach coping and problem-solving skills:

  Managing problems, conflicts, stress, and emotions are critical life skills for dealing with daily challenges such as occupational, school, relationship, and health concerns that may increase suicide risk. School-based social-emotional learning programs can help youth resolve relationship conflicts, communicate more effectively about their needs, and avoid negative influences (e.g., drugs and alcohol). Parenting and family relationship programs also offer skill-building and problem-solving. These programs support caregivers, promote positive parent-child interactions, and improve children's behavioral and emotional skills and abilities.[54] They are effective in reducing suicide-related thoughts and behaviors.[55]

- Identify and support people at risk:

  Approaches that ensure people at risk are identified and connected to services are critical. For example, training community members and others who interact with populations at increased risk so they know the warning signs of suicide and how to respond, called gatekeeper training, can be effective. Additionally, crisis intervention services (e.g., hotlines) and various treatment modalities (e.g., collaborative care, cognitive behavior therapy, brief interventions in EDs) have been shown to prevent suicide attempts and re-attempts.[40]

- Lessen harms and prevent future risk:

  Harm can be direct, such as the death of a loved one or close friend to suicide, or indirect, such as exposure to unsafe media reporting about suicide. Whether direct or indirect, such harms are known to increase the risk of suicide. Programs that support the bereaved (i.e., survivors of suicide loss)—for example, using face-to-face outreach and telephone support can reduce psychological distress and risk of suicide ideation and attempts.[56] Responsible media reporting (e.g., not using sensational headlines or pictures of the suicide decedent, not mentioning the method of suicide, not reducing suicide to one cause, and providing protective factor information and helping resources) can decrease suicides and suicide contagion.[57]

129.4 ROLE OF LIFESTYLE MEDICINE PRACTITIONERS

Lifestyle medicine practitioners look at systemic and population-based interventions to improve the health of people.[58] This basic tenet of lifestyle medicine lends itself to a public health approach.[7,59] and for practitioners to serve several roles in preventing suicide. These roles include clinical responsibilities and support for patients and communities, research, and education.[60]

As a clinician, the lifestyle medicine practitioner may have clinical responsibilities from both the patient and population-based perspectives. Those who work in primary care settings, schools, community centers, homeless shelters, and other related locations have the access and opportunity to play a pivotal role in suicide prevention. Awareness of specialty organization policy statements and guidelines on suicide prevention can help direct practitioners' decision-making and assessment of suicidal ideation, depression, and other risk factors.[61] Evidence-based assessment tools and best-practice models are available.

Some lifestyle medicine practitioners who work in community-based organizations, local or state health departments, or federal health agencies can impact suicide prevention through the public health approach.[7,59] A focus on community health needs related to suicide is also warranted, as is support for comprehensive prevention policies.[62,63] Championing the implementation of evidence-based research can assist effective decision-making about suicide prevention policies and programs.

Practitioners can also serve as compelling advocates for suicide prevention in their communities because of their unique training and practical experience. A clinician's obligation to advocacy is grounded in their professional experience, expertise, and duty to patients.[64] Several physician organizations recognize the role of clinicians in public policy, and some believe activism is a medical responsibility that requires skilled training for effectiveness.[65]

Prevention practitioners have a broad array of expertise in various areas; however, many have little training, experience, or proficiency in suicide prevention, specifically. In these cases, they could seek opportunities to gain knowledge, including information about suicide risk and protective factors, and the latest evidence for screening, treatment, and prevention modalities. Formal learning options include professional development and continuing education conferences. Practitioners may also discover community resources for patients and population-based activities. In addition, sensitivity to the unique characteristics of the population with whom they interact is encouraged. Understanding these cultural differences is critical for communicating with people from diverse geographic, ethnic, racial, cultural, economic, sexual orientation, spiritual, or social backgrounds.[66]

129.5 CONCLUSION

Suicide is an urgent public health crisis in the United States. The COVID-19 pandemic has brought renewed attention to suicide prevention, mental health promotion, and health equity as individuals, families, and communities have struggled under the weight of the pandemic and its effects

on social, physical, and emotional well-being. As the United States and the world continue to bear the consequences of the COVID-19 pandemic, vigilance is needed, both in implementing prevention and identifying and supporting populations disproportionately impacted by COVID-19 and suicide.

A comprehensive public health approach is needed to address the range of risk and protective factors associated with suicide. The comprehensive approach includes both upstream strategies, such as those from CDC's Prevention Resource that aim to prevent suicide risk in the first place, as well as downstream prevention efforts (lifestyle medicine practitioner perspective), which aim to respond to people at immediate risk and prevent re-attempts. These efforts include knowing the risk and protective factors and warning signs for suicide, providing direct clinical care, counseling on access to lethal means for people at risk, discussing cultural and/or behavioral determinants that contribute to suicide, assuring smooth transitions between levels of care, ongoing professional development, and engaging in research, education, and policy.

Lifestyle medicine practitioners care for patients and address conditions in the environment that cause disease and injury. They are trained to approach health concerns and understand the broad scope of an entire community and the context of the patient. This combined perspective is essential in addressing population-based, subgroup, and individual issues that play such a prominent role in suicide and its prevention.

CLINICAL APPLICATIONS

- Physicians can help identify early signs of suicidal thoughts and behaviors.
- Practitioners can seek evidence-based assessment tools and employ best-practice models, such as those from the National Action Alliance for Suicide Prevention (https://theactionalliance.org/healthcare) the "Assessment of suicide risk" from the American Psychiatric Association (APA) Practice Guidelines for the Psychiatric Evaluation of Adults (https://psychiatryonline.org/doi/epdf/10.1176/appi.books.9780890426760), and other APA resources.
- Practitioners can address research gaps by contributing rigorous, evidence-based models for screening interventions. The National Institute of Mental Health (NIMH) conducts ongoing research to address suicidal behavior. See www.nimh.nih.gov/health/topics/suicide-prevention/index.shtml.
- The American Psychological Association (APA) has psychological research, effective treatments, and educational materials for various audiences (decision-makers, researchers, and the public). See www.apa.org/news/apa/2018/suicide-prevention-month.
- Lifestyle medicine practitioners can support suicide prevention policies and programs in their communities and through formal advocacy training through seminars or conference sessions at professional meetings or fellowships.
- Many medical groups and associations (e.g., American Medical Association, APA, American College of Preventive Medicine) have additional resources for clinical practice.

Disclaimer: The findings and conclusions in this manuscript are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Part XXII

Public and Environmental Supports for Lifestyle Medicine



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130 Healthcare Reform and Lifestyle Medicine in the Post-COVID-19 Era: Moving Forward

Gregory W. Heath, DHSc, MPH, FACSM, FAHA and Steven Fox, MD

KEY POINTS

- The COVID-19 pandemic has demonstrated an exacerbation of previously existing health disparities linked to lifestyle diseases and conditions due much in part to the widening gap between private healthcare organizations and public health agencies with misconstrued functions for each in addressing population health.
- The COVID-19 pandemic in the United States and globally can therefore be considered a *syndemic*, where there is an adverse interaction between diseases and social determinants of health (e.g., poverty, education, housing, employment, racism, access to healthcare), in this case, the high prevalence of chronic diseases and their antecedent risk factors among the US population and a highly infectious agent, SARS-CoV-2 and its variants.
- The Affordable Care Act (ACA), having been in place for over 12 years, continues to provide considerable improvement in the number of people with health insurance coverage, however, with the cancelation of the individual mandate, many segments of the population representing diverse race/ethnic groups and people of lower socioeconomic status have seen a downturn in the proportion of those insured.
- The focus on primary care for the delivery of preventive care and lifestyle medicine services is critical for the success of any type of healthcare reform going forward.
- The ACA has demonstrated that significant numbers of US residents have benefitted from increased access to care and coverage of clinical preventive services without cost-sharing.
- The ACA legislation contains elements that could further advance lifestyle medicine and primary prevention, but this opportunity is dependent on the approval of the American electorate to expand the government's role in the regulation of the healthcare delivery system.
- Traditional fee-for-service reimbursement creates an incentive for providers to supply a high volume of expensive services if the payment exceeds the cost of the service delivery.
- Modification of patient health behaviors is central to the practice of lifestyle medicine and primary prevention; however, this requires a combination of the healthcare teams' lifestyle medicine skills, patient responsibility, and community-based supportive policies and environments (cultural, physical, social, etc.) to ensure that lifestyle changes are both initiated and sustained. Currently, this approach is quite variable and only emphasized by employer-sponsored health plans.
- The American healthcare system faces three interrelated challenges: cost, quality, and access to services.
- Support for lifestyle medicine was evident in the CMS recognition of obesity as a disease in 2014, thereby creating the potential for Medicare coverage of obesity-related treatments.
- Policies and evidence-based environmental interventions outlined in this chapter identify primary prevention strategies that hold significant promise for the alleviation of premature suffering from disease, the maintenance of functional health, and the prevention of early death.

130.1 INTRODUCTION

The COVID-19 pandemic at the time of this writing has continued for over 30 months across the globe.[1] The impact in the United States of America (US) has been devastating with an excess of over 80 million cases, 4.5 million hospital admissions, and 977,000 deaths[1] (Figure 130.1 and Figure 130.2).

To say the least, the pandemic has overwhelmed and stretched the healthcare and public health systems of the US well beyond their capacity to keep pace with the COVID-19 outbreak.[2] Healthcare providers have become exhausted, frustrated, and mentally/emotionally challenged throughout the pandemic.[3] During the early weeks of the pandemic in the US, a pattern emerged among cases and deaths that revealed that those most vulnerable to a severe and/or critical course of COVID-19, often requiring hospitalization,

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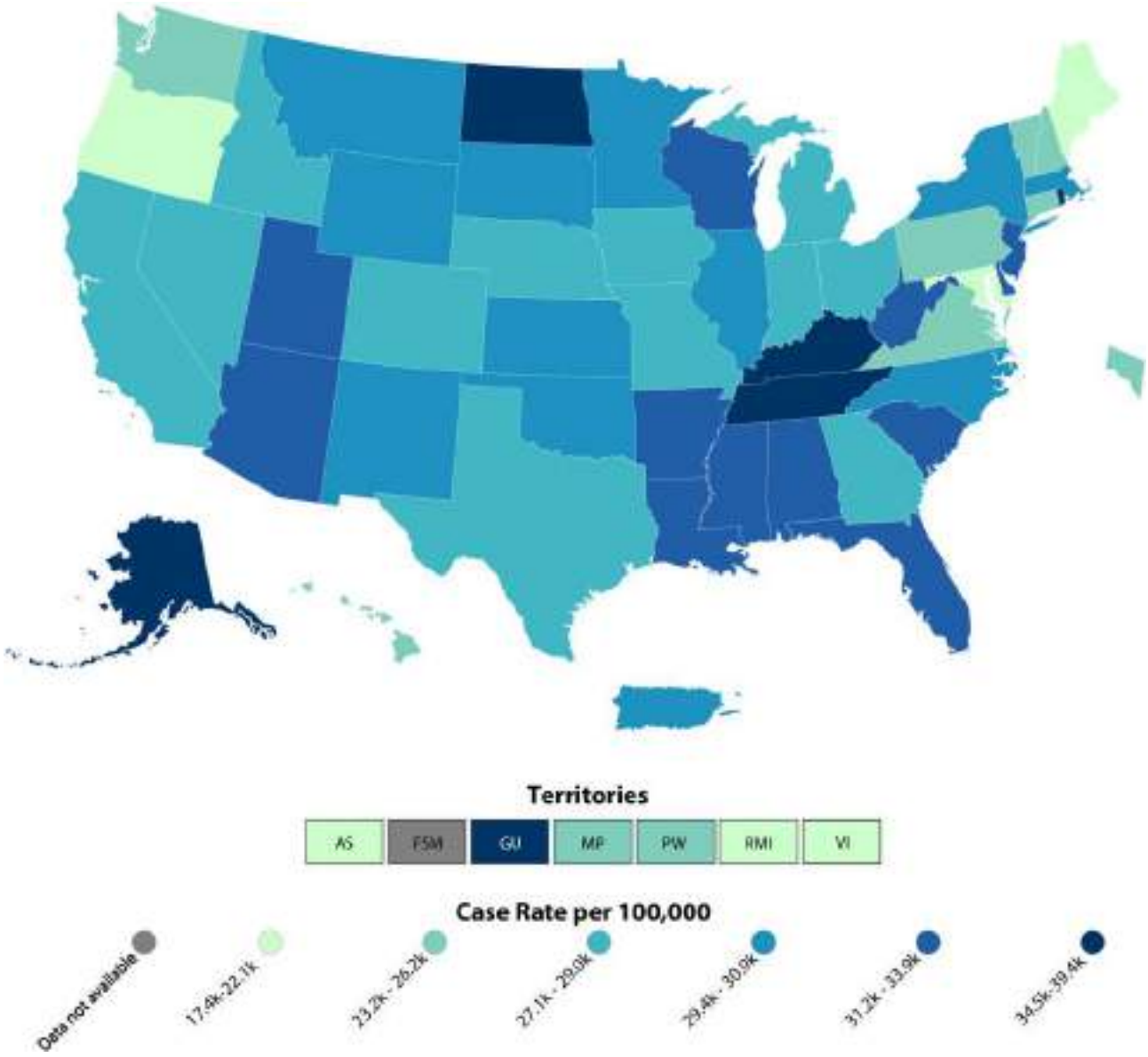


FIGURE 130.1 COVID-19 cases by state (2020–2022) per 100,000 (source: https://covid.cdc.gov/covid-data-tracker/#cases_newcaserateper100k).

suffered from pre-existing conditions and comorbidities that predisposed them to such outcomes.[4,5] These "underlying conditions" most often included lifestyle diseases such as hypertension, type 2 diabetes, chronic respiratory diseases, and chronic kidney disease.[6] Other independent lifestyle risk factors for COVID-19 cases, hospitalizations, and deaths also emerged, including overweight, obesity, and a history of physical inactivity.[7–9] Another pattern emerged during the pandemic that identified a disparate burden for COVID-19 outcomes among African American/Black, Hispanic/Latino, and persons representing lower socioeconomic status.[10–12] These marked disparities reflected pre-existing disparities driven by the social determinants of poverty, lack of access to regular healthcare including preventive/lifestyle medicine, and historical systemic racism.[13] In general, the US population's health status was inadequate to fend off the onslaught of SARS-CoV-2 and its variants, especially among disparate populations, establishing the pandemic as a *syndemic*, i.e., the interaction of the social determinants of health with COVID-19.[14] The high prevalence of non-communicable diseases (NCD) and the lifestyles of poor diet, cigarette smoking, physical inactivity, and obesity among the US population as a whole provided for the "perfect storm" for such a syndemic as can be seen through these series of maps[15] (Figures 130.3–130.9).

Since the Patient Protection and Affordable Care Act, often referred to as the Affordable Care Act (ACA), was signed into law on March 23, 2010, healthcare reform has been on the minds of patients, politicians, and providers alike. The impact of the ACA was much like the impact

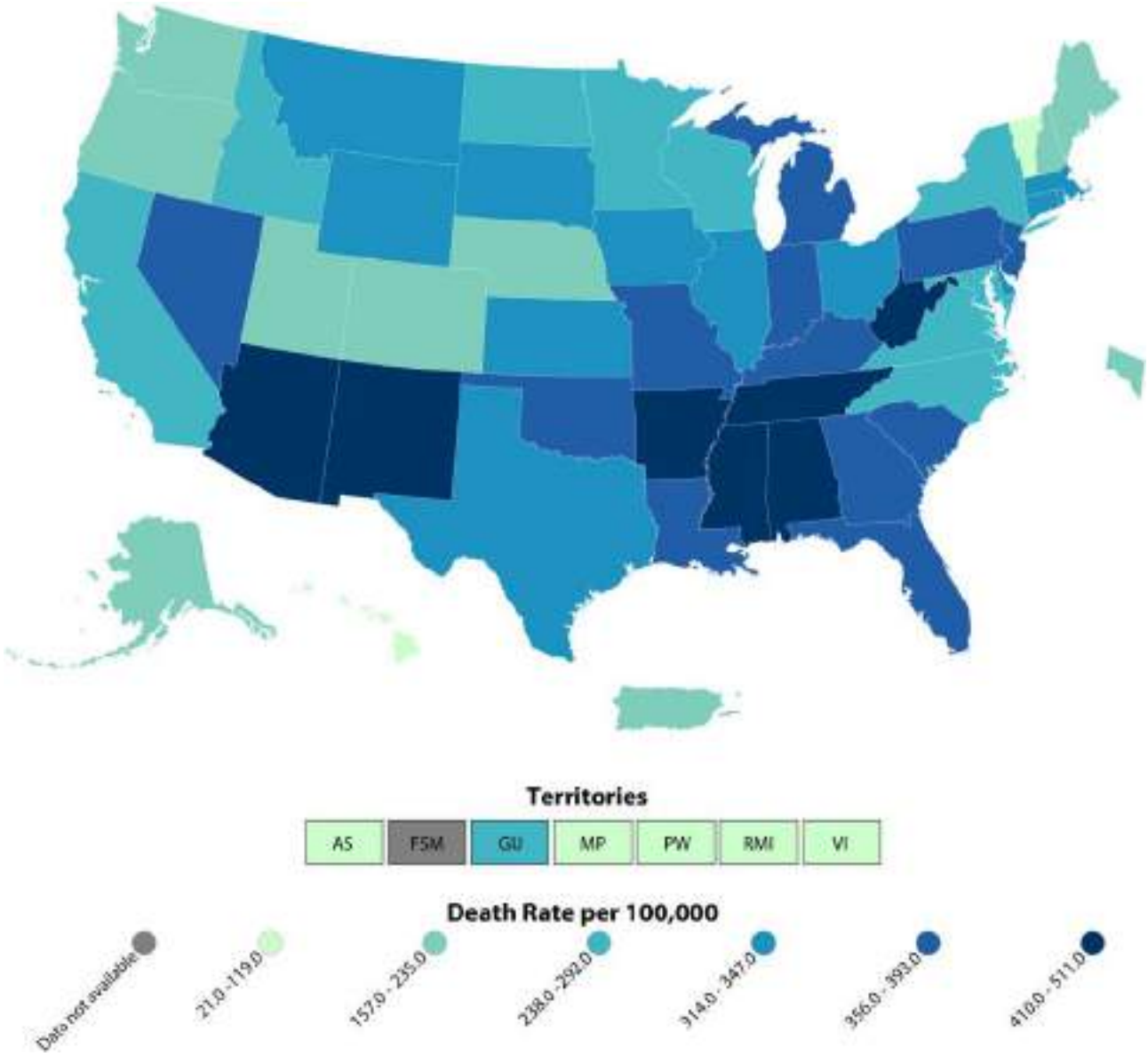


FIGURE 130.2 COVID-19 deaths, by state, USA (2020–2022) per 100,000 (source: https://covid.cdc.gov/covid-data-tracker/#cases_newdeathrateper100k).

of the creation of Medicare and Health Maintenance Organizations, and the law was an attempt to transform healthcare delivery in the US. Over the past 12 years, numerous regulations, and policies, many of which are still in the process of being implemented, have affected the healthcare delivery system. In many cases, planned changes are being modified in response to court decisions and debates in Congress, state legislatures, and communities. The discussion is certain to continue, as government-sponsored programs are estimated to account for 47% of all healthcare spending by 2025, with total expenditures estimated to represent 20.1% of the total US economy.[16]

With the start of ACA in 2014, 20.4 million uninsured individuals obtained coverage, with 43.9% enrolled in Medicaid, 31.8% enrolled in private non-group insurance (mostly through ACA exchanges), and the remaining 24.3% enrolled through employer-sponsored insurance. During the first half of 2020, according to newly released estimates from the National Health Interview Survey (NHIS), 30 million US residents lacked health insurance.[17]

This number indicates a steep decline in the number of uninsured Americans since 2010, before the implementation of the large coverage expansions under the ACA. The ACA produced particularly large coverage gains for Blacks, Latinos, Asian Americans, and Native Americans, as well as for lower-income families. However, the uninsured rate has increased since 2016, even prior to the COVID-19 pandemic. From 2017–2019, the uninsured rate rose by 1.7%, most likely due to new policy changes to coverage options available under the ACA and Medicaid. Estimates from the NHIS show no significant change in uninsured rates during the early months of the COVID-19 pandemic. However, the

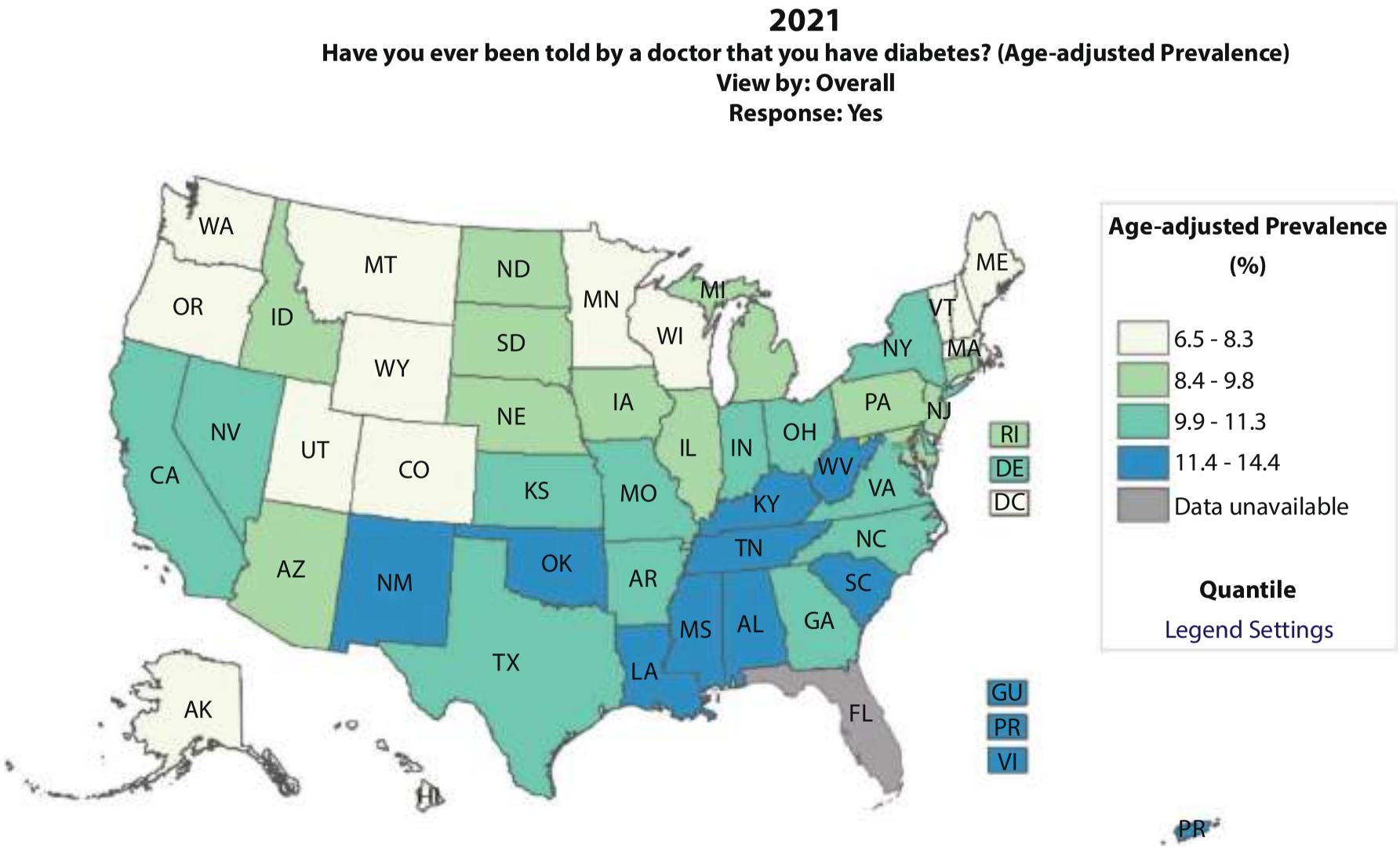


FIGURE 130.3 State-specific prevalence of type 2 diabetes among adults 18 years and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

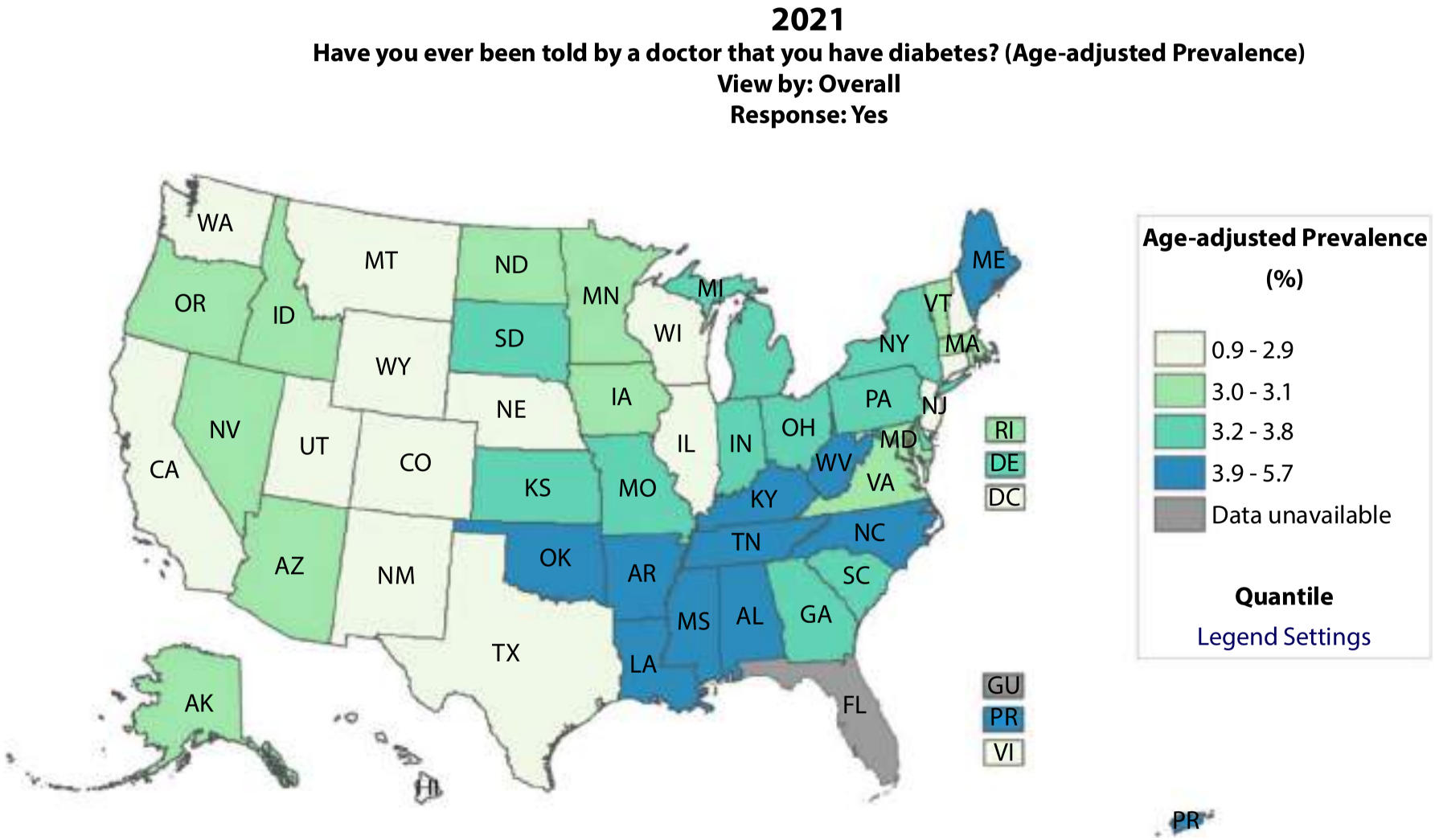


FIGURE 130.4 State-specific prevalence of angina or coronary heart disease among adults 18 and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

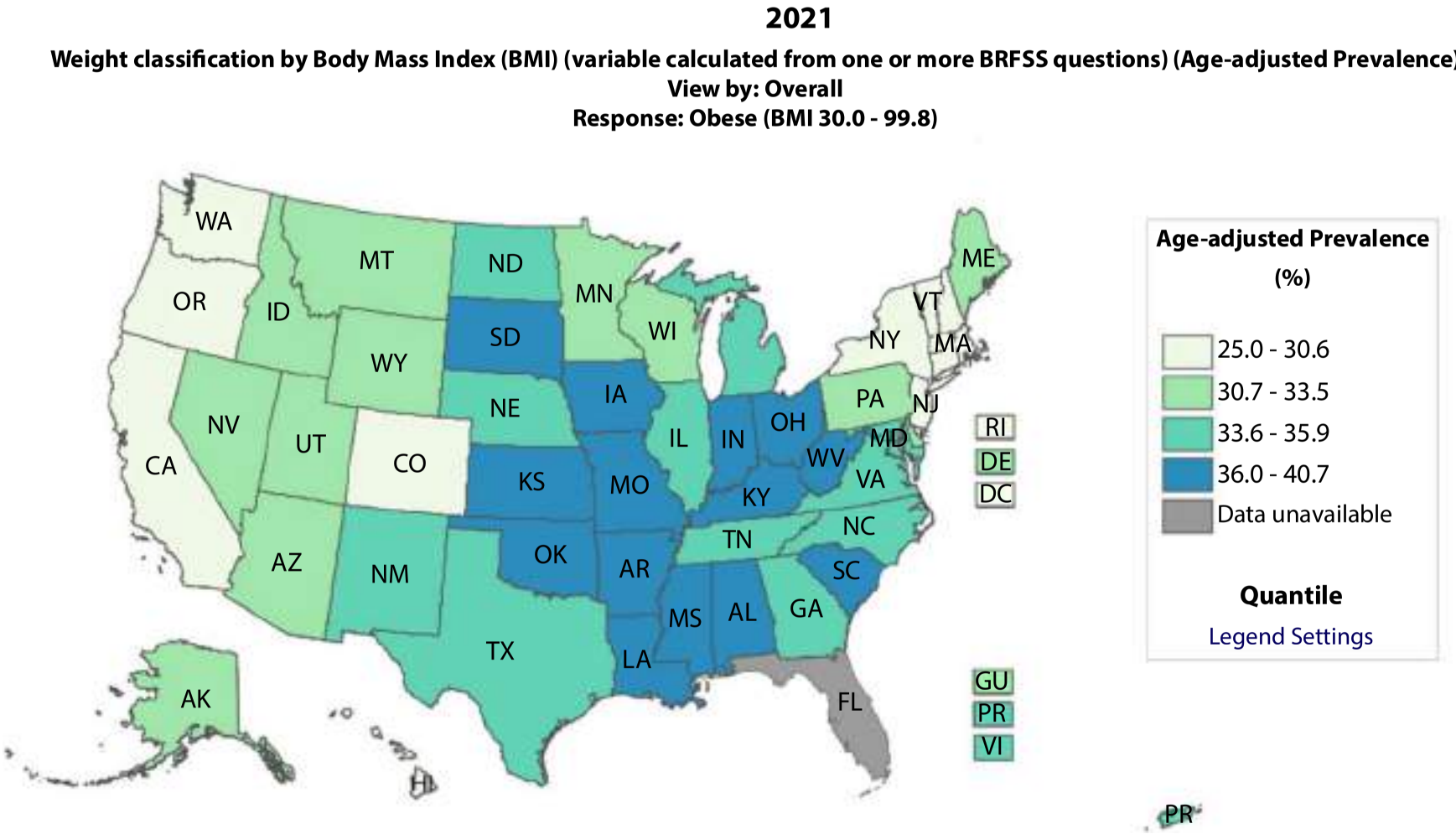


FIGURE 130.5 State-specific prevalence of obesity among adults 18 years and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

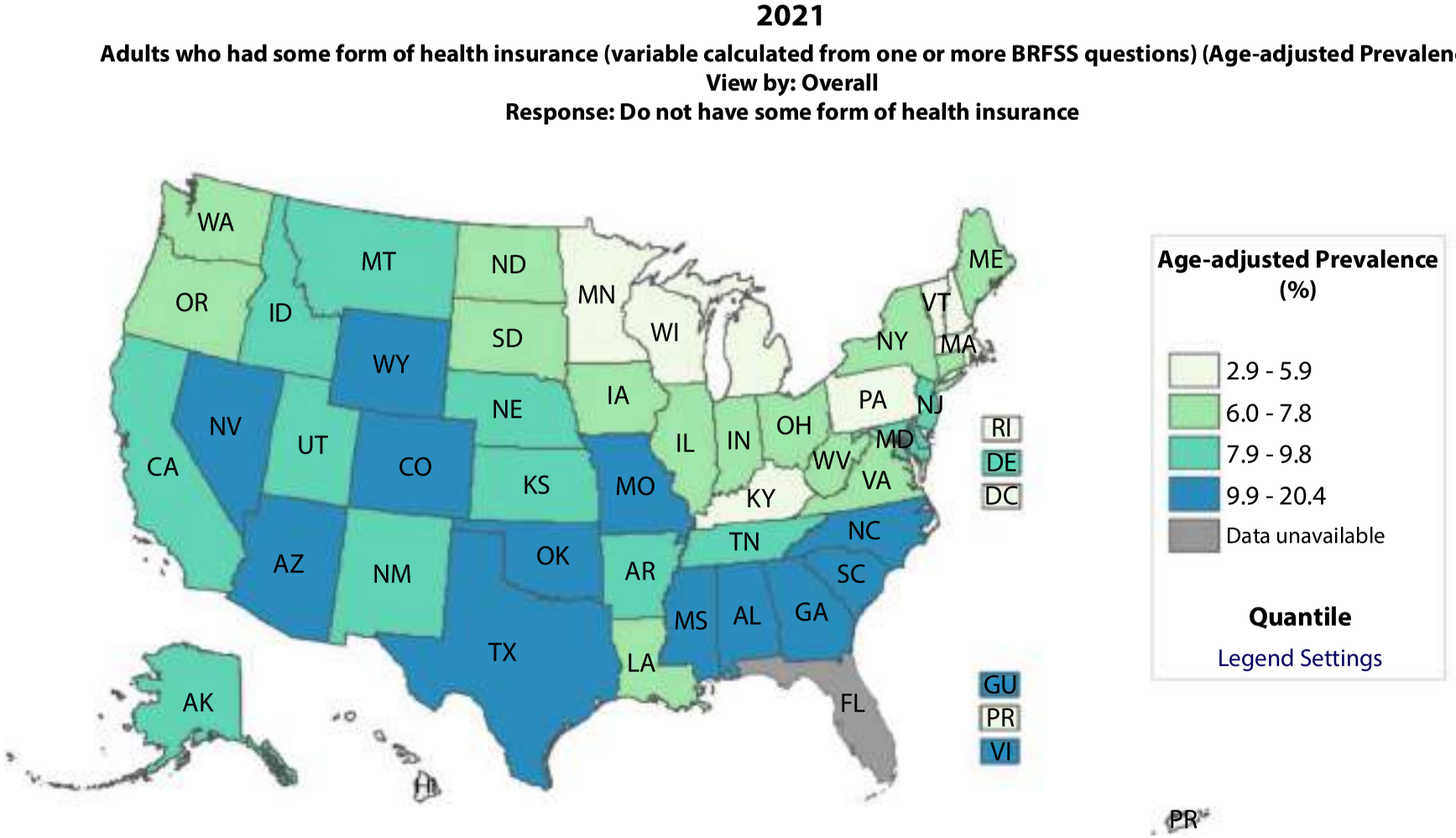


FIGURE 130.6 State-specific prevalence of health insurance among adults 18 years and older, United States, 2021. (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

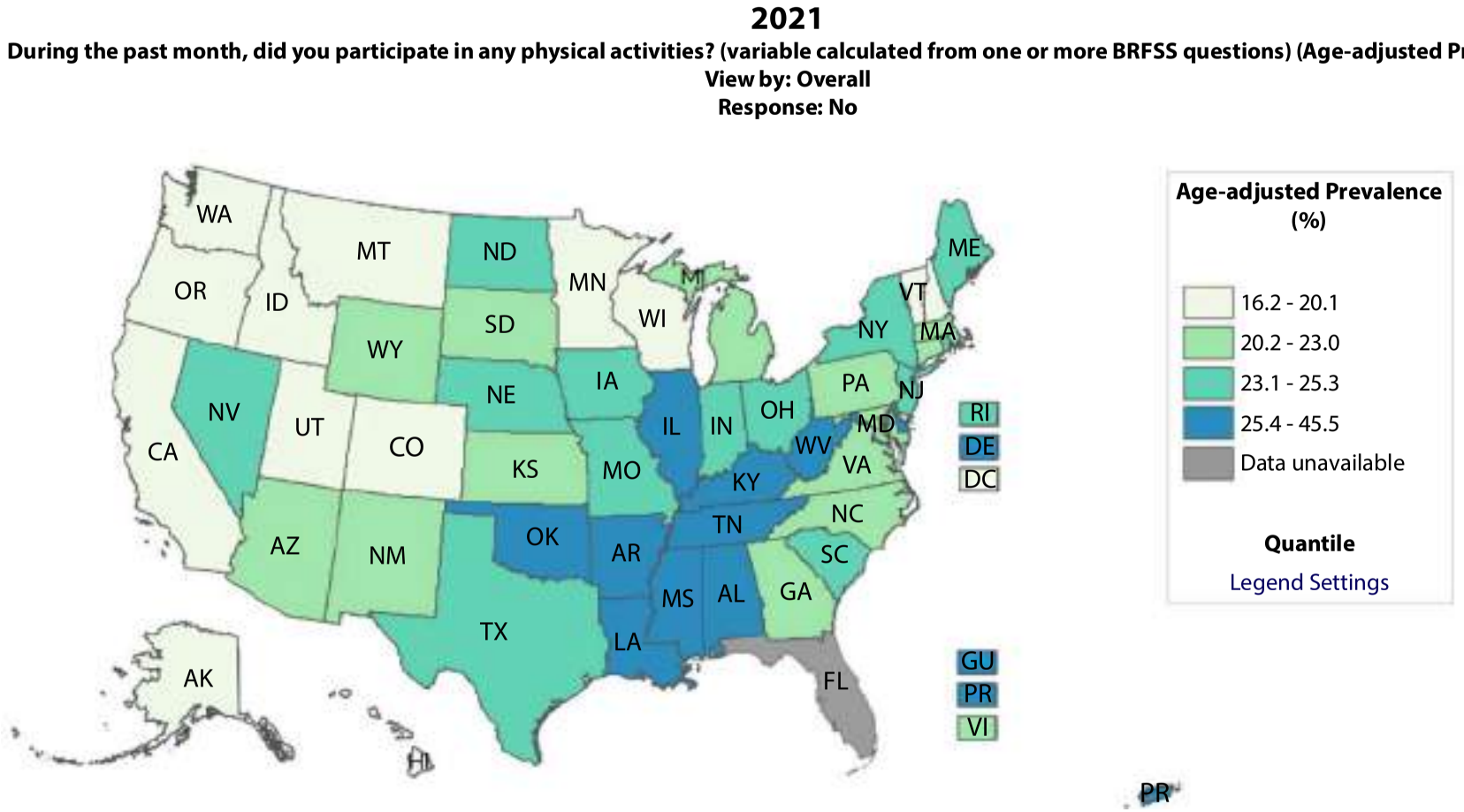


FIGURE 130.7 State-specific prevalence of physical inactivity among adults 18 years and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

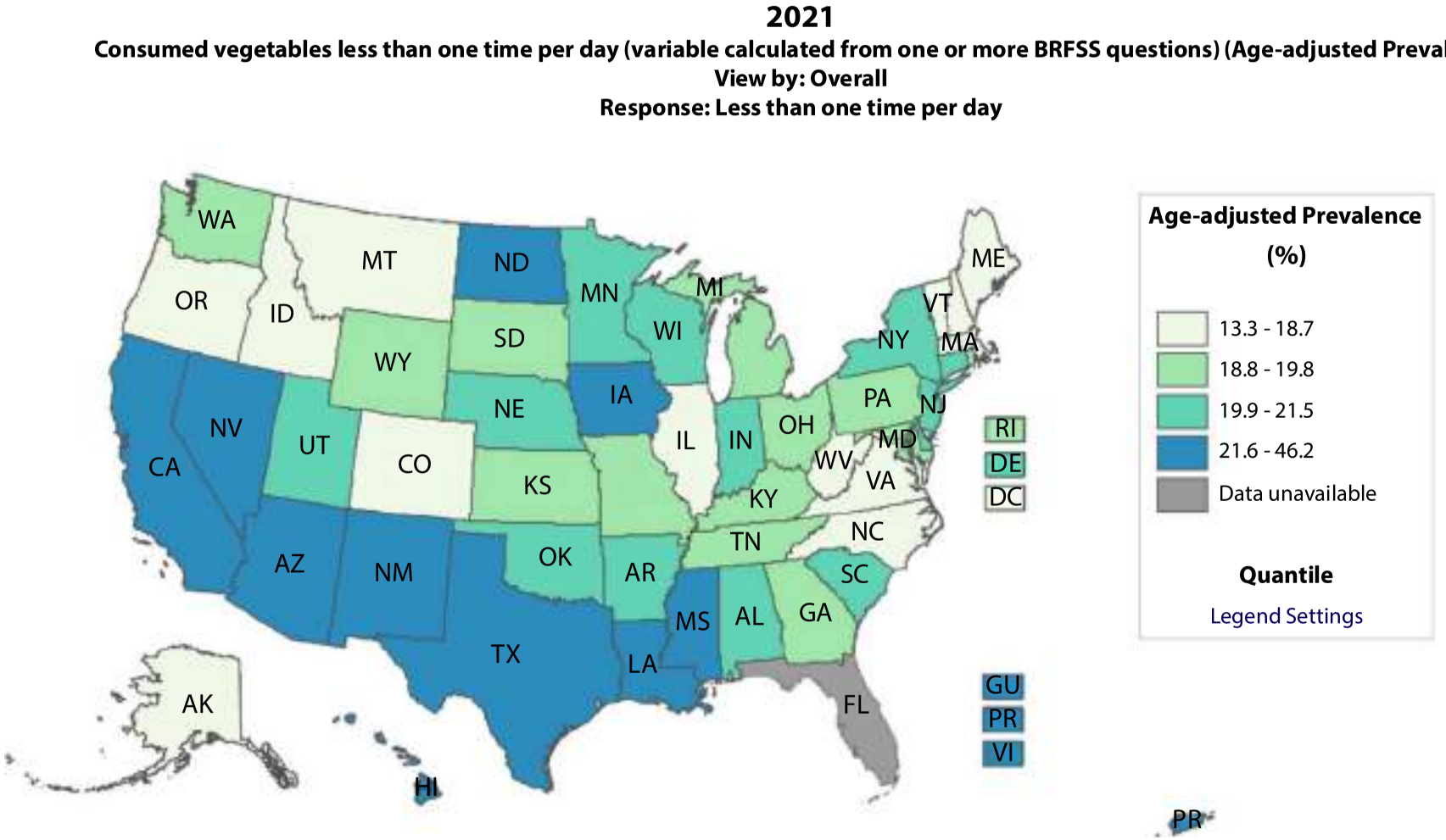


FIGURE 130.8 State-specific consumption of vegetables among adults 18 years and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

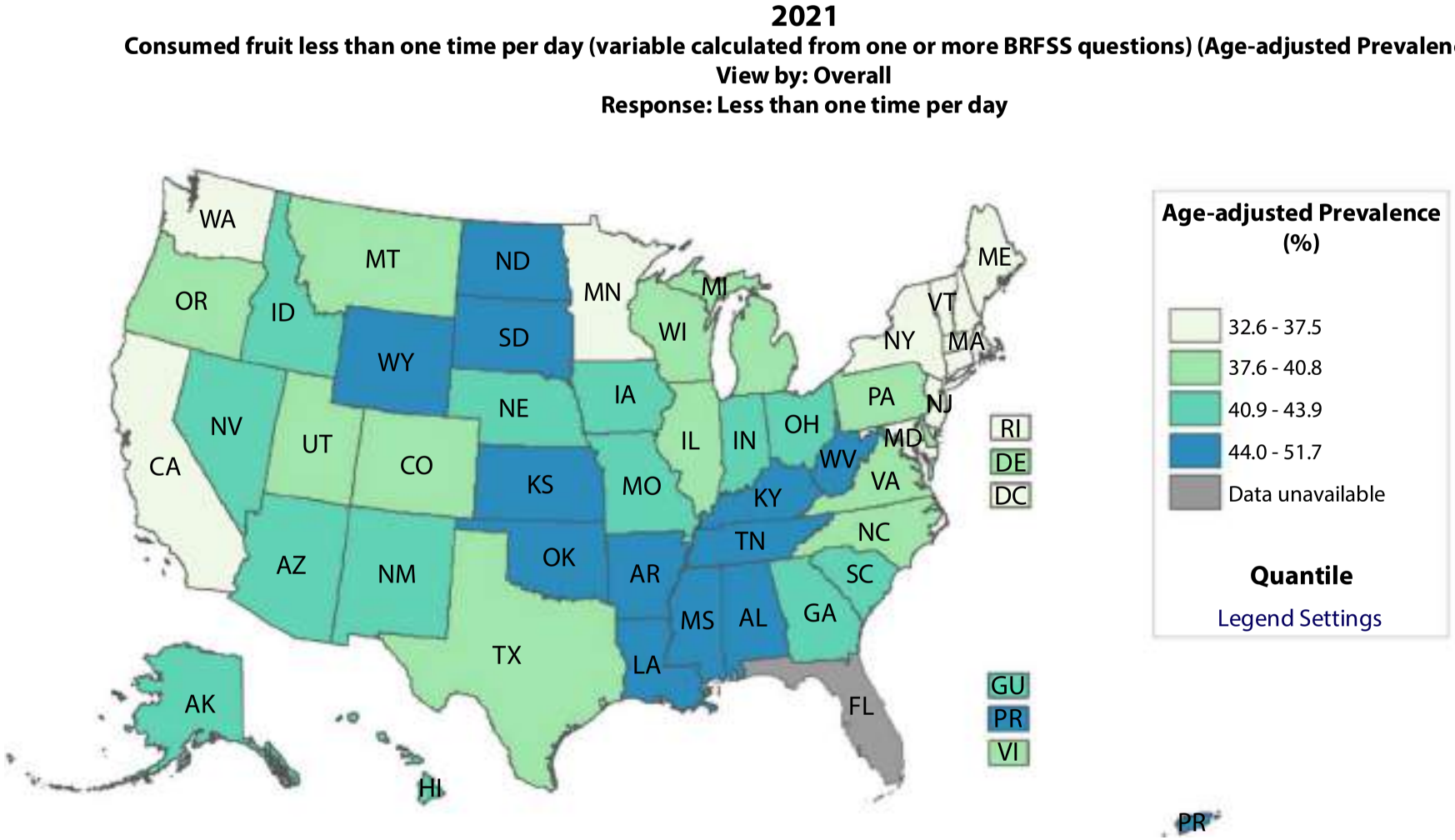


FIGURE 130.9 State-specific consumption of fruits among adults 18 years and older, United States, 2021 (source: https://www.cdc.gov/brfss/brfssprevalence/index.html).

pandemic itself created challenges in conducting the survey that may affect estimates of the uninsured, due to reduced response rates and a temporary shift from an in-person survey to a telephone survey. Compared with other Americans, the uninsured disproportionately represent Black or Latino populations; younger adults; those with low incomes; or live in states that have not expanded Medicaid.[17]

A primary ACA objective is the development of alternative payment models. Currently, there are more than 20 ongoing value-based payment programs that often overlap with one another.[18,19] This has created a challenging environment, especially for healthcare organizations to make decisions about participation, care redesign, and investments.[18] This environment also limits the rigor of model testing. Isolating the effect of a model might be nearly impossible, leading to a situation in which singular models are not deemed successful despite contributing to system-level improvements in quality and cost.[20] As has been stated by Navathe et al.,[20] "Some of these programs have evolved from early CMS projects and ACA provisions, like the Accountable Care Organization (ACO) and bundled payment programs, but the sheer breadth of such programs can be perplexing for providers". Hence, even though there have been several financial incentives, or penalties, these have apparently had little documented effect on healthcare delivery itself but have created healthcare provider exasperation and disappointment.[21]

The most impactful programs for lifestyle medicine probably relate to Primary Care Transformation, episodic care models, and initiatives focused on the Medicare and Medicaid populations. The ACA has substantially increased access to care and coverage of preventive services without cost-sharing for millions of Americans.[22] Many preventive services including vaccinations, well-child visits, screening for HIV and sexually transmitted infections, HIV pre-exposure prophylaxis, contraception, and cancer screening are required to be covered by most group and individual health plans and for many Medicaid beneficiaries without cost-sharing. Such expanded access to recommended preventive services has increased the number of people covered through both private health insurance and Medicaid expansion under the ACA.[22]

The analyses of recent CMS data indicate that more than 150 million people with private insurance (58 million women and 37 million children) currently are able to receive preventive care services without cost-sharing under the ACA.[22] Additionally, approximately 20 million Medicaid adult expansion enrollees and 61 million Medicare beneficiaries can potentially benefit from the ACA's preventive care services provisions.[22] As a result of these non-cost-sharing benefits, evidence from impact studies of the ACA has revealed an increase in colon cancer screening, vaccinations, use of contraception, and chronic disease screening inclusive of opportunities to identify the lifestyle contribution to these diseases/conditions.[22]

The potential success of the integration of lifestyle medicine into the fabric of healthcare in the US hinges on the following important steps: 1) lifestyle healthcare providers need to identify opportunities and incentives to attract previously uninsured Medicaid enrollees as well as privately insured patients to better prevent and manage chronic diseases/conditions; 2) lifestyle healthcare providers need to be better equipped to deliver lifestyle medicine services to their patients; 3) lifestyle healthcare providers need to partner and successfully refer their patients to existing community-based programs and services designed to reinforce behavioral and lifestyle changes among their patients; and 4) lifestyle health providers and their associates should be equipped to assist patients with navigation of the healthcare delivery system with a goal to improve access to the correct care when needed.

Several CMS programs have been implemented to expand the use of preventive medicine to promote health and wellness. The most visible of those programs has increased Medicare payments for some preventive services up to 100% of the actual charge or fee schedule rate (e.g., obesity prevention services).[23] In 2017, the Comprehensive Primary Care Program was designated as the Comprehensive Primary Care Plus (CPC+) program for regionally based multi-payer reform.[24] The CPC + program created a payment structure that includes a care management fee as well as a performance-based incentive beyond fee-for-service payments. This structure continues the fee-for-service payment model while providing funding to expand care management resources that are expected to improve the quality of care provided through the performance-based incentive.

The focus on primary care for the delivery of preventive services is critical to the success of healthcare reform.[25,26] The ACA takes important, but modest, steps to address critical primary care needs: payment reform, workforce training, transformation of practice, and expansion of the primary care safety net. ACA provisions included the establishment of a National Health Care Workforce Commission, increased support for workforce training (Title VII and the Prevention and Public Health Fund), cultural competency training, enhanced payments, expansion of community health centers, and piloting of new care models. ACA provisions have also provided Medicare bonus payments to primary care physicians and eliminated differences in payments between Medicaid and Medicare for primary care services. It further provides Medicare bonuses to primary care physicians who work in shortage areas, thereby helping to minimize geographical disparities in resources available to patient populations with social disadvantage. These reforms could also conceivably reduce de facto segregation by insurance type within healthcare systems that receive federal funding, but regulations prohibiting intra-institutional segregation of care may be needed. Modest increases in payments alone will not be sufficient to address the current geographical distribution of primary care physicians, much less avert a primary care shortage.[27]

The ACA legislation took several steps to promote the quality of healthcare service delivery. A key component of that was the establishment of the Patient-Centered

Outcomes Research Institute (PCORI). This non-governmental entity has been charged with setting research priorities and promoting research that provides a clinical evidence base to help providers and patients make informed healthcare decisions; to assist healthcare delivery systems in providing evidence-based, efficient, and safe healthcare; to ensure that evidence is dependent on and applied to racially and ethnically diverse and geographically distributed communities; and to develop broad prevention and screening strategies that promote health across such diverse populations. Much reporting about the PCORI research agenda has focused on the term "comparative effectiveness research" (CER). Although the foundational basis for effectiveness research has existed for over half a century, the legislation envisioned a far more expansive and inclusive role for CER. In addition to comparing therapeutic treatments, CER has been conceptualized as the rigorous application of science to evaluate and compare health outcomes, clinical effectiveness, and risks and benefits of a much broader set of interventions—from new healthcare delivery methods to medical procedures and devices to drugs and biologicals, and to integrative health practice strategies, as well as prevention strategies. Moreover, the legislation directed that CER must include broad participation across the nation to create a representative evidence base that could help identify and address health disparities and inform decisions by patients in special population groups. Comparative effectiveness research is expected to extend beyond academic health centers (AHCs) and teaching hospitals to include research in partnership with community-based care settings and practice-based networks as well as with community-engaged research, which provides for engagement with communities as partners in research.[28] Such a focus on CER and similar methods that embody rigorous science to determine what interventions/treatments work best for whom, in what settings, and under what circumstances supports lifestyle medicine by translating preventive care and disease management evidence into changes in practice and behavior at the level of individuals, populations, and healthcare delivery systems.[29]

Understanding the role of employers is central to understanding the US healthcare system. At present, almost two-thirds of American citizens under the age of 65 are covered by an employer-sponsored health plan. Some thought that the employer penalty could result in the sudden disappearance of employer-sponsored health insurance,[30] but there has not been an erosion of employer-sponsored coverage since ACA was implemented.[31] The historic linkage of health insurance to employment for over 80 years has presented a problem of access to affordable healthcare services for unemployed individuals, but the private sector system does promote innovation and value through its influences on competing providers.[32,33] Furthermore, the availability and generosity of healthcare coverage for Americans ultimately depends on the economic fortunes of private companies. Government-sponsored health insurance relies on individual and corporate taxes, which are directly linked to employment and economic growth. The less tax revenue collected by the federal and state governments, the greater will be the necessity to ration care among the population that relies upon a government-sponsored program.[30]

Value-based purchasing and pay-for-performance represent employer-initiated innovations that Medicare used on an experimental basis.[34] The Medicare Physician Group Practice (PGP) Demonstration introduced "shared savings" as a mechanism to reduce costs and improve the quality of care provided to its beneficiaries. Participating physician group practices received regular fee-for-service reimbursements but were also eligible to receive an additional performance payment if a CMS-specified cost target was achieved (i.e., an 80% share of the difference between the actual cost of services provided and a risk-adjusted spending trend for treatment of the given condition in each market). The Medicare PGP Demonstration served as the model for a provision of the ACA legislation that established the ACO as a mechanism for providers to become eligible for participation in the Medicare Shared Savings Program.[35,36]

Although the ACA legislation intended to reduce the cost and improve the quality of healthcare for all Americans, CMS payment policies have historically resulted in cost-shifting to private payers. An analysis of the PGP Demonstration suggested that most provider groups would experience a financial loss because of participation in a similar shared savings program, which poses a risk to the entire value-based purchasing movement initiated by employers.[37] The creation of ACOs by dominant providers through mergers and acquisitions could drive up costs for private payers. Market consolidation can also have an adverse effect on the ability of private payers to obtain the service quality data that are essential to value-based purchasing.[35] Although the inclusion of a hospital in an ACO is needed for optimal coordination of healthcare services, a potentially serious conflict of financial interests exists between physician groups and hospitals about the necessity for hospitalization of many patients. Some experts believe that hospital-centric provider organizations adversely affect the potential for physician groups to benefit from a shared savings program[36] and that they will not serve the best interests of the country.[38]

Modification of patient behaviors is central to the practice of lifestyle medicine and primary prevention, but the patient's responsibility to ensure that a high degree of value is derived from clinical medical services has only been emphasized by employer-sponsored health plans. Patient consumerism is promoted by high-deductible health plans that are combined with health savings accounts to incentivize healthy behaviors, and through employer-sponsored worksite health management programs. Because impaired glucose metabolism is the primary underlying cause of numerous high-cost conditions, regular physical activity and healthful dietary behaviors can profoundly influence employers' self-insured health plan costs.[39,40] Because poor employee health decreases corporate profitability through high health plan costs, work absenteeism, and suboptimal

productivity, employers have a strong interest in promoting personal responsibility for healthy lifestyle choices and informed utilization of healthcare services. Unless commercial insurance and government-sponsored health plans incentivize healthy behaviors and healthcare consumerism, no type of provider-payment model alone is likely to produce long-term control of cost escalation. Rather, a conscientious effort to identify key policies and environmental supports for healthy lifestyles that are community-based and accessible to all Americans needs to coincide with provider-based training and incentives to integrate the practice of lifestyle medicine into healthcare with an overall result in improved population health.[41]

Years of fee-for-service reimbursement have produced a provider-centered and process-oriented system for the delivery of clinical services that is highly resistant to change. Both CMS and commercial insurance pay-for-performance initiatives have defined quality of care based on process-of-care measurements (e.g., provider adherence to clinical practice guidelines) rather than patient outcomes.[34,42] Value should be defined as the outcomes achieved per dollar spent. Measuring the total costs over a patient's entire care cycle and relating them to the outcomes realized from the collective set of services could lead to future reallocation of spending among the various types of services. For example, greater frequency of physical activity among obese individuals has been documented to produce greater claims costs related to the treatment of musculoskeletal disorders.[43] Primary and preventive care of obese patients might provide greater value (i.e., better long-term outcomes at lower cost) through substantial involvement of a clinician who possesses expertise in exercise prescription for the avoidance of musculoskeletal disorders or the prudent referral of patients to community programming and/or fitness specialists. Different patient populations (e.g., obese children, healthy adults, patients with multiple chronic conditions) will need different bundles of services, which require different types of outcome measurement. Condition-specific outcome measurement instruments are needed, and no single outcome can fully capture the results of care.[42] The outcomes that are most important to the patient should provide the numerator for the value equation, and the denominator should be the total cost of all services that jointly determine success in meeting the patient's needs.[42]

Although the term "patient-centered care" is widely used, the existing provider-centered and disease-oriented healthcare system often fails to devote sufficient attention to the needs, concerns, and preferences of patients. Patient-centered care involves efforts to inform, educate, and communicate with individual patients, shared decision-making, and continuous advocacy of injury and disease prevention in the context of understanding the patients' living, learning, working, and playing environments. Clinical care is delivered to one patient at a time, but a "population health" perspective is essential for the improvement of the quality of care that is provided to individual patients. Identification of the needs of specific patient populations can be achieved through systematic collection and analysis of patient-centered outcomes data, but it is difficult to accomplish without the utilization of appropriately designed health information technology (HIT). Unfortunately, the current organizational structure of the healthcare system and prevailing financial incentives have focused HIT development on systems for the documentation of billable events rather than the collection of data to support continuous quality improvement.[44] The Health Information Technology for Economic and Clinical Health (HITECH) Act clearly supports the development of a mechanism for the secure exchange of electronic data between providers, but such a platform is not likely to facilitate meaningful improvements in healthcare value without financial incentives that reward patient-centered care.

Support for lifestyle medicine has been evident in the CMS recognition of obesity as a disease in 2014, thereby creating the potential for Medicare coverage of obesity-related treatments.[45] Despite Medicaid being a state-administered program, the CMS decision influenced several states that extended their Medicaid coverage to include both prevention and treatment of obesity. West Virginia[46] and Tennessee[47] offer both full and partial reimbursement for Weight Watchers© programs. Another set of policy supports for lifestyle medicine was initiated in early 2006 through the National Committee for Quality Assurance (NCQA), which approved Healthcare Effectiveness Data and Information Set (HEDIS) measures of health plan performance regarding the measurement of physical activity and BMI as "vital signs" among adults, children, and adolescents. In addition, nutrition and physical activity assessment and counseling for adults, children, and adolescents were also recommended. However, even with the broad implementation of such assessment and counseling interventions, it is clear from recent studies that this alone is not sufficient to facilitate effective and sustained health behavior change among most patients.[48] Most US health plans use HEDIS measures to monitor provider performance that is reported to purchasers of healthcare plans and consumers.[49] The new chronic disease prevention and obesity-related measures target improvements in providers' practice behaviors related to chronic disease and obesity prevention, care, and treatment. Chronic disease and obesity-related HEDIS measures demonstrate the role that a policy intervention can have on preventive care practice behaviors among providers.[49] The ACA expansion of Medicaid appears to have created an improvement in the care for chronic disease care. The states with expanded Medicaid enrollment have found improved adherence to medication use among patients with chronic conditions, increased communication with physicians, and improved health status.[50]

Current policies and practices relating to the delivery of healthcare do not provide adequate incentives, monetary or otherwise, for providers to integrate lifestyle medicine and preventive care into their existing practices.[50,51] Preventive care advocates emphasize the potential cost savings that the US healthcare delivery system could realize but the likely impact has been questioned by many within the medical

community.[51,52] However, critics of preventive care expansion often confuse early detection and treatment with primary prevention and public health efforts, with the latter appearing to provide the best mechanisms for cost savings and prevention of premature morbidity and mortality.[53,54]

As with any governmental legislation, questions about the impact on the public are critical for determining the success or failure of its implementation. The true impact of the ACA will not be known for years to come, but there is substantial data to support the arguments of both its advocates and its critics. For low-income adults, access to primary care, affordability of care, preventive visits, screening tests, and self-reported health have all improved because of the ACA.[50] The reduction of patient cost-sharing for many preventive services has also had mixed results. Research has documented a modest increase in the use of some preventive services.[51–53] However, the early results for critical preventive screening services such as colonoscopy and mammography have been less positive.[54] Administrative barriers, such as a lack of accurate coding for a preventive service, patients' unawareness of policy changes, and insufficient cost-sharing, may be responsible for a lack of increase in preventive service utilization.[54]

With the advent of the 12th anniversary of the ACA, traditional fee-for-service reimbursements to individual providers are unlikely to continue. Should an optimal balance be achieved between government-mandated initiatives and private-sector influences on the US healthcare delivery system, perhaps the cost, quality, and access problems can be collectively resolved. In any case, physicians and other healthcare practitioners who are committed to the delivery of patient-centered clinical care should welcome payment reform that rewards excellence and facilitates the realization of optimal patient outcomes. The transition from fee-for-service to pay-for-performance offers the potential to expand healthcare equity by rewarding providers for high-quality care.[55] However, a reversal in the expansion of healthcare access that the ACA has created, especially among current Medicaid enrollees, would likely have an adverse effect on healthcare equity.[56]

Policies and evidence-based interventions and environmental supports outlined in this chapter identify primary prevention strategies that hold significant promise for the prevention of premature suffering from disease and early death. In addition, the outlined practices can greatly benefit the patient with an existing chronic condition by effectively using lifestyle medicine to manage chronic disease/conditions such as obesity, coronary heart disease, type 2 diabetes, hypertension, and stroke.[57] The future of this field will evolve with payment reforms that will drive care transformation and greater community engagement on the part of the healthcare system. Lifestyle medicine providers need to embrace these opportunities as they develop to align patient needs with the availability of financial resources for payment of clinical services and linkages to community resources that will optimize health for all.

CLINICAL APPLICATIONS

Action	Tools	Comments
1. Engage primary care providers in changing their practice patterns.	Practice in teams; implement and follow professional medical guidelines.	Engaging patients in primary care and lifestyle medicine for the prevention and management of chronic conditions requires clinicians to work in interprofessional teams and implement team-based care.
2. Encourage patients to take an active role in their care through shared decision-making and communication about self-management, medications, and lifestyle changes.	Implement and train all providers in the use of the electronic medical/health record (EHR).	Patients can contribute to the design of the practice and share their experiences of medical visits and access to lifestyle education.
3. Connect EHRs across organizations and spread the implementation.	Clinical care coordinators/navigators; health education videos/presentations in waiting rooms and designated office space.	Hire ongoing health information technology support staff to maintain the functionality of an EHR system, including changing and upgrading the software and incorporating new information on patient management.
	ACOs can help practices adapt EHRs to connect with hospitals and other providers in the ACO that may not be on the same platform.	
4. Standardize lifestyle vital signs within EHR.	ACLM/ACPM guidelines. ACSM/AMA EIM solution.	Training and CME in lifestyle medicine vital signs, patterns of referral to community resources.

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131 Policy and Environmental Supports for Physical Activity, Active Living, and Healthy Eating

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KEY POINTS

- Physical inactivity and unhealthy eating are significant, independent risk factors for the major chronic diseases responsible for premature morbidity, disability, and death in the United States and globally.
- Evidence from community-wide and multifaceted approaches targeting the reduction of unhealthy behaviors and the promotion of healthy behaviors is necessary to improve population health.
- Interventions that increase physical activity are a critical component in the prevention and management of chronic diseases and include social and behavioral approaches; informational approaches and community-wide campaigns; and policy and environmental approaches.
- Environmental supports, such as improved access to healthful foods, access to transportation, online grocery shopping, healthful vending, and behavioral economics are promising strategies for promoting healthy eating.
- Policy and environmental approaches to promoting physical activity and healthy eating have been demonstrated to be effective and significant reinforcers for physicians and other healthcare providers who counsel and advise their patients to be more physically active and to eat more healthfully.
- School settings have been shown to provide effective opportunities to increase physical activity and healthy eating among children and youth.
- Worksites have repeatedly been shown as places where physical activity and healthy eating can be successfully promoted among employees.
- Community organizations can often provide physical activity facilities and programming.
- Public recreational facilities and parks provide places to be physically active and often offer programming for a broad cross-section of participants.
- Environmental infrastructure, both built and natural, provides opportunities for people to participate in active transport, active sports, and recreation.
- Food and nutrition security are critical in promoting healthy eating.
- Individuals and communities experiencing food insecurity may adopt unhealthful coping strategies that, over time, can lead to poor physical and mental health outcomes, such as obesity, diabetes, and cardiovascular disease.
- African American/Black, Indigenous, and people of color experience food insecurity at disproportionately higher rates, making it more difficult for these individuals to consistently exhibit healthful food behaviors.
- Federal nutrition policy (e.g., menu and food labeling) and the *Dietary Guidelines for Americans* provide useful guides for healthy eating patterns.
- Lifestyle medicine clinicians have a key role to play in strategic alliances to promote healthy behaviors and environments, and there is growing recognition that involvement in these types of efforts is a professional responsibility.
- To create policy, systems, and environmental changes that address social determinants of health, it is important to utilize approaches that build on community strengths and acknowledge the interdependence of individuals, their social networks, and the community structures, norms, cultures, histories, and values.

131.1 INTRODUCTION

The burden of chronic disease in the United States is overwhelming. To address this burden, researchers and practitioners are paying increasing attention to environmental and policy interventions.[1,2] Of particular interest are interventions to increase physical activity, a critical component in the prevention of chronic disease. Community-based approaches to promoting physical activity were initially assessed systematically for effectiveness by Kahn et al.[3] and

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TABLE 131.1
Community Interventions to Promote Physical Activity

Informational approaches

- **Community-wide campaigns:** These large-scale, highly visible, multicomponent campaigns direct their messages to large audiences using a variety of approaches, including television, radio, newspapers, movie theaters, billboards, and mailings. ***Recommended with strong evidence***

Behavioral and social approaches

- **Individually-adapted health behavior change programs:** These programs are tailored to a person's specific interests or readiness to make a change in physical activity habits. Teaching behavioral skills such as goal setting, building social support, self-rewards, problem solving, and relapse prevention, the programs help people learn to incorporate physical activity into their daily routines. ***Recommended with strong evidence***
- **School-based physical education (PE):** This approach seeks to modify school curricula and policies, to increase the amount of time students spend in moderate-to-vigorous activity while in PE class. Schools can accomplish this either by increasing the amount of time spent in PE class or by increasing students' activity levels during PE classes. ***Recommended with strong evidence***
- **Social support interventions in community contexts:** The goal of this approach is to increase physical activity by creating or strengthening social networks. Examples include exercise buddies, exercise contracts, and walking groups. ***Recommended with strong evidence***

Environmental and policy approaches

- **Creating or improving access to places for physical activity combined with informational outreach:** Examples include building walking/biking trails or making it possible for people to use exercise facilities in community centers or in the workplace. Informational outreach includes activities such as training on equipment, seminars, counseling, risk screening, and health workshops. ***Recommended with strong evidence***
- **Point-of-decision prompts to encourage stair use:** These signs are placed by elevators and escalators and encourage people to use nearby stairs instead. ***Recommended with sufficient evidence***
- **Community-scale urban design land use policies and practices:** Examples involve the efforts of planners, architects, engineers, developers, and public health professionals to change the physical environment of urban areas consistening of several square miles or more to support physical activity. ***Recommended with sufficient evidence***
- **Street-scale urban design and land use policies:** Examples involve the efforts of planners, architects, engineers, developers, and public health professionals to change the physical environment of small geographic areas to support physical activity. ***Recommended with sufficient evidence***
- **Built environment approaches combining transportation system interventions with land use and environmental design:** Examples include combining policies improving street connectivity, sidewalk and bicycle infrastructure, and public transit access with policies or designs enhancing access to parks and recreational facilities. ***Recommended with sufficient evidence***

Heath et al.[4] Within these systematic reviews, the authors identified three major domains of community-based physical activity interventions. These domains include behavioral/social, informational/community-wide campaigns, and policy/environmental approaches to promoting physical activity in community settings (Table 131.1).[3–5]

In addition to physical inactivity's contribution to the burden of chronic disease in the United States and throughout the world is the role of unhealthy eating, which can take the form of overnutrition or undernutrition.[6] Consuming food is a matter of survival for all human beings and consuming nutritious foods is more complicated than one might imagine. Disparities in both healthy eating and nutrition-related chronic diseases (e.g., obesity, diabetes, cardiovascular disease) are often influenced by various socioecological factors (e.g., food security) outside of an individual's direct control.[7] Food environments should promote healthful eating behaviors via supportive policies, which will improve health outcomes, especially among populations disproportionately affected by chronic diseases.[8]

Successful and sustainable changes have been demonstrated at local and even national levels.[9] The North Karelia Project, for example, demonstrated that relentless campaigning and partnering with local community and social influencers can reduce smoking, cholesterol, blood pressure, and cardiac death outcomes by changing health behaviors over the course of the last 50 years.[9] This model of broad-scope intervention is currently being implemented by organizations like the Blue Zones Project in the United States to help communities align community residents, organizations, institutions, and agencies to impact policies, places, and people using evidence-based interventions, media campaigns, and data tracking to promote health and wellness in the context of local culture.[10]

The current chapter seeks to identify for the lifestyle medicine practitioner evidence-based interventions that address policy and environmental supports for promoting physical activity and healthy eating that can reinforce a healthy lifestyle through active living and healthful eating assessment, counseling, and referral.

131.2 COMMUNITY-BASED APPROACHES TO PROMOTING PHYSICAL ACTIVITY

Adults in developed countries report many barriers to participation in regular physical activity. One commonly cited factor is a lack of access to facilities or safe places for physical activity.[11] Healthcare practitioners can encourage and even prescribe physical activity for their patients, but unless individuals have a place in which to be active, they are often unable to follow such recommendations. Creating or enhancing access to places for physical activity is an example of a policy or environmental intervention.[3,12] Such interventions include creating/enhancing existing walking/biking trails or exercise facilities and increasing access to existing facilities by reducing barriers to their use (e.g.,

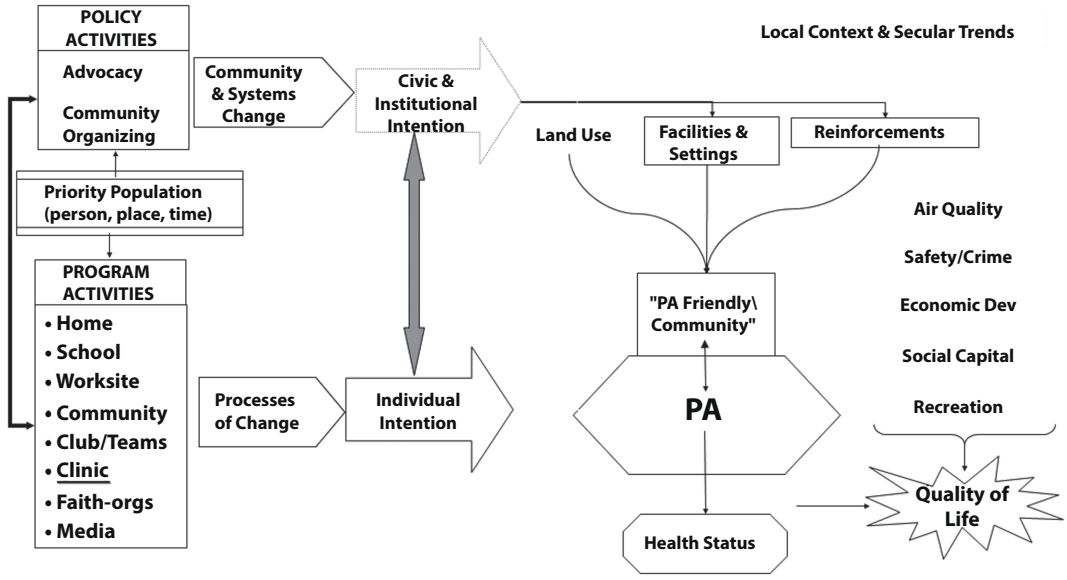


FIGURE 131.1 Community-based physical activity promotion logic model (Dodson EA and Heath GW. Policy and environmental supports for physical activity and active living. In: *Lifestyle Medicine*, 3rd Edition, pp 1367, Figure 123.1 [Rippe JM, editor]. CRC Press, Taylor & Francis Group, LLC, 2019).

increasing safety or enhancing affordability). These efforts often include personnel and/or participant training, social support, and further integration of these structures, facilities, and programs into participants' communities. Policy and environmental approaches for promoting physical activity are predicated on the basis of establishing a foundation on which the concept of a "physical activity-friendly" community/space is created, whereby intersectoral efforts of physical activity programming, promotion, and civic action can yield greater success among community residents.[13] Figure 131.1 provides a detailed logic model illustrating the key intersectoral steps and components of a comprehensive approach to promoting physical activity within the context of a local community. Although such things as civic and individual intent may vary across communities/settings, the principles of social support and intentional linkages between the clinical setting and community support for physical activity appear to be necessary to bring about improvements in a population's level of physical activity.[12,13] An exemplary intervention that embodies such a model, albeit on a smaller scale, is described by Linenger et al.[14] It included new infrastructure (i.e., bike paths), access to facilities (e.g., expanded hours of operation, lighted and integrated paths), and improved programming on a residential US Navy base.[12] More recently, a systematic review of adult physical activity behaviors and their relation to green spaces found that the presence of outdoor fitness equipment promotes physical activity.[15] Multiple studies have documented that developing or installing such infrastructure is reasonable from a cost perspective.[16–18]

Another effective strategy within the domain of policy and environmental approaches has been successfully implemented in Latin America.[19–22] This strategy consists of community-wide policies and planning that place physical activity within the public policy agendas of communities, emphasize the promotion of physical activity guidelines, provide organizational incentives, address institutional and environmental barriers, and use media effectively.[23] Two examples of this promising intervention approach are described by Ribeiro et al.[23] and Reis et al.,[19] who report on the effects of community physical activity programs in Recife, Brazil, and Curitiba, Brazil, respectively. These programs, created in response to the burden of chronic diseases among local populations, involve the dissemination of information about physical activity, assessments of current lifestyle choices, and physical examinations. Concurrent with these interventions, weekly radio programs are broadcast, physical activity classes are offered, strength training equipment is made available, and various races, games, and dance events are sponsored to provide incentives for physical activity.[19–23]

Policy- and environmental-based interventions that are designed to create or provide access to places where people can be physically active often involve the combined efforts of worksites, schools, coalitions, government agencies, and community members.[3] These interventions are characterized by providing improved access to existing exercise facilities, such as fitness centers (both proprietary and non-profit), community centers, and walking/bicycle trails, and by providing access to school grounds.[3,4] In addition to promoting access, many of these interventions incorporate components such as supervision of equipment use, health behavior education and counseling, risk factor screening, referrals to health services, buddy systems, transportation system interventions, and promotion of facility use.[24,25]

A more detailed discussion of each of these areas of intervention follows.

131.3 PLACES THAT MAY PROMOTE REGULAR PHYSICAL ACTIVITY

131.3.1 Schools

Schools present an excellent site for interventions to increase physical activity in children and adolescents. In particular, the Community Preventive Services Task Force (CPSTF) has recently found sufficient evidence to recommend two new types of interventions. Classroom-based physical activity breaks allow teachers to integrate short bursts (lasting four to ten minutes) of moderate-to-vigorous physical activity into daily classroom activities several times per day. Such breaks have been shown to increase student daily physical activity and educational outcomes. Similarly, classroom-based, physically active lesson interventions are recommended to increase time spent engaging in daily physical activity for school-aged children. These lessons allow teachers to incorporate physical activity directly into lessons taught. They may be conducted inside or outside and typically last 10–30 minutes.[26]

School physical education and health education curricula now provide methods of promoting youth physical activity, and many of these strategies have been shown to be effective.[27–29] In particular, systematic reviews have resulted in the recommendation of enhanced school-based physical education, wherein curricula are modified to ensure the engagement of K–12 students in longer periods of moderate- or vigorous-intensity physical activity during physical education classes. These redesigned classes may be combined with other interventions at the school or community levels, including those encouraging family involvement, education about physical activity, and increased opportunities for physical activity through community partnerships.[30]

However, currently, within the United States, a paradox exists in many schools. Although school buildings and grounds may be the most widely available public resources for physical activity within the community, they are often underutilized. Studies of students' engagement in physical activity during leisure time at school (e.g., during lunch, before or after school) reveal that few students use this time to be physically active.[31,32] Many studies have examined associations between physical activity and school physical and social environments. A recent review of these studies highlights several factors associated with increased physical activity in schools: the presence of dedicated spaces for physical activity (e.g., sports fields, gyms); access to sports equipment (although these associations were present only for boys); safe, interesting, and newer playgrounds; and sufficient space for physical activity.[33]

Most schools have policies in place that restrict access to school grounds by students and community members outside of school hours. Thus, these abundant public resources are underutilized; further, these policies may have the most negative impact on low-income communities, which commonly lack other places for safe physical activity. There are several community advocacy groups around the country seeking solutions to this problem. Among them is the Denver Learning Landscapes Alliance.[34] This group seeks to transform school playgrounds and surrounding neighborhoods by designing multidimensional school playgrounds that offer elements of public parks and focus on low-income communities.[32] The addition of more pleasing landscapes encourages participation and park use and has the potential to improve physical, mental, and social well-being.[35,36]

Another approach to increasing the usability of existing spaces for physical activity by community members involves the creation of shared or joint use agreements. These agreements describe costs and risks associated with community use of spaces owned or managed by schools, universities, community centers, faith-based organizations, and so on, and define the terms for their shared use. Such agreements have been implemented in multiple states and may be a way to improve access to places for physical activity, especially among communities with low incomes.[37]

Active transport by walking and cycling to and from school can provide substantial physical activity for children and youth.[38] This has been illustrated by a recent evaluation of the Safe Routes to School program.[39] In 2016**,** advocacy efforts by the Safe Routes to School National Partnership resulted in a revision of transportation performance measures by the US Department of Transportation dictating that performance will be measured by the safety of individuals rather than the speed at which cars travel.[40] As part of its mission, the Safe Routes to School program leverages available federal dollars set aside to promote cycling and pedestrian activities in communities through assistance from state departments of transportation. For example, the California Department of Transportation provided $66 million in funding over three years for Safe Routes to Schools grants to 270 schools.[40] Such funding was used to make physical improvements, such as sidewalk and bike lane construction or enhancements, traffic calming, and street crossing improvements around schools. Some schools added promotional and educational programs to encourage people to use the improved streets. In Marin County, CA, walking to school increased by 64% and biking increased by 114% after a combined intervention.[41] A statewide evaluation of ten schools found that students who passed by the improvements on their way to school increased walking and biking by 15% compared with 4% for those who did not pass the improvements.[42]

131.3.2 Worksites

Many employed adults spend at least half of their waking hours at work, where the pressures of work may contribute to poor activity behaviors; thus, worksites are natural places for physical activity promotion.[43,44] Further, while the number of employees working in sedentary jobs has increased, those in physically active jobs have decreased over time.[44] Meanwhile, sedentary behavior is an independent risk factor for chronic disease and mortality.[45–47] This new reality

highlights the importance of utilizing the worksite as an intervention site for physical activity promotion. A particularly promising type of worksite health promotion strategy involves environmental and policy changes that may assist employees in making healthful choices at work. Research indicates that the presence of worksite supports for physical activity (e.g., on-site exercise facilities, showers, subsidized health club memberships, time or breaks for physical activity during the workday) can increase the likelihood that employees will engage in physical activity and meet national physical activity recommendations.[1,2,43,48,49]

Across worksites, there is wide variation in the types of work performed and the settings in which employees conduct their work. Thus, worksite physical activity interventions that increase physical activity in those employed in manufacturing may not be most effective for those in healthcare or finance. One recent study examined which worksite supports for physical activity were available in various industries and occupations, and which combinations of these supports were associated with the likelihood that employees would meet physical activity recommendations.[50] As part of a large, multi-city study in Missouri, adult participants employed more than 20 hours per week outside the home were surveyed about their occupation and activity behaviors.[51,52] Researchers asked about 16 different worksite supports for physical activity, including the presence of bike storage, availability of showers, incentives to walk/bike to work, and flexible time during the workday for physical activity. Results indicated a wide variety in the availability of worksite supports for physical activity, depending on the type of industry or occupation, suggesting great disparity in access to physical activity supports at worksites. Further, where the availability of one support for physical activity did not always increase the likelihood that employees would meet physical activity recommendations, the combination of certain pairs of support did. For example, when employees have incentives to bike and a place to safely store their bikes, they may be more likely to bike to work. If employees have flexible time during the workday for physical activity combined with exercise facilities, maps suggesting walking routes around the worksite, or showers, they may have reduced barriers to incorporating physical activity into the workday. Of note is the fact that many of the worksite supports examined were of low or no cost to implement (e.g., flexible time for exercise, maps of worksite-adjacent walk/bike routes), hopefully removing one perceived barrier (cost) from employers seeking to encourage physical activity in employees.

Watanabe and colleagues described a recent randomized trial in which the effects of a multi-component worksite intervention were tested in three worksites.[53] Intervention worksites were allowed to select from a variety of intervention programs in which they participated for three months. Intervention options included stair-use prompts, on-site exercise programs, and individual competitions, among others. Control worksites (N = 5) were offered feedback and usual care occupational health services. Physical activity, the primary outcome, was measured at baseline, three months, and six months. The overall physical activity level of employees in the intervention sites increased compared with those of employees at control sites. The proportion of employees achieving a high level of physical activity (defined by levels of physical activity intensity and frequency) increased from 13% at baseline to 21.5% at six months.[53] This flexible intervention showed a positive effect on physical activity among participants and is likely feasible for broad application to other, similar worksites.

131.3.3 Public Recreation Facilities and the Built Environment

Public parks and recreation facilities are widely used, with about 80% of the population making some use of municipal facilities and a smaller but substantial percentage using park programs and services.[54] A major national study of neighborhood parks was conducted in 2016, wherein a representative sample of 114 parks in major US cities was observed and park administrators interviewed.[55] Walking loops and gymnasia were especially well utilized. Parks in low-income neighborhoods were utilized less than those in high-income neighborhoods, where more programs and supervised activities were available.[54] Another recent review of park characteristics, use, and physical activity found that more males than females used parks, older adults were less likely to use parks, and youth were generally more active in parks than adults.[49]

The evidence is strong that the contribution of public recreation facilities and programs to physical activity could be enhanced by optimizing the design of facilities to support physical activity for various population groups and promoting the use of the facilities.[54–56] The potential impact of improved park design was indicated by an Australian study that found adults with very good access to large and attractive public open spaces were 50% more likely to be regular walkers than those without such access.[57]

The research is strong that the presence of parks may enhance physical activity;[58] further, there is some evidence that park and recreation professionals are enthusiastic about participating more in promoting physical activity. A survey of 44 recreation center directors in San Diego County found that most center directors wanted to provide more physical activity programs to youth, 75% were willing to partner with health professionals to train staff in physical activity leadership, and 59% wanted to improve the marketing of their programs.[59] The most frequently cited barriers to offering more physical activity programs for youth were inadequate staff and training, departmental support, and funding.[59] Increased collaboration between public health and recreation professionals to maximize the use of public recreation facilities for physical activity is indicated.[60]

In addition to parks, the design of the built environment (e.g., the presence and condition of sidewalks, location and condition of green space, and availability of

public transportation) has immense potential to impact participation in physical activity. A large body of evidence documents the positive relationship between the built environment and physical activity.[60–62] A recent analysis of urban environments, conducted in 14 cities in ten countries around the world,[63] found that residential, intersection, and public transport density, as well as the number of parks, were significantly and linearly related to physical activity. Further, participants living in the most activity-friendly neighborhoods sampled reported 68–89 more minutes of physical activity per week compared with those living in the least activity-friendly neighborhoods.[64]

Additionally, after a recent review, the CPSTF now includes, among its recommendations for increasing physical activity, built environment strategies combining one or more interventions designed to improve pedestrian or bicycle transportation with one or more land and environmental design interventions.[24] For example, transportation system interventions could include policies aiming to improve sidewalk, bicycle, and trail infrastructure or street connectivity. When combined with a land use intervention, such as a policy or project that enhances access to parks and public or private recreational facilities, there is sufficient evidence that the combination of these interventions can increase physical activity. These new recommendations offer opportunities for community leaders to apply evidence-based interventions to increase physical activity among community residents.

131.3.4 Community Organizations

Many community organizations provide physical activity facilities and programs or have the potential to do so. In the private sector, health clubs, dance studios, martial arts organizations, swimming clubs, and sports leagues are familiar examples. Non-profit organizations include YMCAs/YWCAs and Boys' and Girls' Clubs as well as sports leagues. Faith-based organizations often have physical activity facilities and programs for their members, which could be made available to others in the community. Private and public housing developments often have recreational and fitness facilities. Thus, many resources throughout communities can be used for recreational physical activity, and with improved promotion can become better utilized. However, there do not appear to be any well-designed systematic studies of how the facilities and programs within these community organizations contribute to the physical activity levels of individuals in surrounding communities. Although there are undoubtedly many exemplary programs in these organizations, there currently are no programs that have been systematically evaluated regarding changes in physical activity behaviors due to policy and environmental supports to promote physical activity. A historical systematic review conducted by Kahn et al. identified a strong body of evidence under the category of community-wide campaigns that identified successful collaboration across multiple community sectors, which included many of the community organizations mentioned above.[3,25,65] A conclusion from this work suggests that the public health impact of such facilities and programs can be maximized by increasing the number of participants, increasing the frequency and duration of activity sessions, and sponsoring year-round programs (especially sports organizations). Making resources available to the general community and having reduced fees for low-income participants could help contribute to reduced disparities in physical activity.

131.4 PROMOTING THE USE OF ECONOMICS IN PLACES TO BE PHYSICALLY ACTIVE

Through the systematic evidence reviews by the CPSTF, there has emerged substantial evidence that policies combined with improved infrastructure that supports active transport and active recreation (e.g., walking, biking, and running) results in increased physical activity among children, youth, adults, older adults, and persons with disabilities.[66,67]

King et al. suggested that, where possible, an environmental and policy intervention should be chosen based on likely potency and cost-effectiveness.[68] While evidence supporting the cost-effectiveness of some policy and environmental interventions is still growing, research indicates that such interventions can be cost-effective in schools, worksites, and community settings.

131.4.1 Costs/Benefits and Funding

During the past decade, there has been an emergence of studies supporting the cost-benefit/effectiveness of several community-based interventions to promote physical activity and healthy eating. Earlier efforts focused on school-aged children and the effects of a comprehensive school-based intervention among overweight children.[69] The results of this controlled study demonstrated the cost-effectiveness of preventing weight gain and facilitating weight loss among these students.[69]

Roux and colleagues[70] conducted an econometric simulation based on the systematic reviews of the CPSTF using the effectiveness results for each of the categories of physical activity promotion, behavioral/social, informational/campaigns, and policy and environmental approaches and reported the projected positive cost-benefit and cost-effectiveness of these intervention strategies. Further, Abildso and colleagues recently demonstrated the cost-effectiveness of community rail-trail conversions on the successful promotion of physical activity among community residents.[71]

The most recent findings from the CPSTF addressed interventions to increase active travel to school and found that there were substantial economic benefits associated with the provision of walking/biking infrastructure and the promotion of active transport to school among children and youth.[72,73]

The strategy of combining both physical activity promotion and healthy eating interventions targeting youth and

school-aged children has been recently reported by the CPSTF.[74,75] The use of digital health intervention strategies among overweight and obese youth has resulted in the prevention of further weight gain as well as weight loss.[74] Whereas the combination of healthy snacks (e.g., fruits and vegetables, water) and increased physical activity during school hours (in addition to physical education) have resulted in the prevention of weight gain and a decrease in BMI trends among school-aged elementary students.[75]

Undoubtedly, policy and environmental approaches are essential for sustaining improvements in physical activity behaviors within communities. By creating connections across disciplines, including land use planning, transportation, public health, and economic development, substantial policy changes may be gained. Improving policy and engaging community members may be the important formula for enhancing success.

131.5 FOOD SECURITY AND HEALTHY EATING

Eating behaviors of individuals, families, and communities are influenced, in part, by various socioecological factors outside of their direct control, including food security. Food security, defined by the United States Department of Agriculture (USDA), is "access by all people at all times to enough food for an active, healthy life".[76] Achieving a food-secure home requires adequate quantity, quality, and diversity of foods to meet the health needs of everyone in the household. Closely linked to this concept of food security is the emerging topic of nutrition security. Nutrition security encompasses a variety of additional factors including availability, affordability, access, acquisition, consumption, and education related to foods that promote well-being and prevent disease.[75] As the prevalence of nutrition-related chronic diseases continues to increase, shifts in environmental and policy priorities beyond caloric sufficiency and food quantity to a more health-promoting, nutrition-secure focus are necessary to encourage the adoption of healthful eating behaviors among individuals from diverse communities.[77]

131.5.1 Disparities in Food Security

Food insecurity affects every community in the United States. In the most current 2020 report, the USDA estimated that approximately 10.5% of households were experiencing food insecurity, which equates to over 38 million people.[74] While rates of food insecurity have decreased in the United States from a high of 14.9% in 2011, it is projected that the COVID-19 pandemic has erased much of this progress.[78] Moreover, these rates represent national averages. Although this steady decrease in pre-pandemic food insecurity rates has been noted, a significant gap among rates in different populations persists, making it more difficult for these communities to consistently exhibit healthful food behaviors.[76]

One type of disparity in food insecurity exists among different racial and ethnic groups. On average, both White, non-Hispanic/Latinx and Other, non-Hispanic/Latinx households have low food insecurity rates compared with the national averages.[76] However, there is a significant difference in the food insecurity experiences of Black, Indigenous, and people of color (BIPOC) households. Additionally, other disparities in food insecurity can be seen among different household types, areas of residence, and geographic regions. The 2020 USDA data revealed that households with children had a substantially higher rate of food insecurity (14.8%) than those without children (8.8%), with the highest rates existing among households headed by single mothers (27.7%). The prevalence of food insecurity was higher for households located in principal cities of urban areas (12.7%) and rural areas (11.6%) compared with those located in suburban and other urban areas outside principal cities (8.8%). Regionally, the 2020 food insecurity rate was highest in the South (12.3%) compared with the Northeast (9.3%), and Midwest and West (both 9.5%) US geographic regions.[76]

131.5.2 The Relationship between Food Security and Chronic Disease

The rapid and sustained rise of nutrition-related chronic diseases (e.g., obesity, diabetes, cardiovascular diseases) over the last three decades is a major public health concern in the United States. While these nutrition-related conditions touch all communities across the country, they disproportionately impact lower-income BIPOC communities often experiencing food insecurity.[79] These nutrition-related health disparities stem, in part, from a complex array of health inequities. The interplay between various social determinants of health, including poverty and low food security, and the incidence and prevalence of chronic diseases is well documented.[6–8,80,81]

The relationship between food insecurity and chronic disease development is cyclic in nature.[81] Often, food-insecure households alternate between adequate food supply and scarcity throughout the month and/or year. In response to this inconsistency, households may adopt unhealthful behaviors to cope with times of food insecurity. For example, adults who anticipate future food scarcity may overconsume during times of adequate food supply, which can lead to physiologic changes such as binge eating, efficient energy storage (i.e., fat accumulation), and peripheral insulin resistance. Over time, these unhealthful coping strategies can lead to poor physical and mental health outcomes. With the onset of chronic conditions, healthcare costs may rise (e.g., increased medication and physician visits), household income may decrease (e.g., missing or losing employment due to illness), and spending tradeoffs may be used to cope. When individuals and families are forced to choose between selecting healthful food and paying electric bills, the food insecurity cycle continues.[81]

Although it appears counterintuitive, the high rates of overweight and obesity among food-insecure and

low-income individuals are associated with obesogenic factors experienced by the general American public (e.g., increased portion sizes and sedentary behavior). However, this population faces additional unique challenges in adopting and maintaining healthful eating behaviors, which make them particularly vulnerable to obesity. Factors such as limited resources, limited access to affordable, healthful foods, and greater exposure to the marketing of unhealthy foods and beverages can all lead to poor eating behaviors.[82] Improvements in these factors may promote more healthful eating among all populations, including those experiencing food insecurity (Table 131.2).

131.6 PROMOTING HEALTHY EATING THROUGH ENVIRONMENTAL AND POLICY APPROACHES

Food security, its relationship to nutrition-related chronic disease, and healthful food choices are complex, interrelated issues requiring multifaceted approaches. Story and colleagues propose a socioecological framework illustrating the myriad influences on food choices individuals make.[83] Mounting evidence leads experts to suggest policy and environmental interventions to increase healthy eating[1,83] (Table 131.3).

131.6.1 Environmental and Policy Supports for Healthy Eating

Food deserts and food choices. Adequacy of the food supply, such as certain types of restaurants or fresh produce, impacts the types of foods that are available to individuals and families. Food deserts, or places lacking access to foods that are nutritious, such as fruits and vegetables, whole grains, low-fat dairy products, and others exist in the United States.[84] The body of literature is growing about food deserts in the United States and their impact on health.[85]

As defined by the USDA, a food desert contains several key components: low-access community, number of individuals impacted, and distance an individual lives from a supermarket or grocery store that is not considered a convenience store or quick mart.[82] A "low-access community" must consist of 1000–8000 people and averages around 4000 people; furthermore, at least 33% of the census tract's

TABLE 131.2
Policy and Environmental Interventions for Obesity Prevention and Control

Action	Tools	Comments
The first step in building a strategic alliance is to show consistency, authenticity, and transparency when advocating for a healthier environment with the community within one's own clinic or practice.	Institutionalized policies (i.e., modifying policies to remove soft drinks from the waiting room). Materials are readily available, highlighting the importance of physical activity and eating healthier food. Community partners can help! They include but are not limited to schools, neighborhood associations, clinics, the local health agency, and non-profit organizations.	When committing to healthier communities, physicians and clinicians should first assess the immediate environment of the clinic or practice.
Physicians and clinicians should address the social and environmental determinants of health within the community they serve so to increase their influence on both population and patient health. As an individual citizen, a clinician can be an active community member.	Ask clients where they shop for fruits and vegetables, where their children play, and how they get to work. Walk the neighborhoods and communities to experience the environments firsthand. Public meetings. Testimonials before policymakers. Refer patients to community resources or programs.	Physicians are unlikely to have a full understanding of the specific nature of the community they serve. Community engagement is an important component of the work for multidisciplinary partnerships.
Screen for food insecurity in healthcare settings	Electronic medical record (EMR) embedded Healthy Eating Vital Sign (see reference [120]).	Healthcare providers are increasingly screening for food insecurity in the clinical setting. Individuals who positively screen for food insecurity should be referred to local resources (e.g., food pantries) and nutrition assistance programs (e.g., SNAP) (https://hungerandhealth.feedingamerica.org/explore-our-work/community-health-care-partnerships/addressing-food-insecurity-in-health-care-settings/).

Source: https://www.thecommunityguide.org/topic/obesity. *Source:* https://thecommunityguide.org/topic/physical-activity.

TABLE 131.3
Policy and Environmental Interventions for Healthy Eating

Action	Tools	Comments
Counsel or refer for counseling individuals not meeting the current Dietary Guidelines for Americans.	Multiple materials are available from the NIH, ACP, AAFM, AAP, CDC, etc.	Effective strategies to promote healthy eating involve understanding the patient's access to healthy foods, living/community situation, personal preferences, and health status.
Refer patients to a registered dietitian/nutritionist (RDN)/licensed clinical nutritionist (LCN) and work with public health and other community-based organizations to provide resources and guidance for healthy eating.	EMR-generated referrals to RDN/LCN and community resources that offer places for healthy food and healthy eating.	Healthy eating promotion requires both a public health approach as well as an individual approach to increase the intake of healthy and nutritious foods with policy and environmental (physical, social, cultural) supports holding the greatest promise.

Source: https://www.thecommunityguide.org/topic/nutrition.

population must live in excess of one mile from a supermarket or large grocery store. An additional quantifier is added for rural individuals, such that the distance must be greater than ten miles from the supermarket. Food deserts also contain larger numbers of quick marts and convenience stores that offer mostly sugar- and fat-laden processed foods, which are associated with obesity.[86] While interventions, such as implementing farmers' markets in food deserts, have had some success, access to these healthful food options alone is not always enough to change eating behaviors.[87–89] Additional approaches addressing the knowledge, skills, and behavior related to the preparation and consumption of healthful foods are needed.

Accessibility to full-service grocery stores. Increased consumption of fruits and vegetables has been reported by those who shopped at a supermarket compared with those who did not. Adequate fruit and vegetable consumption has been associated with a more nutritious diet and more improved health outcomes.[90] However, access to nutritious foods is also affected by a lack of transportation and long distances between households and supermarkets or grocery stores. Not surprisingly, residents are at risk for food insecurity and chronic disease in neighborhoods where transportation options are limited, the travel distance to stores is greater, and there are fewer supermarkets. Lack of access to public transportation or personal vehicle limits access not only to food itself but, importantly, to nutritious food.[91] Additionally, some people live in a "food mirage", where individuals reside near grocery stores or supermarkets, but cannot afford the foods sold there. In these cases, individuals must still find transportation to more affordable options.[92]

Shopping patterns, including food purchasing, dramatically shifted to online purchasing during the COVID-19 pandemic. Shoppers can now choose curb-side pick-up and grocery delivery which, according to recent Nielsen research about measuring and understanding the shopper "shift", will likely remain options.[93] Online grocery shopping may improve access to healthful options for some individuals and has the potential to reduce less healthful impulse food purchases. However, elements of online grocery shopping like consumers' reluctance to buy fresh produce online may have a negative impact on food purchases.[94]

Behavioral economics. When behavioral economics (i.e., how individuals are influenced to make choices) is applied to the food environment setting, choice architecture is a key factor in decision-making about nutritious and non-nutritious foods.[95] Choice architecture is a concept in behavioral economics that adjusts the appeal or availability of choices in an individual's mind to encourage one specific choice over another. Choice architecture may preserve freedom of choice while making unhealthy options less convenient or more healthful choices immediately visible to the consumer. Behavioral economics may lead to poor food choices and decision-making and is present in supermarkets, convenience stores, and food pantries. Something as simple as the placement of food at eye level, on or at the front of the shelf can influence a choice for the consumer that may be undesirable, in terms of the nutritional quality of a food item. While more healthful items may be available, they may not be located within immediate view; thus, the attractive packaging, flashy signage, and eye-level placement of food products impact selection by the consumer. By contrast, simply placing healthful foods in prominent locations in stores may encourage individuals to select them. Behavioral economics recognizes that even though consumers may have the required information, skills, and decision bias about a food product, they may still choose a food that is not as nutritious as another due to placement in a store or other elements that are responding to choice architecture.[96] Behavioral economics presents a low-cost, feasible approach to improving food choices but does not address other barriers such as access, transportation, time, or energy required to prepare foods.[95]

Healthy school vending. Although non-nutritious foods in school vending machines are being banned in many states across the nation, schools may be substituting other sugar-sweetened beverages, such as sports and energy drinks. Both the USDA and the CDC support new regulations that determine what may be provided in the vending

machines throughout the school day.[96,97] According to the Food and Drug Administration (FDA), there are now limits on fat, sugar, sodium, and total calories in the food products stocked in school vending machines. According to the Smart Snacks in Schools guidelines,[98,99,100] such snacks must:

- Be a grain product that contains 50% or more whole grains by weight (have a whole grain as the first ingredient); or
- Have as the first ingredient a fruit, vegetable, dairy product, or protein food; or
- Be a combination food that contains at least a quarter cup of fruit and/or vegetable; and
- The food must meet the nutrient standards for calories, sodium, sugar, and fats.

The nutrient standards for smart snacks are:

- Calories: 200 or less
- Sodium: 200 mg or less
- Total fat: 35% of calories or less
- Saturated fat: less than 10% of calories
- Trans fat: 0
- Sugar: 35% by weight or less

Thus, changing the food environment by ensuring that healthful foods are available and affordable, and utilizing choice architecture to make it easier and more appealing to select healthful foods may be effective means of addressing food choices contributing to chronic disease.

Federal Nutrition Policy and Dietary Guidelines for Americans. Federal Nutrition Policy and Dietary Guidelines are useful guides for healthy eating patterns. Every five years, the USDA publishes updated recommendations for Americans through the Dietary Guidelines. The 2020–2025 Dietary Guidelines deliver new key messages with a recently incorporated theme of "make every bite count" and include recommendations for every life stage, beginning with pregnancy and lactation.[90] The recommendations note that:

- At every life stage, meeting food group recommendations, even with nutrient-dense choices, requires most of an individual's daily calorie needs and sodium limits.
- Nutrient-dense food and beverage choices are customizable and should reflect individual and cultural preferences, and budgetary needs.
- A small amount of added sugars, saturated fat, or sodium can be added to nutrient-dense foods and beverages to help meet food group recommendations, but foods and beverages high in these components should be limited.
- Foods and beverages higher in added sugars, saturated fat, and sodium, as well as alcoholic beverages, should be limited.

The contribution of dietetic professionals. The Academy of Nutrition and Dietetics (AND) also plays a role in advocating for federal nutrition policy that supports healthy eating. The Academy is "committed to improving the nation's health and advancing the profession of dietetics through research, education and advocacy".[101] Registered dietitian nutritionists (RDNs) play a key role in chronic disease prevention and treatment, helping to shape food choices of consumers, and improving the overall nutrition status of people. RDNs can translate science into practical recommendations for those they work with. These professionals also work with policy leaders at all levels of government "to promote health and reduce the burden of chronic disease through nutrition services and interventions".[101]

Worksite supports for healthy eating. Because many adults employed full time spend so many hours at work, worksites are excellent places to assist employees in making healthful food choices. Research shows that increasing the selection of fruits, vegetables, and salad, while reducing the prices of these items, increases purchases.[102] Recommended strategies for creating healthy worksite food environments include ensuring access to clean water, providing healthful food in on-site cafeterias and vending machines, and reducing prices for fruits and vegetables.[103,104] In a study designed to examine the associations among worksite environmental and policy influences and physical activity and healthy eating, researchers found that employees reporting the availability of a cafeteria, snack bar, or food services at the worksite were more likely to consume fruits and vegetables more than twice per day and less likely to consume fast food more than twice per week.[105] Further, they found that employees reporting that their worksite cafeteria, snack bar, or food services provided daily fresh fruits and vegetables were also less likely to consume fast food more than twice per week. These results suggest that access to healthful and affordable foods at worksites may improve employee food choices.[105]

131.6.2 Role of Food Labels

The potential of FDA-required food labels to promote healthy eating is limited without expanded and improved consumer education. In 2018, the FDA published the updated and redesigned Nutrition Food Label (see Figure 131.2). Changes were made to make it easier for individuals to make informed decisions about the foods that they eat. This is important because many foods that contribute to chronic disease include pre-packaged, convenience food items. All manufacturers were required to update their product labels by July 1, 2021. The purpose of these updates is to help consumers be better educated about food choices.[106] Specific changes include the following:

- Serving sizes have been changed to reflect what people actually consume, rather than what is recommended. Also, if a package is intended to be



FIGURE 131.2 New nutrition labeling (www.FDA.gov/NewNutritionFactsLabel).

eaten in one or two sittings, the manufacturer must list the entire container as one serving.

- Calorie-count font size is larger and bolder for easier reading.
- The calories from fat information were eliminated as research has illustrated that type of fat consumed matters more than amount.
- "Added sugars" are now listed in grams and as a percent daily value to help people reach the Dietary Guidelines goal of consuming "less than 10% of calories per day from added sugars".
- Vitamin D and potassium have been added to the food label since these are typically nutrients that Americans typically under-consume; vitamins A and C have been removed since deficiencies in these are uncommon.
- A footnote has been updated to help the consumer better understand what the product provides. This is given as a percentage in relation to total daily consumption.

It is recommended that saturated and trans fats be limited to less than 10% of kilocalories per day, added sugars to less than 10% of kilocalories per day, and sodium to less than 2300 mg per day. Alcohol, if consumed, should be in moderation, up to one drink per day for women and two drinks per day for men, and only by adults over the legal drinking age. A standard drink is anything that contains one-half ounce of pure ethanol. Some examples include 5 ounces of wine, 10 ounces of wine cooler, 12 ounces of beer, and 1.5 ounces of 80-proof whiskey, scotch, rum, or vodka[90] (see Figure 131.3). These guidelines are often confusing to consumers who do not have the knowledge or energy to calculate these amounts of sugars in their diets or read food labels to determine a food's sodium content.[107]

131.6.3 Restaurant Menu Labeling

Menu labeling in restaurants is a promising strategy for promoting healthful food choices. Americans are busy and convenience food options are abundant.[106] In addition, more consumers are eating out at restaurants more frequently, and consuming about one-third of their calories from foods that they do not prepare themselves. Therefore, the FDA has established the Menu Labeling Rule for all restaurants and similar retail food establishments covered under this rule. This includes any restaurant establishment that has 20 or more locations. The standard menu items will have the calories listed beside the name or the price of the item (food or beverage). At facilities where there are salad bars, buffets, and so on, the calories will be available to consumers on signs that are near the foods. However, calories will not be required for "condiments, daily specials, custom orders, or temporary/seasonal menu items".



FIGURE 131.3 Standard drink of alcohol (www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink; accessed 4/15/2022).

Restaurants will also be required to provide written nutrition information, which will provide the full nutrition facts of the menu items.[107] When fully implemented, this Menu Labeling Rule will provide additional opportunities for consumers to be aware of the nutritional content of food choices.[108]

131.7 BUILDING STRATEGIC ALLIANCES TO PROMOTE HEALTHY EATING AND ACTIVE LIVING

To create environmental and policy changes that address social determinants of health, it is important to utilize approaches that build on community strengths and acknowledge the interdependence of individuals, their social networks, and the community structures, norms, cultures, histories, and values.[109–111] Because of the importance of these more multilevel, multisector, interdisciplinary changes, many federal, state, and nongovernmental agencies are calling for the development of strategic alliances (i.e., partnerships, coalitions, asset-based community building) to promote healthy eating and active living.

Lifestyle medicine clinicians have a key role to play in strategic alliances to promote healthy behaviors and environments, and there is a growing recognition that involvement in these types of efforts is a professional responsibility. Within the clinical setting, most physicians focus their time and energy on individual- and social- or family-level factors to enhance the health of their patients. This may involve testing, counseling, and referrals to other clinicians and clinical resources (nutritionists, physical therapists, etc.). While these traditional clinical roles are absolutely critical to patient care, many physicians have found that they want to have a role in addressing the other factors that impact the health of their patients. These include but are not limited to employment status, literacy levels, food insecurity, adequate housing, and access to healthcare and transportation. At the same time, professional expectations and spheres of influence are changing to reflect the important responsibility physicians have in advocating for health outside the bounds of the typical patient encounter or the walls of the clinic (Figure 131.4).[112,113]

Bringing organizations and community members together from a range of disciplines, sectors of society, and diverse backgrounds is necessary when striving to enhance healthy eating and active living in a community. The resultant groups have been called strategic alliances, coalitions, or multidimensional partnerships. Each group may go through various stages of development,

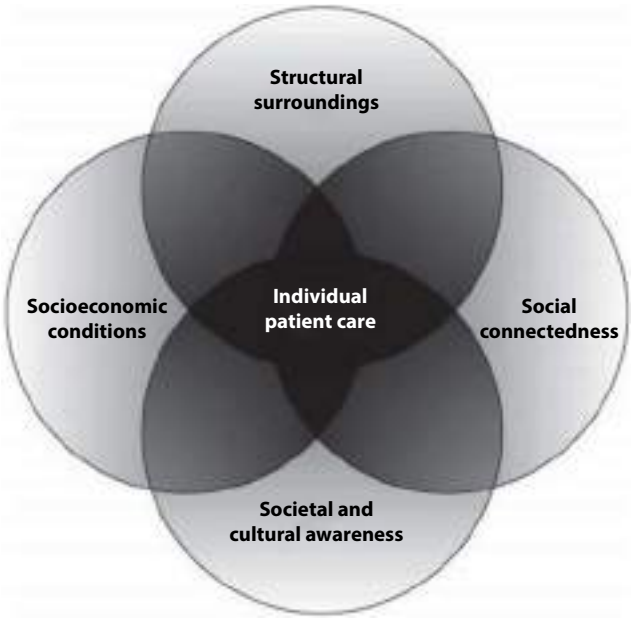


FIGURE 131.4 Assessing community engagement (source: Organizing Committee for Assessing Meaningful Community Engagement in Health and Health Care Programs and Policies. 2022. Assessing Meaningful Community Engagement: A Conceptual Model to Advance Health Equity through Transformed Systems for Health. NAM Perspectives. Commentary, National Academy of Medicine, Washington, DC. https://doi.org/10.31478/202202c.).

progressing from initial conversations, regular meetings, development of an organizational structure, development of partnership capacity, development of a mission and vision, action planning, implementation, evaluation, and eventually to sustainability and maintenance. With time, trust can be developed within a group, and, in turn, the level of collaboration strengthens and becomes more productive. The first level of collaboration might include sharing information and referrals (e.g., between clinics and community programs). The next level might be to jointly define a goal with each partner acting individually toward this shared goal (e.g., sending letters to encourage healthy choices at school events). A third level might be to contribute or exchange resources (i.e., money, space, equipment, or personnel) for a common goal. The last and often most difficult level is collaborating on planning, funding, implementing, and evaluating policy, systems, and environmental (PSE) change activities.[114,115] The benefits of these multidimensional partnerships are wide-ranging. Partnering with community members (schoolteachers, retired nurses, parents of children, etc.) can ensure that goals and activities are culturally relevant and feasible within the community. Also, having a variety of partners from different sectors (transportation, elected officials, schools, businesses, land use planning, etc.) can help a group navigate unique systems and processes and translate professional jargon. As an ongoing process, partners should work together to respond to the demands of the project as well as demands for increased information, resources, communication, community input, and utilization of services to improve outcomes.[116–118]

131.8 SUMMARY

In the practice of lifestyle medicine, healthcare professionals cannot rely solely on effective assessment and counseling of their patients to adopt and maintain a more physically active and healthy eating lifestyle. Indeed, health behaviors are seldom changed or adopted within the confines of the clinical setting. However, the astute lifestyle medicine practitioner committed to promoting physical activity and healthy eating among her/his patients will proactively identify existing physical activity and healthy eating resources and supports within the patient's community and neighborhood as essential in achieving individual health-related levels of physical activity and healthy eating. Such resources and supports are conveyed through programming, policies, and infrastructure in communities, worksites, schools, parks, community organizations, and transportation systems. By linking clinic to community, lifestyle medicine practitioners are thus assured of maximizing the likelihood of their patients adopting and sustaining a healthier eating and physically active lifestyle.

The obesity and overweight epidemic is growing in proportions faster than healthcare professionals or public policy influence can offset, despite research-based recommendations about guidelines for healthy eating. Continued attention and research need to be focused on how the environment, in multiple ways and facets, plays a role in individual choices. Better access to nutritious foods along with perceptions about the quality of food that is available and a focus on the prevention of overeating of non-nutritious and processed foods needs to be an ongoing effort. Food deserts, transportation issues, and affordability in low-income and BIPOC neighborhoods must be remedied in the way of policy change and environmental supports for eating behaviors to ultimately produce reduced chronic disease risk and improved health outcomes.

Physicians and other healthcare professionals can play a key role with strategic alliances in creating sustainable environmental and policy changes that are critical for the health and well-being of their patients and the community. Furthermore, there is growing recognition that this involvement is a professional responsibility and that work to develop community-integrated health systems also clearly advances the "quadruple bottom line" goals of a healthcare system that is rapidly undergoing a number of transformations. Participation can be achieved through a variety of roles and levels of involvement. Regardless of the role, it is helpful to be aware of how alliances can be structured to be most effective in accomplishing their goals. The support of physicians (through participation and/or leadership) can greatly enhance the success of strategic alliances, and their community-based work can also extend the physician's ability to advocate for the health of their patient population

and increase the effectiveness of a physician's counseling for healthy behaviors.

CLINICAL APPLICATIONS

Action	Tools	Comments
Assess physical activity of all patients.	Electronic medical record embedded Physical Activity or Exercise Vital Sign (PAVS/EVS) - Available through Exercise is Medicine (www.exerciseismedicine.org)	Unfortunately, <35% of individuals are routinely assessed for physical activity levels in primary care settings.
Counsel inactive patients or individuals not meeting the current Physical Activity Guidelines for Americans level of physical activity strategies.[119]	Multiple materials are available from the NIH, ACP, AAFM, AAP, CDC, and others.	Effective strategies to promote physical activity involve understanding the patient's living/community situation, personal preferences, and health status.
Refer patients and work with public health, parks/recreation, and other community-based organizations to provide resources and guidance for patients to be more physically active.	EMR-generated referrals to community resources, which offer places and programs for physical activity promotion.	Physical activity promotion requires both a public health approach and an individual approach to increase physical activity with policy and environmental (physical, social, cultural) supports holding the greatest promise.

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