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Editors

The Epidemiology of Aging

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For Frank,
Who understands me and takes care of me, With all my love.

ABN

For Kathryn and Nora,
Who bring me great joy; Their unconditional love keeps me whole.

JAC

Foreword

In recent decades, the field of the epidemiology of aging has grown substantially in breadth and depth. The many cumulative successes in public health over the past century have led to a larger proportion of the population surviving to achieve longevity, but this has come with an increase in the number of individuals who eventually experience disability. The field of the epidemiology of aging evaluates these public health successes and addresses the new challenges that have come with them. The focus is not only on the length of life, but on the quality of life.

As a core discipline of public health, epidemiology serves to identify key problems and the rates at which they occur, determine risk factors for these problems in populations, and then formulate interventions to reduce the rates and risk factors. Ultimately, the purpose of epidemiology is to inform and improve the health of populations. The epidemiology of aging ranges from the study of the process of aging itself to the study of health outcomes in older adults. In spite of the achievement of longevity, the epidemic of aging includes an overall increase in disability and the need for care and prevention, including primary, secondary and tertiary prevention. As the scope of the problems of aging has become better defined, projections for the future now depend on whether the prevention of age-related chronic disease will compress or expand the period of morbidity at the end of life. Thus, the field of the epidemiology of aging has been uniquely focused on improving the quality of life in old age.

The definition of old age itself has evolved over time. The age of 65 has been most commonly used as the threshold for old age. Historically, this threshold comes from the age for pension eligibility, initially established in Europe and later adopted in the US for the Social Security Program. Early epidemiologic studies and clinical trials on aging included adults ≥60 years of age (e.g., the Systolic Hypertension in the Elderly Program [SHEP]) or ≥65 years of age (e.g., the Cardiovascular Health Study [CHS], the Study of Osteoporotic Fractures [SOF]). However, until after age 70, the majority of older adults experience few health problems and mortality risk is fairly low. More recent studies such as the Health Aging and Body Composition Study (Health ABC) and the Lifestyles and Independence Interventions in the Elderly (LIFE) now start at age 70. Life expectancy at age 65 is now close to 20 years and the most rapidly growing age group of older adults is the "oldest old", generally defined as the group over age 80 or 85. Many ongoing studies on aging (e.g., CHS, SOF) continue to follow their participants well into the tenth decade of life. Studies of healthy aging and longevity focus on exceptional

survival and health, generally enrolling adults ≥90 years of age or ≥100 years of age, as in the studies of centenarians.. The longevity phenomenon is unique in human history and it is leading to a new and urgent need to understand the oldest old. Thus, many epidemiologic studies and prevention trials now focus on individuals who are ≥70 years of age.

The early-life origins of age-related disease and disability are also of increasing interest. Long-term follow-up of younger cohorts and retrospective designs offer the opportunity to study aging from a life course perspective. Early life experiences, including exposures *in utero*, are thought to impact the risk of chronic disease and thus impact aging. In effect, all epidemiologic studies, if carried on for many years, can inform the study of aging. The conversion of the Honolulu Heart Study to the Honolulu Asian Aging Study is an example of the rich progress that can be made in understanding the mid-life origins of aging. The continued follow up of women who are enrolled into the Study of Women's Health Across the Nation (SWAN), a study of premenopausal women who were 42–52 years of age at baseline, will provide important information on the transition from "middle" age to "old" age. It is critical that we continue to capitalize on future opportunities to maintain the long-term follow-up of such rich long-term data sets.

The epidemiology of aging draws from important contributions to the field of gerontology that have been made in multiple disciplines. Demography has defined the growth of the aging population, while social gerontologists have identified important interactions between health and social factors in older adults. Psychologists have identified the importance of mental and cognitive health to the quality of life in old age. Physiologists and basic scientists have identified aspects of aging processes that can be measured in population studies. Geriatric physicians and allied health professionals have defined important clinical syndromes—such as falling and immobility, weight loss and frailty—which are best managed by addressing their multiple contributing factors. Advances in our imaging techniques have facilitated the identification of subclinical disease. Together, these diverse disciplines have contributed to the methodology that is used for the multidisciplinary assessment of older adults in population studies and the assessment of solutions to extend the active lifespan.

Aging has proven to be an area of inquiry that is particularly well suited to epidemiologic methods. Age-related health conditions are by nature multifactorial, with contributions from many domains including physical, social and emotional factors. The disabling consequences of disease and of aging are relevant to the entire population, but they are highly heterogeneous. Large population studies are needed to understand this variability and complexity. Older adults have high rates of the common chronic diseases and many risk factors for these diseases have been identified in disease-specific epidemiologic cohort studies. Disability has come to be recognized as a highly variable dynamic process and various aspects of disability have been targeted as key endpoints for identifying risk factors and designing prevention trials. Such trials are currently being designed to encompass these critical issues of variability and the need for generalizability.

Though the demographic imperative is clear, there is a need to attract more investigators to the field of the Epidemiology of Aging. The chapters that follow form a foundation of knowledge that hopefully will serve to propel careers and research in the field forward. We hope that the quality of aging throughout the world can improve as a result.

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Preface

This book was developed to support training and research in the epidemiology of aging. It evolved from the Epidemiology of Aging course that we have been co-teaching at the University of Pittsburgh Graduate School of Public Health since 1989. What began as a single course has since transformed into three courses, a training program that has been funded for 20 years by the National Institutes of Health, National Institute on Aging, multiple United States (US) cohort and randomized clinical trials, a Center for Aging and Population Health and now a focus on aging and global health. It's been a fun train ride—especially in our positions as co-conductors at Pitt. Now we find a need to summarize the seminal findings that have emerged with regard to aging over the past 20 years.

Why create a separate book on the Epidemiology of Aging? There are many reasons why research into older adults requires different considerations than research into younger adults. There is tremendous heterogeneity in the way that individuals age and study designs must take this heterogeneity into consideration. Researchers must distinguish normal age-related physiologic changes from changes that are related to disease. Comorbidity is very high in older adults and it increases with advancing age. Students of aging need to understand this, measure it and adjust for it either as a confounder or as a mediator. The risk factors for disease in middle age differ from the risk factors at older ages. In the epidemiology of aging, we focus on disease outcomes, but also on staying healthy and living well. There is a greater need for social services in older populations, so the consequences of disease are greater. The study of health and disease at older ages must be a study of interrelated changes. The domains of health status and function are key concepts. Also, the goals of therapies will likely differ in older populations compared to younger populations.

The field of epidemiology of aging continues to expand to encompass the many factors that contribute to health and function. Specific methods that address the tremendous heterogeneity in the aging experience have been established. These methods and important key findings have grown to form a substantial body of knowledge. This book is designed to take stock of the progress in the field and to form a foundation for future progress in improving the quality of life of older adults. We hope that it is only the beginning.

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Acknowledgments

The idea of the book came from a need to support our training program in the epidemiology of aging. We want to acknowledge the funding of our program in the Epidemiology of Aging at the University of Pittsburgh by the National Institutes on Aging.

Our program of study began with a single course on the epidemiology of aging when the training program was first funded in 1990. The establishment of this course corresponds to our respective first pregnancies and births of our oldest children. Thus we view the development of the field and this book with our own life course perspective. We would like to acknowledge the support of our families in this venture.

We have always attempted to teach from the perspective of current and active researchers in the field, including invited and visiting faculty. This book would not have been possible without the support of the many contributing authors who are our colleagues in the quest to improve the aging experience for all older adults.

Finally, we would like to acknowledge the expert assistance of Ms. Mary Parker, Sharon Happe, Amy Flaugh. A special thanks to Ms. Michelle Utz-Kiley for her expertise in handling all correspondence and editing of each chapter and successfully carrying the project through to completion.

Contents

Part I

Methods

The Demography of Aging

1

Jane A. Cauley

Abstract

Demography is the study of changes in the size, diversity, distribution and composition of human populations over time. The world's age composition has changed dramatically and these changes continue. The percentage of individuals ≥65 years of age will double from 7 to 14 %, rising from 506 million in 2008 to 1.4 billion by 2040, with the largest increases in developing countries. It is important to note that the older population is getting older, with the largest increases in those ≥80 years of age. Life expectancy at age 65 has increased. In 2003, the average 65-year old woman in the United States was expected to live an additional 19.6 years, and a man, an additional 16.8 years. The older population is mostly female, especially in developed nations. Cardiovascular disease is the major cause of death worldwide. Disability in older adults is declining, though these trends may not continue given the exponential growth of the oldest old population. These demographic changes will profoundly impact public health. Cross-national research must address this unprecedented growth, specifically longitudinal studies to identify links between health, disability, economic status, work and family structure; to establish mechanisms to harmonize and standardize data collection internationally; and to develop multidisciplinary research designs to address issues impacted by population aging.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Demography • Mortality • Disability • Oldest Old • Trends • Minorities • Epidemiologic studies • Demographic studies • Socioeconomic status • Global health • Race/ethnicity • Population • Future Projections

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Abbreviations

ADL	Activity of Daily Living
CVD	Cardiovascular Disease
NRC	National Research Council
ODR	Older Dependency Ratio
SHARE	Survey of Health Aging and Retirement in Europe
US	United States

1.1 Introduction

The age composition of the world's population has changed dramatically during the twentieth century. These changes continue into the twenty-first century. Specifically, the size and proportion of the older population (defined as age 65 and above), especially the oldest old (defined as age 80 and above), have increased substantially and will continue to increase. The purpose of this chapter is to present a broad and general overview of current demographic trends across the world. The main source of information for the United States (US) was the Federal Interagency Forum on Aging-Related Statistics (Older Americans 2010) [1]. For outside of the US, the major sources of information were the International Population Report, An Aging World: 2008 [2]. These data should be considered in light of two caveats. First, the data are based on summary statistics and it is important to keep in mind the heterogeneity in the way that people age. The population age 65 and over is large and very diverse. Second, the population that survives to ≥65 years of age represents only a fraction of their original birth cohort. There may be survivor bias in those who survive to older ages, especially the oldest old.

Demography is the study of the change in the size, diversity, distribution and composition of human populations over time. Demographers have identified a general progression of changes in fertility, mortality, population composition and the demographic transition. The demographic transition is a gradual process where a society moves from relatively high rates of fertility and mortality to low rates of both fertility and mortality. The demographic transition has three stages [3]. In the first stage, birth and death rates are high and the population grows slowly. The age pyramid for this stage has a very narrow top with few older people and the largest number of children 0–4 years of age. In the second stage modernization begins, especially industrialization and urbanization. Medical care and public health improves, leading to a sharp decline in death rates and longevity. Infant mortality declines, but birth rates remain high. In the final stage, death rates continue to decline but birth rates decline, population growth surges and the age pyramid becomes more rectangular. From 1900 to 1950, a steady decline in infant mortality raised the life expectancy in industrialized nations from 45–50 in 1900 to 65–70 in 1950. By 1950, most industrialized nations had experienced their demographic transition. For the purposes of this chapter, per the United Nations, "developed" countries include all countries in Europe and North America plus Japan, Australia and New Zealand. All other countries are considered "developing" nations.

1.2 Global Aging

Virtually all nations in the world are now experiencing growth in the number of residents ≥65 years of age, though there is considerable variability. Most developed countries have relatively high proportions of individuals ≥65 years of age, but the most rapid increases in the older population are in the developing world. Birth rates are also rapidly declining in many countries, including developing countries like India and China, further accelerating the shift toward an aging society. In 1950, about 5% of the world's population was ≥65 years of age while about 13% was <5 years of age. By 2020, individuals who are 65 years of age or older will outnumber children who are <5 years of age. The global population ≥65 years of age was estimated to be 506 million in 2008, which was about 7% of the world's population. By 2040, the world is projected to have 1.3 billion older adults, accounting for 14% of the total population. Eastern and

Table 1.1 Percentage of the population that is older, 2008–2040 [4]

	Age (years)		
Region	≥65	≥75	≥80
Northern Africa			
2008	4.9	1.6	0.7
2020	6.7	2.2	1.1
2040	12.8	5.0	2.5
Sub-Saharan Africa			
2008	3.0	0.9	0.3
2020	3.3	1.0	0.4
2040	4.2	1.4	0.6
Asia (excluding Near East)			
2008	6.8	2.4	1.1
2020	9.3	3.3	1.7
2040	16.2	6.8	3.7
Near East			
2008	4.6	1.7	0.8
2020	5.7	2.0	1.1
2040	9.9	3.8	2.0
Eastern Europe			
2008	14.5	6.0	3.0
2020	17.3	6.9	4.3
2040	24.4	12.6	7.8
Western Europe			
2008	17.8	8.5	4.9
2020	20.9	10.1	6.2
2040	28.1	15.0	9.3
Latin America/Caribbean			
2008	6.5	2.5	1.2
2020	8.8	3.3	1.8
2040	15.3	6.6	3.7
Northern America			
2008	12.8	6.2	3.8
2020	16.5	6.9	4.0
2040	20.8	11.6	7.3
Oceania			
2008	10.8	4.9	2.9
2020	13.7	5.7	3.3
2040	18.5	9.1	5.5

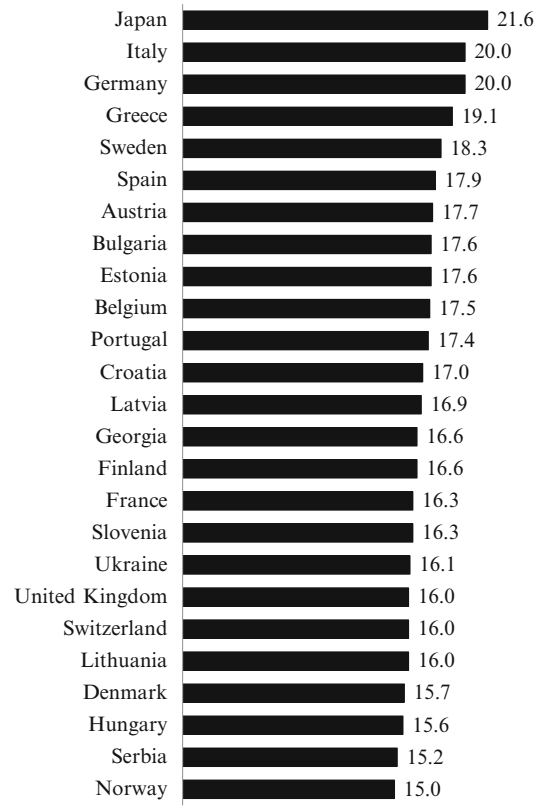

Fig. 1.1 The world's 25 oldest countries: 2008 (percent of population age 65 years and over) [2]

Western Europe will have the highest populations of people ≥65 years of age, including about 8–9% who are ≥80 years of age (Table 1.1). In Europe, by the year 2040, one in four individuals will be ≥65 years of age. In Asia, Northern Africa, the Near East and Latin America, the proportion of residents who are ≥65 years of age will more than double. However, it is important to point out heterogeneity within a region. For example, the population in China and India that were ≥65 years of age numbered 166 million in 2008, nearly one-third of the world's total in that age group. The absolute number will increase to 551 million in 2040 (329 million in China and 222 million in India).

Japan is the country with the world's oldest population (Fig. 1.1), with 21.6% of its population ≥65 years of age. Almost 20% of the populations of Italy, Germany and Greece are ≥65 years of age. With the exception of Japan and Georgia, all of the other countries with the oldest populations are in Europe.

During the period of 2008–2040, the projected increase in the older population in 52 studied countries ranged from a low of 18% in Bulgaria to 316% in Singapore (Fig. 1.2). As shown in Fig. 1.2, the percent increase will be greatest in developing nations compared to developed

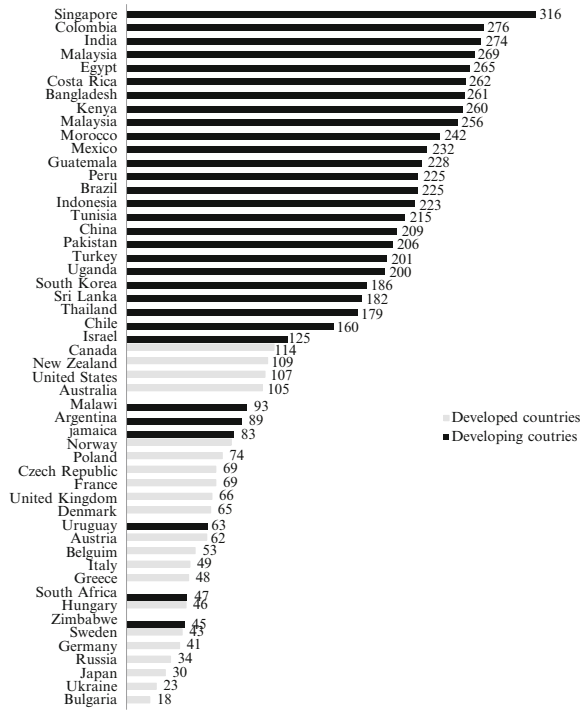

Fig. 1.2 Percent increase in population age 65 and over: 2008–2050 [2]

nations such as the US. The pace at which the world's population is aging is also increasing. From 2007 to 2008, there was a per-month increase of 870,000 individuals ≥65 years of age. In 10 years, the pace will increase to 1.9 million per month.

The median age will rise in all countries of the world. In Germany, the median age was 43 in 2008 and is projected to be 49 in 2040. In China, the increase will be much larger, with the median age of 33 in 2008 increasing to age 44 by 2040. In 2008, many developing countries had median ages younger than 27, but by 2040 the median age in these countries will be in the 30s or early 40s. Japan will have the highest median age at 54, indicating that half of its population will be ≥65 years of age by 2040.

An important feature of population aging is that the older population is getting older. The oldest old (≥80 of age) constituted 19% of the world's older population in 2008, 26% in developed countries and 15% in developing countries. More than half (52%) of the world's oldest old live in six countries: China, the US, India, Japan, Germany and Russia. China has the largest percentage of the

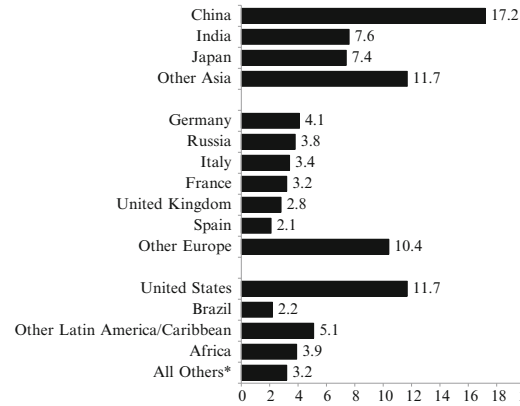

Fig. 1.3 Global distribution of people aged 80 and over: 2008 (percent of world total in each country/region) [2] * "All others" includes Oceania and Northern America except the United States. *Notes*: Individual countries with more than 2% of the world's total are shown separately. Figures may not sum to 100% due to rounding

oldest old, with 17.2% in 2008 compared with about 7% in Japan and India and 2–3% in Europe (Fig. 1.3). In 2008, 11.7% of the world's population ≥80 years of age lived in the US. The number of centenarians is also increasing, especially in

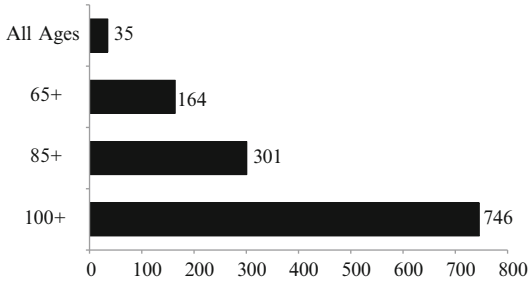

Fig. 1.4 Percent change in the world's population: 2005–2040 [2]

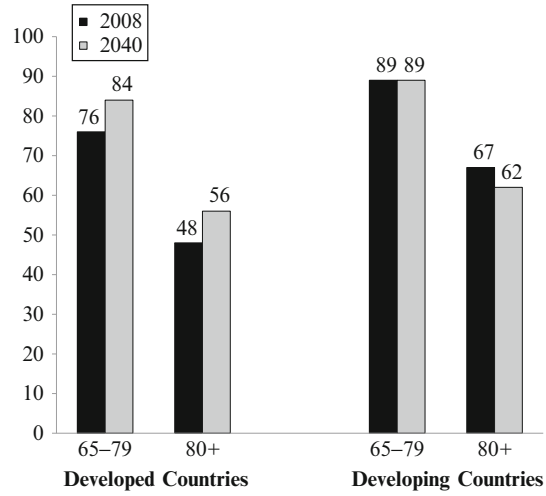

Fig. 1.5 Aggregate sex ratios for older age groups: 2008 and 2040: number of men per 100 women [2]

developed countries (Fig. 1.4). While the overall world population will increase 35% from 2005 to 2040, the percentage that is ≥85 years of age will increase by 300%, and the percentage that is ≥100 years of age will increase by 750%. Researchers estimate that the odds of living to 100 have risen from 1 in 20 million to 1 in 50 for women in low-mortality countries like Japan or Sweden. The United Nations estimated that the population of centenarians was about 270,000 in 2005. By 2040, this number is projected to reach 2.3 million.

The sex ratio, defined as the number of men per 100 women, is a common measure of the gender composition. In 2008, the older population was primarily female. In developed nations, for every 100 women 65–79 years of age there were 76 men of that age, and for every 100 women ≥80 years of age there were 48 men of that age (Fig. 1.5). However, by 2040, with projected gains in the life expectancy in men, the number of men per 100 women in these age groups will increase. In developing countries, the gender differences are less evident and are expected to change little from 2008 to 2040.

1.3 Life Expectancy

Life expectancy at birth is greatest in Japan and Singapore at 82 years of age, with most others developed countries—including the US—in the 78–80 year range (Fig. 1.6). On average, an individual born in a developed country can expect to outlive his or her counterpart in the developing

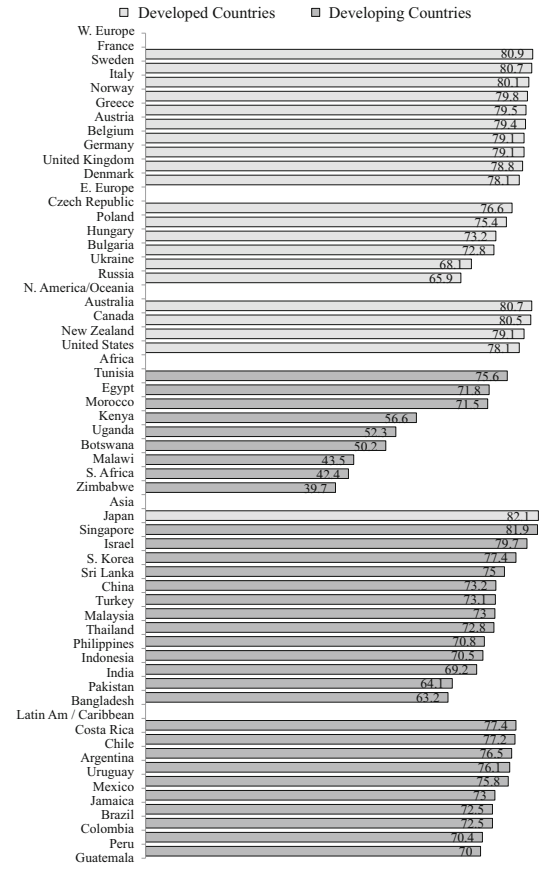

Fig. 1.6 Life expectancy at birth for selected countries by region: 2008 [2]

world by 14 years. Life expectancy has increased dramatically in most parts of the world since 1900. In some countries, life expectancy has more than doubled (e.g., Austria, Greece and Spain). In many developing countries, information on life expectancy prior to 1950 is unavailable. Since World War II, improvements in life expectancy have been fairly common and uniform. One exception is the impact of HIV/AIDS on life expectancy, especially in Sub-Saharan Africa. Almost universally, life expectancy is greater in women than in men, with the average gap in life expectancy at about 7 years. The gender difference is smaller (3–6 years) in developing countries, likely due to higher rates of maternal deaths. The life expectancy at birth exceeds 80 years in more than 45 countries.

Life expectancy at age 65 has also been increasing. Japanese women who had reached age 65 in 2004 could expect to live an additional 23.3 years, and a man who had reached age 65 could expect to live an additional 18 years. In the US in 2003, the average woman at age 65 was expected to live an additional 19.6 years, and a man at age 65 was expected to live an additional 16.8 years.

1.4 The Aging of the United States Population

In 2008, 39 million people ≥65 years of age lived in the US, accounting for 13% of the total population. The older population grew from 3 million in 1990 to 39 million in 2008. The population ≥85 years of age grew from 100,000 in 1900 to 5.7 million in 2008. The baby boomers (born between 1946 and 1964) started turning 65 years of age in 2011. This will result in a dramatic increase in those ≥65 years of age in the US. By 2030, the older population in the US is projected to be twice as large, growing from 35 million in 2000 to 72 million in 2030, with older adults representing 20% of the population. After 2030, the proportion of the population ≥65 years of age will be relatively stable. The percentage of oldest old, however, will grow rapidly because the baby boomers will be entering this age group. There is state-by-state variability in the proportion of adults who are ≥65 years of age. In 2008, Florida had the highest percentage (17%) followed by Maine, Pennsylvania and West Virginia, each at 15%.

As the US population ages, the population ≥65 years of age will become more diverse (Fig. 1.7). In 2008, 80% of the US adults ≥65 years of age were White. By 2050, this is projected to decrease to 59% with increasing proportions of Blacks, Asians and Hispanics. This increase reflects, in part, gains in life expectancy in the minority populations.

1.5 Health Concerns in Older Populations

1.5.1 Mortality

Worldwide, cardiovascular disease (CVD) is the major cause of death, despite declines in overall CVD deaths. A study of the major causes of death in the 25 countries in the European Union (2001) estimated that at age 65–69, CVD and cancer each account for about 35% of all deaths. By age 85, the proportion of deaths due to CVD increases to about 55% and the proportion due to cancer declines to about 15% (estimates taken from graphs) [5].

The major causes of death among individuals in the US are summarized in Table 1.2. Diseases of the heart, cancer and stroke are the top three causes of death, despite an overall decline in death rates of 21% from 1981 to 2006. Death rates for heart disease and stroke declined by about 50%. On the other hand, death rates due to diabetes increased by 20%.

1.5.2 Chronic Health Conditions

The estimated rank order of disease burden differs in high- versus middle/low-income countries (Table 1.3). In high-income countries, most of the disease burden was from chronic conditions, such as CVD and neuropsychiatric conditions. In middle/low-income countries, most of the

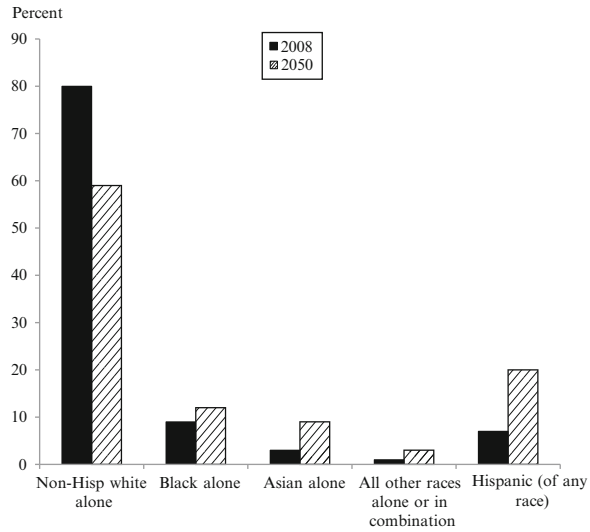

Fig. 1.7 US Population age 65 and over, by Race and Hispanic Origin, 2008 and Projected 2050 [2]. *Note*: The term "non-Hispanic white alone" is used to refer to people who reported being white and no other race and who are not Hispanic. The term "black alone" is used to refer to people who reported being black or African American and no other race, and the term "Asian alone" is used to refer to people who reported only Asian as their race. The race group "All other races alone or in combination" includes American Indian and Alaska Native alone; Native Hawaiian and Other Pacific Islander alone; and all people who reported two or more races

Table 1.2 Leading causes of death: US population ≥65 years of age, 2006

Rank	Cause	Rate per 100,000
1	Diseases of heart	1,297
2	Malignant neoplasms	1,025
3	Cerebrovascular disease (stroke)	297
4	Chronic lower respiratory diseases	279
5	Alzheimer's disease	177
6	Diabetes mellitus	137
7	Influenza/pneumonia	124

Table 1.3 Rank order of disease burden in high-income vs. low and middle-income countries, 2001

Rank	High-income countries	Low and middle-income countries
1	Ischemic heart disease	Perinatal conditions
2	Cerebrovascular disease	Lower respiratory infections
3	Unipolar depressive disorders	Ischemic heart disease
4	Alzheimer and other dementias	HIV/AIDS
5	Lung, trachea, and bronchus cancers	Cerebrovascular disease
6	Hearing loss	Diarrhoeal diseases
7	Chronic obstructive pulmonary disease	Unipolar depressive disorders
8	Diabetes mellitus	Malaria
9	Alcohol use disorders	Tuberculosis
10	Osteoarthritis	Chronic obstructive pulmonary disease

Disease burden measured in disability-adjusted life years [6]

disease burden was due to problems related to maternity and infections. However, these patterns are likely to change. Non-communicable diseases accounted for 85% of the burden of disease in high-income countries compared to 44% in middle/low-income countries. It is estimated that by 2030, non-communicable diseases will account for 87% of the disease burden in low-, middle- and high-income countries.

Figure 1.8 shows the most common chronic health conditions among US populations ≥65 years of age. The most common chronic conditions were hypertension, arthritis and heart disease. The prevalence of certain conditions differs in men

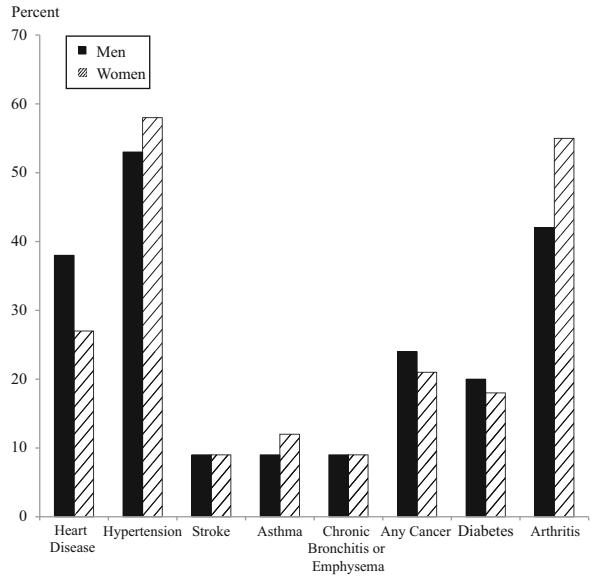

Fig. 1.8 Chronic health conditions among the population age 65 and over, by sex, 2007–2008 [2]. *Note*: Data are based on a 2-year average from 2007 to 2008. *Reference population*: These data refer to the civilian non-institutionalized population

and women, with higher rates of heart disease in men but higher rates of hypertension and arthritis in women. There are also ethnic differences in the prevalence of conditions, with higher rates of hypertension and diabetes in Blacks and higher rates of diabetes in Hispanics compared to Whites.

The rise in the number of individuals who are overweight or obese is a global pandemic and raises the possibility that gains in life expectancy will not be realized. In the Survey of Health Aging and Retirement in Europe (SHARE), 59–71% of men and 41–67% of women were overweight or obese (Fig. 1.9). In the US, the percentage of individuals ≥65 years of age who are obese increased from 22% in 1988–1994 to 32% in 2007–2008 (Fig. 1.10). The prevalence of obesity is higher in individuals 65–74 years of age compared to those ≥75 years of age.

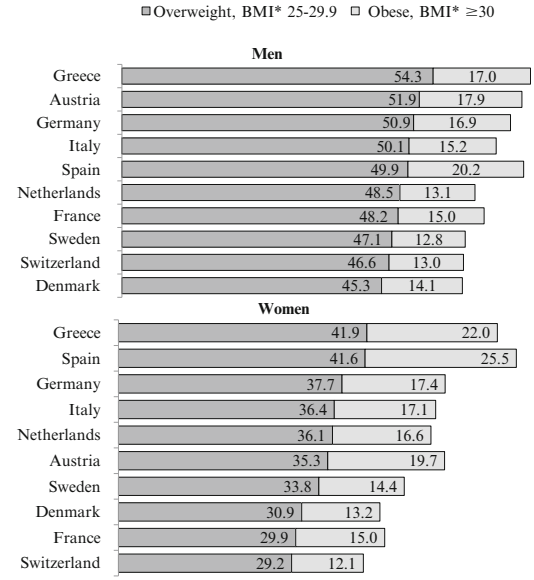

Fig. 1.9 Percent overweight and obese among men and women aged 50 and over in ten European countries: 2004 [2, 7]; * BMI is body mass index (kg/m^2)

1.5.3 Disability

As people are living longer, the quality of that longer life becomes a central issue. This issue will impact national health systems, retirement and the demand for long-term care. Global estimates of disability prevalence rates are difficult to make due to different definitions of disability. One study that examined trends in 2005 in 12 countries defined disability as having one or more limitations in basic activities of daily living (ADLs). A decline in disability was observed in 5 of the 12 countries (Denmark, Finland, Italy, the Netherlands and the US). Disability rates were stable in Australia and Canada, while Belgium and Japan reported increases [9].

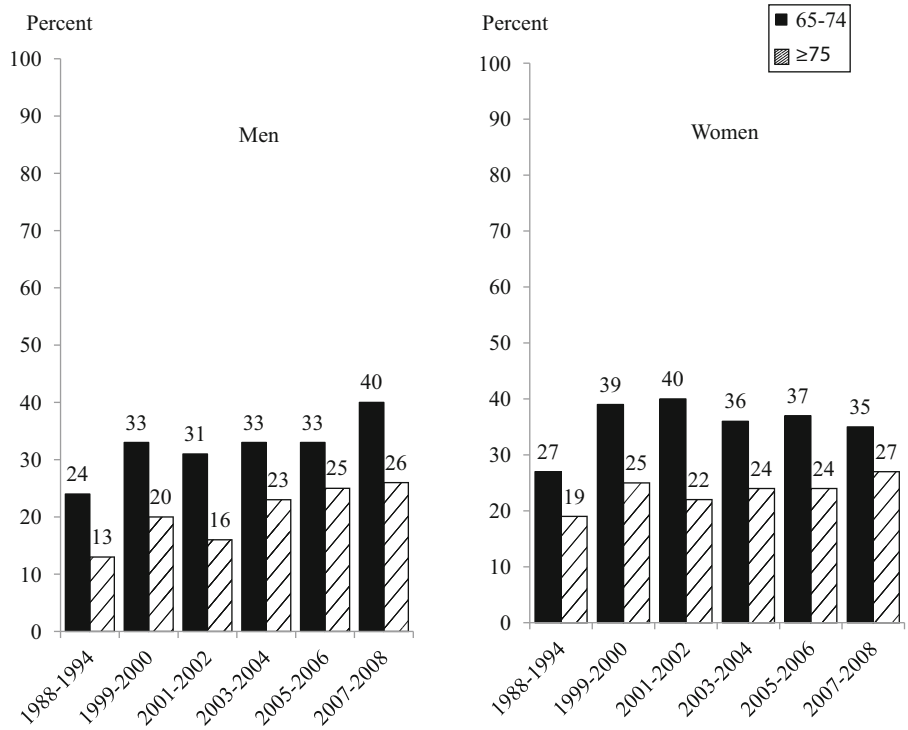

Fig. 1.10 Percentage of US population age 65 and over who are obese, by sex and age group, selected years 1988–2008 [2, 8]. *Note*: Data are based on measured height and weight. Height was measured without shoes. Obese is defined as a Body Mass Index (BMI) of 30 kg/m^2 or greater. *Reference population*: these data refer to the civilian non-institutionalized population

Additional evidence from the US suggests that disability rates have declined in the population that is ≥65 years of age. Data from the US National Long-term Care Survey showed declines in disability from 1982 to 2004–2005 (Fig. 1.11). In 2004–2005, 81% of the US older adult population was not disabled—a decline of about 4% from 1982—and only 4% were institutionalized [10].

1.6 Social Factors in Older Populations

1.6.1 Marital Status/Living Arrangement

Older men are more likely to be married than are older women: 60–85% of men ≥65 years of age are married. Even at ages 75 and older, 70% of men are married. This pattern is true for both developed and developing countries [2], in part because men tend to marry younger women.

Multigenerational living arrangements have been declining in many countries, especially in Europe. Even in Japan, the proportion of older Japanese individuals who are living with children dropped from 87% in 1960 to 56% in 1995. It is expected to further decline to 42% by 2010. Thus, the proportion of individuals—especially women—who live alone has been increasing. In the US in 2008, older women were more than twice as likely as older men to live alone: 40% vs. 19%, respectively. Older Black (41%) and White (42%) women were more likely to live alone compared to Asian (22%) and Hispanic women (27%) [1].

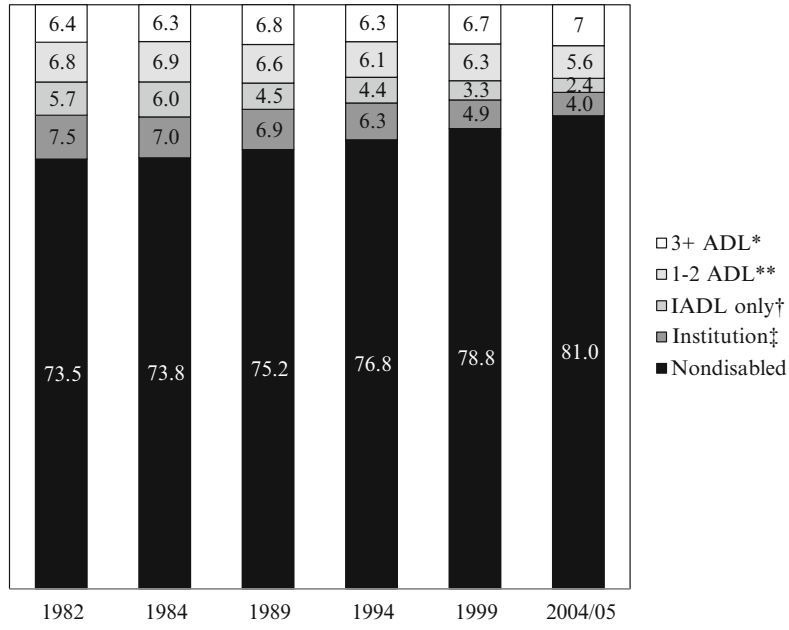

Fig. 1.11 Chronic disability decline in the United States: 1982–2005 (percent of older people in each category) [2]; *"3+ADL" refers to difficulty with three or more basic activities of daily living (ADLs), such as eating, toileting, dressing, bathing and ambulation; **"1–2 ADL" refers to difficulties with one or two of these items; †"IADL only" refers to difficulty with one or more instrumental activities of daily living (IADLs), such as preparing meals, managing money, shopping, performing housework, and using a telephone; ‡"Institution" refers primarily to nursing homes. *Note*: Data refer to the Medicare-enrolled population aged 65 and over

1.6.2 Societal Support

A commonly-used indicator of societal support is the dependency ratio, the ratio between older individuals and working-age individuals. The older dependency ratio (ODR) is defined as the number of individuals ≥65 years of age per 100 individuals 20–64 years of age. The ODR is rising in most regions of the world, except for Sub-Saharan Africa (Fig. 1.12). From 2000 to 2040, the ODR is likely to increase at least two-fold. By 2004 in Western Europe, for every 100 individuals who are 20–64 years of age, there will be 53 individuals who are ≥65 years of age. Thus, the ratio of workers to older adults will only be 2–1.

1.6.3 Education

Individuals with higher education tend to have lower mortality rates and better overall health than do their less educated peers. This may reflect higher income and better access to health care. Educational attainment differs markedly between developed and developing countries. In developed countries, half or more of the populations 55–64 years of age have completed secondary and tertiary education. This compares to about 5% in Chinese men and 10% in Indian men [2, 3], with educational attainment even lower for women in these countries. In contrast, in 2008 in the US, 77% of the total population ≥65 years of age were high school graduates and 21% held a

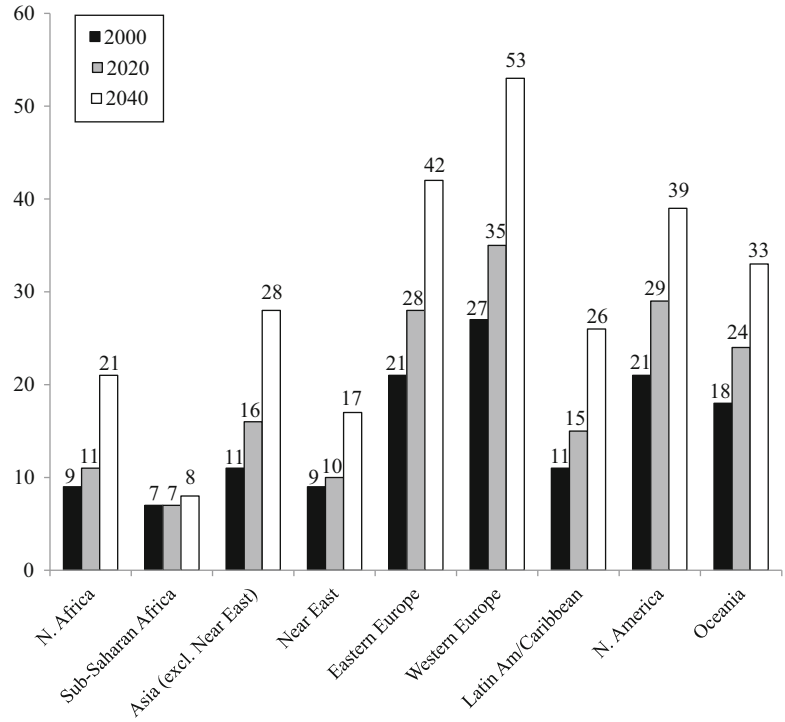

Fig. 1.12 Older dependency ratios for world regions: 2000, 2020, 2040 [2]. *Note*: Older dependency ratio is the number of people aged 65 and over per 100 people aged 20–64

bachelors degree or higher. Despite this high level of educational attainment, there are substantial differences by race/ethnicity. Among Whites, 82% were high school graduates compared to 60% among Blacks, 74% among Asians and 46% among Hispanics [1].

1.7 Impact and Preparation

The demographic changes noted above will have a profound public health impact. In terms of economics, population aging will have an impact on economic growth, savings, investments and labor markets. In terms of health care, the number of geriatricians trained for the care of older adults who have multiple comorbid conditions is woefully inadequate. Population aging will have a major impact on health care insurance plans/premiums—whether private or national—and on other health care resources.

How do we prepare for this aging world? The National Research Council (NRC), part of the National Academies of Science, convened a panel of experts to examine issues that surround global aging and its implications for policy and research [11]. This group noted that the window of opportunity is shrinking to address the gaps in our knowledge about global aging. The report noted the importance of cross-national research to inform policy decisions. The NRC panel recommended that nations coordinate data collection and research in order to leverage resources. Specifically, the NRC panel called for longitudinal studies to identify the links between health, disability, economic status, work and family structure; to establish mechanisms that will help to harmonize and standardize data collected in

different countries; and to develop multidisciplinary research designs to address the many issues that population aging will impact. Hopefully, these efforts will prevent the development of a "global aging" crisis.

1.8 Summary

The average age of the world's population is increasing at an unprecedented rate and this increase is changing the world. From 2010 to 2040, the world population ≥65 years of age will double from about 506 million in 2008 to 1.3 billion by 2040, accounting for 14% of the world's total population. Developing nations will experience the most rapid increase in the older adult population. In China and India, those ≥65 years of age numbered 166 million in 2008, and the number is expected to reach 550 million in 2040. The country with the world's oldest population is Japan. Japan also has a very low birth rate, driving a further acceleration of mean age. Given these facts, population aging is a pervasive global phenomenon.

The aging of the world's population will profoundly affect public health, including effects on economics, healthcare and healthcare resources. Nations will need to coordinate data collection and research to leverage resources if we are to prevent the development of a "global aging" crisis.

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Conducting Case-Control and Cohort Studies in Older Adults

2

Robert B. Wallace

Abstract

Special challenges are involved when conducting primary case–control, cohort and related observational studies in older adults. While the challenges are not unique, there are a host of features that dominate such studies, including the recruitment of older adults into research studies, the ethical hurdles of approaching and gaining consent from participants who may have cognitive impairment, the presence of multi-morbidity, difficulties in data collection such as obtaining interviews from primary and proxy respondents, complexity in interpreting clinical and research biomarkers, different approaches to prevention and treatment in usual clinical care, and altered and complex clinical outcomes. Each of these hurdles, and others, require special design and analytic features when conducting observational research in older adults. Fortunately, some solutions and approaches are available.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Cohort Studies • Case-control Studies • Methods • Proxies • Disability • Dementia • Cognitive Function • Follow-up studies • Epidemiologic studies • Ethics

2.1 Introduction

Methodologically, the frameworks, concepts and study designs that have served epidemiological research well can be profitably applied to the study of health and disease in older adults. However, careful consideration must be given when applying conventional methods to the study of older adults as there are many problems and pitfalls that may complicate the research. This

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chapter provides an introduction to these problems and pitfalls, as well as to some solutions and approaches for overcoming them. Of note, many of these issues apply to other age groups to a greater or lesser extent, but have been more widely popularized in this age group.

2.2 The Ethics of Observational Studies Among Older Adults

Most observational studies that use primary data collection among older adults obtain personal interviews and sometimes physiological measures. These procedures have some innate potential for personal harm (e.g., untoward release of personal clinical information). Although the potential harm is usually not to the severity that could come with various clinical interventions, informed consent is required. While this is a complex issue for all age groups and circumstances, it is a particularly important problem among older adults due to this population's substantial prevalence rates for cognitive impairment, clinical dementing illnesses and psychiatric conditions. For example, it has been noted that dementia is present in more than half of the residents of skilled nursing homes and in at least 20% of community-dwelling older adults at 80 years of age.

Observational studies that approach older adults in general do not diagnose clinical impairment or dementia (or even have the capacity to do so), and thus the question of whether such impairment exists among participants often remains moot and unresolved, with data quality assessed by study staff. One must also be cognizant that some older adults may have guardians or have ceded power of attorney. While respondents and their surrogates may offer useful scientific information, not soliciting guardianship or power-of-attorney status may lead to inappropriate research consent acquisition [1, 2]. Another issue that arises is that participants in longitudinal studies may start out cognitively and psychiatrically intact, but later become clinically impaired. This is a potential problem that requires consideration at the start of a study. There are currently no easy solutions to this problem, but investigators must be aware of the issue and be prepared to address it with Institutional Review Boards.

2.3 General Considerations for Conducting Observational Studies in Older Adults

One useful approach to highlighting many special issues regarding observational research on older adults is to start with clinical observation, an approach that has been the source of many of today's epidemiological methods and hypotheses. Geriatric observations and experience help provide insight into how research studies need to be shaped in order to understand and maximize outcomes. The following is a brief summary of informative geriatric issues and their research consequences. It is important to note that there is no categorical group of the "aged". Clinical changes evolve with normal aging and with the occurrence of age-related diseases and conditions, which challenges analytical attempts to deal with these changes.

2.3.1 Multi-morbidity Is Common in Older Adults

Most older adults have a substantial number of clinical conditions and incumbent treatments. While these conditions and therapies may, on balance, not always be severe and debilitating, they may in various ways change "normal" behavior, dietary patterns, physical activity, cognitive performance and many other characteristics that are represented in population studies, and they may alter disease patho-physiology, manifestations and outcomes. Thus, no matter what the index study condition may be, other diseases must be considered.

2.3.2 Signs and Symptoms Are Common in Older Adults

While not all clinical signs and symptoms necessarily indicate a serious illness, they are common in many bodily systems among older adults. One

consequence of this is that the clinical interpretation of these signs and symptoms, whether through clinical interviewing or structured questionnaires, can yield different results in older adults than might be found in younger adults.

2.3.3 Disease Presentation and Clinical Manifestations May Be Different in Older Adults

For various reasons which are often related to age-related physiological, metabolic and immunological changes, various "classical" diseases may have different clinical manifestations in older adults. For example, pulmonary or abdominal infections may not manifest in the usual manner among older adults, and myocardial infarction may be clinically "silent" more often in older adults than in younger adults. This has implications for the detection and designation of cases in epidemiological studies, as well as for disease surveillance in general.

2.3.4 Clinical Information on Older Adults May Be More Difficult to Acquire

Cognitive decline with age may alter the ability to recall and report disease experiences, making interviews and data collection more complex. Of course, older adults also have more years to recall. Older adults are more prone to delirium, particularly under various types of clinical and social stress, and this also impedes the reporting of information. Older adults may also have a lesser availability of suitable proxy respondents to help collect otherwise missing information.

2.3.5 Distributions of Clinical Biomarkers and Other Physiological Measures May Be Different in Older Adults

Distributions of blood tests and other tests, even those with well-accepted normative standards, may be different among older adults due to age-related physiological change, varying environmental exposures and frequent co-morbidity. This may lead to different levels of disease definitions and occurrences, and may raise difficult issues of interpretation and prediction.

2.3.6 Older Adults Have Increasing Vulnerability to Environmental Challenges

Older adults are likely to have altered responses to "usual" environmental exposures such as physical (e.g., heat or frigid temperatures), social (e.g., hospitalization or other institutionalization) or chemical (environmental contaminants). Most of the responses are likely to be adverse, but it is possible that the reverse can occur in some instances. For example, decreasing liver enzyme function with age may alter the ability to convert a harmless chemical precursor to a harmful toxin.

2.3.7 Bodily System Dysfunction Plays a Prominent Role in the Health Status of Older Adults

The geriatric emphasis on human function (physical, mental, cognitive and social) and on defined diseases adds phenotypes that become both predictors and outcomes in epidemiological studies of older adults. Many such investigations are aimed at preserving function and preventing functional loss. Several "geriatric syndromes", such as declining cognitive function and sleep disorders, also reflect functional decrements that often come with increasing age.

2.3.8 Usual Medical Care Practices May Be Altered in Older Adults

Morbidity and causes of death are mostly defined and named through patient interaction with the health care system, and that interaction can be different among older adults. Care is more intense in order to deal with progressive acute and chronic

illnesses, and it often involves more practitioners and institutions, each contributing to the list of disease occurrences and treatments. Therapies—particularly medications—are much more common, and these alter clinical manifestations and outcomes. Also, there is likely to be an altered propensity for diagnostic procedures and disease surveillance in general, in part due to the imperatives of managing existing clinical priorities and in part because practitioners may believe that intensive diagnosis will lead to more severe therapeutic procedures which may yield adverse outcomes. All of this may alter the disease-labeling experience in older adults from that found in younger adults, who tend to have single illnesses. This could possibly alter the meaning and findings of epidemiological studies with increasing age.

2.3.9 Preventive Interventions, Such as Disease Screening, Decrease with Increasing Age

As has been noted above, there are many reasons why preventive interactions decrease with increasing age. This is important to epidemiological study because this decrease will tend to make it appear that, in some instances, age-related disease rates may not increase in older old adults as rapidly as in younger old adults. In fact, such rates may even appear to decline, at least in part due to altered surveillance rates and related diagnostic biases. It is worth noting that many screening modalities that have a proven value in mid-life adults do not have evidence for efficacy in the eighth, ninth and tenth decades of life. This is an area of research in which epidemiological studies could make important contributions.

2.3.10 Clinical Outcomes Are Often Different in Older Adults

Two issues are worth noting here. First, some treatments that have a certain outcome in young and middle-aged adults may have varied outcomes among older adults. This may be due to altered age-related physiology or to less responsiveness to stressful treatments. It may also be due to altered treatment intensity or the altered propensity to treat, as noted in Sect. 2.3.8 above. Second, older adults tend to have more secondary adverse clinical outcomes from primary illnesses, the so-called "geriatric syndromes," such as falls and fractures, delirium, mental symptoms, sleep disorders and physical dysfunction. All of this adds complexity to case definitions ("caseness") in epidemiological studies.

2.3.11 "Younger Old Adults" Are Different from "Older Old Adults"

Individuals in their seventh decade of life are different from those in their ninth and tenth decades with regard to many clinical, functional and socio-psychological dimensions. Therefore, when individuals across this broad age range are considered in population studies, it is necessary to adjust critical areas such as participant ascertainment and data collection methods to account for these differences.

2.3.12 Many Older Adults Reside in Institutional and Other Long-Term Care Settings

In the United States, about 5% of older adults currently reside in nursing homes and other long-term care settings. Many of these individuals have serious functional deficits, including physical and cognitive impairment. Therefore, conducting observational studies in institutional settings has several special challenges, including appropriately gaining access and informed consent, and obtaining study information through direct participant contact. Thus, institutional care research decisions have to be made as to whether such residents should be included, and how to obtain credible research information. Because of these challenges, research is often conducted on secondary data sources, which is not without its own set of methodological issues [3].

2.4 Conducting Observational Studies of Older Adults

Even after considering the above general issues in approaching older adults for participation in case-control and cohort studies, important logistical concerns remain that must be considered in the design of these fundamental studies. In this section, issues regarding the conduct of case-control studies on older adults will be addressed first, recognizing that many of these issues will apply to cohort studies and other study designs. It has been said many times that the choice of a study design depends on many factors, the most important of which is choosing the design that optimally answers the scientific questions at hand. All robust study designs, including case-control and cohort studies, have substantial costs to participants, investigators and sponsors. Potential research outcomes must always be considered in terms of the investment. The complementary use of experimental designs, either separately or as part of an observational study, may improve scientific yields in these undertakings [4].

2.4.1 Case-Control Studies

There are a number of special methodological issues with regard to in the conduct of case-control studies among older adults, several of which were introduced in the section above. Some of the more general issues follow.

2.4.1.1 What Is a "Case?"

There is every reason to believe that a new case of incident disease in an older adult may have some different clinical, physiological or biological properties than are found when that same disease occurs in a younger adult. Many of the reasons are noted above, but the major determinants include distractions from already existing conditions and differences in clinical presentation and communication, and diagnostic surveillance and practices. Newly diagnosed conditions may have different stages of advancement and severity. Conditions diagnosed in later life may also be different biologically than that "same" condition diagnosed earlier in life. For example, changes in weight, diet and substance use that occur in late life may alter the pathogenetic mechanisms of the disease. Many important chronic illnesses, such as atherosclerotic disease or breast cancer, clearly have antecedents early in life, so diseases that become clinically overt in the senium may be on a different biological trajectory. Similarly, the occurrence of various infectious diseases in older adults may reflect prior organism exposure earlier in life, yielding different clinical behavior and outcomes.

The situation may be more complex because those who survive to have "conventional" conditions late in life likely have a set of biological characteristics that allowed this survivorship, and such characteristics could alter the nature of late-occurring conditions. As one example, it is axiomatic that diseases that occur earlier in life are more likely to have an overt genetic basis than those that occur later in life. The higher mortality of older adults leads to the issue of competing mortality [5]; it is possible that certain diseases are less likely to occur among older old adults if some other diseases supervene earlier. Special care is required in the design of case-control studies of general longevity as the "controls" are, by definition, deceased and unavailable. Some type of nesting within previously-assembled cohort studies may be necessary for this type of study.

The above has several important implications for the conduct of case-control studies. One is that risk factors may be different for the "same" condition in different parts of the life course, even within the senium. For example, all other things being equal, a given blood cholesterol level may predict different clinical outcomes in an 80-year-old than in a 45-year-old. Another is that biological case homogeneity across the life course should be assessed with biomarkers and other related methods to explore or determine case homogeneity across the age spectrum. A third is that case heterogeneity will likely lead to varied clinical outcomes and responses to treatment, and so comparative effectiveness research needs to consider this problem as well. It should also be noted that these issues are not limited to studies

in older adults. Many of these problems are global and in search of innovative approaches.

As in other age groups, sometimes "cases" in older adults are not discrete clinical entities but rather are defined from the categorization of continuous biomarker measures. For example, among older adults, a "case" may be defined as someone who has a hip bone mineral density below a certain level, or has a usual walking speed above or below a certain rate. Such definitions can be very productive if clearly articulated, but there must be assurance regarding the accuracy and reliability of the measures or case misclassification can occur.

2.4.1.2 Ascertaining Cases and Controls

The general techniques for identifying older patients as cases with a particular health condition are probably not different from those in other age groups: patient registries, clinical records, clinical referrals, population contacts, etc. In the United States and in many other developed countries, older adults appear on nearly-universal health insurance or health system lists (e.g., in the United States: Medicare), making participant sampling easier and more complete. However, in general, older adults have a set of special impediments to case ascertainment:

- Many older adults live in protected environments, such as assisted-living or chronic-care institutions, and direct contact through telephone or mail may be more troublesome even in the absence of illness or dysfunction. Also, older adults are still somewhat less likely to have access to electronic mail or other online devices [6].
- Older adults living in the community may be protected from public contact by family members or others, and this may make access for studies problematic.
- Higher prevalence of clinical conditions, various functional deficits and age-related cognitive dysfunction may all act to decrease the ability or willingness of older adults to participate in studies. Cognitive decrements are a common and difficult problem for observational studies in older adults, and the solutions are difficult. Cognitively-impaired potential study participants, even those living in the community, may be protected from various types of social or professional contact, even if the study burden is minimal and appropriate, and the proxy "guardian" may be an equally-impaired spouse or other relative. Cognitive dysfunction can decrease interview data quality and has been shown to lead to lower-quality interview data [7], as well as decreases in the capacity for decision-making of many types.
- Older adults who are able to participate from a health perspective may have social or economic deterrents to such participation, such as having substantial care-giving obligations or a lack of transportation.

All of these factors lead to decreasing participation rates for older adults in case-control studies, and most would apply to the ascertainment of control participants as well. This is made worse by a general trend for increased population reticence to participate in research using community-based ascertainment [8]. Remediating these problems is difficult. One general approach is to use proxy respondents where needed [9], and that raises the issue of using proxy respondents for control participants as well. A related problem is that older adults have higher mortality rates, requiring the use of surrogates for decedent cases who may die in the interval between disease onset and scheduled data collection, and for some methodological nuances in selecting controls for deceased cases [10]. Other approaches include exploiting secondary data sources for appropriate hypotheses and providing older adults with more convenient modes of data collection, such as cell phones, devices that overcome sensory impairments, personal digital assistants or even home computers. In the end, however, non-participation of older adults increases with age and few efficient solutions have been devised.

2.4.1.3 Collecting Data on Older Adults

Several general problems may decrease the quality of interview data collected from older adults who participate in case-control studies. As noted above, declining population cognitive abilities are a central problem when it comes to recalling remote health events or exposures.

However, each item or hypothesis should be evaluated on its own terms to determine whether interviews can be a viable and accurate source of information. It is possible that memory aids, such as timeline techniques [11], may improve the accuracy of information. A general problem for all case-control studies is that validation of historical information is often not available, such as from clinical, employment or environmental records, and the problem is exacerbated among older adults. Even proxy respondents may be less available for older adults than for younger index participants.

Of course, problems with interview studies may be less important if biochemical, physiological or other biological measures can overcome the problems of interview recall. Studying, for example, immunological memory for prior infectious exposures or xenobiotic levels such as DNA adducts may offer exposure indicators that might not be easily obtained through interview methods.

2.4.1.4 Matching Cases and Controls

Controls are often matched to cases for the purposes of statistical precision, the avoidance of confounding factors and for other reasons [12]. This may be technically more difficult in case-control studies of older adults because there are so many potential variables on which to match. Thus, matching must be done carefully, with consideration given to hypothesized causal pathways. Some assumptions of case and control homogeneity may not be correct due to the potential variations in long-lived individuals. For example, older adults often have one or more retirement relocations [13], and thus have different exposures than would be assumed from older adults who have lived only within a particular geographic area. Biomarkers, particularly gene variants, may play an important role in determining the homogeneity of case and control populations regarding factors other than biological indicators of risk of a particular disease. An example would be comparing the groups in terms of ancestry-informative markers [14]. This could be very useful so long as these markers are not associated with the hypotheses of interest.

2.4.2 Cohort Studies

Cohort studies of older adults have many issues in common with case-control studies and share many of the methodological and logistical issues. For example, information collected from cohort members at study inception is subject to all of the recall problems noted in retrospective studies. Many cohort analyses are now being conducted on existing data sets, including administrative records, health care records and even data from well-documented clinical trial populations, depending on the scientific questions at hand. However, cohort studies often require primary data collection. The following discussion addresses many of the important requisite issues in the design and analysis of such studies. A recent set of papers in the Journal of the American Geriatric Society [15, 16] has provided updated, useful information on cohort study methods.

Prospective cohort studies can be particularly resource-intensive, and the potential scientific payoff must be carefully calculated. Some scientific questions take many years to address, but many changes may take place during the observation period: various measures may be improved or discredited, participants are increasingly censored (permanently dropping out of the study) due to intervening illnesses or death, conceptualizations of diseases change, study equipment may fail and laboratories may change their methods, and some scientific questions and hypotheses may lose their cogency. These problems have no easy resolution, but extensive advice and consultation will help in deciding whether various cohort studies are well rationalized.

2.4.2.1 Recruiting and Retaining Cohorts of Older Adults

Recruiting cohorts of older adults depends, as always, upon the scientific questions being asked. A fundamental issue is whether the cohort should comprise a geographically-representative sample or whether volunteers would suffice. In general, the former is much more challenging to ascertain and its use depends on many factors, including the availability and accuracy of sampling frames and the scientific persuasiveness of the study

themes. Bonk [17] has provided a useful review for the recruitment and retention of volunteer cohorts of older adults, but difficulties remain, particularly with regard to the oldest older adults. Since, as noted above, almost all older adults have a number of chronic conditions or risk states, the question arises as to how these characteristics selectively affect participation. In general, the older the cohort, the greater the non-participation rate will be. Further, when an older cohort is founded, it should be expected to have increased dropouts relative to younger cohorts. The reasons for this loss of study population are likely to be complex and possibly related to the broad distribution of conditions already in place. However, it is the experience of several recent cohort studies that once enrollment is complete, periodic follow-up rates can be credible—in the range of 75–95%.

2.4.2.2 Selecting a Minimum Age for Establishing Cohorts of Older Adults

If cohorts of older adults are founded with the intent of interviewing participants and collecting other data, an important conceptual problem is the minimum age at which the cohorts are established. Starting at later ages may be more efficient in terms of higher rates of age-related changes and disease, and therefore in terms of study resource consumption; younger cohorts may simply be less informative on a per capita basis. However, so many characteristics of older adults (e.g., behaviors, age-related organ changes, diseases) have origins earlier in life, and form the important basis for life-course studies [18], that starting a prospective cohort in later decades may impede the possibility of accurately studying and documenting earlier life events and exposures that are related to outcomes of interest. Also, as noted elsewhere in this chapter, starting at a later age may decrease the amount of information collected due to cognitive decline and declining institutional access, and may exclude certain individuals with earlier deaths who had characteristics relevant to the scientific questions, such as certain genetic or genomic properties or determinants. Of course, the import of this issue depends upon the major research questions and hypotheses for which the cohort is being constructed.

2.4.2.3 Study Interval for Data Acquisition in Cohorts of Older Adults

Another important issue in cohort studies is how frequently to collect primary data. Health, functional and social changes occur at varying rates and intervals, and may change with age and risk status, so as always, the interval depends upon the scientific issues being addressed. Typically, fixed intervals are chosen for reasons which, understandably, often depend upon available resources. A fixed interval probably decreases analytical complexity, but at least some consideration should be given to using combinations of fixed and varying or flexible intervals for various measures to maximize data precision without producing undue participant burden. For example, there has been a suggestion to incorporate a "measurement burst" design [19], where data collection intervals change when critical epidemiological events occur. Table 2.1 lists some of the considerations in selecting the data collection interval. Basically, shorter intervals lead to more textured data collection and are responsive to short-term changes that are often not otherwise well studied. However, shorter intervals involve trade-offs that make decisions regarding study intervals difficult, including greater respondent burden. This can be mitigated by subsampling participants for various measures, varying the study intervals,— mixed modes of data collection (e.g., personal and telephone interviews, postal and "leave-behind" questionnaires, Internet interviewing, record linkage) and employing other hybrid approaches that may reduce resource consumption while maintaining scientific productivity.

Another issue related to study interval is the possibility of participant "training effects" when identical or similar items or performance tests are repeated at periodic intervals. There is evidence that many respondents can recall test items or procedures, such as those for psychological performance, and subsequently "practice" them.

Table 2.1 Factors affecting the choice of study interval in cohort studies

Shorter study interval	Longer study interval
More available study resources	Fewer resources available
Frequently changing measures	Less secular change in measurement variables
Frequently-occurring study events	Less frequent events
High need for cohort maintenance	Less need for cohort maintenance
Lower participant burden	Higher participant burden
Fewer proxy respondents available	More proxy respondents available

Scores can thus improve over time unless other forces intervene [20]. These effects are one source of measurement error that may occur when using short inter-survey intervals.

2.4.2.4 The Primacy of Assessing Cognitive Function in Cohort Studies of Older Adults

Cohort studies of older adults have many goals, only some of which concern the nature, causes and outcomes of cognitive function and clinical cognitive illnesses. In this author's view, a strong case can be made for measuring at least some important dimensions of these outcomes in most general, multi-hypothesis cohort populations. Cognitive measures can be considered in two general categories within cohort studies: indicators of possible dementing illness and full-spectrum assessment of various cognitive dimensions. Performance of cognitive measures will enable (a) the assessment of the quality of interview information [7]; (b) the prediction of subsequent participant behaviors and function, including the ability to learn new study procedures; (c) the prediction of health and social outcomes; and (d) insights into participants' clinical decision-making, which can be increasingly important in making preventive, diagnostic and treatment choices. There may be value in periodically performing cognitive measures because these functions change over time [21] and they will be relevant to many research hypotheses and continued cohort participation. The problem is that even simple cognitive measures can consume precious study time and may be subject to participant distractions or refusals that add measurement error.

2.4.2.5 Proxy Respondents in Cohort Research

A critical issue in conducting cohort studies among older adults is to acquire as much information as possible. One potent source of such information is proxy respondents. There are some types of information that can't be acquired this way, such as opinions, attitudes and various self-perceptions of health and social events. However, index respondents in older cohorts may be unable to offer useful information in some domains due to cognitive impairment (e.g., Alzheimer's disease) or psychiatric illnesses, symptoms (e.g., fatigue), sensory deficits, serious clinical conditions, or the adverse effects of medications or other treatments. It is also possible that specialized family functions, such as money management, have been delegated to someone else. This yields the general point that for some relevant information, proxy respondents may be better sources of information than the index respondent. Optimal information may require the use of multiple proxy respondents, including healthcare and other professionals, paid helpers, and relatives and friends. Some cohort studies invoke proxy interviews as part of the protocol to obtain certain types of specialized information.

One problem with the use of proxies is their availability. Another is the quality of their reports if they are of similar age or health status to the index participant. On occasion, there is also a consent issue when primary respondents name other potential persons to part of a research study. Using proxy respondents also generally raises the cost of data collection, but it can be extremely helpful under the right circumstances. Methodological issues in using proxies have been usefully reviewed by Snow et al. [9].

2.4.2.6 Analytical Issues in Cohort Studies

There are many useful reports on the analysis of longitudinal data in general, so this topic will not be reviewed here in depth. However, some

general issues will be highlighted. In addition to standard analytical methods for longitudinal data, two ancillary approaches to analyzing cohort data are the nested case-control study and the case-cohort study [22]. Both approaches are basically used to simplify the analysis and improve efficiency in working with large and complex cohort data sets. In nested case-control studies, cases of interest that meet certain definitions are selected from the cohort, and controls are selected from non-cases who have a similar time interval of follow-up. These data are then analyzed in the manner of typical case-control studies. In case-cohort studies, cases are selected in a similar manner, but controls come from a random sample of non-cases in the cohort irrespective of the time interval of follow-up. Unfortunately, the gains in efficiency, such as achieving lesser use of expensive biomarker determinations that come with using these approaches may come at the price of certain limitations in data outcomes. Such analyses must be conducted carefully, particularly given the complexity of diseases and the risk factors in older adults.

Another important issue is missing data. This can be a problem in all data collection, but is particularly important in cohort studies because there are multiple participant contacts and usually substantial data collection opportunities. While there is a well-established literature on dealing with missing data, newer techniques are always emerging that should be considered [23]. However, all of these techniques are not a substitute for cohort study protocols that minimize the problem with effective study designs. These protocols include being flexible with data collection opportunities, such as allowing short delays in data collection during periods of illness or intensive care-giving and using proxy respondents more readily where feasible.

One general issue in analyzing cohorts of older adults is the problem of censoring, which in some respects is a type of missing data. Censoring may be due to many factors, but the most common general reasons are death, illness, care-giving duties and burdens of being in the study. Access to and use of transportation to study sites can also be a common problem, particularly after the seventh decade [24], and health factors related to selective participation can be substantial [25]. One approach to collecting information on events prior to and surrounding death is the use of informative proxies. For example, in the Health and Retirement Study, an American nationwide cohort study of older adults (hrsonline@isr.umich.edu), there is a successful "exit interview" process that captures health, social, economic and medical care utilization events in the months prior to death. All causes of censoring except death can lead to the loss of important study outcomes, and one must resort to proxy respondents or to secondary data sources where available.

An important conceptual issue arises in the analysis of death events, relating to the nature of the scientific question. If it is desired to know the rates and risk factors for outcomes had the participants lived a reasonable period beyond their death, then consideration should be given to excluding the decedents from the analysis altogether. However, other analytical methods are possible due to the accelerated rates of many adverse functional and health characteristics in the months and years prior to death. This problem has been addressed by analyzing health events that occurred prior to the time of death using retrospective reports from proxies and prospective study designs [26]. However, it should be acknowledged that there are variations in these patterns, ranging from long, slow declines to sudden death in the face of insignificant health problems. Exclusion of the decedents eliminates much of the problem of co-mingling age-related "natural history" changes with pre-terminal events. On the other hand, if the question involves determining the net effect of various exposures or interventions on outcomes among the entire population, including decedents, then all participants should be included.

The problem of co-mingling non-terminal with terminal events was approached in the psychological literature a few decades ago, and became known as the "terminal drop" [27]. Here the issue was trying to dissect out patterns, predictors and causes of long-term cognitive trajectories among

older adults and differentiating them from those patterns occurring in the pre-terminal period. There have been fewer analyses in other functional domains, such as physical, social and mental function, but the same patterns likely apply. One consequence for data collection in cohorts is that there may be value in continuing to follow cohorts of older adults with mortality surveillance even after primary data collection is completed in order to address this issue.

A related issue is the problem of competing mortality [5] or competing risk. For example, one may wish to determine the likelihood of certain outcomes in a population if some participants had not died at all or had died only of certain causes. Dealing with competing mortality, and sometimes even competing morbidity, is analytically challenging and has been discussed in detail [28].

Overall, there are great challenges remaining in the analysis of longitudinal studies, not least of which is dealing with short-term fluctuations in health and functional measures—one of the frontiers of cohort studies—because the methodology may be demanding and expensive. This problem may be exacerbated due to the lesser availability of data with which to estimate sample sizes for various hypotheses. The incorporation of various types of physiological, biochemical and other biomarker data into cohort studies may also make analyses more complex. Nonetheless, many statistical modeling approaches to longitudinal data are available, including those dealing with death or other censoring. These include Cox proportional hazards models, extended Cox multistate transition models, generalized estimating equations, generalized linear models, and joint modeling methods [28]. Biostatistical assistance in the planning and analysis of longitudinal models is almost always indicated.

2.5 Conclusion

While many of the logistical and conceptual issues related to case–control, cohort and other observational studies of older adults apply equally to other age groups, there are a host of special issues and problems that pertain to studying older adults. Many of the study issues are logistical, related to ascertaining study populations, collecting accurate data and maintaining participation in longitudinal studies with multiple contacts. However, there are also complex conceptual issues concerning the nature and interactions of health, disease and dysfunction among older adults that should guide both the hypotheses and the analyses of these pursuits.

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Study Design: Randomized Controlled Trials

3

Marco Pahor and Matteo Cesari

Abstract

Due to the growing need to make clinical decisions based on scientifically valid, standardized and objective grounds, the number of randomized controlled trials (RCTs) has steadily been increasing over the last three decades. RCTs represent the most rigorous study design that is aimed at comparing the effects of different interventions on specific outcomes. Nevertheless, evidence-based medicine still has limited applicability, especially for older adults who are often excluded from clinical trials. Clinical trials in older adults present special challenges with regard to ageism in research, recruitment of high-risk participants, multiple comorbidities and polypharmacy, adherence to the protocol, compliance with the interventions, safety, adverse events reporting and standardization of geriatric-specific outcomes. To provide clear and reliable results for translation into clinical practice, RCTs need to be based on a solid rationale and apply state-of-the-art methodologies. A number of key issues must be considered when planning and conducting RCTs, with special attention given to challenges that are related to the inclusion of older adults in clinical research.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Randomized controlled trials • Study design • Masking • Exclusion criteria • Inclusion criteria • Informed consent • Generalizability

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Abbreviations

ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attract Trial
ASPREE	ASPirin in Reducing Events in the Elderly
CAST	Cardiac Arrhythmia Suppression Trial

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CONSORT	Consolidated Standards of Reporting Trials
CRT	Contract Research Organization
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
HERS	Heart and Estrogen/progestin Replacement Study
HMO	Health Maintenance Organization
HYVET	Hypertension in the Very Elderly Trial
IRB	Institutional Review Board
LIFE	Lifestyle Interventions and Independence for Elders
MTD	Maximum Tolerated Dose
PPO	Preferred Provider Organization
RALES	Randomized Aldactone Evaluation Study
RCT	Randomized Controlled Trial
SHEP	Systolic Hypertension for the Elderly Program
SPPB	Short Physical Performance Battery
T-Trial	Testosterone Trials
US	United States
WHI	Women's Health Initiative

3.1 Introduction

Randomized controlled trials (RCTs) are considered to be the gold standard for the assessment of intervention efficacy and effectiveness. To provide reliable results, an RCT needs to be carefully planned and follow well-defined rules in its conception, design, implementation and reporting. Individuals who are ≥65 years of age constitute the most rapidly growing age group. Older adults are the patients seen in more than one third of all outpatient clinic visits and utilize more than half of all hospital days. Therefore, the need to specifically focus clinical research and scientific evidence on aged populations is a growing research priority. Nevertheless, older age represents a frequent criterion of exclusion from clinical research [1, 2]. Clinical trials in older adults present special challenges with regard to ageism in research, recruitment of high-risk participants, multiple comorbidities and polypharmacy, adherence to the protocol, compliance with the interventions, safety, adverse events reporting and standardization of geriatric-specific outcomes.

In this chapter, we discuss the key points to consider when conducting RCTs with a special focus on older adults. To ease the discussion, we provide several practical examples derived from the ongoing Lifestyle Interventions and Independence for Elders (LIFE) study, a multicenter Phase 3 RCT designed to assess whether physical activity or health education is more effective for the prevention of major disability in 1,600 high-risk sedentary older adults [3] (from the pilot of the LIFE study, which was completed in 424 participants [4]), as well as other RCTs that were conducted with older adults.

3.2 Basic Concepts

A "clinical trial" is usually defined as a prospective study that is aimed at comparing the effect and value of one or more interventions against a control [5]. Thus, a clinical trial must be prospective, compare different interventions and consider a control group. Random allocation of participants to the study arms and a blind assessment of the effects are also innate components of modern RCTs.

The reason for considering the design and conduction of an RCT is the existence of uncertainty or clinical equipoise regarding the effects of an intervention (i.e., there is a question without an answer). Even if the researcher truly believes in a hypothesis, that researcher is ethically justified in addressing the question in an RCT if that researcher has no preference for the possible answers and has sufficient doubt regarding which intervention is better.

Clinical trials are either explanatory (i.e., testing efficacy under ideal conditions) or pragmatic (i.e., measuring effectiveness in routine clinical practice) [6]. This differentiation is relevant because the two approaches may lead to different conclusions regarding the same intervention. In fact, a beneficial treatment in a selected population and specific setting may not work equally well in a real-life setting. These two natures of a

trial will also determine different and substantial decisions regarding its design. An explanatory approach will be based on the selection of a homogenous population to test the scientific validity of a hypothesis. In contrast, a pragmatic trial will rely on participants who mirror "real" variation found among patients in clinical practice.

3.3 Design of Randomized Controlled Trials

RCTs may be designed along the following formats [7]:

- *Parallel-group design.* This type of trial entails separate groups, each randomized to a different intervention (or placebo). The groups are followed-up to estimate the outcome differences among interventions.
- *Crossover design.* A crossover trial is based on repeated measures/assessments of participants who receive different interventions in a random sequence. For example, in a crossover trial to compare the efficacy of two treatments A and B, participants are initially randomized to these two interventions. After a follow-up period *t*, the crossover (with a mid-term assessment) occurs and participants who received treatment A during the first phase of the study start receiving treatment B, and vice versa. At the end of the second follow-up period *t*, the close-out visit is performed and participants are reassessed. Advantages of this design include the ability to control for all known and unknown confounding variables with implicit matching of data (each participant is their own control), improved recruitment (every participant receives the intervention) and a substantially higher statistical power compared to the independent parallel-group design. Three major issues need to be carefully considered in the design phase: the "order" effect (i.e., the order in which treatments are administered may modify the outcome), the "carry-over" effect (an adequate wash-out period between treatments is required to avoid a confounding of the estimated effects) and the "learning" effect (i.e., when an intervention administered in the first phase of the trial cannot be completely eliminated in the second; for example, the learning of a specific skill or behavior) [5, 8].
- *Split-body design.* This trial design is based on testing different interventions (or placebo) on separate parts of the body of each participant (e.g., intervention on the left arm versus placebo on the right arm).
- *Cluster design.* This type of trial is used when pre-existing groups of participants (e.g., clinics, hospitals, study sites, schools) are randomly allocated to the different interventions (or placebo). In other words, the randomization process does not deal with single participants, but with groups of individuals.
- *Factorial design.* When this type of trial (also called "fully crossed design") is adopted, participants are randomly assigned to different study arms which are considering different combinations of interventions and placebo (e.g., group 1: treatment A and treatment B; group 2: treatment A and placebo B; group 3: placebo A and treatment B; group 4: placebo A and placebo B). In this way, it is possible to study the effect of each single factor on the response variable as well as detect the presence of possible interactions in the relationship between factors and the study outcome. Usually, a factorial trial entails four treatments (i.e., a 2×2 factorial design). If the number of combinations is too high to be feasible, some possible combinations can be excluded, leading to a "fractional factorial design".
- *Standardly-tailored design.* Standardly-tailored multicomponent trials have been proposed to study multicomponent interventions for complex geriatric conditions [9–11]. The study population is selected according to modifiable risk factors for the outcome of interest. Only participants who have an individual risk factor are randomized to the control or active interventions that are targeted towards that risk factor. Consequently, participants are not randomly assigned to all or some pre-planned combinations of interventional

components as in a full factorial design. In the standardly-tailored design, participants randomized to the intervention arms are given only those interventional components that correspond to the risk factors that the participant possesses at the time of enrollment.

- *Nested design*. In nested design RCTs, participants are randomized to active or control interventions and, according to baseline characteristics, may participate in one or more nested trials that are investigating diverse outcomes. For example, the Testosterone Trials [12] are a set of multi-center RCTs that involve 12 centers across the United States. The primary aims are to test the hypotheses that testosterone treatment of older men who have low serum testosterone concentrations—and who have symptoms and objectively-measured abnormalities in at least one of five areas (physical or sexual function, vitality, cognition and anemia)—will result in more favorable changes in those abnormalities than will placebo treatment. Participants may enter into one or more of the five outcome trials according to their baseline inclusion criteria. This design may efficiently save on sample size if a relevant number of participants qualify for more than one trial. However, it also presents challenges in projecting the sample size, as it is often difficult to accurately predict how many participants will actually qualify for multiple trials.

An RCT may also be categorized based on the blinding procedures. "Blinding" indicates strategies implemented to prevent participants, caregivers and/or outcome assessors from knowing the intervention allocation [13]. Unlike allocation concealment (see Sect. 3.4.4), it is sometimes impossible or inappropriate to perform entire blinding in RCTs (e.g., when comparing surgery to radiotherapy in cancer patients, or in behavioral interventions such as physical activity or health education in the LIFE study). The recent Consolidated Standards of Reporting Trials (CONSORT) statement suggests avoiding the terms "single-blind", "double-blind", or "triple-blind" as they are potentially misleading. It is instead recommended that researchers explain who was blinded and how it was done after the allocation to the interventions [14]. For example, in the LIFE study, the interventionists and participants are aware of the randomized intervention allocation, but the outcome assessors are blinded.

Before a new intervention (either pharmaceutical, surgical or behavioral) can be implemented in clinical practice, it needs to demonstrate a higher efficacy compared to current standard treatments. Therefore, several preliminary phases of research, which are outlined below, are required for approval by the regulatory agencies. Regulatory approval is usually a lengthy process, sometimes lasting years. However, a recent survey has found that despite criticism of the United States (US) Food and Drug Administration (FDA) review process, new cancer drugs are approved more quickly in the United States than in Europe [15]. "Compassionate use" or "expanded access" programs allow medicinal products that are not approved, but are in the development process, to be made available to patients with a severe terminal disease (e.g., cancer, Alzheimer's disease) who have no other alternative treatment available to them [16, 17]. The main phases of RCT research are as follows:

3.3.1 Phase 0 Trials

Phase 0 trials are used to establish whether the pharmacokinetic and pharmacodynamic properties of a drug correspond to those expected from preclinical studies. Since these studies are based on the administration of very low, subtherapeutical doses, no data regarding safety or efficacy can be obtained. On the other hand, these studies provide useful information for identifying the best drug candidates according to the pharmacokinetic and pharmacodynamic parameters.

3.3.2 Phase 1 Trials

Phase 1 trials represent the first step in the evaluation of an intervention in humans. They usually

enroll a small number of participants (less than 100) with the aim of understanding how well the intervention is tolerated. Phase I trials are particularly required to estimate the Maximum Tolerated Dose (MTD), which is the maximum dose of a drug that a patient can receive before the onset of unacceptable toxicity. Moreover, Phase 1 trials need to provide definitive information regarding the pharmacokinetic and pharmacodynamic properties of the tested drug.

The MTD is usually estimated by recruiting a small number of participants and sequentially entering them at a particular drug dose. If no adverse side effects are exhibited, a new group of participants is entered into the trial at a higher drug dose. This is continued until unacceptable toxicity shows up or pre-calculated safety levels of pharmacokinetics are reached. That dose, or perhaps the previous one, is referred to as the MTD.

3.3.3 Phase 2 Trials

After the initial safety of the study drug is established, the next goal (to be accomplished in Phase 2 trials) is to assess whether the drug has any biological activity or effect. During this second phase, the drug safety will continue to be monitored in a larger group of participants (a few hundred). Early Phase 2 trials (or Phase 2A trials) are designed to determine the required dosing of the treatment. The following Phase 2B trials are conducted to estimate the efficacy of the intervention at the established doses.

Phase 2 trials are sometimes designed as case series and sometimes as small randomized clinical trials (in a sort of hybrid Phase 2-Phase 3 design). The success of a Phase 2 trial depends on the quality and proper conduction of the Phase 1 study. If the Phase 1 study is not qualitatively acceptable, the investigator may use a dose of the tested intervention that is either too low (thus, falsely ineffective) or too high (thus, falsely harmful). Results from Phase 2 trials are required to design the comparative Phase 3 trials.

3.3.4 Phase 3 Trials

A Phase 3 RCT enrolls several hundred or several thousand participants at multiple sites to assess the efficacy of a new intervention and, consequently, its possible role in clinical practice and public health. Since Phase 3 trials are the most expensive, difficult and time-consuming, the strongest evidence coming from the preliminary phases is required. Phase 3 RCTs are also required for regulatory approval of new interventions.

An intervention may fail or show specific issues years after its approval. Therefore, long-term surveillance is necessary. This "post-marketing surveillance" is usually referred to as Phase 4 trials.

3.4 Randomized Controlled Trials in Older Adults

The participation of older adults in clinical trials is still far from being quantitatively and qualitatively adequate [18]. Trial participants rarely mirror the typical older patients evaluated by geriatricians or those living in long-term care facilities. In fact, the typical older participants in clinical trials are younger, present less comorbidity, take fewer medications, and are cognitively intact and independent in activities of daily living. This type of participant hardly represents the socially, biologically and clinically complex geriatric patient population [19]. Although it is commonly thought that older adults are not particularly willing to participate in clinical studies, a growing body of literature shows that older adults have a positive opinion regarding their enrollment into a clinical trial [20].

Why are older adults often excluded by RCTs? First, their clinical and pharmacological heterogeneity and complexity might significantly influence the effect of the tested intervention. Concerns about safety might be raised by physicians due to the increased risk of adverse events. Second, older participants are more likely to drop-out from the study due to frail health status. Third, there is the key issue of the availability of an efficient social support. Limited support from

family or a caregiver makes it extremely difficult to guarantee adherence to the study protocol and to plan the proper follow-up evaluations. Fourth, the enrollment and maintenance of older participants in a trial requires extra time and resources, and consequently extra expenses.

3.4.1 Evidence-Based Medicine

Modern medicine is based on evidence. Physicians constantly look for standard and objectively valid treatments for their patients who have special needs. Patients and their families increasingly require an informed choice for the planned or proposed interventions. These certainties can be provided only through methodologically-correct state-of-the-art clinical research [21].

Evidence-based medicine is the judicious and systematic application of research evidence to the care of individual patients, integrated with clinical judgment, expertise and patient's values and preferences. The applicability of evidence-based medicine in older patients is a commonly debated issue for geriatric medicine. It has been estimated that only 5% of the RCTs reported in four major journals in 2004 were designed specifically for older adults, and 72% of trials reported in nine major journals between 1994 and 2006 excluded older adults [2]. This (often poorly justified) exclusion makes information that comes from scientific evidence unreliable and potentially harmful for older adults. What works for a younger adult patient without comorbidities or concurrent therapies is unlikely to similarly work for a frail older adult who has multiple comorbidities and is taking numerous drugs.

The need of evidence to directly apply research findings to everyday clinical practice has led to a significant increase in RCTs and meta-analyses over the last three decades. It has been estimated that 75 trials and 11 systematic reviews of trials are now published every day, and a plateau has not yet been reached [22]. Given this enormous body of data, we need to be extremely careful in selecting what is indeed relevant, what is coming from methodologically correct sources, and what might be biased or of limited interest. In this context, it is noteworthy that a major source of bias in clinical research is caused by the obsessive need for obtaining "positive" findings from a trial [21], particularly when dealing with small trials focused on surrogate outcomes.

Phase 3 RCTs are designed to gather the necessary scientific evidence to impact clinical practice. Several examples from large RCTs demonstrate the problems of relying exclusively on intermediate or surrogate outcomes and on observational data. These studies include the pharmacological treatment of arrhythmias (Cardiac Arrhythmia Suppression Trial [CAST]) [23] and hypertension (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attract Trial [ALLHAT]) [24], as well as others that focused on hormone replacement therapy (Heart and Estrogen/progestin Replacement Study [HERS], Women's Health Initiative trial [WHI]) [25, 26]. Findings from these studies suggest that results from trials that use surrogate outcomes may not always apply to generalized prevention of events. This concept applies equally to prevention of disability studies in older adults, for which conclusive evidence is currently lacking. The LIFE study was designed to fill this important gap in knowledge for the practice of evidence-based geriatric medicine.

3.4.2 Planning and Pilot Testing

Pilot testing plays a critical role for the successful conduction and completion of an RCT. Pilot studies are particularly useful for the following reasons:

- To refine the protocol and assess its feasibility;
- To verify the recruiting feasibility. Too stringent criteria of eligibility may negatively affect the recruitment of the population, and may be adequately modified during the pilot study;
- To assess participant adherence and retention. In older persons, it is important to evaluate the rates of intercurrent illness that may compromise adherence to the protocol;

- To assess the feasibility and yields of recruiting older populations from diverse communities and ethnic subgroups, and to refine the recruitment strategies;
- To obtain data that will allow a more accurate projection of the sample size needed for a full-scale study by assessing the outcome incidence rates and the drop-in, drop-out, and loss to follow-up rates;
- To refine the definition of the primary and secondary outcomes; and
- To obtain preliminary data regarding the expected effect size on primary and secondary outcomes.

For large Phase 3 studies, pilot studies are used to optimize the multicenter infrastructure needed to conduct the full-scale study, including:

- Establishing a prototype for the infrastructure for the main study (field centers, administrative coordinating center, data coordination center, reading center, biological samples repository and committees);
- Developing and refining study forms;
- Developing a Web-based communications system;
- Programming a data management system;
- Preparing study documents (including intervention materials and a manual of operations);
- Establishing a study-wide system for quality control; and
- Developing a comprehensive system to monitor and ensure participants' safety.

Pilot data can be gathered both by conducting smaller trials in the field and by performing secondary data analyses using existing databases of epidemiologic cohort studies and previously completed trials.

One of the first steps in designing and planning an RCT is the determination of the required sample size. This estimate should be based on:

- The estimated outcomes event rate in the control group for dichotomous variables or the standard deviations of the outcome measures for continuous variables;
- The planned minimum detectable effect size;
- The expected drop-out, drop-in, and loss to follow-up rates;
- The required statistical significance; and
- The power for the trial.

The p-value (or probability, or alpha; conventionally 0.05) defines the accepted risk of type I error (i.e., the risk of finding false-positive results, or detecting a difference between interventions where one does not exist). The power (or beta) value defines the accepted risk of type II error (i.e., the risk of finding false-negative results, or missing a difference where one is indeed present; conventionally 0.80 and set to 0.90 for Phase 3 trials). If a trial has several primary outcomes of interest, the power should be set at a higher level to adjust for multiple comparisons [27]. If the trial is underpowered, it might falsely reject a true effect of the intervention. It is important to power the trial to detect the minimal effect size that is deemed to be clinically relevant rather than the expected effect of the intervention.

It is important to devote sufficient time to designing the data collection forms. Well-designed forms will significantly reduce the risk of errors and the variability of results. The forms should be easily administered, as short as possible, focused on the topic, avoid open-ended questions, and the questions should follow a logical sequence. It is useful to draft the main results and tables of the trial to identify the key information that needs to be collected. A literature review and results from pilot studies will support the choice of the specific variables and provide the best instruments to assess them [28]. To refine the data collection, the forms should be tested before the beginning of recruitment in simulated interviews and examinations with participants who are similar to the future participants. To plan a successful recruitment before the start of the trial, the investigator should estimate the number of potential participants that are expected to be screened by taking into account the eligibility criteria.

Announcements of the trial in the media and information provided to health care professionals in the area should precede the initiation of recruitment. Although it is not possible to establish *a priori* which recruitment strategy is more

efficient, several approaches have proven to be effective in older persons, as outlined below. The yield often depends on the sociodemographic characteristics and cultural background of the area. Therefore, starting at the trial initiation, all the efforts, expenses, contacts and recruited participants related to each strategy should be monitored.

3.4.3 Design of Interventions for Older Adults

To verify the efficacy of the tested intervention, the investigator may seek to maximize the potential benefit and minimize possible toxicity. Accordingly, special attention needs to be given to the dose and duration of administration, the composition and nature of the control group and placebo, and the target population. These aspects are particularly relevant in older adults.

For complex syndromes, such as disability in older populations, multi-component intervention trials are being proposed in which several combined intervention approaches in one group are compared to alternative combined interventions or control in another group. The main issue to be resolved in such trials is the interpretation of the results, as it would be difficult to assess which individual intervention did or did not work.

In this phase, investigators should also define who will guarantee the availability of the intervention for the entire study, evaluate whether special approval is needed from the regulatory agencies, design the randomization and blinding procedures, and plan interim safety assessments [5].

3.4.4 Randomization and Concealment of Randomization Scheme

The aim of randomization is to minimize potential bias. The random allocation of participants to the study groups will promote an equal distribution of their known and unknown characteristics among interventions. Therefore, differences in the study outcome will likely only be explained by the tested treatments [29].

The design of the "restricted randomization" (or "permuted blocks", or block randomization) is intended to achieve a sufficient balance in the number of participants assigned to different treatments at any stage of the recruitment period [30]. In addition, a common procedure in multicenter trials is to separately apply the block randomization to each individual study site [31, 32].

Another randomization technique for balancing groups according to prognostic factors is the so-called "minimization". It consists of keeping a running total of participants allocated to prognostic factor subgroups (which are previously defined by the investigator according to those parameters at higher risk of biasing the final results and, consequently, to be balanced across interventions). In this way, randomization is mainly driven toward a balance of the prognostic factors [31, 32].

The process of allocation needs to guarantee that randomization cannot be deciphered [32]. Therefore, a concealment procedure of the randomization scheme is needed. If the randomization is unconcealed, the investigator may modify the scheduling of potential participants, consequently biasing the allocation of participants to the trial interventions.

The best methodology to conceal randomization is to perform it "at distance". Distance randomization adopts a central randomization service that receives the basic participant details and provides the participants' allocation by phone or internet to the investigator. In this way, randomization is kept distant and separate from both investigator and participant.

3.4.5 Outcomes in Older Adults

The study outcomes need to be scientifically valid, but also clinically relevant (especially in older adults). The question to be answered by the trial should arise from a scientific rationale and be based on preliminary evidence that supports it.

The definition of the outcome (e.g., prevention of disability) needs to take into account not only

the study hypothesis (e.g., physical exercise may prevent the onset of disability), but the nature of the intervention (e.g., what kind of physical exercise), the target population (e.g., older adults who are not disabled) and the measure of the endpoint (e.g., how disability is defined).

When defining the outcome of a trial, the preliminary essential requisite is a careful review of available evidence on the topic. If evidence is well-established and definitive, there may be no need for a new study. However, in a well-studied field, a trial may be needed to test unknown aspects and refine specific concepts (e.g., verifying the hypothesis in understudied populations). A literature review will help to establish an outcome that is seen as relevant by most researchers in the field and is consistent with other studies in the area. This approach will facilitate the inclusion of the trial in future systematic reviews and comparisons of its results with those from different trials [28].

Phase 3 trials that use disability, mobility and physical function outcomes are currently under way. These include the Testosterone Trials (or T-Trial), the ASPirin in Reducing Events in the Elderly (or ASPREE trial) and the LIFE study. The LIFE study has operationalized mobility disability as the objectively-assessed capacity to walk 400 m and it uses the Short Physical Performance Battery (SPPB) as the main tool to assess physical performance [3, 4, 33]. In this respect, standardization and consistency of the outcome definitions across studies is of critical importance. Physical function, mobility disability and sarcopenia are currently being examined as clinically relevant geriatric outcomes and therapeutic indications which could be approved by regulatory agencies in the US and Europe [34]. Regulatory approval of such therapeutic indications will represent a major step forward toward the development of new treatments and trials specifically targeted to older adults.

3.4.6 Selection of Older Participants

With advancing age, a parallel increase of comorbidities (and consequently medication use) occurs. This puts older adults at higher risk of adverse events in RCTs, potentially resulting in selective attrition and missing data. Moreover, diseases and medications act as major confounders in the evaluation of any tested intervention. Industry-sponsored RCTs may be more focused on evaluating the efficacy and internal validity of a specific drug to be marketed rather than assessing its effectiveness and safety in high-risk older adults. The main consequence of this approach results in the exclusion of some older adults due to their comorbidities and multiple pharmacological treatments. This approach provides a relatively healthy study sample and significantly reduces the risk of interactions between intervention and intercurrent diseases. However, due to excessively restrictive inclusion and exclusion criteria, the resulting sample would not be representative of the general geriatric population. In turn, the generalizability of the findings would be limited.

The inclusion of older adults in clinical trials has been strongly encouraged in a recent report from a roundtable discussion among two geriatric societies (the European Union Geriatric Medicine Societies and the American Geriatrics Society) and two regulatory agencies (the US FDA and the European Medicine Agency) [19]. Authors of the report provided some examples regarding biased messages that can be derived from clinical trials which limit access to older adults. For example, although treatment of systolic hypertension is commonly considered as beneficial, this evidence is controversial with regard to individuals who are ≥80 years of age due to the paucity of data in this age group. In this context, it is worth noting that studies that supported the treatment of hypertension in very old adults adopted higher target levels of systolic blood pressure compared to the levels typically considered in younger adults [35]. Therefore, it is possible that modifications to hypertension treatment may be required when guidelines are translated from younger to older patients. Similarly, the initial relevant benefits reported for spironolactone in the treatment of severe heart failure in older adults were reconsidered when, after a few years, an increased rate of

hospitalizations due to hyperkalemia and associated excess mortality was observed in very old patients [36]. This was easily explained by the differences that exist between the selected sample of the Randomized Aldactone Evaluation Study (RALES, promoting the spironolactone use) [37] and the more complex older population (with higher prevalence of diabetes and renal failure) to which the medication was administered in the "real world" [19, 38].

When RCTs are specifically conducted in older adults, they can also be confirmatory of guidelines that have been established for younger or middle aged adults. Recently the Hypertension in the Very Elderly Trial (HYVET) has demonstrated the benefits of the treatment of hypertension in individuals who are ≥80 years of age [35].

3.4.6.1 Inclusion and Exclusion Criteria

The definition of reasonable eligibility criteria for participant recruitment is particularly important for a successful trial. Excessively restrictive criteria (aimed at obtaining an extremely homogeneous sample) are likely to raise difficulties in getting a sufficient number of participants and will limit the generalizability of the results. On the other hand, criteria that are too loose may facilitate recruitment, but may also undermine the study findings due to their recruitment of a heterogeneous sample population. Therefore, special efforts should be given to determine the study entry criteria, keeping in mind that age and gender are the two major criteria to consider.

Ideal eligibility criteria would exclude individuals for whom the treatment may be harmful, who would be unlikely to benefit from the intervention, or who have the potential to be noncompliant. Similarly, each inclusion criterion needs to be scientifically and clinically justified.

If recruitment is slow and limited due to narrow and excessively selective criteria, investigators may need to reconsider the criteria. This decision is always problematic because it requires a revision of the study protocol and a reevaluation of the trial aims, design and safety. Expanding the entry criteria may facilitate recruitment, but dilute intervention effects (thus, losing the benefits of the extra participants).

Typically, healthier and lower-risk people tend to volunteer for RCTs. This is particularly relevant when older adults are targeted. Such a "healthy cohort effect" will likely result in a lower incidence of study outcomes and may substantially undermine the projected power of the trial. An efficient approach for addressing this issue is to establish inclusion criteria that involve a pre-set proportion of high risk participants. For example, the LIFE study is screening participants based on the SPPB score (range 0–12, with 0 indicating the lowest-performing participants) [3]. To ensure a sufficient proportion of participants who are at high risk of major mobility disability during follow-up, all participants should have an SPPB score of 9 or below, and 45% of the participants should have an SPPB score of 7 or below. In the pilot study, this approach was shown to be very efficient in yielding the expected outcome rates [4].

3.4.7 Recruitment and Screening of Older Participants

The recruitment of participants for clinical trials is an essential task and one of the most difficult, especially when minorities or special populations are targeted, such as older frail populations [39]. Preliminary recruitment estimates should generally be reduced by a factor of one-third to one-half, unless thorough preliminary pilot testing is conducted to accurately assess the recruitment yields of various strategies. Given its importance, this field has itself become an area of investigation.

Although most evidence suggests that, overall, older adults are willing to participate in clinical trials, some factors have been shown to reduce this positive attitude (e.g., low education; low socioeconomic status; and the perception of excessive burden from the study in terms of collection of biological specimens, other procedures, duration of interviews, and transportation problems) [1, 19, 40].

There are several barriers that potentially affect participant recruitment which should be analyzed when planning an RCT, especially when older adults are specifically targeted. Under-recruitment of older and higher-risk participants may negatively impact the statistical power of an RCT due to a lower-than-expected incidence of outcomes. For example, the Women's Health Initiative trial on calcium and vitamin D supplementation was likely underpowered because the trial recruited fewer women >70 years of age than was initially projected [41]. To minimize the impact of potentially recruiting participants who are too healthy, the LIFE study was designed so that 45% of recruited participants would have low physical performance, and therefore be at higher risk of major mobility disability—the primary outcome of the trial [3]. This approach will preserve the power of the study. Townsley et al. [42] recently categorized recruitment barriers into four main groups:

- *Protocol design barriers.* The study protocol should be designed to pose as few barriers to participants as possible. For example, the exclusion of older patients due to poor functional status is usually justified by safety concerns. However, this approach is likely to overestimate the problem, because older participants may present low physical function for conditions that limit mobility but not necessarily enhance the risk of adverse events (e.g., orthopedic diseases).
- *Physician's barriers.* The potential toxicity of the study treatment is the most common concern raised by physicians when excluding older adults from clinical trials. Moreover, other common barriers to recruitment include the physician's perception of older adults with regard to limited social support, lack of awareness regarding the trial availability, and personal beliefs regarding clinical trials.
- *Participant's barriers.* Older adults do not cite their concerns regarding treatment tolerance as a major factor for refusing participation in clinical studies, as do physicians. The most important reason for older adults to consider non-participation is usually related to the older adults' desire to choose their own treatment. When targeting older adults, it should be kept in mind that a lower level of education or the presence of illiteracy (which is more common among older adults compared to younger adults) may limit the understanding of some unfamiliar terms (e.g., clinical trial, placebo, intervention, randomization, informed consent) which can make the older adult diffident to participation. These individuals may benefit from additional time and effort on the recruiter's part, and from explanations given in simpler and clearer words. Moreover, older adults often live alone with limited social support. A trial that involves older adults may need to establish a network of support (e.g., by solving transportation issues, and more closely monitoring adherence and the incidence of adverse events) to facilitate their enrollment and retention.
- *Trial logistical barriers.* Sometimes, physicians are not aware of ongoing trials, and consequently they may not refer potentially eligible participants. Also, potential participants who are required to incur extra costs to be in a study will be less likely to enroll, which will bias the sample selection toward participants with higher socioeconomic backgrounds. Conduction of RCTs in multiple countries that include diverse languages and socio-economic backgrounds may also represent important barriers to recruitment and the standardization of the methods. However, the HYVET, which randomized and followed 3,845 hypertensive patients ≥80 years of age from Europe, China, Australasia and Tunisia has shown that such barriers can be efficiently surmounted [35].

The investigator should constantly monitor a study's ongoing recruitment. If it starts to lag, the investigator should immediately determine the reasons and try to address them as soon as possible. Therefore, frequent feedback to the staff and study sites of a multicenter trial is extremely useful for updating and encouraging the staff, discussing possible issues, and optimizing the trial conduction. This feedback should be based on continuously updated tables and graphs (e.g., Fig. 3.1) which show the actual and expected recruitments.

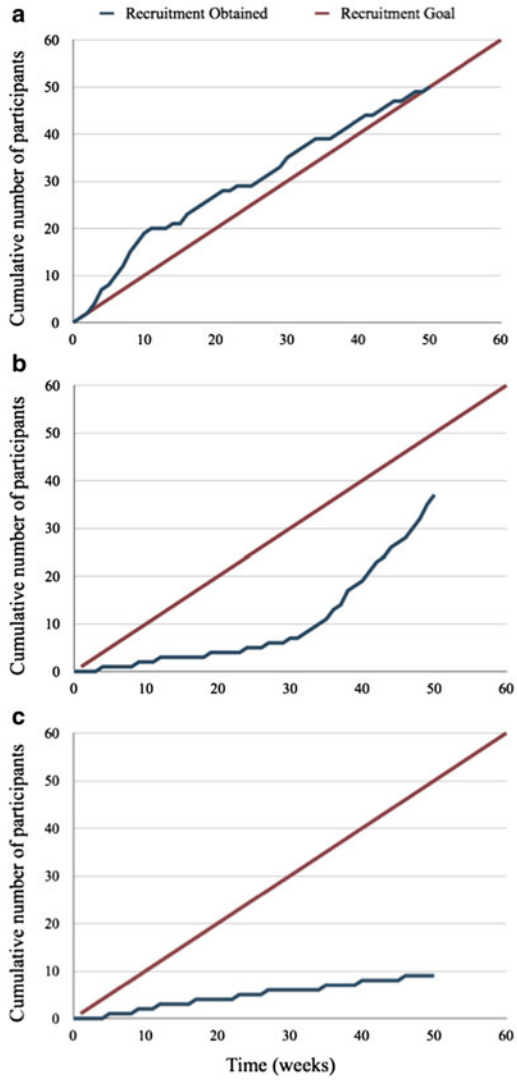

Fig. 3.1 Examples of participants' recruitment in a clinical trial. (**a**) Recruitment consistently performing at the goal rate (**b**) Recruitment starting slowly and then performing at greater than the goal rate. (**c**) Recruitment consistently performing poorly

Several strategies have proven efficient for recruiting high-risk older populations in the community, including issuing press releases about the trial to produce media stories; use of newspapers, magazines, church bulletins, newsletters, radio and television advertisements; placing brochures and fliers in doctor's offices, senior centers and retirement communities; mass mailing brochures and recruitment letters to age- and gender-eligible individuals by using commercially available mailing lists; contacting participants from previous studies; participating in health fairs; and making presentations at senior centers, community centers, retirement communities, and organizations that provide services for older adults (e.g., local agencies on aging).

In several studies and in our experience, mass mailing is the most successful and cost-efficient strategy, followed by telephone calls and newspaper advertising. Radio and television advertising is the least cost-efficient method [43]. Nevertheless, because different recruitment strategies target different portions of the public, all strategies should be considered and implemented to maximize the recruitment yield. The simultaneous implementation of multiple recruitment methods produces an overall reinforcement of the marketing effort for the trial. For example, a prospective participant who reads a newspaper ad and hears a radio message about the trial may be more likely to respond when they receive a study brochure in the mail. Professionally designed study brochures and other recruitment materials which are graphically appealing and include appropriate wording to entice the interest of the target population are of critical importance for the success of the recruitment efforts. Figure 3.2 shows an example of the recruitment brochure that was successfully used in the LIFE study.

We have recently found that establishing effective institution/community relationships may be an effective way to enhance participation in clinical research by underserved ethnic minority older populations [44]. This would include open communication and cooperation, mutually beneficial programs, holistic approaches to health and disease, participatory and balanced partnership with communities, and the establishment of multiethnic advisory boards.

Additional recruitment sources include participants in health plans such as Health Maintenance Organizations (HMOs), Preferred Provider Organizations (PPOs) or Medicare. The advantages of this approach include comprehensive information regarding the participants, ease of follow-up for health events, and usually enhanced retention and adherence.

Fig. 3.2 The LIFE study recruitment brochure used at the University of Florida field center

3.4.7.1 Informed Consent

Obtaining consent for participation in clinical trials is essential, but not easy [45]. This procedure should be considered as a process that enables the participant to make an informed choice regarding the treatment being offered [46]. Therefore, before considering participation in a trial, the participant needs to be informed about their

diagnosis/condition and the availability of alternative treatments. A consent is reasonable only if the participant's aspirations match those of the study.

The informed consent needs to be obtained before performing any procedure. It represents a crucial task, and the investigator is responsible for having the informed consent form and the protocol approved by the Institutional Review Board (IRB) before the study begins. The informed consent does not ask participants to refuse their own rights and it does not liberate the investigators from their duties.

When designing a trial, the following considerations should be made related to the informed consent procedure:

- *How information is provided to the participant.* Both verbal and written information should be provided to potential participants. Handouts that provide information related to the trial should be written in clear language; use short sentences; avoid scientific jargon (or explain it when necessary); and pay attention to layout, typeface and design. All of the written material ought to be pre-tested to check for missing or unclear information. Cognitively impaired participants need a proxy with power of attorney to act on the participant's behalf.
- *The use of written consent forms.* The consent form registers the participant's decision to participate in the trial and should help to reinforce information regarding the voluntary nature of the trial and the trial's implications. A consent form must specifically relate to the trial or to the procedures in question. Consent is only limited to a specific trial or treatment, and the participant cannot be considered to have given consent for anything else.
- *The setting in which consent is obtained.* The setting may influence the participant's ability to give consent, particularly for older adults (especially if cognitively impaired) who may feel more comfortable in their own home than in unfamiliar surroundings.
- *The timing of obtaining consent.* Participants should not feel rushed into giving consent. It might be helpful, after a first contact with a potential participant, to schedule a separate appointment in a quiet place. In this way, the participant will also be able to discuss the decision with their family, friends and physician. The presence of a witness or a second opportunity to discuss the consent may also help to reduce anxiety and improve communication.

The amount and type of information expected by potential participants may vary. However, there is always a minimum of information that all participants should receive, and this includes the potential risks that are associated with the trial. When informing the participant about the study's potential risks, a good rule is to disclose any significant event which is either severe (for example, paralysis or blindness) or fairly likely to occur (for example, a 30% likelihood of nausea). At the same time, the potential participant should be instructed regarding procedures to be activated if adverse events occur and whether compensation is available for serious injuries.

The informed consent form must describe the trial design and duration, and clarify all study implications. All evaluations, measurements and procedures need to be described and explained, with special attention given to any inconvenience associated with them.

It is important to explain that participation is voluntary and that deciding not to participate will not change the physician-patient relationship or the way the patient will be followed in the future. It should be clear that participants are free to withdraw at any time and do not need to provide an explanation, and that withdrawal will not prejudice their future treatment.

Explaining scientific and methodological concepts to older adults may not be easy, but it is necessary for a fully informed consent. Sometimes, the idea of being included in the placebo group (often wrongly considered as "untreated") or receiving an unknown treatment may scare the possible recipient, reducing their willingness to participate. It is important, therefore, to clarify these concerns by describing in plain words what will happen and the reasons for such choices.

An RCT is mainly conducted due to uncertainty regarding the best treatment for a specific condition.

Thus, randomization may sound less threatening to a potential participant if it is explained as the way to fairly distribute the hoped benefits and the unknown risks between the study groups. It might also be helpful to explain that randomization is used to reduce possible bias. Double blinding will be better appreciated if it is explained that results may otherwise be affected by the expectations of either the patient or the researcher.

The acceptance of the informed consent requires the signature of the investigator and the participant on the specific form. Because of this, a participant may feel that the consent is a signed agreement to complete the trial. The investigator should explain that the form aims to ensure exactly the opposite, which is to guarantee the rights of the participant and the correct conduction of the study. A copy of the signed informed consent should always be given to the study participant.

A major challenge for older adults in fully understanding the informed consent is its length and complexity as mandated by regulatory agencies and local IRBs. The informed consent is often better designed for protecting the parent institution than for making it user-friendly and comprehensible for the participants. Typically it takes 30–60 min, or even longer to fully administer and explain the informed consent, which often exceeds 40 pages. This represents a major burden, particularly for older frail adults, who may lose interest and not fully understand the study. This, in turn, may jeopardize their safety.

Another major challenge for multicenter clinical studies is represented by the heterogeneity of the local IRBs regarding the informed consent requirements. A viable solution is to use a central IRB, but this is not always accepted by all institutions. A major advance in the field will be achieved when regulatory and IRB requirements for the informed consent are standardized and simplified.

3.4.8 Adherence to Protocol, Retention and Participant Burden

Participant retention and adherence to the study protocol are relevant indicators of the quality of the trial. Frequent reasons for which older adults tend to be excluded from clinical trials are the higher probability that they will be lost to follow-up, drop-out from the intervention, and experience poor adherence to protocol. These aspects are particularly challenging when conducting trials with older adults, and such differential loss to follow-up can bias the study results. For example, the Systolic Hypertension for the Elderly Program (SHEP) showed no benefit of antihypertensive treatment on disability and cognitive function, likely due to a higher attrition for disability and cognitive assessments among participants who experienced cardiovascular events [47]. Such participants were also more likely to be randomized to placebo. Consequently, in SHEP, the cognitive and functional evaluations were biased toward the null effect by differential drop-outs.

Efficient ways to promote the adherence of participants to the study protocol are to exclude participants who are at risk for poor compliance and adopt specific interventions to improve compliance. Before enrollment, preventive measures should be taken to minimize non-compliance. Because the study requires a dedicated commitment to examination schedules, the study should enroll only those individuals who appear likely to follow the study protocol. Some studies use a run-in period to assess compliance and exclude those who do not meet pre-specified adherence criteria. The judgment of staff is essential in determining overall eligibility with respect to adherence. It is usually advisable to exclude persons who are addicted to drugs or alcohol, live too far away, are likely to move before the scheduled termination of the trial, or are involved in other clinical research that may interfere with the proposed study. Algorithms should be developed to address non-attendance at the clinic. These should involve procedures that will facilitate documentation of these cases and formulate how best to rectify the attendance problems.

Missed visits. The following procedures should be implemented to monitor missed clinic or home visits: (1) making the appointment and giving instructions for the next visit at the end of each current visit; (2) sending visit reminders; (3) monitoring clinic attendance; (4) immediately

contacting participants (usually by telephone) when they miss a visit; and (5) rescheduling a missed visit if possible.

Refusals. Some randomized participants may not actively participate in the study, perhaps by not adhering to the intervention and/or not attending the clinic. This may be due to a number of reasons, such as lack of transportation, family objections to participation or the participant's decision. Regardless of the reason(s), these participants should be followed until the end of the study, and clinic staff should attempt to make contact at the time scheduled for each interim follow-up visit and for the close-out visit. These contacts are intended to remind the participant that they are welcome to fully rejoin the study at any time. Considerable effort should be expended to collect the main outcome data at appropriate times.

The following guidelines will promote adherence to the protocol, in terms of intervention adherence and clinic attendance.

Participant-staff relationship. A key element that contributes to participants' continued commitment to the trial involves fostering personal relationships between study participants and individual staff members. Personal contacts are more likely to succeed in keeping a participant interested in the trial than impersonal form letters or phone calls from someone who is not known to the participant.

Continuity of care. In general, participants' appointments should be scheduled so that they can be seen by the same clinic staff members during each visit.

Clinic environment. The clinic environment should be warm and pleasant, and oriented toward the comfort of the participant. Personal notes should be made in study charts regarding important events in the participant's life (e.g., the birth of a grandchild), and these can be brought up at the next visit. Lunch or snacks should be provided as appropriate.

Participant-staff communications. Good and consistent communication between participants and staff is essential. Instructions should be clear and interactions should be friendly and individualized. The participant should be reminded of the benefits of study participation. Written reminders about clinic appointments will further enhance communication efforts.

Convenience and accessibility. Study adherence is promoted by an easily accessible clinic location, availability of transportation, and convenient clinic hours. When appropriate, participants should be reimbursed for transportation and parking should be available.

Time in clinic. The time necessary to complete each visit is critically important to participants' long-term retention. Total clinic visit time should be kept to a minimum, consistent with maintaining quality. If waiting is necessary, the situation should be explained to the participant. If possible, the option to reschedule the visit should be offered when the participant feels burdened or tired. Participants should not be rushed or made to feel unwelcome. Coffee, magazines and newspapers should be made available in the waiting area.

Appointment reminders. Written appointment reminders should be mailed.

Interim contact between scheduled follow-up visits. Such interim contact is often useful to maintain participants' interest in the study.

Identification with the study. Regular communication with participants facilitates identification with the study. This includes holiday cards or notices of special events, and periodic newspaper ads that promote the study. Small gifts such as socks, calendars, pens, mugs, and bags which display the study logo should be distributed.

Monetary incentives. To maximize retention and adherence to the intervention protocols, participants should be compensated at a reasonable monetary value for the time spent either in the clinic or during home visits.

Involvement of proxy informants. The involvement of proxies should be encouraged. When appropriate, proxies (which may include the spouse, another family or household member, or any other person who is close to the participant) should be informed regarding the study purpose, design and interventions, and should be invited to attend the clinic visits or any study group meetings. Compliance is more likely to

improve if proxies or family members become involved. Proxies may be given written materials regarding the trial, and they should be encouraged to notify the clinic regarding any unexpected events that the participant may have experienced.

Staff meetings. Regular staff meetings enable clinic staff to discuss participants' adherence problems and develop strategies for improvement. An adherence chart that contains clinic visit summaries should be developed and reviewed for each participant.

Participant ID cards. Participants should be given an identification card bearing the name of the study and a telephone number for medical advice, with instructions that the number be called in case of a medical emergency.

Relationship with private source of care. Good communications and a positive relationship with the participant's primary care physician or other outside source of care are important for enhancing retention and compliance. The physician should be made aware of their patient's participation in the research study, and should be kept advised of abnormal laboratory findings, physical examination findings and other pertinent information, including any clinical problems encountered.

Re-education. A periodic review with the participant of the purpose and general features of the study can be a strong motivator for adherence. It may also be useful to provide participants with calendars that display the expected times for scheduled follow-up visits.

To enhance adherence and retention of participants in a trial, it is crucial that investigators and staff believe in what they are doing, fully understand the study protocol, are adequately trained to perform the study procedures, and have the adequate time and enthusiasm to follow the study and attend participants.

3.4.9 Safety and Adverse Event Reporting

When conducting clinical research studies, the highest priority is to ensure participants' safety. Investigators should constantly verify that the study protocol is being correctly implemented and that recruitment of participants is proceeding as planned. A data and safety monitoring plan typically outlines the oversight and monitoring procedures for ensuring the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks, size and complexity of the clinical trial. A Data and Safety Monitoring Board (DSMB) is usually needed for multi-site clinical trials which involve interventions that entail potential risk to the participants, and are generally needed for Phase 3 clinical trials.

Interim data monitoring for safety and efficacy needs to be planned to check for possible positive or negative treatment effects that are larger than initially expected. If the interim analyses do not find relevant results, the trial can continue without any modification. Alternatively, if relevant results are found, the trial can be stopped early [28].

Procedures for detecting the onset of adverse events to the study interventions need to be carefully designed and implemented. The informed consent form should always indicate the name and contact information of the study personnel designated to assist the participant if a possible adverse event may occur. When a serious adverse event is reported to the study staff, the investigator must communicate it to the IRB within a short time (typically 24–48 h) and try to obtain as much information as possible about the event. Serious adverse events are defined as events that may be harmful to the participant and/or may be serious enough to warrant either temporary or permanent discontinuation of the study intervention, either because the events are intolerable or because they are judged to be potentially harmful. All serious adverse events require immediate reporting and an assessment of the implications for the continuation of the study and/or modification of the consent form. The following events are considered to be serious and relevant to older populations: (1) acute or life-threatening events; (2) events that result in prolonged, permanent or severe disability; (3) another severe illness, including the worsening of a pre-existing condition, injury or accidents;

(4) inpatient hospitalization or surgical procedure, or a treatment to prevent a serious event; (5) death; and (6) a clinically significant abnormal laboratory or diagnostic test.

All adverse events must be described on an appropriate form (including the date and time of the event, what has been done to treat the event, and whether the study intervention was stopped or reduced). If needed, the investigator may also break the randomization concealment to determine which treatment is being received by the participant (in such a case, the participant will be dropped out from the trial).

Adverse event reporting and interpretation may be particularly demanding in high-risk older participants due to the high number of events reported. For example, in the LIFE pilot study, over 97% of participants experienced at least one adverse event over approximately 1 year [4]. An efficient approach to address this problem is to prompt participants using a check-list of expected adverse events for the type of intervention, in addition to open-ended reporting. To ensure that adverse event reporting is unbiased, data collection should be conducted by personnel who are masked to the treatment allocation.

A trial can be stopped early or suspended for several reasons, all of which should be described in the protocol. It is important that the study record all participants who withdraw from a trial or fail to comply with the protocol, and the record should include the reasons reported by the participant. Sometimes a participant might be lost to follow-up due to an intervention-related adverse event. This information will be crucial for avoiding potential bias when evaluating the study findings. Therefore, non-compliant or dropped-out participants should be always followed up. The evaluation of the trial data should always follow the "intention-to-treat" strategy, which is to analyze the study results based on the randomized treatment allocation. The intention-to-treat approach will pragmatically estimate the outcome as if the intervention was tested in all of the participants as randomized, regardless of whether participants continued to satisfy the entry criteria, whether the treatment was correctly and consistently received, and regardless of subsequent withdrawals or deviations from the protocol [48]. Secondary analysis restricted to only participants with high levels of adherence to the protocol may also be considered. Although the smaller sample may negatively influence the statistical power, such analyses might still suggest the presence of trends in the intervention effects according to the participants' adherence. This information may support the primary findings of the trial and provide insights on how to maximize the intervention effects.

3.4.10 Quality Control

The quality of an RCT needs to be constantly monitored. To obtain high-quality data, investigators must ensure that all the information is correctly collected, recorded and interpreted. There are some key data in every trial that cannot be missed without severely affecting the trial's quality. For example, the outcome variables and the baseline characteristics of the enrolled participants (especially those related to the eligibility criteria) are clearly fundamental. It is not possible to monitor everything, but special effort must be directed to these key data (which should be as error-free as possible). For the other variables, a degree of error or missing values can be decided in advance.

Data can present three types of problems [5]:

- *Missing data.* The percentage of missing data is an indicator of data quality, and consequently the quality of the entire trial. Missing data is due to an inadequate evaluation, a laboratory problem, carelessness in completing the data collection forms or the participant's inability to provide the requested information.
- *Incorrect data*. An error in recorded data can happen at several levels. For example, an error might be due to a misunderstanding when retrieving the data from the participant, an erroneous recording in the forms or an incorrect data entry.
- *Excessive variability.* Sometimes, some repeated assessments can be extremely variable in an unsystematic (or random) and/or a

systematic way. Results of the same parameter that are too variable reduce the capacity to detect real changes.

The complete understanding and appropriate use of definitions and methodologies among investigators and staff is vital for the successful completion of a high-quality trial. All of the study definitions and procedures must be clearly written and included in the study protocol. A manual of operations and procedures should also be prepared for every trial. This manual contains the detailed description of all definitions and procedures adopted in the trial so that investigators and staff will work in a standardized and consistent manner. This information needs to be accessible to study personnel at any time. The manual of procedures should also include the scientific background, as well as the rationale, aims and design of the trial. Laboratory methods are also described in detail so as to standardize all the measurements. This document should always be kept updated, especially if the protocol has been amended.

Training sessions for investigators and staff (including laboratory personnel) will help to promote the standardization of procedures and minimize errors. Moreover, specific training (and possibly certification of competence) should be planned for staff who perform special tasks (e.g., blood pressure measurement, electrocardiograms, pulmonary function tests, laboratory tests). Periodic retraining and recertification of personnel should be considered for long-term studies.

After a training session, all of the involved personnel should have a debriefing. This is essential to improve the understanding and interpretation of ambiguous procedures. If such a discussion is done before the study begins, the investigator will be able to identify weaknesses in the forms and the procedures, and thus adequately address them in advance.

A monitoring system of the data and periodic site visits for multicenter trials are vital for ensuring that data will be of high quality. Monitoring is most effective when it is current and when feedback is provided to the staff. Automated monitoring for missing, extreme or inconsistent values helps to improve the data quality. Double data entry can also be used to reduce the error rate. When the forms disagree, the person(s) who filled out the forms should be queried and the data checked from the source. Dates and times are particularly prone to error.

For research that involves investigational drugs, the FDA may conduct audits of individual researchers, research sites, IRBs and sponsors, and contract research organizations (CROs) to ensure the safety of research participants and guarantee the accuracy of research data.

3.5 Reporting Results

RCTs represent the "gold standard" study design for evaluating differences between different interventions. However, to obtain reliable results, the trial must be appropriately designed, conducted, and reported. As mentioned above, to fully evaluate the findings of a clinical trial, authors must provide their readers with a complete, clear and transparent description of study methodologies and results. Unfortunately, too many trial reports are still qualitatively inadequate due to an incomplete description of critical information.

In an attempt to regulate, optimize and standardize the reporting of clinical trials in literature, the CONSORT statement was first published in 1996, and was revised and updated in the following years. Just recently, the CONSORT Group developed a new version of these guidelines to (1) assist authors in writing RCT reports, (2) promote a more complete evaluation of papers by peer-reviewers, and (3) facilitate a critical appraisal of papers by readers [14, 49].

A major source of bias in clinical research comes from the unfair reporting of findings in the attempt to privilege positive results. The greater appeal that a positive study has resides in the larger interest it may have at different levels, for industry/pharmaceutical companies (interested in obtaining positive results for the experimental intervention in the interest of financial benefits), government sponsors (claiming successes in medical research and enhancements of health care quality), scientific journal editors (looking for studies more likely to be cited), academic

researchers (having publications as a mirror of their professional reputation, timing of promotion and salary) and even for caregivers and patients (more interested in looking at what is working rather to what is not). These disparate interests may generate biased scientific evidence [21]. To minimize such bias, it is important to carefully evaluate each study for its quality, applied methodology and scientific relevance. Scientific jargon that uses words like "positive", "significant", "negative", or "null" should be discouraged because it is implicitly non-neutral or potentially misleading. All results have equal relevance to science, as long as they are produced by a logical rationale and correct methodologies [50].

3.6 Conclusions

The progressive aging of our societies and the incredible burden of geriatric syndromes (both at personal and societal level) impose the development of interventions able to prevent and treat age-related conditions. The conduction of RCTs adequately modified to address the multiple issues concerning the participation of older persons should be encouraged. Hopefully, the provision of high-quality data from rigorously conducted intervention studies in elders might contribute in solving the long-lasting "evidence-based medicine" issue in geriatrics.

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4 Target Populations, Recruitment, Retention, and Optimal Testing Methods: Methodological Issues for Studies in the Epidemiology of Aging

Elsa S. Strotmeyer and Rachel E. Ward

Abstract

Epidemiologic studies in older populations are important for defining the breadth of health conditions in older adults, but there are key barriers that such studies must overcome. Older adults who participate in and remain in epidemiologic studies are likely healthier and less disabled than are their peers who do not respond to recruitment efforts, participate in studies or return for ongoing participation in longitudinal studies. Unbiased target populations, sampling, recruitment and retention are critical for a well-designed epidemiologic study of older adults. Given the range of cognitive and physical function in older adult populations, study instruments and methods must address feasibility as well as reliability and reproducibility for the specific population of interest.

Keywords

Bias • Disability • Feasibility • Generalizability • Impairments • Inclusion criteria • Longitudinal cohorts • Optimal testing methods • Participant selection • Precision • Recruitment • Reliability • Representative • Reproducibility • Retention • Sampling • Sensitivity • Target population • Validity • Aging • Epidemiology • Geriatrics • Older Adults • Longevity

Abbreviations

3MSE	Modified Mini-Mental State Examination
AUC	Area Under the Receiver Operating Characteristics Curve
BI	Barthel Index
CT	Computed Tomography
DXA	Dual-energy X-ray Absorptiometry
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly

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MMS	Mini-Mental State
NHP	Nottingham Health Profile
OARS-IADL	Older Americans Resources and Services Instrumental Activities of Daily Living
R^2	Coefficient of Determination
ROC	Receiver Operating Characteristics
SES	Socioeconomic Status
SF-36	36-item Short Form Health Survey
SPPB	Short Physical Performance Battery
SQLI	Spitzer Quality of Life Index
TICS	Telephone Interview for Cognitive Status

4.1 Introduction

Epidemiologic studies in older populations present recognized methodologic challenges [1–4]. Many of these challenges result from the high prevalence of disease and wide range of physical and cognitive function found among older adults. Mody et al. [4] detailed the general principles for the recruitment and retention of older adults in research studies: achieving a representative sample, promoting participation, considering feasibility and retaining participants. Factors that are critical for attaining a representative group of participants from the desired target population are the optimal identification of participants, a detailed plan for recruitment and comprehensive retention techniques. Older participants in research studies may be healthier than older adults who do not participate due to multiple morbidities and a high prevalence of cognitive and physical disability. This participation bias likely affects the results of even the most well-designed studies. Furthermore, researchers must select study instruments that are practical, reliable and reproducible for older adults who have a wide range of cognitive and physical functioning. Studies must be designed from the start to include solutions to these potential barriers in order to ensure that the full spectrum of health and function is included and guarantee the highest quality of epidemiologic research among older populations.

This chapter reviews common challenges in conducting epidemiologic studies of older adults and details solutions for overcoming them.

4.2 Target Populations and Sampling

A target population represents the group of older adults that is of interest for studying a specified health issue. The specific target population predominantly depends on the study design and the study question. Effective participant selection is essential for obtaining a sample of participants that is representative of the target population, and poor participant selection will result in an epidemiologic study that is fundamentally flawed. Ideally, a study should have a detailed and comprehensive plan for obtaining a representative sample of the target population. Different definitions for a representative sample are applied depending on the target population. For example, study criteria may specify a study population that has a minimal level of physical functioning while being representative across age ranges, sex and race. Although some exclusion criteria may be necessary, extensive exclusions in older populations will render results that are not generalizable to the more diverse groups within the overall population. Therefore, utmost care should be taken to have inclusive criteria for participation.

While older participants who directly volunteer from advertising are easier to recruit, they are healthier and differ in demographic characteristics (e.g., younger, more likely women, higher education) from a random sample of a population-based list [5]. If population registries are not available, population-based lists exist that may be used for recruitment. These include census or zip code tracks; random digit dialing; and Medicare-eligible, motor vehicle or voter registration lists [6]. Other sampling populations for studies in older adults include those in health care organizations, hospitals, nursing homes or other care facilities, or housing complexes [4, 6]. In a longitudinal study, the targeted population and the type of representative group chosen must be balanced with the estimated retention rate for

participants and the number of outcomes needed over a specified time period.

4.3 Recruitment

A well-designed recruitment plan is essential to ensure a representative sample of older adults from the target population. Recruitment is the process of communicating information about the study to targeted groups with the goal of generating participants for the proposed research. The strategies employed for communicating with prospective participants must be effective for the targeted older population. The use of marketing and public relations techniques are highly recommended [6–9]. The recruitment materials should be designed to convey the importance of the study objectives in lay language, emphasize the benefits vs. the risks of study participation, and describe the minimum eligibility criteria [4, 6, 7].

Certain targeted populations may need special consideration (e.g., minority, non-English speaking, low socioeconomic status [SES], limited education, and cognitively impaired groups) [2, 3, 9–15]. Some minority populations have been shown to be less likely to participate in physiologic assessments that use biologic samples or certain invasive tests [9, 10, 13]. The social and cultural barriers to study participation by older adults have been summarized—along with proposed solutions—by Mody et al. [4]: perception of the research or medical community, general mistrust, gatekeepers to participants (e.g., family, community leaders), culture, privacy, motivation, language, literacy, geographic location of research, and competing responsibilities (e.g., caregiving for family). Advisory boards or community groups from the targeted populations are often utilized to refine the recruitment campaigns [2, 4, 6, 9, 16–19], though it is not clear whether this community involvement directly increases the response to the recruitment materials [20].

Well-designed recruitment techniques often include a direct-contact person describing the study to the potential participants [6, 21, 22]. Recruitment materials should be factual and not contain subjective characterizations of the study (e.g. fun, exciting). A direct-mailing campaign can be expected to have an estimated 1–6% response rate, with campaigns that are more focused on the targeted population for the study (e.g., age, sex, race, health condition) yielding a higher response than a less focused mailing [6]. Potential participants may be additionally contacted by telephone after the initial mailing. A more intensive approach may be associated with obtaining a more representative sample of the older population [5, 23, 24], but it has also been shown to obtain participants who have higher education [25]. Although the current cohort of older adults likely retains landline telephones (96%), a landline telephone recruitment approach will become less feasible as technology evolves and as younger cohorts transition into the >65-year-old age groups [26]. In the future, studies that use telephone recruitment or follow-up should employ a dual approach of sampling landline and mobile telephone lists. Internet and email recruitment is likely to play an important role in future studies of older adults as well. To ensure representative samples, some studies have identified potential participants through direct visits to their homes [5, 27, 28]. While this technique may be the most staff-intensive, it may overcome bias in the response to a recruitment campaign in older adults [2, 5]. Within epidemiologic studies, the type of recruitment campaign must be balanced with the cost, as more staff-intensive recruitment activities are associated with a greater cost per participant enrolled [25, 29].

4.3.1 Recruitment Incentives

Recruitment incentives are often based on consideration of the travel, time and effort that participants will expend for the study, but they should not be coercive. Commonly used incentives are money, a gift card or a small gift for participation. Small gifts could include a canvas bag, key chain, magnet, mug, pen, etc., and these are usually imprinted with the study name, logo and contact information. Studies also typically provide clinically relevant study results to participants and/or their personal physicians, because medical test

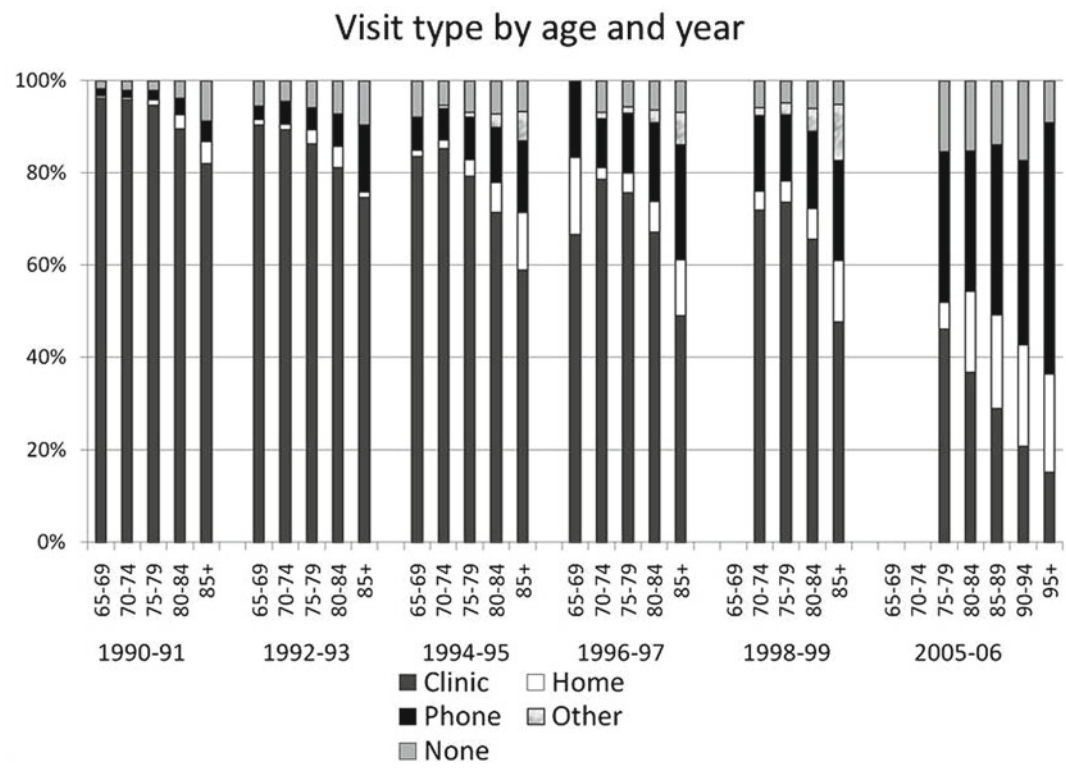

Fig. 4.1 Retention for visits in a longitudinal cohort study varies by age and visit type: example of the Cardiovascular Health Study (CHS) [33]

results have been shown to be an important motivator for participation in some older participants [30, 31].

4.3.2 Recruitment Monitoring

It is crucial to monitor the initial response to types of recruitment techniques. At a minimum, the monitoring should include the target numbers over a time period for recruitment vs. the actual participants enrolled (for an example, see Fig. 3.1, Chap. 3 by Pahor, this volume). Comprehensive recruitment monitoring will include some limited information collected from non-participants to assess possible differences from enrollees. Strategies may be adjusted during the recruitment phase to increase the response from the targeted population or certain groups within the targeted population (e.g., sex, race, SES). In multicenter studies, strategies may need to differ by geographic region since substantial variations in response occur by location [6, 29, 32, 33].

Recruitment rates from eligible older adults may vary based on the perceived benefit vs. burden of the study [4, 34, 35]. Researchers need to examine whether particular components of the exam are associated with poor enrollment and consider allowing participation without requiring certain tests [9]. Additionally, the types of exams offered affect the recruitment response. A cross-sectional study that has one survey may have a higher recruitment rate than a study that has an in-person exam with multiple physical measures. A longitudinal study with multiple clinic exams or an intervention in a clinical trial is likely to be perceived as a burden to some older adults, causing a poorer response to the recruitment campaign compared to studies that are less time-intensive. Studies need to employ flexible visit types in order to overcome the burden of participation among certain older adults. "Split exams" in which some data is collected over the telephone and limited data is collected in person may reduce the burden of participation. Offering

Table 4.1 Solutions to overcoming challenges in recruitment and retention of older adults: accommodate the needs of participants

Challenge	Criteria	Solutions
Impairment	Mobility and/or driving inability	Provide transportation for in-person clinic exams
	Vision	Increase font sizes on all study materials
		Staff read informed consent and questionnaires
	Hearing	Staff speak clearly and loudly
		Conduct exams in quiet offices or over the telephone
		Provide handouts or questionnaires to read
	Cognitive	Utilize proxy contacts
		Staff read and explain informed consent and questionnaires
		Staff assesses participant understanding and need for proxy consent
Fatigue	Capability	A la carte visits – allow 'opt out' of components
		Schedule home or phone visits or split visits
	Time	Provide wide time frame to schedule visits
		Allow ample time for testing
		Schedule ≤3 h per visit
	Pace	Break up physical/cognitive testing
		Provide encouragement
Inability to locate	Contact information	Collect multiple contact information: social security number, full name, address, phone numbers (landline and mobile), seasonal address changes, e-mails
	Proxy contacts	Obtain multiple contact information for family and friends
	Maintain contact	Frequent contact with participants by phone interviews, newsletters, cards, etc.
Demographic/social diversity	Minority, non-English speaking, low SES, limited education	Advisory boards or community groups
		Request feedback on protocols and issues from groups with additional barriers for participation
Nurturing Participation	Incentive	Offer money, gift cards, gifts, etc.
		Provide meals/snacks for long clinic exams
		Provide clinical test results
	Engagement	Retention of friendly, empathic staff
		Study newsletters and calendars
		Send birthday, sympathy, and holiday cards
		Occasional receptions

an in-person exam at the home as an alternative to exams at a clinic may diversify participants with respect to age, overall health status and function [33].

4.3.3 "Health Participant" Bias

A "healthy participant" bias likely occurs in the initial recruitment of older adults [23, 33]; however, this bias may diminish over time in longitudinal studies [33, 36]. Initial approaches may be taken during the recruitment phase to reduce the "healthy participant" bias. Basic solutions for obtaining a diverse sample of older adults initially and over time include designing protocols with accommodation for impairments in vision, hearing, mobility and cognition (Table 4.1). Such accommodations could include providing transportation for in-person clinic exams, increasing font sizes on all study materials for participants, reading informed consent forms and questionnaires

aloud for those who have vision difficulties, and conducting exams in quiet offices or over the telephone for those who have hearing difficulties. Mody et al. [4] included an expanded discussion on strategies for overcoming health conditions that affect recruitment and retention, with greater detail on problems that result from impairments and additional health barriers that are particularly relevant to studies of older adults who are in very poor health (e.g., nursing home or acute care patients), such as those who have major emotional decline, frequent hospitalizations, acute illness, severe pain, shortness of breath and limited life expectancy.

4.3.4 Participant Fatigue

Participant fatigue must be considered when designing the study exam. In this context, one must take into account that the time needed to complete the exam may vary substantially depending on the participant's level of function. For example, it may take more time to conduct and collect measures in older adults who have cognitive and physical impairments than in more functional older adults or those of younger populations. Longer study exams may include a meal or snack, often a light breakfast if a fasting blood draw is being collected. Generally, it is not advisable to include an in-person examination that will take longer than 3 h to complete. If the time needed to collect measures exceeds 3 h, it is recommended that the exam be divided and a second in-person exam be scheduled on a different day. If the exams are on multiple days, exams at the clinic should be required only when necessary and, if possible, consideration should be given to replacing one or more visits with a home visit or a telephone interview to complete the study with the least burden to participants.

In-person examinations should be organized to collect the most critically important physical measures first, in case certain participants cannot complete the entire exam. Physical function measures and questionnaires should be given alternatively to avoid physical fatigue. Multiple questionnaires or cognitive tests should not be given consecutively in order to avoid mental fatigue. If the participant cannot complete all of the questionnaires at the time of the in-person exam, some may be collected later over the telephone. These accommodations are not only important for initially recruiting a representative sample of older adults, they are also particularly important for increasing participant retention in longitudinal studies.

4.3.5 Informed Consent

After a potential participant expresses an interest in participating in the research and has passed the first phase of eligibility for entry into the study, the informed consent process is conducted. Accommodations similar to those noted above apply to the informed consent process (e.g. reading forms aloud, conducting consent process in quiet office). The consent form is often mailed to the participant ahead of time to allow adequate time to review the study materials. The study staff that is responsible for conducting the participant consent not only provides a full description of the study and its objectives, they also clearly outline the study risks and potential benefits and fully answer any questions the potential participant may have.

Many studies exclude participants who cannot give informed consent or those beyond certain cutpoints on cognitive tests. However, many participants who are incapable of providing informed consent do benefit directly from research, and it is important to include them since they are likely to be less healthy and at a higher risk for health outcomes and mortality than are those who can provide informed consent. It may be difficult for a study staff to quantitatively determine a potential participant's capacity to make a decision, which is related to—though different from—cognition. Approaches are available to assess decision-making ability [37, 38]. For older adults who lack the capacity for decision-making, studies use alternative methods of consent by identifying a surrogate for consent (e.g., legally-appointed guardian, durable medical power of attorney, spouse, child, other family, health care

provider). However, even if consent is obtained by a proxy, is vital to obtain the participant's assent for their participation in the research study.

4.4 Retention

Retaining older participants for longitudinal cohort studies and clinical trials is essential for obtaining unbiased results and precise estimates of predictors for outcomes of interest. In a longitudinal study, retention is defined as the continued follow-up of participants who initially enrolled at baseline and have survived for subsequent assessments. Longitudinal studies of epidemiologic cohorts often cite an overall follow-up rate of >90% [39–41], with 70–80% attendance at a clinic exam that occurs within the first several years from baseline [33, 40–44]. Retention varies dramatically by age and visit type, [10, 33] as shown in Fig. 4.1 for the Cardiovascular Health Study. In a longitudinal cohort of older adults, follow-up for telephone interviews remains high (>80% of survivors) over several decades [33]. However, the reliability of self-reported telephone data is uncertain in a population that has a high prevalence of cognitive decline. Cognition may be an important confounder in self-reported data at the oldest ages and is likely critical to assess in telephone interviews. The Cardiovascular Health Study has validated the Telephone Interview for Cognitive Status (TICS) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to assess cognitive function over the telephone [45].

Lower attendance at in-person visits after baseline is common in a longitudinal follow-up. It is also not random, with decreased attendance attributed to dementia, disability or end-stage disease, and strongly related to age, health and function scores measured at earlier points in the study [10, 33, 39, 40, 46]. In a longitudinal epidemiologic study, the retention rates for follow-up will be driven by the age and overall health of the sample when they are recruited. At the oldest old ages (>80 years), retention for in-person visits becomes exceptionally challenging, with approximately 50–70% of participants attending in-person assessments that include home exams [33, 47–50]. Home visits represent a feasible alternative to clinic visits for the collection of physiologic measures, and they are often acceptable to participants who are unwilling to attend a clinic visit [50]. Importantly, offering in-person home exams has been shown to substantially increase retention for physiologic measures in the oldest age groups, and it diversifies the participants who are retained for follow-up with respect to older ages, poorer health and poorer function [33].

High retention at subsequent in-person exams that include physiologic assessments is essential given the accelerated change that can occur in older adults (e.g., bone loss, strength, gait speed, cognition) and the goal of identifying preventable risk factors for accelerated changes [41–43, 51, 52]. Retention bias predominantly occurs in participants who have the highest burden of disease or disability, and those who have the worst starting values. Potential retention bias may be most likely to impact the magnitude of changes seen in physical function [52], body composition [41], strength [40, 52, 53], and cognitive function [45, 52], though studies have also shown an effect on changes seen in lung function and brain white matter grade [46, 54]. Therefore, the inclusion of participants who have the full spectrum of health and disability is critical for defining true physiologic change and its predictors.

4.4.1 Improving Retention

Techniques to improve retention rates at subsequent in-person visits include the above-mentioned solutions to improve recruitment rates (e.g., accommodating impairments in vision, hearing, mobility and cognition; addressing fatigue) and also additional recommendations that are unique to longitudinal studies (Table 4.1). In general, retention will be facilitated by treating the participants with utmost respect and care to accommodate any hardship that could possibly limit their participation. The staff in close contact with participants must be empathetic though also creative at overcoming barriers to participation.

Staff retention over the course of the study is important, as participants often value their long-standing relationships with the staff. A monetary incentive is usually offered for each in-person visit, with the amount often based on the participant's costs for travel and time. As is done in recruitment, many studies often give small gifts—imprinted with the study name, logo and contact information—at each subsequent exam. "Split visits" in which data are collected by two different visit types (e.g., telephone and home exam, or telephone and clinic exam) are an option to ensure that maximal data is collected with the highest level of flexibility for participants as their abilities change. Participants can also be permitted to "opt out" of certain components that they do not wish to complete.

Frequent contact with participants is critical for updating health outcomes and contact information, and for maintaining participants' connection to the study and the staff. Obtaining multiple types of contact information for participants is necessary for successful longitudinal follow-up, including social security number, full name, address and telephone numbers (landline and mobile), email addresses, and the same information for several family members or friends in case the participant cannot be reached [6]. Participants that spend portions of the year away from their primary residence (e.g. residing in warmer geographic locations during northern winter months) may need to have alternate contact information. Longitudinal studies often collect data every 3–6 months through mailed surveys or telephone contact. Additional mailings throughout the year may include birthday cards, holiday cards, study calendars or regular newsletters about the study and its findings [6]. Sympathy cards may be sent when participants inform clinic staff of the recent loss of a close family member or friend, which is common among the peer group of older adults. Some studies have receptions for participants and their families so they can learn about study outcomes and meet study investigators and personnel [6].

A proxy specified by the participant (i.e., someone who the study staff could call if they cannot reach the participant) is needed to ensure completeness of follow-up in situations such as residence changes, impaired decision-making capability, cognitive impairments, serious illnesses or death. Over time, as the population ages, a larger proportion of the exam types will become proxy exams. The research protocol should clearly specify when a proxy will be called. Often the proxies are peers and may be lost to follow-up for similar reasons as the participants, so frequent updating of proxy information is necessary. It is recommended that studies obtain the names of multiple participant proxies who have different contact information, particularly if participants are in the oldest old age groups during follow-up. Potential solutions to the continued follow-up of participants who have impaired decision-making capability or cognition include proxy exams in which a proxy completes a limited telephone interview for a participant or in which a proxy consents for the participant to complete a limited in-person exam. Although the information collected via the proxy contact may be more limited than that collected directly from the participant, investigators will be able to reliably obtain important risk factors and key outcomes [1].

4.4.2 Minimizing Missing Data

Missing data due to loss to follow-up or missed visits is unavoidable in longitudinal studies in aging. During the study design phase, studies must create a plan for handling missing data in order to have sufficient statistical power for main outcomes, including a consideration of the sample size needed based on the target population demographics and health and estimated loss to follow-up. The goal is to prevent missing data by using various techniques throughout the study design [55], such as those that follow. Primary outcomes should be easily determined and have valid alternate definitions. Data collection sequences should be prioritized to collect the most pertinent information first. For participants who have follow-up data, questionnaires and physiologic measures must enable the categorization of multiple reasons for missing responses

so that this data may be analyzed. Missing data should be monitored in real time, particularly for tests that have not been previously performed in a certain population. A missing data level of <5% is usually considered acceptable, though certain tests in older adults may have more missing data if there are health exclusions to the testing (e.g., spirometry, functional reach test, grip or knee extensor muscle testing) [50]. It is recommended that missing items be characterized according to participant characteristics and examiners. Caution should be exercised when using statistical techniques that require imputation because data is rarely missing at random, the missingness is usually informative, and use of imputation techniques may violate principles of the modeling. Ideally, measurements should be designed to minimize missing data while capturing the full range of functioning.

4.5 Optimal Testing Methods

Long-term epidemiologic studies often require a great deal of time and resources, and considerable thought and planning should go into the decision of which study measures to include. Gold-standard methods of measurement for studies of older adults may not be established, which leaves the burden of identifying, developing and validating optimal methods to the investigators. As the field of aging epidemiology increasingly encompasses the measurement of longitudinal changes and clinical trials, it is critical to develop and use appropriate and rigorous testing methods to detect small changes over time. The goal of this section is to provide tools for the evaluation of various methods of measurement in aging research. This section will focus on the assessment of validity, reliability, sensitivity to change, ceiling and floor effects, and feasibility and practicality of measurements. This section features commonly used approaches, though it is not intended as an exhaustive list of important criteria to evaluate methodology or of tools to assess criteria.

The first step in choosing a method of measurement is to detail the scientific rationale for its use (Table 4.2) [58]. The measure's role as an outcome, a predictor, a mediator or a potential confounder should be thoroughly considered and adequately laid out in study documentation. Additionally, investigators should evaluate whether potential measurement methods differ in their association with key outcomes in older adults. Once the scientific rationale behind using a measure has been established, investigators must consider whether the method has been adequately documented in the literature as valid and reliable in their target population. This is important not only for novel methods, but for previously-used methods as well. The investigators should not assume that methods shown to be valid and reliable in younger populations are as valid and reliable in populations of older adults (Table 4.3). There are often additional considerations specific to older adults, such as increased variability due, in part, to comorbid conditions, recovery from illness or injury, and cognitive impairments. Moreover, additional validation and testing may be required to extend methods of measurement to specific populations of older adults, such as the oldest-old, the frail, the highly functional, the cognitively impaired, institutionalized older adults, or those who have multiple chronic health conditions [56, 59, 60, 66, 67]. In addition, as discussed in Sects. 4.3 and 4.4, given the range of abilities and the risk of fatiguing older participants, practical aspects of the study

Table 4.2 Applicability to study population, feasibility and practicality

Assessment criteria	Components
Applicability to study population	Physical ability
	Cognitive status
	Vision/hearing
	Health-status
	Culture
	Education
Feasibility/ practicality [45, 56, 57]	Proportion able to complete
	Time to complete
	Cost
	Equipment needed
	Ability to perform outside of clinic (home or phone)
	Use of a proxy

Table 4.3 Assessing optimal methods of measurement for aging studies

Assessment criteria	Components	Methods of assessment
Validity [45, 56, 57, 59–65]	Sensitivity	Comparison with "gold standard"
	Specificity	ROC curves
	Internal validity	Comparison to alternative measures
	External validity	
	Conclusion validity	Association with outcomes
		Correlation
		Regression
	Construct validity	Factorial validity
		Correlation matrices
Reliability [65–70]	Test/Retest	Intraclass correlation coefficient (ICC)
		Coefficient of variation
		Bland Altman plot
		Kappa
	Internal Consistency	Cronbach's Alpha
Sensitivity to change [40, 56, 71]	Responsiveness	Effect size
		Standardized response mean
		Relative efficiency
Ceiling or Floor effects [56, 60, 65, 72]		Assess distribution

must also be considered, such as length of testing time, the abilities of the study population and whether the test can be administered over the phone, during a home visit, or by proxy. Other practical considerations include available study resources, necessary equipment and comparability to previous studies.

Many of these criteria for evaluation are not unique to aging research, as they are useful for all types of epidemiologic assessment. However, due to aspects which are unique to an older adult population (e.g., a wide range of function and higher rates of comorbidity and disability), these criteria are particularly important for this group. This section will attempt to put these criteria in the context of aging research—using examples from the literature—to address the unique aspects of studying older adult populations.

4.5.1 Validity

The overarching goals of epidemiologic studies, both in general and when studying older adult populations, are to accurately measure the frequency of a disease or condition and to assess the effect of an exposure on an outcome of interest. It may be more difficult to assess these accurately and over time in an older adult population due to the variability that occurs in this age group. Therefore, to successfully achieve the goals of an epidemiologic study, the two components of accuracy—validity and precision—must be assessed. This section will address various components of validity and provide examples of how to assess the validity of a measure in older adults. Precision, also known as reliability, will be discussed in the next section.

In epidemiologic research, validity is defined as the ability to correctly identify those with and without a disease, condition or trait. The two main types of validity are internal and external validity. Internal validity refers to the absence of methodological issues that result in systematic errors or biases within a study. To ensure adequate internal validity, care should be taken in the design phase of the study. Much of the discussion in this section on assessing and avoiding measurement error falls under the realm of internal validity.

External validity describes the representativeness of the study sample to a target population. The generalizability or applicability of study findings to a broader population is related to but not synonymous with external validity. For studies of older adults, balancing external validity with generalizability may be challenging and is dependent on the goal of the study. For example, when initially evaluating the Short Physical Performance Battery (SPPB) for assessing lower extremity function in older adults, the goal was to capture a broad spectrum of physical function [57]. One challenge for such a study is the recruitment and retention of more infirmed, physically-impaired participants (see Sects. 4.2, 4.3 and 4.4). In this case, the SPPB had to include activities that were safe for older adults who have physical impairments and limitations, while containing more challenging components to distinguish those who have higher physical function. Conversely, the goal may be to expand or tailor current measures to a specific study population, such as Simonsick et al. [60] did when they expanded previously-used measures of physical function to capture high levels of functioning in older adults. Eligibility criteria were used to ensure that this study population was well-functioning at baseline. These criteria included having no difficulty walking a quarter of a mile, climbing ten steps, or performing activities of mobility-related daily living. Another common tradeoff is balancing generalizability with the need to recruit individuals who are most at risk for developing a disease or condition of interest. In either case, caution must be used to avoid generalizing results to a population that differs significantly from the study sample.

One key element of evaluating internal validity is assessing information bias, which results from errors in measurement. Information bias or measurement error, can lead to the misclassification of participant exposure or disease status. This component of validity is often broken down into sensitivity, the ability to correctly identify those who have a condition or trait of interest, and specificity, the ability to correctly identify those who do not have a condition or trait of interest. To evaluate the sensitivity and specificity of a measure, it is necessary to compare it to a previously validated measure or preferably a "gold standard" method of measurement, if one exists. For example, Arnold et al. [45] validated the TICS and the IQCODE—both of which can assess cognitive function in older adults who are unable to return to the clinic—against a current standard method, the Modified Mini-Mental State Examination (3MSE). The TICS and the IQCODE were performed within 30 days of administering the 3MSE on a subset of participants from a population-based study of older adults ≥65 years of age at baseline. When choosing the amount of time between measures for an assessment of validity, it is crucial to consider the population-specific progression of the disease or condition in order to avoid comparing measurements at different stages.

One statistical method used to determine validity is plotting the sensitivity by the false positive rate (1 – specificity) to yield the receiver operating characteristics (ROC) curve [73]. The area under the ROC curve (AUC) represents the overall accuracy of classifying the disease or trait of interest, taking into account the tradeoff between sensitivity and specificity. Values range from 0.5, which indicates chance or the worst possible accuracy, to 1, which indicates perfect accuracy. In Arnold et al. [45], the TICS had an AUC of 0.89 and the IQCODE had an AUC of 0.75. The interpretation of these areas is that there is an 89% and a 75% probability that the TICS and the IQCODE, respectively, would correctly rank a participant with low cognition as having a higher suspicion of low cognition compared to a participant with normal cognition [74].

Recent concern that the ROC curve may only be suitable for detecting very large differences between the validity of different measures has lead to the development of novel reclassification methods that can distinguish smaller yet meaningful differences [61]. Reclassification methods use r x c tables based on the number of risk categories. This allows for the evaluation of measures with categorical outcomes, eliminating the need to dichotomize them, as is necessary with the ROC curve. In aging research, reclassification methods have been used to test the validity of

biomarkers [62] and risk models for predicting cardiovascular disease risk, such as the Framingham Risk Score, [61, 63, 75] and risk of osteoporotic fracture, such as FRAX model [64].

Additional options for validating a measure that does not have a dichotomous outcome include comparing the measure to an alternative measure using correlation coefficients or using regression to estimate the amount of variance one explains of the other (captured by the coefficient of determination [R^2]). One advantage of using regression is the ability to account for other parameters that may affect results of the measure. Guralnik et al. [57] used multiple linear regression to estimate the amount of variance of the SPPB summary score that was accounted for by an alternative method of measurement, self-reported function, adjusting for age and sex. They found that self-reported function alone accounted for 42% of the variance and that adding age and sex to the model accounted for an additional 4%, which illustrates that while the proportion of variance explained by self-reported function was high, there was still a considerable proportion of variance that remained unexplained. From this, the authors concluded that self-reported function may not adequately capture all of the parameters of physical function, and that an additional performance measure, such as the SPPB, provides a more complete assessment. However, correlation and regression analyses should be used with caution, given that they both have weaknesses [76, 77]. Correlation coefficients suggest a relationship between the two measures, and do not necessarily infer that the measures capture the same parameter. With regression, different variances may be observed depending on the assignment of measures to independent and dependent variables.

It is often useful to compare the measure being validated to relevant outcomes of interest. This can be done using regression techniques. Using Cox proportional hazards regression, Guralnik et al. [57] tested the association of SPPB summary scores and self-reported function measures with two outcomes that are highly salient to older adults: nursing home admission and mortality. Adjusting for age, men and women who scored 5 points poorer on the SPPB summary scale had a 2.3 (95% CI: 1.8–2.9) and 2.6 (95% CI: 2.0–3.5) times greater risk of mortality, respectively, and a 3.4 (95% CI: 2.5–4.6) and 2.8 (95% CI: 2.2–3.6) times greater risk of nursing home admission, respectively. This is the first step in evaluating conclusion validity, a term that is commonly used in social science research, but is equally important in epidemiology. Conclusion validity assesses whether the relationship between the measure and a related outcome is plausible. Additional methods of assessing conclusion validity include confirming that the measure is reliable (discussed in the next section) and ensuring that there is adequate power to draw the conclusion.

Construct validity refers to the amount to which the method of measurement captures what is intended to be measured. While there are certain parameters that can be measured directly (e.g., height, weight and blood pressure), other parameters (e.g., mental well-being) must be measured using indirect means. Mental well-being is an example of a construct, or an abstraction for which there is no direct measure. To indirectly measure a construct, several items are often used, such as multiple questions in a survey.

One method of assessing construct validity is to test factorial validity [78]. High factorial validity means that an item correlates well with the intended construct (referred to as convergent validity), while correlating poorly with other unintended constructs (referred to as discriminant validity) [79]. In an analysis designed to validate the 36-item Short Form Health Survey (SF-36) in frail older adults, factorial validity was tested to assess how well the survey captured the constructs of physical and mental well-being in this target population [56]. Using principal components analysis [80], the authors extracted two factors from the subscales of the SF-36, and retained factors that had an eigenvalue ≥1. The principal components were then rotated and the correlations among the subscales were tested based on *a priori* hypotheses. They chose the following cut-points for correlations: $r \geq 0.70$ to indicate a strong relationship; $0.30 < r < 0.70$ to indicate a moderate relationship; and $r \leq 0.30$ to indicate a weak

relationship. As an example of the results, the subscales Physical Function and Role-Physical strongly correlated with the Physical construct (r = 0.80 and 0.81, respectively) and weakly correlated with the Mental construct (r = −0.10 and −0.20, respectively), as hypothesized, exhibiting adequate factorial validity. In contrast, the subscale Bodily Pain moderately correlated with both the Physical construct (r = 0.42) and the Mental construct (r = 0.46), exhibiting poor factorial validity.

4.5.2 Reliability

Reliability or precision refers to the degree to which an instrument measures the same way each time it is used with the same participants under the same conditions. When evaluating longitudinal change, it is particularly important to take into account the degree of reliability of a method of measurement so as not to mistake the variability of the measurement for actual change. Some examples of when it may be necessary to assess reliability include when developing new measures, when existing measures have been tested in younger adults but not in older adults, when adapting measures or administering them in study populations for which they were not initially designed, when choosing an optimal method among a number of different options, and when a learning effect is thought to occur [56, 65–68].

The two components of reliability are test/retest reliability and internal consistency. Test/retest reliability, also known as reproducibility, measures the consistency of the instrument when implemented on two separate occasions for each participant. As when comparing two different measures to assess validity, when assigning the amount of time between test and retest trials, one must take into account the population-specific progression of the disease or condition that is being assessed. Tools for assessing test/retest reliability include (1) coefficients of variation [81], which assess the dispersion between the two measures while accounting for the magnitude of the measures' values; (2) intraclass correlation coefficients [82], which evaluate how much variability can be attributed to differences between individuals rather than measurement variability within individuals; (3) Bland Altman plots [76, 77], which illustrate whether there is systematic variation between the repeated tests, and (4) kappa coefficients, which compare the agreement of nominal outcomes, while adjusting for chance agreement [69]. Each of these tools was used to evaluate the test/retest reliability of motor nerve conduction measures in older adults [67]. While nerve conduction measures have been found to be reproducible in young healthy and diabetic populations [83], their test/retest reliability had not been previously assessed in older adults, for whom poor nerve function is common [84]. Tests were repeated on the same day, by the same examiner, 1–3 h apart. Ward et al. [67] observed low coefficients of variation (<5%) and moderate-to-high intraclass correlation coefficients (≥0.75), which indicates good test/retest reliability in their study population. Bland Altman plots were created by plotting the differences between the test/retest measures against the means of the test/retest measures. These plots illustrated that the mean differences between the measures were not significantly different than zero and that most of the data points fell within 1.96 standard deviations above and below the mean differences, which suggests minimal systematic variation. Finally, reproducibility of nerve conduction waveforms that had abnormal morphology could not be assessed in this study using the above described methods, since no numerical results were obtained. Instead, kappa coefficients were used to assess the agreement of waveform morphology status (normal vs. abnormal) between primary and reproduced measures. All measures had high Kappa coefficients (0.82–0.90; all $p < 0.05$), indicating very good agreement [70]. This technique allows for evaluating reproducibility of whether or not a result can be obtained.

Internal consistency tests the extent to which a group of items, such as a group of questions in a questionnaire, measure the same concept. Unlike test/retest reliability, to assess internal consistency, the measure is only administered once. Internal consistency can be measured using

Cronbach's alpha [85] by separating items in an instrument into groups and calculating correlation coefficients for items within the groups. Cronbach's alpha values range between 0 and 1, where 0 indicates no internal consistency and 1 indicates the highest internal consistency. To evaluate the internal consistency of the SF-36 for clinical application in their population of frail older adults, Stadnyk et al. [56] used a cutoff of 0.90 for an acceptable Cronbach's alpha. They found that most of the subscales did not meet this cutoff, which indicated unacceptable internal consistency for the use of this instrument in frail older adults [56].

4.5.3 Sensitivity to Change

In epidemiologic studies of older adults, it is often an important goal to detect longitudinal change in measures of interest to study the progression of a disease or condition with age. For example, the goal may be to detect declines in physical or cognitive function, where it may not be enough to simply identify participants who are impaired as small continuous declines may have occurred, even in those classified as functionally intact [52]. In addition, the sensitivity of a measure is also crucial when classifying change using clinical cutpoints, since some participants may be on the border of the cutpoint. Classification of risk factor stability, which also requires that a measure be sensitive to change may also be of interest. For example, participants maintaining high homocysteine levels over time may have poorer nerve function than those with levels that changed over time [86]. The ability to detect small changes in outcomes or risk factors of interest is necessary for the earlier identification of diseases, conditions, declines in function, or prolonged exposure to risk, which can lead to earlier intervention and more successful prevention. Therefore, when choosing an optimal method of measurement, it is important that it be sensitive to change.

Sensitivity to change often requires a quantifiable measure with a certain level of precision, so as not to mistake actual change for measurement variability (see Sect. 4.5.2). For example, advanced imaging methods such as dual-energy x-ray absorptiometry (DXA), which can measure change in lean mass as low as 1% [71], and computed tomography (CT), which has minimal test/retest and inter-observer variability (coefficients of variation <5%) [40], have been used to elucidate the relationships between declines in muscle mass, muscle quality content and strength with age. These direct and sensitive measures of muscle mass have led to findings that support the hypothesis that age-related declines in muscle quality, rather than in muscle mass alone, could play a major role in loss of strength in older adults [40]. Previous to this work, the use of less precise and sensitive measures of muscle mass had produced conflicting results [87]. Therefore, when studying the relationship between risk factors and the progression of a disease or condition, the inability to detect change could lead to misclassification that erroneously biases results toward the null.

Sensitivity to change, or responsiveness, can be examined using effect size [88], standardized response mean [89] and relative efficiency statistics [90]. Stadnyk et al. [56] used these statistics to measure the ability of the SF-36 to detect change in health-related quality of life in frail older adults from admission to discharge from various rehabilitation programs. The effect size, which estimates the magnitude of change observed with the measure, was calculated by dividing the mean change by the variability of the measure in a stable situation (in this case, the standard deviation of the measure at baseline). Similarly, the standardized response mean, which is also a measure of magnitude of change, was calculated by dividing the mean change of the measure by the standard deviation of the mean change. For both the effect size statistic and the standardized response mean, greater magnitude signifies a greater capacity to detect change. Stadnyk et al. calculated the effect size and standardized response mean statistics for each subscale of the SF-36 and compared them to statistics that were calculated for alternative health assessments, including the Nottingham Health Profile (NHP), the Spitzer Quality of Life Index

(SQLI), the Barthel Index (BI) and the Older Americans Resources and Services Instrumental Activities of Daily Living (OARS-IADL), all performed in the same target population. They found that the subscales of the SF-36 were generally less responsive (effect size: 0.00–0.35; standardized response mean statistics: 0.00–0.31) than comparative health assessments (effect size: 0.00–0.73; standardized response mean statistics: 0.00–0.94).

Stadnyk et al. also calculated the relative efficiency, which is a ratio of the ability to detect change of one method of measurement to the ability to detect change of an alternative method. It is calculated by dividing the paired *t*-test statistic that compares the measure of interest at two time points (in this case the score of each SF-36 subscale at admission and at discharge) by the equivalent statistic of an alternative method of measurement. Since there was no standard assessment of quality of life in frail older adults, they used the SQLI as their alternative method. If the method of measurement being tested and the alternative method have the same efficiency, the relative efficiency will be equal to 1. A score of >1 denotes that the measure being evaluated is more efficient than the alternative method, while a score of <1 means that the measure being evaluated is less efficient than the alternative method. Using relative efficiency statistics, they found that each SF-36 subscale was less responsive than the SQLI (relative efficiency statistics: 0.03–0.14) [56].

4.5.4 Ceiling and Floor Effects

Ceiling and floor effects indicate that the variance of a measure cannot be estimated at high or low ranges. These effects are common in research in older adults and are problematic given the variability that occurs with older age. Consequences of ceiling and floor effects include reduced sensitivity in detecting outcomes of interest [91–93] and the inability to detect important associations between risk factors and outcomes. They may also result in the inability to characterize true changes over time (see Sect. 4.5.3) that occur within the ceiling or floor.

The presence of a ceiling or floor effect can be evaluated by examining the variance of the measure within the study population. A ceiling or floor effect may be present if the resulting distribution is skewed at the low or high end of the spectrum, respectively. For example, a ceiling effect may occur if the researcher chooses a measure of physical function that is not challenging enough for a higher-functioning population. On the other hand, a floor effect will likely occur if the researcher chooses a physical function measure that is too challenging for their study population to complete.

Alternatively, ceiling and floor effects can be evaluated by comparing the method of interest to a method that is known to capture the desired range of variability. For example, Simonsick et al. [65] sought to assess measures that could capture a full range of physical function and exercise tolerance in older adults. Measures with low cardiovascular demands, such as the 4-m fast- and usual-paced walks, the 20-m fast- and usual-paced walks, and the seated step test—all of which can be completed in the event of limited space and time, or by those who would be excluded from more demanding measures—were compared to measures with high cardiovascular demands, such as the graded treadmill walk and the 6-min walk. Performance for each test was ranked from 0 to 4 by sample-based quintiles, and was compared between the tests. A reasonable substitute measure was defined as being within 1 point of the comparative measure at least 80% of the time and being within 2 points of the comparative measure 100% of the time. The investigators observed mostly poor comparability between the low-demand and high-demand measures. Only the 4- and 20-m fast-paced walks approached the cutoff for variability with the 6-min walk, as 82% were within 1 point and 96 and 98%, respectively, were within 2 points. The investigators also used linear regression to evaluate the amount of variance that the low-demand measures explained of the high-demand measures. The unadjusted variances ranged from 0.13 to 0.42, with the 20-m fast-paced walk explaining 42% of the 6-min walk, which suggests that it could be an adequate substitution [65].

Ceiling and floor effects can often be overcome by modifying the method of measurement to better suit the study population. For example, methods of measurement that were created to identify those who have impairments or limitations are likely to be inappropriate when studying highly functioning older adults. Simonsick et al. [60] sought to overcome ceiling effects of physical function measures by increasing the difficulty of the tests. By lengthening the duration of tests, adding progressively more challenging activities to the exam and altering scoring to raise the measurement ceiling, the investigators were able to distinguish higher levels of physical function in this study population of older adults.

With certain measures, both ceiling and floor effects may occur depending on the target study population. The Mini-Mental State (MMS) examination is a brief cognitive test that has been shown to be somewhat reliable and valid for screening dementia [94, 95]. However, ceiling and floor effects limit its suitability for detecting mild cognitive deficits in individuals who do not have dementia and for differentiating more advanced stages of dementia [96]. The 3MSE was developed to overcome these ceiling and floor effects. This was achieved by adding additional test items and altering existing test items (some to increase difficulty and some to increase ease); giving credit for some coaching or aided recall; and broadening the scoring range from 0–30 to 0–100 [72]. Compared to the MMS, the 3MSE has been found to be a more reliable [92, 93, 97] and sensitive measure [91–93] for detecting dementia and cognitive deficits in a variety of study populations.

Depending on the target study population and the goal of the study, ceiling and floor effects can be prevented by carefully matching the method of measurement to the ability of the study population, or by selecting a method that captures a wide range of variability. However, if ceiling and floor effects cannot be avoided or minimized in the design, then statistical methods should be carefully chosen to adjust for these effects, such as Tobin regression [98].

4.5.5 Feasibility and Practicality of Measurements

The feasibility and practicality of a measurement may depend not only on the characteristics of the study population (see Sects. 4.3 and 4.4), but also on the resources available and the goal of the study. The most advanced method of measurement is not always the gold standard for epidemiologic studies. Comparability with similar studies and consistency with a previously-used method may be more important than implementing the latest technology. In addition, extensive testing and costly equipment may be exchanged for ease of implementation in a large study population or a clinical setting. Therefore, investigators should consider the tradeoff between using the most advanced, innovative study measures and the practicality of implementing such measures.

4.6 Conclusion

Demographic and health characteristics differ among older adults who participate in research and who continue to actively participate in longitudinal studies. Although the higher burden of disease and impairments in older adults compared to younger populations may pose recruitment and retention challenges, there are viable solutions for achieving participation across a range of health and functioning. These solutions focus on accommodating the needs of older adults to facilitate participation, which will reduce participation bias in studies and increase the representativeness of participants. Measures used in studies of older adults must be valid, reliable and sensitive to change over a wide range of functioning. In general, to maximize participant retention and the collection of critical health information that characterizes the dynamic longitudinal changes in older adults, key data must be obtained through frequent telephone follow-ups with the option of a proxy completion of the interview, and in-person exams that are offered should include the option of a home exam.

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Nursing Home Research

5

Susan Hardy

Abstract

Nursing home utilization is common among older adults, and it represents a costly and growing sector of the health care system. As the length of hospital stays has declined, nursing homes increasingly provide short-term rehabilitative and medical care to patients who have recently been discharged from acute-care hospitals. Nursing homes may also provide palliative, hospice, and respite care. With the impending entry of the baby boom generation into Medicare eligibility and old age, there is an urgent need for information to guide the medical care of nursing home residents and to direct policy regarding long-term care. Although challenging, high-quality nursing home research is achievable with careful attention to methodological and administrative issues. Multiple publicly available data sets are available for use in nursing home research.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Competency • Informed consent • Vulnerable populations • Frailty • Rehabilitation • Comorbidity • Assistive device • Nursing home • Assisted living • Personal care

Abbreviations

CASCADE	Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-Life
CMS	Centers for Medicare and Medicaid Services
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MDS	Long-term care Minimum Data Set
NLTCS	National Long-Term Care Survey
NNHS	National Nursing Home Survey
OSCAR	Online Survey and Certification Reporting System

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5.1 Introduction

Nursing homes were initially developed as residential facilities intended to provide medical care and supportive services to individuals who have chronic illnesses and disabilities. As the length of hospital stays has declined over recent decades, nursing homes have begun to provide short-term rehabilitative and medical care to patients who have recently been discharged from acute-care hospitals [1]. Nursing homes may also provide additional services such as palliative and hospice care, as well as respite care designed to relieve family caregivers. Nursing homes vary widely in size, may be hospital-based or free-standing, and offer differing arrays of special services.

Nursing homes are one of the most heavily regulated parts of the health care system. In addition to observing state laws, the vast majority of nursing homes must be certified by the Centers for Medicare and Medicaid Services (CMS). Without this certification, facilities may not receive payments from Medicare or Medicaid. CMS certification requires compliance with extensive regulations that concern the provision of care, the frequency of physician assessments, the availability and use of a variety of medical services, and many other issues [2]. Facilities are evaluated for compliance at least annually, and the results of the surveys are available online: http://www.medicare.gov/NHCompare. Available results include compliance areas in which the nursing home was considered deficient, staffing level (total hours the nursing staff worked divided by the number of residents), and a selection of quality indicators.

In 2004, more than 16,000 nursing homes were operating in the United States (US), with a total of over 1.7 million beds. Of these facilities, 88% were certified for both Medicare and Medicaid payments, 62% were for-profit, and 54% were part of a chain. The facilities had an average of 108 beds, with 14% having fewer than 50 and 6.2% having 200 or more [3].

In this chapter, we will review the characteristics of nursing home residents and the need for conducting nursing home research. We will also address some of the unique methodologic challenges of nursing home research and provide an overview of the most relevant large databases that are available for nursing home research.

5.2 Nursing Home Residents

The nursing home population comprises two major groups: long-term residents and short-term rehabilitation patients. Long-term residents live permanently in the facility because a combination of physical and cognitive problems results in their needing 24-hour nursing care. Most short-term residents are receiving post-acute care after a hospitalization, with the intention of returning to the community upon discharge. A smaller portion of short-term residents are receiving palliative or respite care. Since Medicare limits post-acute care to 100 days, residents who stay longer than 3 months are generally considered to be long-term. Of the almost 1.5 million individuals who were residing in US nursing homes in 2004, 80% were long-term [3].

The vast majority (88.3%) of nursing home residents are ≥65 years of age. Characteristics of older nursing home residents by time since admission are presented in Table 5.1. Both long- and short-term nursing home residents have a high burden of medical problems and disability. The prevalence of cognitive impairment, as indicated by either a diagnosis of dementia or the inability to make decisions, is higher among long-term residents (73%). However, cognitive impairment is highly prevalent among short-term residents as well (53%). Short-term residents are more likely to be discharged because they have recovered or stabilized, while long-term residents are more likely to eventually die at the facility or be transferred to a hospital.

5.3 Why Conduct Nursing Home Research?

Nursing home utilization is high among older adults, and it accounts for substantial healthcare costs. In 2003, 18% of adults ≥65 years of age spent some time in a nursing home. Among

Table 5.1 Characteristics of United States nursing home residents ≥65 years of age by time since admission[a]

	Time since admission	
Characteristic	<90 days	≥90 days
Age in years, mean	82.5	84.5
Female, %	67.9	76.0
Non-Hispanic White, %	83.7	84.4
Married, %	25.4	19.4
Active chronic diseases (of 7), mean	1.5	1.6
Dementia, %	36.0	53.3
Chronic kidney disease, %	5.3	3.3
Chronic obstructive lung disease, %	17.0	12.8
Diabetes, %	26.7	23.0
Heart failure, %	21.3	20.3
Coronary artery disease, %	21.6	20.6
Arthritis, %	17.2	24.5
Total number of medications, mean	8.8	8.9
Able to make daily decisions, %	56.8	37.3
Require no hands-on assistance with ADLs[b], %	3.0	4.4
Require hands-on assistance with all ADLs, %	29.4	34.1
Fell in the past 6 months, %	42.4	35.5
Discharge reason (for patients discharged at the time of the survey)		
Recovered or stabilized, %	44.3	6.8
Deceased, %	17.8	44.5
Hospitalized, %	23.3	37.5
Transferred to another nursing home, %	5.6	6.6
Other[c], %	9.0	4.7

[a]All data is from the 2004 National Nursing Home Survey with the exception of discharge information, which is from the 1999 survey

[b]ADL: activities of daily living; includes transferring, walking, dressing, eating, toileting, and bathing

[c]The majority of 'Other' discharges were discharges to home or to assisted living/personal care

the oldest older adults (≥85 years of age), 44% spent some time in a nursing home [4]. In 2010, the lifetime risk of nursing home use among individuals 65 years of age was 44% for any use and 24% for a stay of at least 1 year [5]. The number of older adults who will require long-term care services is expected to double as the baby boom cohort ages [6]. This extensive use has driven US health expenditures for nursing home care steadily upward, from $85 billion in 2000 to $137 billion in 2009 [7]. Medicare beneficiaries who were living in long-term care facilities for at least part of 2006 accounted for 6% of the Medicare population, but accounted for 17% of total Medicare spending, even though most nursing home costs are paid either privately or by Medicaid [8].

Despite the obvious medical, fiscal, and policy challenges connected with nursing homes residents, there is remarkably little scientific evidence to guide the care of this diverse and ever-expanding population. Knowledge regarding the incidence, prevalence, and course of many diseases and impairments in nursing home residents is conspicuously lacking, and even less is known regarding the interaction among the multiple chronic problems that are common in this population [9]. The differences in health status between nursing home residents and their counterparts who live in the community are great enough that even the limited research done in community-dwelling older adults cannot easily be applied to the nursing home population [10, 11]. For example, 48 of the 50 clinical trials used to support Canadian clinical guidelines on osteoporosis treatment were conducted with community-dwelling participants [11]. None of the trials of bisphosphonates—the mainstay of osteoporosis treatment—were conducted with nursing home residents, and the mean age of participants was 70 years. In addition to the difference in age, nursing home residents have a higher prevalence of dysphagia and other impairments that could alter the safety profile and effectiveness of bisphosphonates. Few medications and interventions have been tested in nursing home residents, and most trials that have enrolled nursing home residents have been small and of poor quality [12]. In order to improve the medical care provided in nursing facilities and to formulate reasonable healthcare policy, it is vital that high-quality research be conducted in the nursing facility setting.

Several investigators have demonstrated that high-quality nursing home research is feasible and can have a high impact. The Choices, Attitudes, and Strategies for Care of Advanced

Dementia at the End-of-Life (CASCADE) study provides an example of a rigorously conducted prospective cohort study of nursing home residents with advanced dementia and their healthcare proxies that is designed to elucidate major gaps in knowledge regarding the end-of-life experience in advanced dementia. Gaps addressed by the study include: (1) disease trajectory and clinical course of advanced dementia, (2) resident comfort, (3) clinical decision-making, (4) family satisfaction with end-of-life care, and (5) complicated grief among bereaved family members [13]. The study has identified pneumonia, febrile episodes, and eating problems as frequent complications of advanced dementia that are associated with distressing symptoms, burdensome interventions, and high 6-month mortality rates [14]. Marcantonio et al. [15] conducted a randomized controlled trial of a delirium-abatement program in older adults who were admitted to skilled nursing facilities for post-acute care. Although the intervention did not reduce the duration of delirium, the study dramatically increased our knowledge with regard to the prevalence and duration of delirium in post-acute care and its adverse outcomes, including poor functional recovery and institutionalization [16].

5.4 Methodologic Issues in Nursing Home Research

5.4.1 Ethical and Regulatory Issues

The ethical conduct of research in nursing homes requires balancing the residents' right to participate in and benefit from research with the protection of a vulnerable population from the potential risks inherent in research. Although federal regulations on human participant research do not specifically recognize nursing home residents as a vulnerable population, the general consensus in the research and bioethics community holds that nursing home residents are entitled to special protection due to their high rates of cognitive impairment and their dependence upon the facility to meet their physical, emotional, and social needs [9, 17]. The American Medical Directors Association, while strongly supporting the involvement of residents of long-term care facilities in research, emphasizes the need for the facility and its medical director to approve and provide an ongoing review of the project, and to ensure the resident's or surrogate's right to refuse participation at any time [9].

In addition to securing the nursing facility's permission, researchers will also need to obtain approval from an Institutional Review Board (IRB). Given the dearth of nursing home research, very few nursing facilities have established their own IRBs, so researchers will have to apply to another appropriate IRB, likely that of the research institution with which the principal investigator is associated. Often these IRBs have minimal expertise on nursing homes and no representation from the key stakeholders, such as nursing home staff or resident advocates. Further, individual states may have additional legal requirements with regard to nursing home research. For example, Pennsylvania requires that its Department of Health approve all research that involves nursing home residents. State regulations may also dictate who may provide surrogate consent for participation in research, and under what circumstances surrogate consent may be provided. Many states limit the ability of court-appointed guardians to consent to research participation on behalf of an impaired individual.

In addition to providing guidance on who is able to provide informed consent, ethical concerns limit the types of research in which vulnerable and decisionally impaired older adults can participate. Generally, research should be directly relevant to the participant's condition or circumstance. For example, the testing of an experimental medication for the control of behavioral symptoms in dementia would be relevant to a nursing home population and thus would be ethically acceptable. On the other hand, an early-stage trial of an experimental diabetes medication that is intended to benefit anyone with that disease would be more appropriately conducted in the community and with a cognitively intact population. A selection of topics appropriate for nursing home research is presented in Table 5.2.

In most cases, research should pose minimal risk to the participant; that is, the probability and

Table 5.2 Conditions and issues that should be studied in nursing homes

Dementia
Neurodegenerative diseases
Osteoporosis and fractures
Delirium
Depression and other mental health issues
Heart Failure
Disability
Dysphagia
Sarcopenia
Frailty
Chronic pain
Polypharmacy
Palliative Care
Infectious Diseases:
Multi-drug resistant organisms
Pneumonia
Urinary tract infections
Influenza and other respiratory viruses
Norovirus and other gastrointestinal infections

magnitude of harm or discomfort that is anticipated in the research should not exceed those ordinarily encountered in daily life or during routine physical or psychological examinations or tests. However, the exposure of participants to more than minimal risk can be justified if the research offers the possibility of direct benefit to the participant, or if it seeks knowledge directly relevant to the understanding or the eventual alleviation of a condition that afflicts the participant [17].

Like all other research in clinical settings, research in nursing homes must comply with the regulations that govern healthcare information in the Health Insurance Portability and Accountability Act (HIPAA) [18]. Initial contact regarding study participation must be made by the clinical staff that cares for the resident, and specific consent or a HIPAA waiver is required to gain access to medical records.

5.4.2 Decisional Capacity and Informed Consent

Although many nursing home residents are cognitively impaired, researchers cannot assume that residence in a nursing facility, or even a diagnosis of dementia, necessarily precludes the capacity to consent to participate in a study. Rather, decisional capacity—the ability to understand options and choose between them—should be assessed clinically, taking into account the nature and complexity of the decisions involved. An individual might well have the capacity to decide to participate in one study, yet lack that capacity for another study that has, for example, a more elaborate design or more medically esoteric risks. Decisional capacity requires individuals to understand the relevant information (such as procedures, risks and benefits), appreciate how this information applies to their situation, weigh the pros and cons of each option in reasonable terms, and then make and express a choice [19]. Protocols for nursing home research should include a formal assessment of the potential participants' capacity to consent. When a potential participant is determined to lack this capacity, the researcher should obtain the impaired person's assent to defer the decision to a legally authorized representative. Even after the representative has provided surrogate consent, a decisionally impaired older adult retains the right to refuse participation at any time [17]. A number of tools have been developed to assess an individual's capacity to consent to participation in research. While the MacArthur Competence Assessment Tool for Clinical Research has the most empirical support, briefer tools may be more efficient for initial screening or minimal-risk studies [20].

5.4.3 Participant Selection and Recruitment

Given the varied categories of nursing home residents, careful attention should be paid to enrollment criteria. For example, researchers who are conducting studies of functional recovery after hospitalization will want to enroll participants upon admission for post-acute services, and to exclude those admitted for palliative or long-term care. Studies of the effect of non-pharmacologic interventions on behavioral disturbance in dementia may want to limit enrollment to long-term

residents. Even with well-devised criteria, the enrollment of appropriate nursing home residents presents particular challenges because both long- and short-term patients typically arrive following hospital discharge [4]. Determining whether a resident will be short- or long-term at the time of admission can be very difficult, and the subsequent exclusion of initially eligible residents should be taken into account when determining sample size. The high mortality rate of nursing home residents also generally necessitates the recruitment of large sample sizes for longitudinal studies of outcomes other than mortality.

Recruitment actually begins with the selection of facilities that will participate in the research program, because facility characteristics (e.g., ownership, staffing levels) are associated with outcomes for residents [21, 22]. Generalizability therefore demands the recruitment of participants from a range of facilities. The recruitment of a broad participant sample becomes even more critical in intervention studies, in which cluster randomization by facility is often necessary to prevent contamination of the control group by exposure to the intervention or to test changes in the organization or provision of care [23, 24]. While it is important to secure the support of a facility's administrator, medical director, and director of nursing, it is equally vital to ensure the cooperation of the direct-care staff—who often have little obvious incentive to assist researchers—because timely patient identification and recruitment cannot occur without effort on their part [10, 24, 25].

The recruitment of nursing home residents for research studies is unusually costly and time-consuming. In addition to high rates of cognitive impairment, this chronically ill population may have multiple sensory and communication deficits that require adaptation of the informed consent procedure. When potential participants are unable to provide consent, a surrogate decision-maker must be identified and contacted. Seeking proxy consent, while often quite burdensome for the researcher, remains essential because the exclusion of participants who are unable to consent will severely limit the generalizability of any research results. Given these obstacles, the process of consent, screening, and enrollment often requires multiple visits and phone calls. These hindrances for the researcher accompany a need to encourage initial recruitment and retention by minimizing the burden of the research on the resident. Lengthy assessments may often require multiple sessions, and patients and surrogates may be reluctant to undergo even minimally invasive procedures, such as blood draws.

5.4.4 Selection of Appropriate Measures

All measures used in research with nursing home residents should be validated in the nursing home population and be selected with the specific challenges of nursing home research in mind. Many measures commonly used in studies of community-dwelling adults may be too difficult for nursing home residents to perform, which could result in high rates of missing data or high floor effects. For example, many nursing home residents cannot complete common performance measures, such as hand grip strength, or timed chair rise and ambulation, due to cognitive or physical impairments [26]. Cognitive, visual, or hearing deficits may also render residents unable to complete questionnaires or interviews unless the procedures can be modified to compensate for their deficits. Anticipating high rates of cognitive impairment in particular is critical for valid results; a study will be of little use if, for example, it fails to distinguish those who are unable to stand when asked from those who do not understand the request. For some measures, cognitive impairment may also necessitate adding a proxy's response to that of the resident. The preferability of using a family or a staff proxy depends upon the nature of the particular assessment and the frequency of family contact [27]. The deliberate selection of a measure that a proxy can complete will help to prevent missing data.

5.5 Publically Available Data Sets for Nursing Home Research

Data from administrative sources and large national epidemiologic studies is available for the study of nursing homes and their residents. While some data sources, such as Medicare and Medicaid claims data, contain information on nursing home residents and are used in nursing home research, we will focus on data sets that are specific to nursing homes and their residents.

5.5.1 Long-Term Care Minimum Data Set (MDS)

The MDS is a comprehensive, standardized health status assessment tool which must be completed at regular intervals on all residents in nursing homes that are certified by Medicare or Medicaid. Initially developed in response to the 1987 Institute of Medicine Report on Nursing Home Quality, the MDS was designed to assess residents for health problems or risks, guide the development of individual care plans, and drive improvements in care quality. In addition, data from the MDS is used to create quality indicators which guide certification and are available to the public. A third function of the MDS is to determine reimbursement under the prospective payment system. The MDS was nationally implemented in 1991, updated in 1995 (MDS 2.0), and updated again in 2010 (MDS 3.0) [28]. The MDS 3.0 development process sought to improve the clinical relevance and accuracy of MDS assessments, increase the voice of residents in assessments, improve user satisfaction, and increase efficiency [29]. After extensive national pilot testing, MDS 3.0 was implemented in all nursing facilities in October 2010. Both MDS 2.0 and MDS 3.0 data are available from the CMS for use in research.

The MDS contains information on each resident's functional, medical, mental, and psychosocial status. Specific areas that are included are presented in Table 5.3. When comparing "gold standard" research nurses with facility nurses, the MDS 3.0 items were shown to be recorded with excellent reliability, and several MDS 3.0 assessments—including those for cognition, depression, and behavioral disturbances—have been validated against gold standard assessment tools [29]. The MDS is completed upon patient admission and at least quarterly thereafter. For post-acute care patients, the MDS is completed at days 5, 14, 30, 60 and 90 after admission. The MDS can be linked to other data sources, such as Medicare or Medicaid claims data.

The use of the MDS can result in research that is highly clinically relevant because the sample is representative of nursing home patients and the information is collected as part of routine care. For example, a tool to predict 6-month mortality among nursing home residents with advanced dementia that is based upon items from the MDS performed better than other existing tools, and can easily be used to identify residents who might benefit from hospice and palliative care services [30].

Additional information on the MDS (and other CMS data) as a research resource is available from the Research Data Assistance Center: http://www.resdac.org/.

5.5.2 Online Survey and Certification Reporting System (OSCAR)

Provider of services files, which are derived from CMS's OSCAR database, provide information on nursing homes that are certified by Medicare, Medicaid, or both. Available information includes ownership, specialized units, number and types of staff, and the availability of ancillary services such as laboratory testing or radiology. In addition, OSCAR includes the number of Medicare, Medicaid, and other residents, and summarized information on the condition of residents with a focus on conditions with quality indicators. The facility information in OSCAR can be linked to the MDS and Medicare/Medicaid claims data. Additional information is available from the CMS website: http://www.cms.gov/NonIdentifiableDataFiles/04_ProviderofServicesFile.asp.

Table 5.3 Content of the MDS 3.0 assessment

Area	Items
Identification information	Sociodemographics, administrative information
Hearing, speech, and vision	Ability to hear, speak, understand speech, and see; use of hearing aids or corrective lenses
Cognitive patterns	Brief Interview for Mental Status (or staff assessment if patient unable to complete interview), delirium
Mood	Depressive symptoms
Behavior	Psychotic symptoms, behavior symptoms (presence, frequency, and impact), rejection of care, wandering
Preferences for customary routine and activities	Preferences about basic daily activities and leisure activities
Functional status	Assistance received for activities of daily living, bathing, balance, range of motion, assistive devices, rehabilitation potential (on admission)
Bladder and bowel	Appliances, continence, toileting program, constipation
Active diagnoses	Checklist of medical diagnoses with ability to list additional diagnoses
Health conditions	Pain management, pain (presence, frequency, impact on function, intensity), shortness of breath, tobacco use, limited life expectancy, fever, vomiting, dehydration, internal bleeding, fall history
Swallowing/nutritional status	Signs and symptoms of swallowing disorder, height and weight, weight loss, nutritional approaches
Oral/dental status	Signs and symptoms
Skin conditions	Pressure ulcer risk, pressure ulcers (number, stage, duration, dimensions), venous/arterial ulcers, other skin conditions, current skin treatments
Medications	Injections, insulin, psychiatric medications, anticoagulants, antibiotics, or diuretics
Special treatments, procedures, and programs	Cancer treatments, respiratory treatments, IV medications, transfusions, dialysis, hospice care, respite care, isolation/quarantine for infectious disease, vaccinations, therapies (speech, physical, occupational, respiratory, psychological, recreational), restorative nursing programs, physician examinations, physician orders
Restraints	Type and frequency of physical restraints

MDS = long-term care Minimum Data Set

5.5.3 National Nursing Home Survey (NNHS)

The NNHS is a continuing series of surveys of nursing homes, their residents, and their staffs which are conducted by the National Center for Health Statistics. Surveys have been conducted periodically since 1969, with the most recent in 2004. Each survey had its own specific focus, but a subset of information was collected across years, which enables the evaluation of trends over time. Weights provided can be used to extrapolate results to the entire US nursing home population. Facility-level topics include certification, bed availability, services provided, staffing, and financial information. Resident-level data include demographics, health and functional status, and sources of payment. The 2004 NNHS included—for the first time—prescribed medications and a survey of nursing assistants.

Nursing home residents who were included in the 1985 NHHS were followed longitudinally through the National Nursing Home Survey Follow-up, which had three waves: one each in 1987, 1988 and 1990. The follow-up surveys investigated hospital and long-term care utilization patterns, and include data on vital status, living arrangements, and nursing home and hospital stays.

Researchers have used NNHS data to study many topics, including psychoactive medication use [31, 32], falls [33, 34], and palliative care [34].

The NNHS data from 1995 onward is available for free download at http://www.cdc.gov/nchs/nnhs.htm. The site also provides detailed documentation on the survey methods and questionnaires. Older data is available from the Inter-university Consortium for Political and Social Research: http://www.icpsr.umich.edu/icpsrweb/ICPSR/index.jsp.

5.5.4 National Long-Term Care Survey (NLTCS)

The NLTCS, conducted by the National Institute on Aging and Duke University, is a longitudinal survey designed to study changes in the health and function of older Americans. Six waves of data collection are available from 1982 to 2004. Each wave used a screening questionnaire to divide the sample into three groups: the non-disabled, the disabled who are living in the community, and the disabled who are living in an institution. All of the disabled individuals and a subset of the non-disabled individuals receive a detailed survey on medical and functional status, formal and informal care received, and healthcare utilization. A next-of-kin survey was conducted for deceased participants in 1984 and 1999. Surveys of informal caregivers were conducted in 1989, 1999 and 2004. Blood and buccal swab samples were obtained from a subset of participants in 1999. These data can be linked to Medicare claims data.

The NLTCS is particularly useful for examining the factors that lead to nursing home admission and for following nursing home use over time. For example, data from the survey have been used to identify potential problems when older adults transition into and out of post-acute and long-term care services [36], to predict future needs for long-term care after a diagnosis of Alzheimer's disease [37], and to determine the effect of the availability of informal help in the community on permanent nursing home placement [38]. Detailed information on the NLTCS is available at: http://www.nltcs.aas.duke.edu/.

5.6 International Differences in Long-Term Care

In both developing and developed countries, the growth in both the absolute number of older adults and the proportion of the population that is >65 years of age is leading to the increased need for long-term care services. Resident characteristics, services available, care practices, and the financing of long-term care are highly variable factors across countries [39]. The proportion of older adults who live in nursing homes ranges from 0.2% in Korea to 4.3% in the US to 7.9% in Sweden. Total (public and private) long-term care expenditures range from 0.6% of GDP in Spain to 1.3% in the US to 2.9% in Sweden. Spain has the highest percentage of private spending at 72%, and Sweden has the lowest at 5%. In the US, 42% of expenditures are private [40].

In spite of these differences, many long-term care issues (e.g., quality of care, medication use, functional status) are similar across countries. In addition, many countries use assessment tools based on the MDS. Nevertheless, it is important to consider cross-national differences when generalizing research between countries, particularly when research addresses predictors of institutionalization, health care utilization, and other factors that are highly dependent on health system characteristics. The Organisation for Economic Co-operation and Development has an excellent publication that compares and contrasts long-term care services among member nations [40].

5.7 Summary

Nursing home utilization is common among older adults, and it represents a costly and growing sector of the health care system. The need for information to guide the medical care of nursing home residents and to direct policy regarding long-term care has become increasingly urgent with the impending entry of the baby boom generation into Medicare eligibility and old age. Although challenging, high-quality nursing home

research is achievable with careful attention to methodological and administrative issues. A number of publicly available data sets are available for use in nursing home research.

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Use of Proxies and Informants

6

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Abstract

A proxy or informant is an individual who provides reports on behalf of, or about, a study participant. Proxies are essential in studies of older adults for minimizing selection bias and preserving external validity. Important items to consider when designing studies that will use proxies include determining the wording of questions, determining how the proxies will be selected, determining the proxy perspective, and selecting appropriate analytical methods. Future research directions on the use of proxies include the development of new analytical methods. In summary, the use of proxies should be thoughtful, well-documented, reported in results, and—wherever possible—assessed for bias in the populations and domains that are utilized in the studies.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Proxies • Informants • Reliability • Validity • Self report • Performance • Disability • Cognitive impairments • Epidemiologic studies

Abbreviations

ADL	Activities of Daily Living
BMI	Body Mass Index
CCC	Concordance Correlation Coefficient
FDA	Food and Drug Administration
ICC	Interclass Correlation Coefficient
NeuroQOL	Quality-Of-Life in Neurological Disorders
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NPHS	Canadian National Population Health Surveys
PROMIS	Patient Reported Outcomes Measurement Information System
PROs	Patient-Reported Outcomes
US	United States

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6.1 Introduction

The quality of information that is used in research studies (e.g., reliability and validity) is vital to researchers. For many measures, respondent self-report is the easiest, preferred or only way to obtain information. For example, quality of life, mood, opinion, values, and percent of disability and difficulty with physical functioning can only be obtained by asking study participants. However, study participants are not always able to answer for themselves, often due to physical or mental limitations. In these situations, studies will either have missing data or they will use responses from a "proxy" in lieu of the participant's self-report. Because the use of proxies is common in studies of older adults, epidemiological studies in aging must be concerned with the reliability (i.e., participant-proxy agreement) and validity (i.e., whether there is a systematic bias in responses of proxies relative to participants) of proxy data, and the impact that proxy reports have on study results.

In this chapter, we provide an overview of the role and choice of proxies in research, important methodological considerations regarding the types of questions that can be asked of proxies, ways to improve the wording of questions when the use of proxies is anticipated, and the impact that different participant and proxy attributes have on participant-proxy correspondence. The chapter concludes with a discussion of some limitations of proxy data and analytical techniques that can be used to understand proxy data.

6.2 Proxies

6.2.1 What Are Proxies or Informants?

A proxy or informant is an individual who provides information on behalf of, or about a study participant. Proxies are commonly used (1) when information cannot be obtained from the study participant, (2) when the perspective from another individual is sought to better understand a construct (e.g., to improve physician classification of disease diagnoses and symptoms) [1], or (3) to complement or reinforce a participant's self-report [2]. This chapter focuses on the use of proxies when data cannot be obtained from the participant, as this is most common in studies of older adults. Hereafter, we will use the term "proxy" to refer to proxies and informants.

6.2.2 Why Use Proxies?

The use of proxies is common in health surveys of older adults, where more than 20% of community-dwelling adults and 50% of long-term care residents are unable or unwilling to respond for themselves [1–3]. Age-related cognitive impairment, physical impairment and use of long-term care increase with age, thus increasing the need for and use of proxies. The rationale for recruiting proxies for health surveys is to minimize selection bias and preserve external validity. If proxies were not used, the most ill and cognitively impaired participants would be excluded [1, 4]. Unfortunately, issues of bias still remain even when proxy assessments are collected due to dyadic disagreement of responses between participants and proxies.

6.2.3 Discrepancies Between Participant and Proxy Reporting

The use of proxies can change results. For example, an analysis of the Canadian National Population Health Surveys (NPHS) found that prevalence estimates for chronic conditions based on the 1996/1997 cross-sectional Health file (in which proxy reporting was less common) were significantly higher than prevalence estimates derived from the General file (in which proxy reporting was more common) [5]. Individuals for whom data were proxy-reported in 1994/1995 and self-reported in 1996/1997 had higher odds of self-reporting new cases of certain health conditions [5]. Perruccio and Bradley [6] used the NPHS to examine changes in arthritis from 1994/1995 to 1998/1999 and found that the prevalence of arthritis using information from proxies

was stable over time (approximately 8.5%) while prevalence in self-respondents increased from 15.8 to 17.4% over time. The authors also found that the disparity between self- and proxy-reporting was higher for women and for younger older adults [6]. Thus, it is important to report and document the use of proxies in any study, and to consider the implications when interpreting results.

6.2.4 The Benefits of Proxies

The use of proxies provides several benefits. A proxy can provide information that would otherwise be missing for participants who are unable to respond for themselves. This information can provide important insight regarding these participants, who are often different from those who provide self-reports [7]. A study of Medicare beneficiaries found that those who needed proxies were significantly less educated, older, and had poorer physical and mental health than those who did not need proxies [7]. Thus, studies that use proxies can examine a participant sample that is more representative of the target population being studied.

Although proxy responses can be poor direct substitutes for missing participant data, they are still beneficial for aging research. When proxy data are not collected, participant characteristics such as demographics (e.g., age, sex, marital status) are often used for adjustment or to impute missing participant data. However, participant characteristics only overcome the part of the selection bias that can be explained by participant characteristics. Because the most impaired participants are also the most likely to require a proxy [7], information from proxy reports can help explain some of the selection bias that is not explained by participant characteristics alone. Also, in a validation sample or subsample in which both proxy and participant data are collected, information on the concordance between proxies and participants can be used in analysis. As a result, the use of proxy responses plus participant characteristics can lead to more externally valid results than only using participant characteristics for adjustment or imputation, or simply substituting missing data with the proxy response. An additional benefit of using validation data from proxies (reports from proxies on behalf of a participant who also provides self-report) is that the researcher can determine the relationship between proxy responses and whether a study participant requires a proxy response. For example, one can use validation data to estimate whether the proxy report of disability for activities of daily living (ADL) is worse for study participants who require a proxy than for study participants who provide self-reports. These arguments support using proxies in aging research, but not as simple substitutes for missing participant data.

6.3 Reasons for Discrepancies Between Participant and Proxy Reporting

There are several potential explanations for why participants and proxies do not give the identical response to a specific question on a health survey or measure. These include the nature of the question, characteristics of the participant, characteristics of the proxy and the setting in which the participant resides, and the psychological perspectives underlying their potential discrepancies [8]. Each of these explanations must be considered when designing a study that may involve proxies.

6.3.1 Considerations Regarding the Types of Questions in a Health Survey or Measure

6.3.1.1 What Is the Gold Standard?

For many studies of proxy and participant reporting, the study participant's response is assumed to be the correct answer, or the "gold standard". However, the gold standard should be defined based on the purpose of the information obtained [1]. The gold standard could be an underlying construct, observed performance, or the participant's response.

Many constructs are measured with low reliability or large bias using self-reports even though

an "objective" measure is available. For example, self-report is sometimes used to gather participant height, weight and Body Mass Index (BMI) even though these can be measured objectively using scales and tape measures. Bias in self-reports of these measures include the well-known factor that older adults often misreport their height and weight [9]. They may do so differentially by weight (heavier people are more likely to under-report weight) or by other demographic characteristics (women under-report weight more than men) [9]. Older adults may under-report height, perhaps due to the effect of osteoporosis on height [9]. Proxies may also misreport height and weight. Reither and Utz [10] found a larger-than-expected increase in mean BMI between 1996 and 1997 in the National Health Interview Survey (NHIS). Analyses confirmed that proxy reports of weight tended to be biased downward in the 1996 survey, with the degree of bias varying by race, sex and other characteristics [10]. As such, proxy reports of height and weight (in lieu of participant self-report) were discontinued as part of the 1997 NHIS redesign.

For many areas of participant functioning, a gold standard may either not exist or may be difficult to measure. For example, large epidemiological studies often rely on participant-reported symptoms because large-scale physician assessments are often impractical. For many aging studies, key endpoints include quality of life and disability measures, which can only be assessed from the participant's perspective and in their own living setting.

6.3.1.2 Measurement of Objective and Subjective Outcomes

When proxies are used to examine an underlying construct, any bias that arises may depend upon characteristics of the construct. Objective, observable and concrete outcomes or domains have better participant-proxy agreement than do subjective outcomes [7, 8]. Examples of these objective outcomes are physical health, cognitive status, and performance of physical ADLs and instrumental ADLs [3].

Many large epidemiologic studies rely on the self-report of health conditions and symptoms. While these conditions are typically reported in discrete categories (presence or absence), many of them vary in their ability to be observed. Also, proxies may vary regarding the accuracy with which they report conditions. Quinn et al. [11] compared participant versus proxy reporting of 14 physical signs and symptoms. The best participant-proxy agreement was found with extremity swelling (a concrete, observable sign) and the worst was found with abdominal bloating (a subjective sign). Similar results were reported by Magaziner et al. [12, 13] with regard to the reporting of chronic conditions and symptoms. Researchers have typically found large bias and low reliability for subjective domains that tend to be more private and less observable, like depressive symptoms [1, 14] and quality of life [1]. Previous studies have reported that proxies tend to over-report depressive symptoms [14, 15] and disability [16]. There is also evidence that agreement is better on discrete (yes/no) questions versus exact points on a continuum. Better agreement has also been found on issues related to the frequency of an event as opposed to intensity.

Research participants are often reluctant to report sensitive information, such as income and expenditures. As a result, many surveys use a single question to collect information about all household members from a single respondent. This method has been found to be unreliable and leads to under-reporting [17].

6.3.1.3 Appropriate Choice of Question Wording

When designing epidemiological studies, researchers have proposed that questions be refined for proxies [12, 13, 18]. It is generally recommended that questions ask about facts rather than about subjective perceptions. For example, to obtain information about a study participant's disability, it is best to ask the proxy whether the participant received assistance in performing ADLs rather than whether the proxy perceived a need from the participant for assistance in performing ADLs. While the former question may help to acquire factually correct information, there may still be bias when participants and proxies answer different questions

(i.e., whether the proxy observed receipt of assistance by the participant versus whether the participant thinks that they *require* assistance).

One principle to keep in mind when designing questions for proxies is that any design feature that might impact the reliability or validity of a self-reported question is as likely, or more likely, to impact reliability and validity of the proxy response. When participants answer questions, they must engage in a number of mental processes, including comprehension, retrieval, estimation, judgment and reporting. Thus, less ambiguous questions improve comprehension and therefore improve reliability and validity. Similarly, it is known that participants have more difficulty recalling older events than recalling recent events, so the accuracy of proxy reports are also likely to be worse for older events. As with all questionnaires, proxy versions of questionnaires should be validated prior to use so that inherent biases and limitations to reliability are known in advance [19].

6.3.1.4 What Is the Perspective the Proxy Uses to Answer?

A further example of question wording is the perspective implied in the questions. There are two perspectives from which a proxy can provide information: the "proxy-patient" perspective and the "proxy-proxy" perspective [20]. The proxy-patient perspective asks proxies to respond as they believe the patient would have responded (i.e., proxies respond from the patients' perspective). The use of the "imagine-patient prompt" has been effective in reducing discrepancies between the patient and proxy when the proxy-patient view is used [20]. Questions from the proxy-proxy perspective ask the proxy to report on the patient from the proxy's own view, using the proxy's own thoughts and opinions (i.e., proxies respond from their own perspective). Gundy and Aaronson [21] performed a randomized trial to investigate whether proxy perspective impacts differences in responses between cancer patients and proxies, and hypothesized that the proxy-patient perspective group would have better agreement relative to the proxy-proxy perspective group. However, the few differences that were found were in the unexpected direction (e.g., the proxy-patient perspective group did not always have the best agreement).

6.3.2 Who Are the Participants?

Many participant-proxy validation studies have shown bias (i.e., systematic over- or under-reporting) and imperfect agreement between study participants and proxies across several sub-populations of older adults, including patients with hip fracture [12, 18], Alzheimer's disease [15], epilepsy [22], stroke [8, 23, 24], heart failure [11], cancer [20], and other disease subgroups [4, 13, 25]. Different participant groups also vary in the magnitude of bias and the reliability of responses. For example, among stroke patients, stroke severity is very predictive of participant-proxy agreement, such that greater severity is associated with poorer agreement between stroke patients and their proxies [23, 24]. Greater discrepancies in responses regarding functional and emotional well-being have been reported with regard to persons who have dementia or other cognitive impairment [3]; proxies tend to describe more impairment in function and emotional well-being than do participants. Studies in other populations have not always seen a marked relationship between participant illness and proxy reporting [1] and find that variables relating to the relationship between the proxy and participant have the strongest association with participant-proxy agreement [1].

6.3.3 Who Are the Proxies?

In general, a good proxy is one who knows the participant well enough to report for, or about, the participant. Most studies rely on spouses, partners or other housemates [26], especially for information regarding daily activities and contemporary events. This is because it is assumed that these individuals know the most about the participant and spend the most time with the participant. Spouses [7, 20] and cohabitating proxies [19] have better agreement with the participant

on measures of health care experiences and health-related quality of life [19] than proxies who are not living with the participant. Spouses are in better agreement with study participants in the rating of memory and physical and instrumental ADLs than are more distant relatives and those not living with the participant [12, 27]. In general, proxies who are in daily contact with the participant have better agreement on quality of life scores than do those with less contact [19]. When there is no spouse, adult children often serve as the proxy. However, for information regarding the participant's childhood or other historical information, an adult sibling may be a better proxy than an adult child or even a spouse [26].

A list of available proxies should be identified before the start of any research study, especially for longitudinal studies. It is also important that the method of identification of proxies and how their data were used be specified in the methods and results sections of any written documentation for the study.

6.3.4 The Impact of Living Situation on Choosing Proxies

The living situation of the participant may dictate the most appropriate proxy. Older adults have a much higher likelihood of residing in assisted living facilities or nursing homes, or of receiving home-based long-term care from a non-family caregiver. In nursing homes, for example, nurse's aides provide much of the direct care and may be the best proxies for reporting participant function and type of care received [18]. For participants who live in the community, a family member who has regular contact with the participant may be the best choice for a proxy. The identification of proxies will be easier for some participants than for others, which may also lead to biases. The identification of a proxy for community-dwelling older adults who live alone (30% of older adults) [28] may be challenging. It may be especially difficult to find an appropriate proxy for childless, single or widowed older women who live alone. Some gender, ethnic or socioeconomic status groups also may differ in the availability of appropriate proxies.

6.3.5 The Psychological Reasons for Discrepancies Between Participants and Proxies

Psychological perspectives impact both self-report and proxy reports. Older adults may alter responses regarding quality of life, disability and function over time as a result of adaptations or changes in standards, values and definitions, a phenomenon referred to as response shift [29, 30]. Often, a response shift occurs to maintain positive perceptions of one's quality of life even in the face of marked changes in actual health [29]. Response shifts also may affect how proxies report on participants. One study found that participants who had a recent health event reported higher levels of disability than did their proxies [30]. One theory for this finding is that the health event may have led to changes in social comparison, such as comparing oneself to peers who have had the same health event, which resulted in response shift.

Relevant psychological theories that may impact participant-proxy agreement include cognitive dissonance theory, self-awareness theory and self-schemas, which have been summarized in a review by Lynn Snow et al. [1]. In addition, social psychology has found evidence that "correspondence bias", the belief that a person's behavior is attributed to disposition rather than situation, increases with age [31]. Furthermore, this bias is usually external and not internal; that is, we judge others as behaving due to their "nature" but understand that our own behavior is sometimes dependent on the environment or situation. Thus, a proxy may ignore situational aspects that relate to a participant's health while a participant may attribute problems to recent changes in situations, leading to a lack of correspondence.

Proxy responses to questions may also be affected by the burden that some proxies may experience due to providing care for participants. When the proxy is a caregiver who suffers from

psychological distress or the burden of caregiving for the participant, responses from the proxy are less likely to agree with the participant than when the proxy is not distressed or burdened [25]. This may explain, in part, why proxies tend to report more disability than do participants. Agreement is also poor when the proxy has symptoms of depression [20, 25]. Thus, for some patient groups (e.g., participants with dementia), if studies select the person in closest contact with the participant as a proxy, this proxy may also be more likely to have care-giving-related burden or depression, which would decrease the proxy's ability to accurately report.

6.4 Analytical Strategies to Evaluate and Utilize Proxy Data

There are a number of methodological and analytic strategies for using proxy data, including methods for evaluating the quality of proxy data (i.e., agreement and bias estimates), statistical methods to account for proxy data (i.e., adjust for the effects of using proxy data), and newer United States (US) government initiatives in patient-reported outcomes using modern test theory (i.e., item response theory) that are beginning to include proxy data evaluation.

6.4.1 Analytic Methods for Evaluating Proxy Data

Participants who are unable to provide self-reports are typically different from those who can provide their own responses. Examples of groups that require proxy respondents include those with cognitive limitations, serious physical health problems and those who cannot be located. The exclusion of these groups exemplifies non-random missingness because such non-responders tend to be sicker and/or more cognitively impaired than responders. Thus, the amount of bias between proxies and participants who require proxy respondents (those unable to respond) can never be empirically measured. Despite this quandary, proxy report bias can be evaluated by comparing proxy reports to participant self-reports among participants who are able to respond.

When participant self-report is the gold standard, the evaluation of proxy data involves the assessment of two characteristics: reliability and validity. Reliability refers to the closeness of proxy responses to participant responses, and validity refers to the lack of systematic bias of proxy responses relative to participant responses. Reliability is often measured using agreement percent, which can be unduly inflated by chance or by sensitivity/specificity assessment, which relies on the gold standard. Many studies of categorical assessment now use the Kappa statistic or the weighted Kappa statistic (for low frequency responses) [32]. The Kappa statistic measures chance-adjusted inter-rater agreement for categorical variables (e.g., whether or not the participant is able to perform an ADL). Standards for Kappa have categorized agreement as poor-to-slight ($K \leq 0.2$), fair ($K = 0.21–0.40$), moderate ($K = 0.41–0.60$), substantial ($K = 0.61–0.80$) and almost perfect ($K \geq 0.81$) [32].

Reliability correlations measure the strength of relationship between proxy and participant responses for continuous variables (e.g., a measurement scale for depressive symptoms such as the Center for Epidemiological Studies Depression Scale). Correlation measures can include the Pearson correlation coefficient, the intraclass correlation coefficient (ICC), and the concordance correlation coefficient (CCC). The Pearson correlation coefficient should be used when variation in the same direction is expected, the ICC should be used when differing values within a fixed range of responses are expected, and the CCC should be used when values are expected to be close between all or most of the participants [11]. The ICC is typically assessed using the same criteria as the Kappa. The CCC can be computed using multiple methods (i.e., Lin's method, Variance Components, U-statistics, Generalized Estimating Equations) [33]. Categories for descriptors of the CCC are: poor agreement (<0.90), moderate agreement (0.90–0.96), substantial agreement (0.95–0.99) and

almost perfect agreement (>0.99) [34]. Many studies have found similar conclusions from analyses using either the ICC or CCC [11].

Validity is typically assessed by measuring bias, the average discrepancy between proxy and participant responses. Bias can be calculated by taking the arithmetic mean of the discrepancy score (proxy response minus participant response). The degree of bias can depend on the measurement units. To produce a standardized measure of bias (remove measurement units), the mean discrepancy score can be divided by the participant standard deviation or the mean participant response; the latter standardization can be converted to percent bias by multiplying by 100.

When the proxy and participant are conceptualized as two raters of a latent gold-standard construct, then the aforementioned measures of reliability are interpreted as measures of concurrent validity. In this case, the proxy response *per se* is not being evaluated; rather, the measurement scale of the latent construct is being evaluated [1].

6.4.2 Statistical Analysis to Account for Proxy Data

Despite the empirical evidence of proxy bias [1, 3, 8, 12, 13, 18], little attention has been given to developing statistical methods that adjust for proxy bias. Most commonly, proxy data are simply substituted for missing participant data. In many cases, authors do not mention the use of proxy data in the statistical analysis sections of their research reports. This approach implicitly assumes that proxy responses are perfectly correlated with participant responses [1], an assumption that is likely false. Empirical data regarding proxy bias suggest the need for statistical methods that can model theories about proxy bias and utilize information about proxy characteristics (e.g., relationship and living arrangement with the study participant). One major barrier to the development of statistical methods that are specifically designed to handle data from proxies is that proxy bias cannot be empirically tested for participants who do not provide responses, though this bias may still impact study conclusions [35]. Because collecting proxy data was designed to solve the missing-data problem, the greatest potential lies in statistical methods that use a missing-data framework.

To date, there have been two published statistical methods that were developed for proxy data [35, 36]. The paper by Huang et al. [36] was specifically motivated by randomized treatment cross-over trials. The authors proposed simultaneously fitting two models, one for proxy responses and one for participant responses, while assuming no selection bias (i.e., participants who required a proxy were no different, on average, from those who did not require a proxy).

The paper by Shardell et al. [35] was motivated by observational studies of older adults. The authors proposed performing multiple imputation [37] for missing participant data using proxy reports, participant demographic information (e.g., age and sex) and proxy characteristics. In most studies, only reports from either the proxy or the participant are collected, which means that the actual degree of bias between proxies and participants can never be calculated. To address this concern, Shardell et al. [35] recommended performing a sensitivity analysis by incorporating an assumed level of bias (e.g., from published participant-proxy validation studies) into the imputation, and repeating the analysis multiple times using different plausible assumptions to ensure that the conclusions were robust.

When designing future studies with proxies, there may be additional value in collecting data from proxies for a random validation sample of participants who are able to provide self-reports. In this case, bias between participants and proxies can be determined for the validation sample and used as an "anchor" to determine plausible levels of bias for participants who cannot provide self-reports. This may be especially important in longitudinal studies of older adults, where a large loss to follow-up may occur due to cognitive or health decline.

The two published statistical methods that have recently been developed for handling proxy data are limited in that they only handle normally distributed outcome data. New methods are needed that can handle (1) non-normally

distributed outcome data and (2) proxy-measured covariate data. In the meantime, we recommend that researchers focus on recruiting proxies who have characteristics associated with low bias (e.g., participants' spouses and cohabitants) and avoid, to the extent possible, proxies who are stressed by the caregiving relationship.

6.4.3 Patient-Reported Outcomes and Item Response Theory

The National Institutes of Health (NIH) has initiated new patient-reported outcomes (PROs) initiatives (e.g., Patient Reported Outcomes Measurement Information System [PROMIS], NIH Toolbox, Quality-Of-Life in Neurological Disorders [NeuroQOL]) in an effort to provide standardized measures of important domains for research studies. The NIH PRO projects all use Item Response Theory (e.g., Rasch analyses) to test scales on their measurement properties and provide the basis for Computerized Adaptive Testing. Item response theory can be utilized to examine item bias (at respondent and item levels) and create a hierarchy of items, which could put proxy-rated items on a similar scale as patient-reported items to create a common metric across the measures [38]. Currently, none of the existing PROs incorporate proxy responses into their frameworks, though there is increased interest in how proxies may be used. Conversely, the US Food and Drug Administration (FDA) recently issued guidelines for PROs [39] that actively discourage proxy measures, including their use for the cognitively impaired. The FDA does suggest that when proxies are used, researchers should rely solely on reports of events or behaviors that can be observed.

6.5 Conclusions

The benefits and limitations of using proxies can be summarized as follows:

Benefits

- Enables the inclusion of more participants
- Provides data on the sickest and most impaired
- Ensures a more complete follow-up

Limitations

- Proxy characteristics can influence reporting
- Proxies can be difficult to find
- Proxy responses tend to be biased

Researchers who study the epidemiology of aging need to design studies to address these issues. Strategies include the improved assessment of potential proxy reliability and bias, perhaps through the statistical methods outlined above. What is most important is having a thoroughly developed plan for the use of proxies that is well-documented, reported in results and—wherever possible—includes assessment for bias in the populations and domains utilized in the studies. Proxy use should be reported and the use of proxies should be considered when interpreting results. The use of proxy data is particularly important when considering the design of longitudinal studies and randomized clinical trials, where selective loss to follow-up or changing respondents over time could seriously alter study results.

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Assessing Functional Status and Disability in Epidemiologic Studies

7

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Abstract

In epidemiological studies of older populations, the assessment of functional status and disability plays an important role in comprehensively characterizing the population. Epidemiological research in aging has used functional measures to examine the overall health status of older adults, understand the consequences of chronic diseases and behavioral risk factors, and identify individuals at high risk of a variety of adverse outcomes. Important domains are personal roles, social roles and physical capacity. The selection of instruments and questions is guided by the specific population in which they will be used and the objectives of the functional assessment. A variety of approaches have been used to meaningfully summarize multiple disability items. Objective physical performance measures, most of which assess physical capacity, offer a means of assessing functioning in a standardized environment and have found many uses in aging research. Describing trajectories of functioning over time, including both improvement and decline, is crucial for understanding the disablement process. Population trends in disability are a critical measure of health status changes in the older population. Active life expectancy, a

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measure of the remaining years of life from a specific age that are free of disability, reflects both survival and length of high-quality life. Its extension is an important public health goal.

Keywords
Aging • Epidemiology • Geriatrics • Older adults • Longevity • Functional status • Disability • Epidemiologic studies • Assessment • Physical performance • Measurement • Proxies • Self-report • Mobility disorders

Abbreviations

ADL	Activity of daily living
ANCOVA	Analysis of covariance
CAT	Computer adaptive testing
CI	Confidence interval
IADL	Instrumental activity of daily living
IL	Interleukin
IRT	Item response theory
LIFE-P	Lifestyle Interventions and Independence for Elders Pilot
NHANES	National Health and Nutrition Examination Survey
NHATS	National Health and Aging Trends Study
PEP	Precipitating Events Project
PF-10	Short Form 36 Health Survey physical functioning subscale
PPT	Physical Performance Test
SF-36	Short Form 36 Health Survey
SPPB	Short Physical Performance Battery
US	United States
WHO	World Health Organization

7.1 Introduction

While much epidemiologic research is targeted at understanding the distribution and determinants of a particular disease or pathological process, a hallmark of epidemiologic research in aging is the study of the functional consequences of diseases and physiologic changes that occur in aging. Although the epidemiologic study of individual diseases that are important in aging is a high priority, the joint impact of diseases and multiple other physiological, psychological, social and environmental factors in the older population can best be understood by evaluating the functional status of the individual. Assessing functional status in older adults is useful because it is:

- Prognostic of adverse medical outcomes
- Prognostic of further decline in function and loss of independence
- An indicator of level of independence
- An indicator of need for formal and informal care
- A global measure of the burden of disease
- A relevant measure of quality of life.

A large body of epidemiologic research over the past three decades has treated disability as a condition that can be studied in much the same way as is a well-defined chronic disease: by using epidemiologic tools to assess prevalence, incidence and a wide range of risk factors. This work has led to a greater understanding of the occurrence, determinants and consequences of disability in the older population and has provided insights into strategies for the prevention of disability.

7.2 Models of Disablement and Domains of Function

7.2.1 Models of Disablement

Epidemiologic research has found a long list of diseases to be associated with disability onset. The most important disease categories include musculoskeletal, cardiovascular and neurologic conditions. In certain cases, such as stroke or hip fracture, it is obvious how disability results from the disease. In others, however, the onset of

disability may occur over years and the effects of a single or multiple diseases, health behaviors and other risk factors (e.g., obesity, social isolation) are more difficult to understand. In these cases, epidemiologic research into the mechanisms and pathways that lead to disability can be substantially enhanced by modeling steps along this pathway that represent the consequences of disease on impairments and body functions. Ultimately, disability is best conceptualized as the gap between an individual's physical/cognitive capabilities and the demands of the environment, which leads to an inability or difficulty in fulfilling one's social or role functions.

The most prominently employed model of the disablement process was originally developed by Nagi [1] and updated to include environmental influences by Verbrugge and Jette [2]. In 1980, the World Health Organization (WHO) introduced a model that included disability and handicap. More recently, the WHO updated this disability model with a framework that introduces new terminology and is less focused on the disablement process or pathway. Instead, it proposes that disability represents a complex interrelationship of factors [3]. A new model, based on both the Nagi and WHO approaches, was begun in 2011 [4]. It was developed for the National Health and Aging Trends Study (NHATS) and funded by the United States (US) National Institute on Aging. NHATS is a new panel study of individuals ≥65 years of age that will support research on national trends in late-life disability and factors that influence these trends. The steps in these three models are shown in Fig. 7.1.

Most empiric research that addresses the pathway from disease to disability has relied on the Nagi framework, which operationalizes the steps so that specific assessments can clearly be classified as to where they fit in the pathway. In the Nagi model, impairments are defined as dysfunction and structural abnormalities in specific body systems (e.g., cardiovascular system, musculoskeletal system), functional limitations are defined as restrictions in basic physical and mental actions (e.g., ambulation, reaching, grasping, climbing stairs, speaking) and disability is defined as difficulty in or inability to perform life activities (e.g., self-care, household management, jobs, hobbies) [2]. Functional limitations, which are often measured using objective tests of physical performance, are a critical link between impairments, such as poor strength, and disability, such as difficulty transferring from bed to chair or shopping.

The WHO model does not specifically use the term disability, but considers it a general term for the whole process. Instead, it introduced the term "participation" to indicate the degree to which an individual can engage in the activities that are important and relevant to their life. The strengths of the WHO framework include:

- It changes the language we use in approaching disability, which may have a strong effect on perceptions and reactions to disability
- Main domains are framed in a neutral way so that each has positive as well as negative aspects and can represent individuals across the functional spectrum
- The concept of participation provides a strong focus on the ultimate goal of maximizing the opportunities for all individuals with limitations
- There is clear emphasis on the effect of the environment and society on the experience of disability.

However, the WHO model has not been used to any degree by epidemiologists who study the disablement process because it does not outline a clear pathway to be investigated; does not clearly operationalize the components of the model; and while it defines activities and participation differently, it does not discriminate between them in its combined, very-detailed list of activities and participation, so further guidance is needed as to how to discriminate these two domains.

The NHATS model provides clear steps in the pathway to disability, which meet the purposes of the study by operationalizing the concepts so that underlying factors that are responsible for trends in disability can be easily understood. Measurements of both capacity (the same as functional limitations in the Nagi model) and accommodations are important for understanding trends. For example, if improvements are seen over time in self-report of ability to carry out self-care

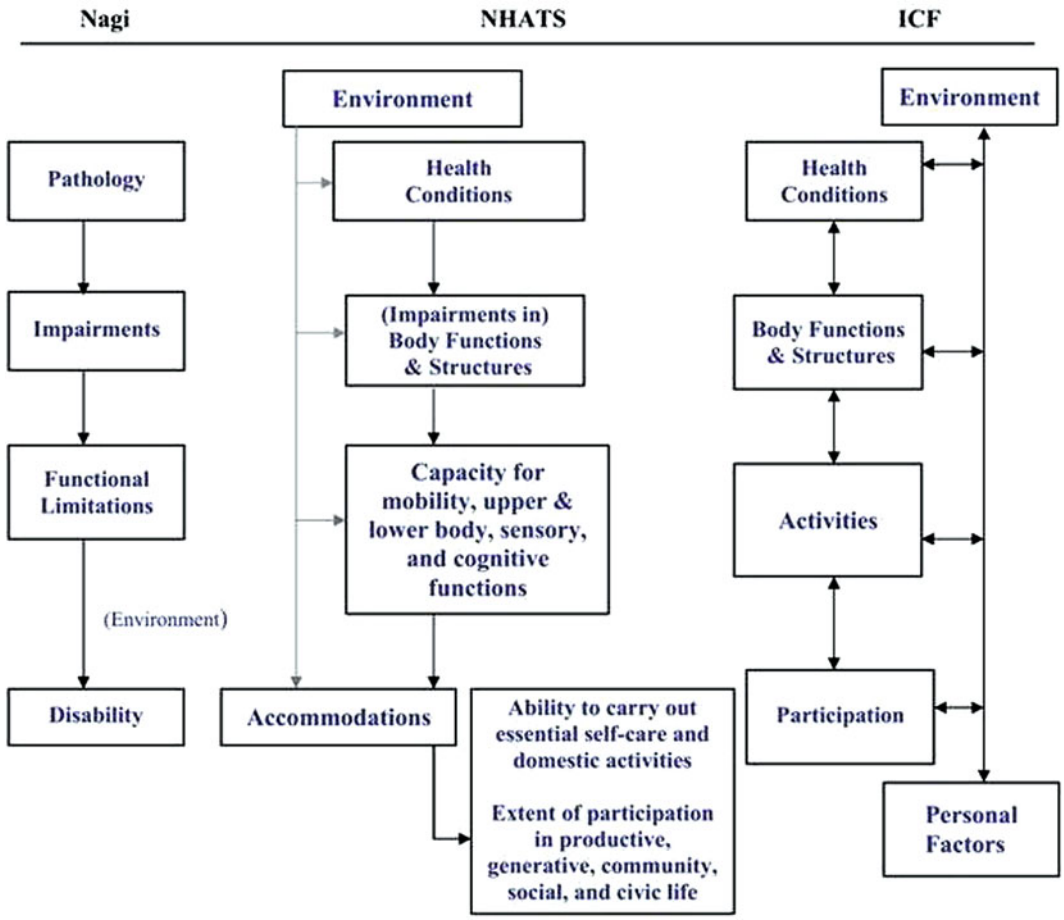

Fig. 7.1 The Nagi International Classification of Functioning, Disability and Health (ICF) and National Health and Aging Trends (NHATS) disability frameworks [4]

or domestic activities, capacity measures can be assessed for changes and—if they have not improved—measures of accommodation may reveal improvement, indicating that accommodations rather than better physical function are responsible for the decline in disability. This model is similar to the Nagi model, but it has not been specifically evaluated with empirical data, which will be possible when the study has collected data on a representative US population.

7.2.2 A General Approach to Domains of Function

Whatever disability framework may be used, there are basic domains of functioning that are relevant in the older population. Function itself has multiple domains, including physical, cognitive, sensory, psychological and social. Within physical functioning, three general domains are highly relevant for the older population: *personal roles, social roles* and *physical capacity*. The most commonly assessed disabilities related to *personal role* are self-care tasks, known as activities of daily living (ADLs). The items assessed usually include the following:

- Eating
- Dressing
- Bathing
- Transferring from bed to chair
- Using the toilet.

Also critical for personal roles are tasks that are required for independent living in the

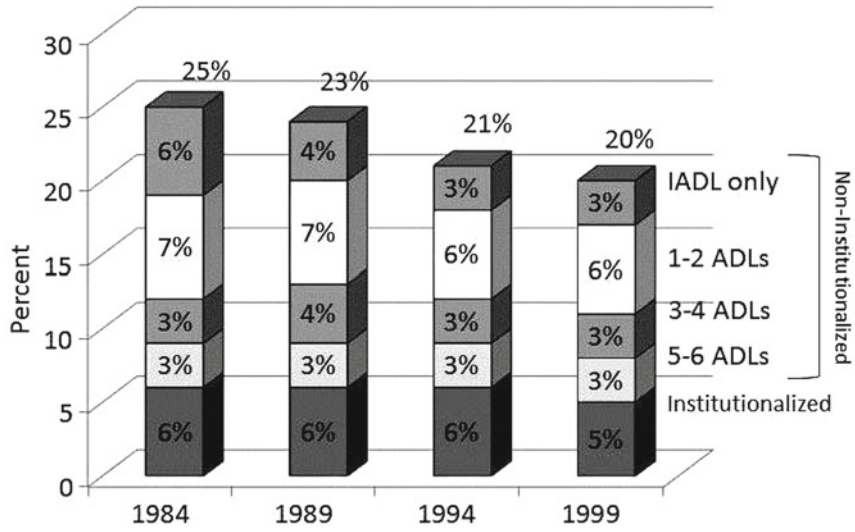

Fig. 7.2 Age-adjusted percentage of Medicare enrollees ≥65 years of age who are chronically disabled (receiving help, needing supervision, using equipment or not able), by level and category of disability: 1984, 1989, 1994, 1999 [5]. Abbreviations: *ADL* activity of daily living; *IADL* instrumental activity of daily living

community. These are termed instrumental activities of daily living (IADLs) and generally include the following:

- Preparing meals
- Shopping
- Housekeeping
- Managing money
- Taking medications
- Using the telephone.

There is generally a hierarchical relationship between ADLs and IADLs, such that nearly everyone with disability in ADLs also has IADL disability. National and local disability statistics often take this into account when presenting rates of disability in these areas. Figure 7.2 shows US data that illustrates the percentage of the US population with disability in specific numbers of ADLs (who generally have IADL disability as well), the percentage with IADL disability only, and the percentage who live in long-term care facilities.

Social roles are an important component of a satisfying and full life, and restrictions in participation in these roles due to illness are an important aspect of disability. There has been less research and less assessment of these roles in national surveys than for the ADLs and IADLs. An instrument that illustrates these kinds of roles is the Late Life Disability Instrument, which includes ADL- and IADL-type measures but also has a strong emphasis on social roles [6]. These social role functions include:

- Visit friends
- Travel out of town
- Go out to public places
- Work at a volunteer job
- Keep in touch with others
- Participate in social activities
- Invite family and friends into home
- Participate in active recreation
- Provide assistance to others.

The third general domain of function is *physical capacity*. In developing his model, Nagi saw this as representing functional limitations and he developed questionnaire items that have been extensively used to represent this domain. These include:

- Pulling or pushing a large object, such as a living room chair
- Stooping, crouching or kneeling
- Lifting or carrying weights under 10 pounds
- Lifting or carrying weights over 10 pounds
- Reaching arms above shoulder level
- Handling small objects.

Mobility is also an important aspect of physical capacity. Numerous questionnaire batteries and objective performance tests have been used to

assess walking and lower extremity functioning. The Short Form 36 Health Survey (SF-36) [7] is a commonly used scale of overall health status, but a large part of the SF-36 is directed toward physical functioning (physical functioning subscale [PF-10]). Most of the questions on the PF-10 assess capacity, with a majority of those aimed at mobility assessment. The PF-10 includes:

- Vigorous activities, such as running, lifting heavy objects or participating in strenuous sports
- Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf
- Lifting or carrying groceries
- Climbing several flights of stairs
- Climbing one flight of stairs
- Bending, kneeling or stooping
- Walking more than a mile
- Walking several hundred yards
- Walking 100 yards
- Bathing or dressing oneself.

Many self-report items related to capacity were evaluated in the development of the Late Life Disability Instrument's function domain [8]. It was found that they aggregated into three specific domains, which include:

- Upper extremity function (e.g., unscrew lid without assistive device, pour from a large pitcher, use common utensils, reach behind back)
- Basic lower extremity function (get into and out of a car, get up and down from a curb, get on and off a step stool, stand up from a low soft couch)
- Advanced lower extremity function (carry while climbing stairs, walk a brisk mile, run to catch bus, walk on slippery surface).

Many aspects of capacity are addressed using measures of physical performance that are assessed using standardized tests in a controlled setting. A wide range of performance measures have been developed, and the reason they work well is probably because they likely capture the impact of multiple chronic conditions and physiologic changes that are related to aging and a sedentary lifestyle. Physical performance tests have been found to predict multiple adverse outcomes, including mortality. Even a simple measure, such as usual gait speed tested over a short course, has a strong relationship with multiple characteristics of the study participant and is highly predictive of adverse outcomes. A meta-analysis that included gait speed data from nine cohorts showed a clear and consistent relationship with mortality risk (Table 7.1) [9]. There was a steep gradient of 5-year survival across baseline gait speed for men and women in each of three age groups, the greater baseline gait speed being associated with greater 5-year survival. For example, for age group 75–84, comparing those with the slowest gait speed (<0.4 m/s) to those walking at 1.4 m/s or faster, the proportion surviving for 5 years was 60 and 93%, respectively, in men and 69 and 95%, respectively in women. Physical performance measures will be further described later in the chapter.

7.3 Assessment by Self- and Proxy-Report

Disability is most often assessed using a self-report format in which the patient or study participant is asked to respond to a series of closed-ended questions which have specific response categories. If a study participant is too ill or too cognitively impaired to provide responses, a proxy may be used for certain types of questions. Disability assessment was originally used in the clinical setting, most often to follow-up patients in rehabilitation programs. However, over the past few decades, its value has developed in assessing the health of the population as a way to characterize older adults in epidemiologic studies and, eventually, as an outcome in clinical trials. Various methods of assessing disability were created for use in different types of studies, but standard sets of items and instructions on how to ask questions regarding these items have never established. The basic ADLs were proposed by Katz et al. in 1963 [10], but even his short list has been modified over time (e.g., his incontinence item is generally not included in current ADL disability definitions).

Table 7.1 Percentage (95% confidence interval) of men and women surviving 5 years by gait speed and age group

	Men			Women		
Gait speed m/s	Age 65–74	Age 75–84	Age ≥85	Age 65–74	Age 75–84	Age ≥85
<0.4	68 (47–82)	60 (38–76)	25 (15–36)	80 (71–86)	69 (58–78)	47 (40–54)
≥0.4 to <0.6	77 (72–81)	57 (49–64)	31 (24–39)	88 (85–90)	75 (68–80)	61 (50–70)
≥0.6 to <0.8	79 (74–83)	65 (57–71)	49 (35–61)	91 (89–93)	82 (78–86)	74 (69–78)
≥0.8 to <1.0	85 (82–88)	75 (69–79)	54 (43–64)	93 (91–95)	89 (86–91)	73 (59–83)
≥1.0 to <1.2	90 (85–93)	83 (76–87)	68 (57–77)	96 (94–98)	91 (87–94)	61 (35–79)
≥1.2 to <1.4	93 (86–96)	85 (79–89)	62 (46–74)	96 (94–97)	93 (87–96)	67 (5–95)
≥1.4	95 (89–97)	93 (86–96)	91 (51–99)	97 (94–99)	95 (72–99)	NE
All gait speeds	87 (82–91)	74 (65–81)	46 (39–53)	93 (91–94)	84 (80–87)	64 (58–70)

Source: Adapted from Studenski et al. [9]. *Abbreviations*: *NE* not estimable due to small numbers of participants in categories

In addition to item selection, choices on how to ask the questions and categories of response were often newly created for each survey or epidemiologic study, limiting the ability to compare disability rates across studies. It is certainly important to use measures that meet the requirements of a study, but even in a small study with a narrow focus, the use of a battery that is used for national surveys enables one to evaluate how the study sample compares to the general population of older adults. In the following subsections, we will discuss a number of issues that exist regarding decision-making for the selection of self-reported disability assessments.

7.3.1 Instrument and Item Selection

When planning a new study, an initial decision must be made whether to utilize an existing battery of items or to pick and choose a specific set of items to meet the study requirements. As in any measurement decision, is advantageous to retain a full battery of items when the battery has had extensive methodological work on validity, reliability and sensitivity to change because selected components of the battery will not have these characteristics. A number of considerations (outlined in Table 7.2) go into determining what kinds of disability items are appropriate for a particular situation. At the most basic level, items used in a clinical setting may be different than those that are most appropriate for a research setting that is evaluating a specific population group. A clinical setting may have the advantage of a trained medical professional, such as a nurse or physical therapist, compared to an epidemiologic research setting that uses assessors with little medical training and in which assessor decision-making about the study participant needs to be minimized. In studies that have many assessors, especially multi-site studies, full training and quality control should be implemented to maximize inter-rater reliability and avoid site-specific deviations in assessment that can result in biases.

A key consideration in item selection is the general health status of the population under study. For example, although it is extremely important to identify ADL disability, only about 10–15% of the total population ≥65 years of age will have ADL disability. Therefore, if no other items are selected, there will be no way to discriminate across the functional spectrum for the remaining 85%. While ADL assessment alone may be adequate for individuals who live in a nursing home or assisted living facility, more information is critical for understanding the functional level and needs of older adults who live in the community. Other characteristics of the study population (e.g., a specific disease that is the focus of the research, impairments of the study sample, educational level) may play a role in the selection of items, construction of questions and mode of administration. A study of a population with arthritis and a study of a population with heart disease may use the same general measures of disability, but each study may choose to add

Table 7.2 Selecting measures of functioning

Measure specifics	Information
Individual, in clinical setting	Minimize false positives and false negatives, even at the expense of ease and economy of administration
Group or population, in research setting	Often administered by multiple assessors with lower levels of professional training
	Requirements:
	• High levels of inter-rater reliability
	• Minimize dependence on professional judgment
	• Be able to administer in reasonable time, with minimal burden on the respondent
	May differ by use – describe population vs. study functional consequences of specific disease or intervention
Must consider general health status of population to be studied	Nursing home
	Disabled in community
	Healthy aging
	Community-dwelling, heterogeneous
Specific characteristics of population	population with a specific disease
	Impairments that affect functional evaluation (hearing impairment, cognitive impairment
	Educational status
Cross-sectional vs. longitudinal measurement	For longitudinal studies, must be sensitive to change
	Continuous measures may be more sensitive to change the dichotomous measures

items that assess aspects of functional loss that are specific to the respective diseases. Finally, the selection of disability measures should reflect whether they will be used only in cross-sectional analyses or whether assessment of longitudinal change will be an important study goal. For example, it is important to identify the subset of a population that has ADL disability at the baseline of a study, but in the remainder of the population there can be a lot of functional change over time that will not be severe enough to be detected by ADL measures.

7.3.2 Formulation of Questions

Three general issues must be considered when determining the formulation of disability questions:

- The actual performance of a task vs. the capacity to perform
- The time interval for the respondent to consider
- Query difficulty, the need for help, or both.

For basic self-care tasks, virtually everyone will need to perform or get help to perform all of the tasks. More difficult tasks may be discretionary. Getting a negative response to a question about whether an individual has walked a quarter mile in the past month may give concrete evidence that the activity was not performed, but it gives little indication as to whether this individual simply didn't choose to do the task, didn't have the opportunity to do the task, or was incapable of doing the task. On the other hand, asking whether the individual is able to do the task may force them to make a decision about their potential ability or capacity to do the task when they have not actually attempted it recently. There is no simple solution to this dilemma. Some surveys query both aspects by asking those who report not doing a task if they believe they could do it if they tried. When asking about discretionary kinds of tasks, it is advantageous to add to the question a phrase about whether they don't do it "for health reasons", particularly when individuals report that they are unable to do tasks such as IADLs, which they may have never done.

Research has shown that there is a great deal of short-term change in functioning, so the time interval that the study participant is asked to consider may have a substantial impact on their response. Many disability instruments simply query the current time (e.g., "do you now have difficulty…"), which is easiest for the respondent. However, more disability will be identified if a time interval is attached to the question, and asking about "in the past year" will give higher prevalence rates than asking "in the past month."

Response categories that are used in disability questions vary across studies and types of questions. The simplest outcome to assess is whether the participant needs help to perform a task, with the option of clarifying whether this means help from a person, help from equipment or both. An alternative to asking whether help is needed is to ask whether help is received, but it should be kept in mind that there are individuals who need help who don't receive it, and they will not be identified if the question is worded to ask about receiving help. Needing or receiving help is at the more severe end of the disability spectrum and there is some advantage to using questions about level of difficulty to characterize the remaining population that does not need or receive help. Questions about difficulty should include a response option to identify that the respondent is unable to do the task in order to not miss this important subgroup that is not able to report on difficulty (response categories to questions about difficulty can be: none, a little, some, a lot, unable to do).

Prevalence estimates of disability in epidemiologic studies and population surveys can be substantially affected by the way that questions are asked and the possible response categories provided. This is illustrated in Table 7.3, which shows percentages of those with disability in a survey for three different assessment outcomes of ADL and mobility items [11]. Looking at a summary of these measures, the percentage with a positive response for 1 or 2 items was 15.0% for difficulty, 9.0% for human assistance and 12.6% for human or mechanical assistance. The percentages for a positive response on three or more items were 8.7, 4.2 and 9.4%, respectively.

7.3.3 Innovative Approaches to Self-Report

In addition to the traditional assessments of the need for help and difficulty with disability items, recent years have seen the development of innovative approaches to assessment. For example, it has been shown that individuals who don't report disability by traditional criteria may report that they have modified the way they do a task or how often they do it. In fact, a substantial percentage of individuals who do not report difficulty will say that they have changed the way they do an activity (e.g., climbing stairs, doing housework) or that they do the activity less often. The predictive validity of this approach has been demonstrated by showing that this subgroup has intermediate rates of adverse outcomes compared to those with difficulty and those without difficulty or modifications [12]. An additional approach to assessment in individuals who report no difficulty is to query how easy it is to do a task, such as walking a quarter mile. Table 7.4 shows objective performance test results for non-disabled individuals (report no difficulty walking ¼ mile) that report whether walking ¼ mile is not so easy, somewhat easy or very easy, and whether or not the participant is doing the task less often [13]. It is clear that for all of these performance tests, there is a gradient of function that increases as the task is perceived to be easier and if the individual has not resorted to doing the task less often.

The use of video images to demonstrate an activity solves some of the difficulties individuals may have in deciding how to answer questions about activities that they have not recently performed [14]. In this approach, stick figure images are shown doing multiple mobility tasks, calibrated for specific speeds of walking and stair climbing. The animations also include certain environmental challenges, such as carrying bags of groceries, stepping across obstacles and walking over rocky terrain. This approach still relies on someone's self-perception of their capacity, but it standardizes the tasks on which participants are reporting.

Table 7.3 Disability estimates for New England states using three different scaling methods

	Difficulty/does not do		Human assistance/does not do		Human or mechanical assistance/does not do	
ADL activity	%	95% CI	%	95% CI	%	95% CI
Walking	8.1	(6.9, 9.4)	1.6	(1.0, 2.2)	10.0	(8.9, 11.7)
Bathing	12.2	(10.7, 13.7)	8.6	(7.3, 9.9)	12.5	(11.0, 14.0)
Dressing	7.3	(6.1, 8.5)	5.0	(4.0, 6.0)	5.3	(4.2, 6.3)
Eating	3.2	(2.4, 4.1)	1.2	(0.7, 1.7)	1.2	(0.22, 2.2)
Getting to toilet	4.3	(3.3, 5.2)	2.0	(1.4, 2.7)	7.5	(6.3, 8.7)
Bed/chair transfer	13.4	(11.8, 15.0)	3.0	(2.2, 3.8)	5.5	(4.4, 6.5)
Getting outside	9.7	(8.3, 11.0)	7.8	(6.6, 9.0)	15.4	(13.7, 17.1)

Source: Adapted from Jette [11]. *Abbreviations*: *ADL* activity of daily living; *CI* confidence interval

Table 7.4 Mean performance by category of reported functioning in walking ¼ mile among persons reporting no difficulty. Health ABC Study

Difficulty/modification	6 m usual walk (m/s)	SPPB score	Completed 400 m walk (%)
How easy?			
Not so easy	0.94	8.69	41.7
Somewhat easy	1.09	9.48	62.5
Very easy	1.21	10.28	81.9
Do less often?			
Yes	1.07	9.39	64.2
No	1.19	10.13	77.4

Source: Adapted from Simonsick et al. [13]. *Abbreviation*: *Health ABC* health, ageing and body composition; *SPPB* short physical performance battery

A particular challenge in using self-report measures is comparing rates across countries, ethnic groups and racial groups. This is due to differences in the way that individuals perceive the questions and relate them to the kinds of activities in which they engage. In the section on physical performance measures (Sect. 7.5), there is a discussion about using objective measures to calibrate responses to self-report questions. Researchers have also used vignettes to anchor assessments of health states. In this approach, a hypothetical person with a specific problem is presented and the respondent is asked to evaluate that hypothetical person using the same format grading scale used to assess respondents. The vignette standardizes the specific nature and severity of a condition, and enables the detection of different reporting styles across countries or cultures. These differences can then be used to adjust observed differences in rates of self-reported disability. This technique and others are described in a comprehensive overview of innovative methods for approaching the measurement of disability in older adults in population surveys. The overview is published by the National Research Council and based on a meeting it convened with leaders in the field [15].

7.3.4 Mode of Administration

Various modes of administration are available for ascertaining self-reports of functioning and disability in survey research, epidemiologic studies and clinical research. Most assessment tools were developed for interviewer administration, but many have been shown to be easily adapted for telephone administration and for self-administration using a paper form at the study site or at the participant's home. Questionnaires that are completed by the participant have a number of advantages [16]: participants can complete the form

when convenient to them; their use reduces staff time spent in administering interviews and reduces the burden on participants when they are seen by the staff; participants can obtain information that they need, such as dates of hospitalization and contact information for physicians and hospitals; the instructions that are written into the form are standardized; and the privacy of the situation encourages more honest responses to uncomfortable questions. A methodological study in the Netherlands demonstrated greater reporting of disability in a self-administered questionnaire compared to a face-to-face interview [17]. On the other hand, interviews have advantages that should be considered when deciding the mode of administration for a study [16]. An interview is easier for the participant in many ways and may avoid difficulty with vision problems or low literacy. An interview may be more enjoyable, ensuring the completion of the full protocol. An interviewer can clarify questions to some degree, according to the guidelines set forth by the study. Interviewers can collect more complex data and can minimize missing and inappropriate responses. Finally, the respondents' appearance and behavior can be directly observed by the interviewer.

7.3.5 Proxy Report

Proxy respondents may be required for research on older populations if the study participant is too ill to respond or has dementia. If a study has a longitudinal component, then even if all participants can participate fully in the study at baseline, a certain percentage of participants will eventually need a proxy respondent to provide information for them. It is of critical importance to construct proxy interviews to maximize the validity of proxy responses related to functioning and disability, as these deficits are often the reason that an individual cannot participate and there can be substantial bias in a study that misclassifies these individuals. A full chapter in this book deals with issues related to the use of proxies (Chap. 6). These issues are vital for obtaining proxy assessments of functional status.

7.4 Summarizing Multiple Disability Items

Disability is most often assessed using multiple self-report items in a battery or formal scale. Often these items are all scored in the same manner, such as yes or no to questions about the ability to perform without the help of another person or equipment, or selection from a standard set of ordinal responses regarding level of difficulty. Occasionally, a battery may have different response frameworks for different items. Regardless of what types and patterns of response categories are utilized for a set of items, it is usually necessary to aggregate responses to multiple items of functioning and disability in order to represent the true nature of functional status in the individual. This may not be ideal in clinical care, where it is important to understand the specific functions in which someone is having difficulty or needs help, but is important in research settings to be able to summarize an individual's functional deficits for analytic purposes. Common approaches to summarizing multiple items that assess disability include the following:

- Difficulty/inability in one or more items
- Summated scale
- Hierarchical scale
- Computer-adaptive testing.

When utilizing a large number of items, it is necessary to understand whether the items represent a single underlying concept or multiple concepts, which items should be aggregated and which should be deleted. A variety of statistical techniques (e.g., factor analysis, Rasch modeling) are used to develop scales that represent underlying or latent constructs that validly represent a domain of functioning (for an example of this process, see [8]).

7.4.1 Disability in One or More Items

The most common summarizing technique for frequently used batteries such as ADLs and IADLs is to classify someone as disabled in the domain if they have difficulty or are unable to

perform one or more items in that domain. A great deal of publicly available data are produced in this way, showing the percentage of the population with disability in one or more ADL items or one or more IADL items, stratified by various demographic variables. For certain purposes, a cutpoint that requires a specific number of ADL items may be set (e.g., eligibility for long-term care that requires inability or the need for help in performing three or more ADLs).

7.4.2 Summated Scale

Summated scales are more complex than the simple dichotomy of disability vs. no disability. They can be constructed in a variety of ways. The simplest is to count up the number of items in which disability is present. In the presentation of public data, these counts are often aggregated into a few categories, such as 1 ADL, 2 or 3 ADLs, and >3 ADLs (Fig. 7.2). More complex summated scales may add up the difficulty score for a number of items to get a continuous summated score of disability. This has been the case in a number of large clinical trials with functional outcomes. An important trial of both aerobic and resistance exercise in individuals who have osteoarthritis of the knees utilized a comprehensive summated scale of lower extremity functioning [18]. This scale contained 23 items on ambulation and stair climbing, transfer, upper extremity functioning, and basic and complex ADLs. Possible responses to each item were no difficulty, a little difficulty, some difficulty, a lot of difficulty, and unable. Each was scored from 0 to 5, and the composite score was an average of the items. The trial demonstrated a significant difference in the two exercise groups compared to an education control group. A continuous variable such as this offers more statistical power to show benefit in a clinical trial, but a limitation is difficulty in understanding what a change of a certain number of points means in terms of real improvement in the disability that result from this intervention. The section on change in function (Sect. 7.6) will describe how clinically meaningful change can be assessed for summated scales and continuous variables.

Another example of a summated scale that worked well in a clinical trial is from a study that was done to evaluate the benefits of a home physical therapy program in frail older adults which focused on improving underlying impairments [19]. The ADLs were scored as (0) having no difficulty and needing no help in the past month, (1) having difficulty but not needing help and (2) needing help. The ADLs were walking, bathing, upper- and lower-body dressing, transferring from a chair to a standing position, using the toilet, eating, and grooming. The scores on these eight items were then summed. The intervention group had an increase in disability from 2.3 at baseline to 2.7 at 12 months, but the control group had a significantly greater increase in their disability scores, from an average of 2.8 at baseline to 4.2 at follow-up.

7.4.3 Hierarchical Scale

Many self-report items have a hierarchical response pattern that is very useful in scoring the items. In the example above, ADLs were scored according to a hierarchy that went from "no difficulty, no help required" to "difficulty but not needing help" to "needing help". It is important to recognize that the scoring of items in a hierarchical manner is distinct from a hierarchical scale, which has separate items that are themselves hierarchical. A simple example of the latter is a scale that queries the ability to walk across a room, walk 50 ft, and walk one-half mile. Knowing that the study participant can walk a half mile indicates that they are also able to do the two easier tasks.

A simple hierarchical scale that has been useful in epidemiologic studies includes ADLs and higher mobility, often defined as the ability to walk ¼ mile and climb a flight of stairs. This scale is hierarchical because nearly everyone who has difficulty performing basic ADLs also has difficulty with one or both of the higher mobility items. Figure 7.3 illustrates research that demonstrates the predictive validity of this hierarchical scale. It shows the joint contribution of serum albumin level and the three-item hierarchical

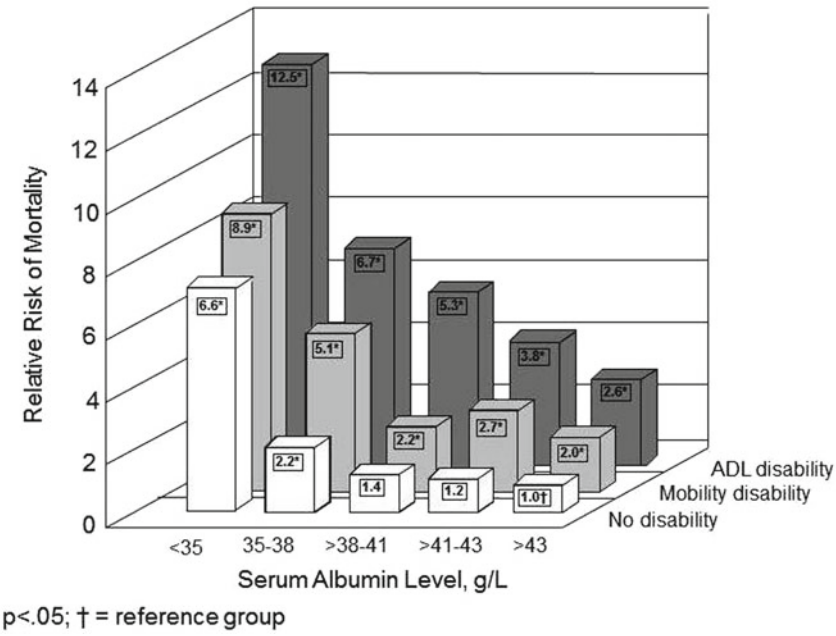

Fig. 7.3 Four year age-adjusted risk of death according to serum albumin in disability status, Women, EPESE 1988–1992 [20]. *Abbreviation*: *ADL* activity of daily living

disability scale in predicting mortality. At each level of serum albumin, there is a gradient of risk for mortality that goes from no disability to mobility disability to ADL disability [20]. In addition to being a predictor of adverse outcomes, this hierarchical scale has also been utilized as an outcome measure in studying predictors of disability [21].

7.4.4 Item Response Theory (IRT) and Computer Adaptive Testing (CAT)

An innovative approach to using a large number of items to efficiently assess the full range of a domain is using IRT to develop an item bank that is then utilized by CAT to score an individual [22]. IRT was originally developed for educational testing and assumes an underlying latent trait that is manifested by responses to a wide range of items, with the level of the latent trait related to the probability that a particular item will be answered in a specific way. This implies a unidimensionality to the underling trait and a range of items that cover the full spectrum of functioning represented by the trait. In practice, a large number of items that are hypothesized to be related to the trait under study are administered and an item bank of appropriate items is developed using IRT. Once this has been accomplished, CAT can be used to efficiently hone in on the level of functioning of an individual by using the knowledge gained from IRT to sequentially select relevant questions from the item bank until a predetermined level of precision is obtained regarding where the individual stands on the scale of functioning. Using this approach, individuals on each end of the functional spectrum may be asked very different questions from the item bank, but their position on the functional spectrum can be determined to similar degrees of precision and with a minimal number of items utilized.

This approach is illustrated in Table 7.5, which shows the correlations between a CAT-based approach and criterion physical function scores that come from the full-item bank of 124 items. These correlations are compared with

Table 7.5 Intraclass correlation coefficients between CAT-based and random-based scores with IRT-criterion physical functioning scores after administering 5, 10 and 20 items, for three score ranges

Items administered	Low-range (N = 131)	Mid-range (N = 521)	High-range (N = 150)
CAT – 5 items	0.87	0.88	0.83
Random – 5 items	0.64	0.77	0.53
CAT – 10 items	0.92	0.93	0.91
Random – 10 items	0.80	0.89	0.76
CAT – 20 items	0.97	0.97	0.95
Random – 20 items	0.92	0.96	0.93

Source: Adapted from Haley et al. [22]; *CAT* computer adaptive testing; *IRT* item response theory

correlations between randomly selected sets of questions from the data bank and the criterion physical function score. It is impressive that in the middle range of functioning, a CAT approach that used only five items has a correlation as high as 0.88 with the full bank of items, with correlations nearly as high at the high and low ends of function. This is in comparison with correlations of ≤0.77 if the items were selected randomly rather than chosen using the CAT process. Using ten items selected by CAT increases the correlations to above 0.90. It is thus clear that CAT is a very efficient method of determining where an individual is on the spectrum of functioning.

While this approach has many advantages, it should be kept in mind that it is very different than using a standard set of assessment items in an evaluation. Individuals at different ends of the functional spectrum may start out with the same question, but will then be presented with a very different set of questions. This can efficiently provide a precise measure of their level of functioning. However, in longitudinal studies or clinical trials, a participant who has a change in functioning may get completely different questions when returning for a follow-up visit. Theoretically, this is the way CAT is supposed to work, but the research community will have to become more familiar with this approach and accept the results of CAT. Researchers who design clinical trials will have to develop methods to assess the power of a randomized trial that uses this type of outcome.

7.5 Objective Physical Performance Measures

Objective measures of physical performance have received increasing attention as assessments that can measure functioning in a standardized manner in both the research and clinical settings. These measures can be defined as assessment instruments in which an individual is asked to perform a specific task and is evaluated in an objective, standardized manner using predetermined criteria, which may include the counting of repetitions or the timing of the activity as appropriate. As per the Nagi model of the disability framework that was discussed earlier in the chapter, these measures can be utilized to represent impairments, functional limitations or actual disability. However, most are indicators of functional limitations and can be thought of as representing the building blocks of functioning [23]; discrete actions that can be readily tested and that are necessary components of the ability to function independently in the community.

The development of performance testing was in response to concerns that self-report of functioning and disability may not be accurate. Additionally, disability is meant to be a measure of how well people are functioning in their own environments and, while this is critical to know in understanding their abilities to function independently, it is highly related to the environmental challenges that are specific to their situation. For example, the ADL that assesses bathing may

have very different responses if the participant has a walk-in shower vs. a bathtub that is difficult to climb into. Standardized performance tests avoid this limitation. Self-reported measures of disability identify a small fraction of the population that is disabled, but the remainder of the population is not characterized according to their functional abilities in most self-report measures. Performance testing has the potential to expand the spectrum across which people can be characterized, and is therefore able to identify both low and high functioning. While there are clear benefits with performance testing, understanding an older adult's ability to function independently in his or her own environment is best described using disability assessment. Research has shown that rather than replace disability assessment, the use of performance measures appears to complement disability assessment in characterizing an individual, especially with regard to individuals who are not severely disabled.

7.5.1 Examples of Performance Tests

A wide range of performance tests have been developed for use in the older population.

Examples of performance tests that assess both upper and lower extremity function include:

- Pegboard test
- Picking up object
- Lifting 10 pounds
- Gait speed
- Timed up and go test
- Chair rise – single and repeated
- Stair climb.

These tests all evaluate a single task except for the timed up and go test, which combines chair rise and gait speed, asking the participant to rise from a chair, walk 10 ft and then return to the chair [24]. The tests listed above are commonly employed, but there are others that have been developed for specific studies or for use in specific populations. This list does not include tests of aerobic capacity, which also assess physical functioning and may be valuable in identifying problems in older adults, but are more targeted toward endurance. The most commonly used of these tests include the 6-min walk and the 400 m walk.

In addition to individual items used for performance testing, several batteries of performance tests have been developed to give a broader picture of functional abilities. The most commonly used of these batteries are the Short Physical Performance Battery (SPPB) [25] and the Physical Performance Test (PPT) [26]. Items used in these tests are as follows:

SPPB

- Side-by-side, semi-tandem and tandem stands, each held for 10 s
- Four-meter walk at usual pace
- Single chair stand and if successful, five timed chair stands as quickly as possible.

PPT

- Writing a sentence
- Simulated eating
- Turning 360°
- Putting on and removing a jacket
- Lifting a book and putting it on a shelf
- Picking up a penny from the floor
- 50-foot walk test
- Climbing stairs (scored as two items).

The SPPB is more purely a lower extremity function test, while the PPT is multidimensional. Both batteries have been used in observational studies and as outcomes in randomized controlled trials. Each of the three components of the SPPB is scored categorically from 0 to 4, and a total SPPB score of 0–12 is created by summing the three components. The SPPB has been found to predict mortality, the need for nursing home admission, and health care utilization in the overall older population. Furthermore, in a population that had no disability at the time the performance battery was administered, the score was found to be highly predictive of those who developed ADL and mobility disability 1 and 4 years later (Fig. 7.4). These findings have been replicated in other populations and with other, similar performance measures, and indicate that there is a state of preclinical disability—expressed as impairments and functional limitations—that indicates a high risk of proceeding to full-blown disability. This finding also provides a way of identifying

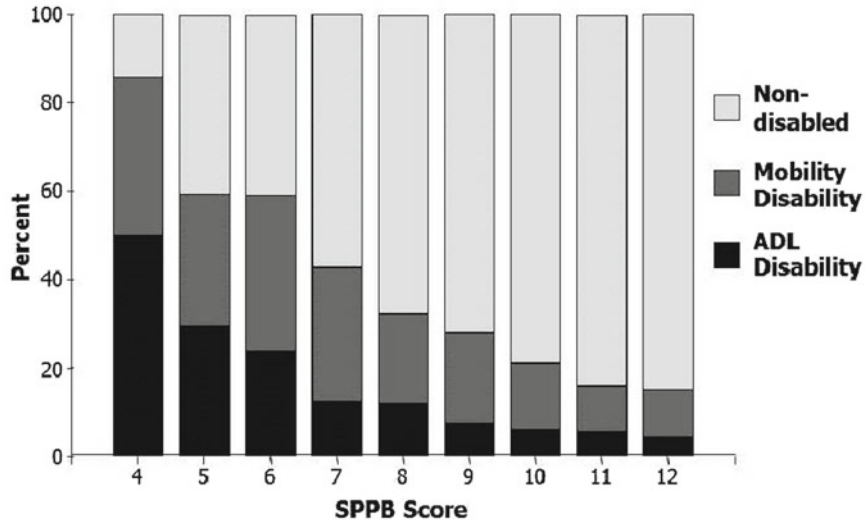

Fig. 7.4 Disability status at 4 years among individuals who were not disabled at baseline, according to baseline Short Physical Performance Battery (SPPB) score [21]

high-risk older adults for whom preventive interventions may be highly effective.

7.5.2 Overview of Uses

Physical performance measures have the following potential applications:

- Identifying high levels of functioning
- Identifying non-disabled individuals at risk of disability
- Clinical "vital sign"
- Evaluating change in functioning and health status
- Intervention studies
- Cross-national and cross-cultural studies.

The ability of performance tests to describe the full spectrum of functioning, including the high end of function, has already been described. This is not an inherent quality of performance measures, and only certain measures will actually identify the highest level of functioning. For example, the balance tests in the SPPB were designed to be done safely in a population starting at age 70 and with no upper age limit. Younger, healthy individuals will generally be able to hold all three stands for 10 s, and the highest performers cannot be identified. This ceiling effect would be useful if identifying and characterizing very high performers were an important part of a research project. For this reason, in some instances investigators have added more difficult balance tests, including walking on a narrow course, a single leg stand with eyes open for up to 30 s and, if the participant is successful at that, a single leg stand for up to 30 s with eyes closed, a task that few people can fully accomplish [13, 27].

The identification of non-disabled individuals at risk of disability is related to the ability of performance measures to tap into the higher end of the functional spectrum, but it is not necessary to identify the very highest level of functioning in order to accomplish this. For example, the SPPB is scored from 0 to 12, with 12 being the best functioning. While additional testing might be able to stratify individuals with scores of 12 into a further hierarchy of very high functioning, the 0–12 range works very well in generally classifying the full older population. Individuals with scores >8 generally self-report no disability, but study of those with scores of 9–12 reveals a clear graded risk of multiple adverse outcomes (e.g., disability, mortality, nursing home admission, hospital use), indicating that in these non-disabled

individuals it is possible to use a performance test to characterize level of risk.

Even in individuals who have lower SPPB scores, there will be a subset that reports no disability, but these individuals will have a higher risk of adverse outcomes than those who report no disability and have a score >8. This is illustrated in Fig. 7.4, which is restricted to non-disabled individuals at baseline (when the SPPB was measured) and demonstrates the graded relationship between SPPB scores and the future risk of ADL and mobility disability. This kind of relationship between performance in non-disabled individuals and adverse outcomes has been examined in many studies that extensively adjust for multiple measures of demographics, health status, behavioral and other risk factors, with virtually no weakening of the performance–adverse outcome relationship. Cooper et al. [28] reviewed the associations of multiple physical performance measures and a variety of adverse outcomes. In the Health, Aging and Body Composition (Health ABC) study, which included only non-disabled individuals who have no difficulty walking a quarter mile or climbing stairs, individuals who had a gait speed slower than 1.0 m/s had greater risk of future persistent mobility limitation, death and hospitalization than did individuals who had a gait speed of 1.0 m/s or faster [29]. What is not yet clear is what it is about the performance tests that make them independent predictors of aging outcomes. It is likely that they are capturing diverse aspects of health in older adults—including comorbidity severity, physiologic decline and motivation—that are not represented by the usual kinds of potential confounders that are studied.

Objective performance testing is beginning to be applied in the clinical setting, though research in this area is sparse. Busy clinicians rarely observe the functional abilities of their older patients but could gain much by knowing whether the patient had functional declines over time, which may occur even while their patient's disease status apparently remains stable. Studenski et al. [30] integrated the SPPB into two geriatric outpatient settings and found that after training the staff, the battery could be performed efficiently and was well accepted by those who administered the tests and by the patients. It showed predictive features similar to what was found in epidemiologic studies of representative community-dwelling populations. In a study in Italy, the SPPB was performed within 24 h of hospitalization and before discharge in geriatric patients who were hospitalized for several different diagnoses [31]. It was demonstrated that the testing was feasible and safe, and that the SPPB score at admission was a significant predictor of length of stay, even after adjustment for a comprehensive measure of comorbidity. Furthermore, a poor SPPB score in the test done just prior to discharge predicted greater rehospitalization, mortality and decline in ADLs over the year subsequent to discharge [32]. There is thus evidence for the potential advantages of utilizing physical performance testing in both the outpatient and hospital settings, but further work will be necessary to examine just how this might influence clinical decision-making and, ultimately, patient outcomes.

Observing change in function and disability are an important part of epidemiologic studies on aging. Transitions in states of self-reported disability are a critical part of this research, but performance measures offer a way of measuring change in a setting that is standardized rather than within the context of an environment that itself may be changing and affecting a disability outcome. Having measures that are precise, reliable and sensitive to clinically meaningful change is of particular importance in clinical trials, and trials that use performance tests as primary and secondary outcomes are becoming increasingly common. Figure 7.6a, b show results from randomized controlled trials that used the SPPB and PPT as primary outcomes.

One limitation of physical performance measures in longitudinal studies is that, over time, individuals with the most disability are less likely to return to the clinic for evaluations. Obtaining high follow-up rates often requires the use of home visits, telephone contacts and proxy interviews [33]. Certain performance measures, such as the SPPB and usual gait speed, have been successfully performed in the home setting. However if only telephone contacts can be used, then it

may be necessary to follow-up individuals using self-report or proxy.

Objective performance measures also provide a means of comparing functional status across countries or cultures, where disability measures may lose comparability due to environmental differences or differential access to assistive devices. Figure 7.5 shows results from the English Longitudinal Study on Aging, a nationally representative sample of older adults in England. It demonstrates the prevalence—by age and sex—of poor physical performance, documented as an SPPB score of ≤8 and gait speed of <0.5 m/s. Longitudinal studies have shown performance below these cutpoints to be strongly associated with multiple adverse outcomes. Poor performance affects only about 10% of individuals in their 60s, but the prevalence rises rapidly in the 70s and attains very high levels in those ≥80 years of age. Women have higher rates of poor performance than do men at all ages. When a US national study that is doing these same tests (the National Health and Aging Trends Study [4]) is completed, results across the US and England will be readily comparable, as will results from other countries that are using these tests.

It is not always practical to utilize performance measures of functioning in large surveys, but methodological work with performance measures may help in the interpretation of differences in self-report that are observed in the self-report of functioning and disability. This approach, first developed by the WHO, uses performance measures of functioning to calibrate responses to self-report items. Using the modeling technique Hierarchical Probit Modelling, Iburg et al. [36] used performance tests from the National Health and Nutrition Examination Survey (NHANES) III to create a vector of performance that represented a latent variable which indicated the true underlying level of performance. They then looked at how different subsets of the population reported disability at different levels of this background latent variable. Utilizing this approach to assess differences in self-report across countries, Melzer et al. [37] compared disability self-reports from the US with the Longitudinal Aging Study Amsterdam. A lower prevalence of disability was observed in the Netherlands, but this approach revealed that individuals in the Netherlands did not report disability until they had more reduced levels of background performance. This indicated that differential reporting of disability across countries might be at least partially explained by cultural differences in how individuals perceive and report their disability level. This calibration technique can thus be used to adjust disability rates to make them comparable across countries, or across cultural or ethnic groups.

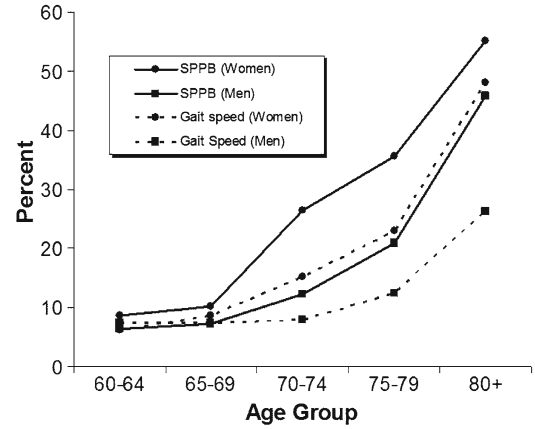

Fig. 7.5 Percentages of men and women with a SPPB ≤8 and gait speed ≤0.5 m/s [39]. *Abbreviation*: *SPPB* Short Physical Performance Battery

7.5.3 Psychometric Properties

Psychometric properties of many physical performance tests have been studied and they have generally been found to have excellent validity and reliability. Predictive validity has been extensively examined by demonstrating the high predictive power of these tests for important adverse outcomes in the older population, as previously described in this chapter. Test-retest reliability is very high when two examiners observe the same test, and intra-observer reliability—when tests are done 1 or 2 weeks apart—has also been found to be high. For example, in the Women's Health and Aging Study, a subset of participants was seen at home weekly and administered the SPPB

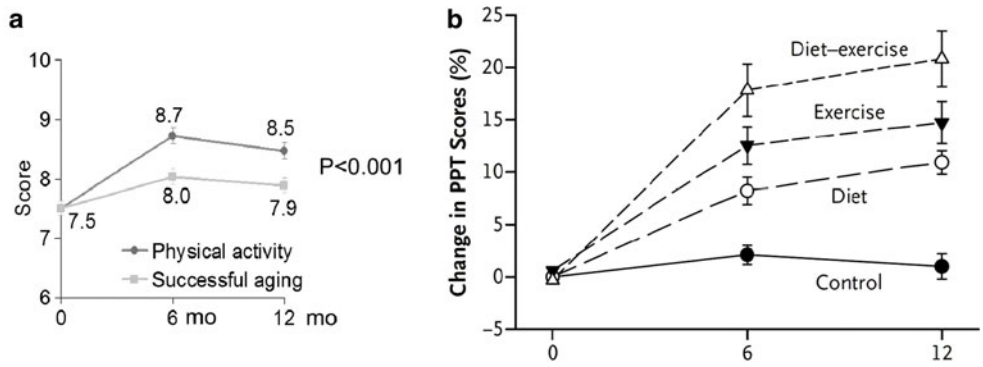

Fig. 7.6 Results from randomized controlled trials that used the SPPB and PPT as primary outcomes. (**a**) LIFE-P SPPB scores at baseline, 6 and 12 months. Means estimated from repeated measures of ANCOVA adjusted for gender, field center and baseline values [34]. *Abbreviations*: *ANCOVA* analysis of covariance; *LIFE-P* Lifestyle Interventions and Independence for Elders Pilot; *SPPB* short physical performance battery. (**b**). Mean percentage changes in Physical Performance Test (PPT) during 1 year intervention [35]

[38]. The test-retest reliability was examined for 1-week intervals at the beginning, middle and end of the 24-week substudy. The total SPPB score had the highest intraclass correlations for these three 1-week intervals, ranging from 0.88 to 0.92. The walk and multiple chair rise tests were nearly as high, ranging from 0.80 to 0.89 and 0.76 to 0.90, respectively. The reliability of the balance tests was somewhat lower, ranging from 0.70 to 0.82.

In addition to validity and reliability, it is critical to examine sensitivity to change in any measurement that is used for longitudinal studies or clinical trials. Figures 7.6a, b indicate that the SPPB and PPT respond to behavioral interventions. In the Women's Health and Aging Study, in which women were followed-up every 6 months, it was found that the SPPB was very responsive to clinical events that occurred sometime within the 6-month interval between which SPPB scores were measured [38]. This is illustrated in Figure 7.7, which shows the change in SPPB in women who were admitted to the hospital with specific diseases. The largest decline was for hip fracture, followed by stroke and myocardial infarction. These declines were much larger than the decline observed in participants who had none of these events over 6 months.

7.6 Change in Function at the Individual and Population Levels

A key aspect of physical function and disability measures in older adults is to represent the change that occurs—both decline and improvement—in response to aging, chronic disease, acute disease events, psychosocial and behavioral factors, and therapeutic interventions. All of the assessment strategies discussed to this point have been used to assess change, and formal evaluations of sensitivity to change have been made for some of them. It was previously described how interpreting change in a summated scale (e.g., the self-reported disability scale used for the FAST trial) can be difficult. A more obvious kind of change that is easy to understand is the onset of incident disability (e.g., ADL, mobility disability) in individuals who were previously not disabled. This approach is useful in prospective epidemiologic studies, but investigation of change across the total population may also require the use of function and disability scales. The interpretation of change is particularly challenging in characterizing physical performance measures, which, due to their excellent psychometric properties, are ideal for capturing change with high precision,

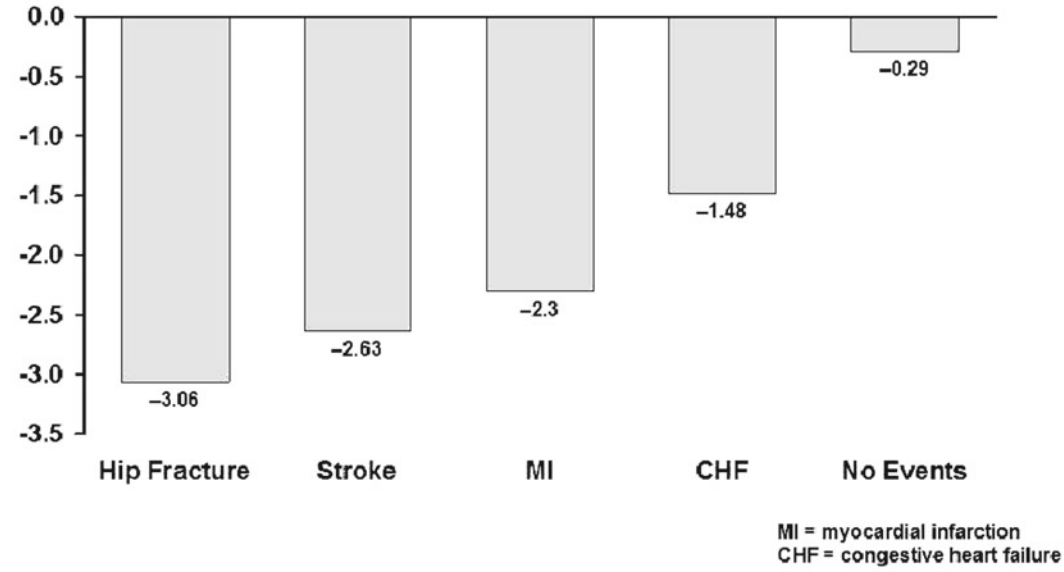

Fig. 7.7 Change in summary performance score over interval during which participants were hospitalized for specific events [38]. Abbreviations: *CHF* congestive heart failure; *MI* myocardial infarction

but for which it is not inherently obvious what the change means.

An important contribution in this area was the work on clinically meaningful change done by Perera et al. [40]. They used both of the techniques that are commonly used to define change, distribution-based and anchor-based analyses, and found similar results for both approaches. Using data from observational studies and a clinical trial, they evaluated both usual gait speed and the SPPB and found generally consistent results for both distribution-based and anchor-based analyses that determine small meaningful and substantial change. Small meaningful change was found to be 0.05 m/s for gait speed and 0.5 points for SPPB score. Substantial change was 0.1 m/s for gait speed and 1 point for the SPPB. In the example shown in Fig. 7.5a (Lifestyle Interventions and Independence for Elders Pilot [LIFE-P] study), the physical activity intervention group had a 1-point improvement in the SPPB score from baseline to 12 months, indicating substantial change, while the successful aging health education group had improvement that could be classified as small meaningful change [34].

7.6.1 Trajectories of Functioning

Many longitudinal studies measure functioning and disability repeatedly over time, and these studies provide data for examining trajectories of functioning. In particular, it is important to understand how various risk factors, both those measured at baseline and those that may change over time, affect trajectory of functioning. An excellent example of research aimed at examining trajectories of gait speed and how they relate to the inflammatory cytokine interleukin (IL)-6 is shown in Fig. 7.8 [41]. These data are from the Women's Health and Aging Study, and the population is stratified by tertiles of IL-6. There is a graded relationship between IL-6 tertile and baseline gait speed, with slower gait speed related to higher IL-6. Women in all strata of IL-6 had a decline in gait speed over a 3-year follow-up but there is a significantly steeper decline in those who had higher IL-6. This difference in trajectories was further examined to evaluate whether muscle strength was a mediator of the IL-6–gait speed association. In models that added muscle strength data over time, there was a substantial attenuation of the IL-6–gait speed relationship,

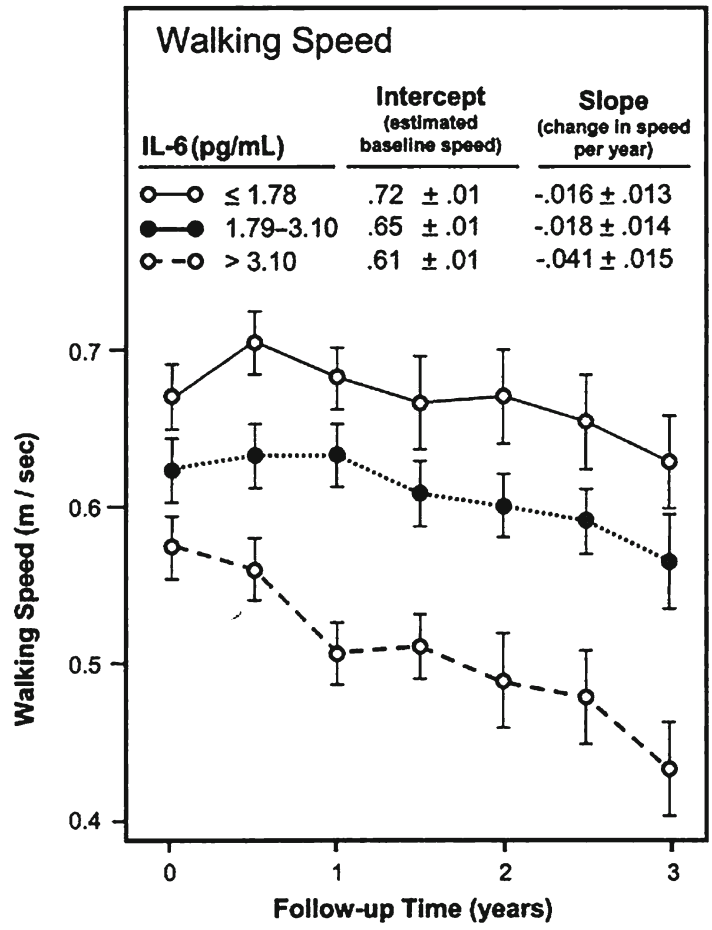

Fig. 7.8 Change over time in walking speed according to interleukin (IL)-6 tertiles [41]

giving evidence that IL-6 may affect gait speed through its impact on loss of muscle strength.

Trajectory of change in measures of functioning may be more powerful predictors of subsequent outcomes than are baseline measures alone. For example, in the Women's Health and Aging Study II, the trajectory of decline of handgrip and hip flexion strength in up to six subsequent assessments was a significant predictor of subsequent mortality in a sample of non-disabled women who were 70–79 years of age at baseline, even after adjusting for baseline values of strength [42]. Trajectories of functioning can also be quite valuable as outcome measures in studies of predictors of functional status as they may be more accurate measures of change than a single outcome assessment. In studying patients with peripheral artery diseases, McDermott et al. [43] evaluated changes in a number of functional outcomes and found that study participants who were more sedentary at baseline (operationalized by asking about number of hours spent sitting per day) had a steeper decline (over up to 4 years) in usual gait speed, fast gait speed and distance covered in a 6-min walk test.

7.6.2 Progression: Catastrophic and Progressive Disability

Longitudinal data provide a means of examining differences in trajectories of functioning or disability in those who develop substantial disability. This is illustrated in the concepts of

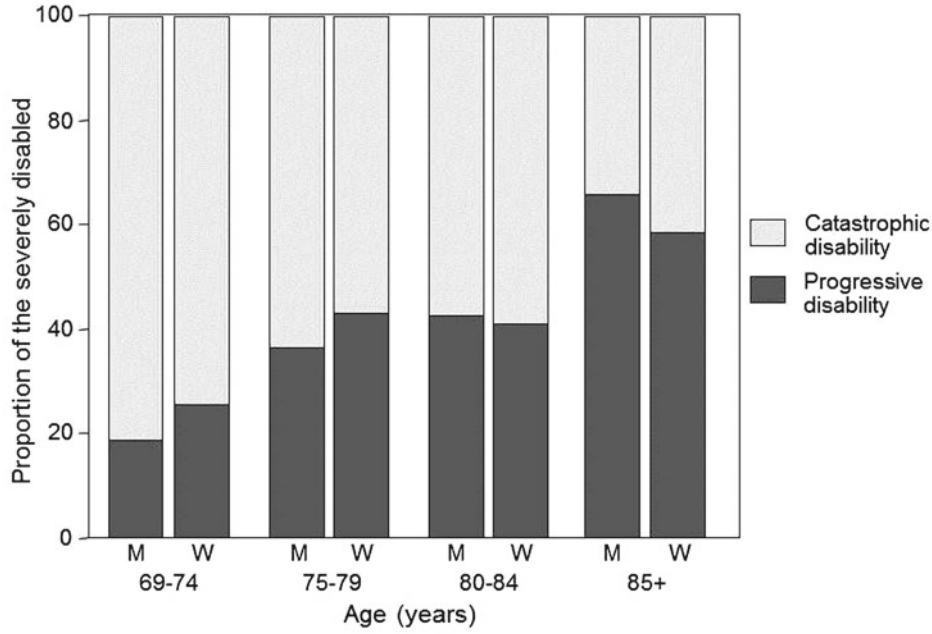

Fig. 7.9 Proportion of individuals with catastrophic and progressive disability among those who developed severe disability during the follow-up period, by age group and gender [44]. Abbreviations: *M* men; *W* women

catastrophic and progressive disability. These concepts were developed by examining trajectories of disability in individuals who eventually developed severe ADL disability, defined as the need for help or inability to perform three or more of six ADLs [44]. Using longitudinal data collected annually prior to the development of severe disability, catastrophic severe disability was defined as having no ADL disability in the 2 years prior to the onset of severe disability, while progressive severe disability was defined as having disability in one or two ADLs in the year prior to the onset of severe ADL disability. Among individuals who developed severe disability, the distribution of catastrophic and progressive severe disability by age group and sex is illustrated in Fig. 7.9. Catastrophic disability is the main type of disability in men and women 65–74 years of age, but this pattern is reversed in the ≥85-years-of-age group, where 60% of severe disability is progressive. The prevention of disability is quite different for these two patterns of disability onset. The main way of reducing catastrophic disability is the prevention of diseases that lead to catastrophic disability (e.g., stroke, hip fracture), whereas an important means of preventing progressive disability is the reduction in the impairments and functional limitations that accompany many chronic diseases of aging and lead to steady functional decline, the so-called geriatric model of functional decline.

7.6.3 Recovery, Interval of Recall

As experience with longitudinal studies of aging was acquired, it became evident that the transition to disability is not an absorbing state and that recovery from disability is common. This was first demonstrated in prospective studies that had intervals of at least 1 year between assessments, so the true dynamics of recovery and then potential return to disability in the short term was unclear. Recovery has best been characterized in the Precipitating Events Project (PEP) [45], a cohort study of 754 community-dwelling adults ≥70 years of age who were not disabled in ADLs at baseline and were followed-up with monthly

telephone interviews over several years. Individuals who were termed frail (determined by slow gait speed) were oversampled. During a follow-up period of >4 years, 56% reported disability (the need for help or instability in one or more of four ADLs: bathing, dressing, walking, transferring). Overall, 81% of these individuals recovered, becoming non-disabled in all four ADLs over the subsequent year, and among those who recovered, a full 57% remained non-disabled for at least 6 months. Recovery was less likely in individuals who had cognitive impairment, physical frailty or severe disability (three or four ADLs at the onset of their disability).

The PEP study also enabled the exploration of recall of disability in individuals who were not currently reporting disability, but who had a month or more of disability reporting in the previous year [46]. Only about half of individuals who had reported in the monthly phone assessments that they needed help with one or more of the four ADLs recalled that they had this disability when queried at the end of the year following the year in which they had recovered. Since even a short disability episode has been found to put older adults at higher risk of long-term adverse outcomes compared to those who never had disability, it is important to note that half of disability episodes are not recalled when participants are interviewed on an annual basis. Accordingly, with longer time intervals between assessments, there will be greater under-ascertainment of incident disability cases.

7.6.4 Joint Effect of Disability Transitions and Death: Active Life Expectancy

There is interplay among age at transition to disability, duration of disability, and length of life that determines the number of years that older adults live in the disability-free state (termed active life expectancy) and the number of years spent in the disabled state. Life table analyses have been used to partition total life expectancy from a specific age into active and disabled life expectancy, utilizing data from population-based longitudinal studies on transitions from the nondisabled state to disability and death, and from the disabled state to nondisability and death. This approach is important for understanding how factors that affect both death and disability have their impact on active and disabled life expectancy. The approach is also critical for determining whether population increases in total life expectancy that are occurring throughout the world are due to the prolongation of years spent in the disabled state, or to increases in active life expectancy, years free of disability and with higher quality of life. The reduction of years spent with disability has been termed compression of morbidity, and it represents a decrease in disabled life expectancy that results from compressing chronic disease and disability into a smaller number of years between disease and/or disability onset and mortality.

There has been little nationally representative longitudinal disability data collected using identical instruments over time to allow for the examination of trends in active and disabled life expectancy. One example of where this has been possible is in the Current Beneficiary Survey, a multistage, longitudinal survey of the US Medicare population that was sponsored by the US Centers for Medicare and Medicaid Services. Figure 7.10 shows data from samples whose evaluations started in 1992 and 2002, and went on for up to 4 years [47]. All 1-year transitions for which data were available contributed to the estimates. Women had a modest increase in total life expectancy of 0.3 years, which resulted from an increase in active life expectancy of 0.7 years and a decline in disabled life expectancy of 0.4 years. Disability in this case was defined as having difficulty in any one of six IADLs and six ADLs. The analyses partitioned disabled life expectancy into three categories, years lived with IADL disability only, moderate ADL disability and severe ADL disability (difficulty with three or more ADLs). In women, 0.3 of the 0.4 years of decline in disabled life expectancy resulted from a decline in severe ADL disability years. Men had a substantial gain in total life expectancy of 0.8 years, which was due entirely to increases in active life expectancy. Overall disabled life

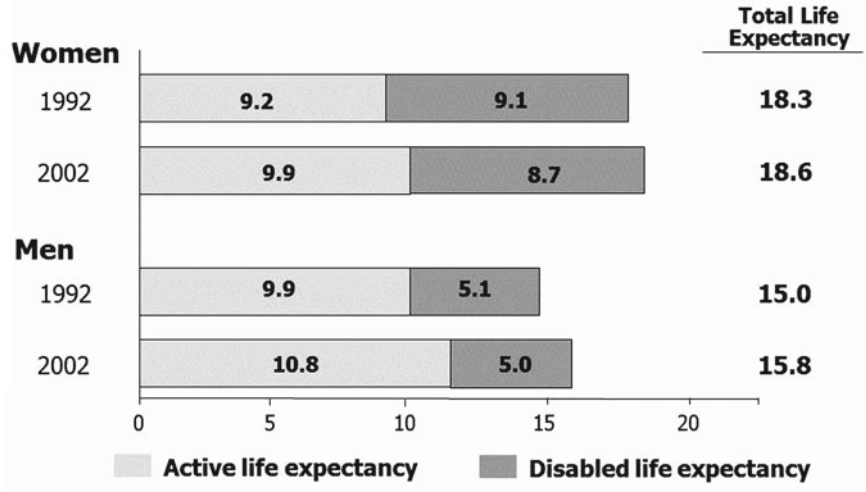

Fig. 7.10 Total active and disabled life expectancy, 1992 and 2002, from the Medicare Current Beneficiary Study [47]

expectancy was virtually unchanged, with no change in life expectancy with IADL disability, a 0.1 year increase in moderate ADL disability and a 0.2 year decrease in severe ADL disability. On the whole, this presents an optimistic picture of improvements over time in the older population, with substantial increases in active life expectancy and moderate to slight decreases in disabled life expectancy.

7.6.5 Trends in Disability

Because disability status is a good way of representing overall health status in older adults who have complex patterns of disease, and because disability also has direct implications for the long-term care needs of an older adult, there has been much interest in evaluating disability trends over time. Although a number of cross-sectional national surveys now assess disability, uniform disability assessment done over time has been available only since the mid-1980s in just a few studies that have nationally representative samples. Although these studies use different assessment instruments, a convincing decline in age- and gender-specific rates of disability was observed from the mid-1980s through the 1990s [48]. The National Long Term Care Survey has similar assessments of ADL and IADL disability available from 1982 through 2005, and recent findings indicate that the decline in disability observed for the first 12 years of the study continued and actually accelerated from 1994 through 2005. In another study that utilized reports of functional limitations—including lifting and carrying 10 lbs, climbing stairs, walking ¼ mile and seeing words in a newspaper—changes in prevalence were evaluated between 1984 and 1993. Declines were seen in the inability to perform all four of these tasks in the ≥65-years-of-age population and in the ≥80-years-of-age population. The functional limitations evaluated in this study, which assess more basic tasks than disability, are an excellent way to follow trends over time because they are less influenced by changing roles that can affect disability assessment (more men cooking in more recent surveys and more women managing money).

The observed declines in disability and functional limitations through the 1980s and 1990s were attributed to a number of factors. Educational status is strongly associated with disability, and it has been estimated that in more recent cohorts, from 25 to 75% of the observed functional declines are related to a higher educational level in more recent cohorts. Improving educational level and socioeconomic status in general likely

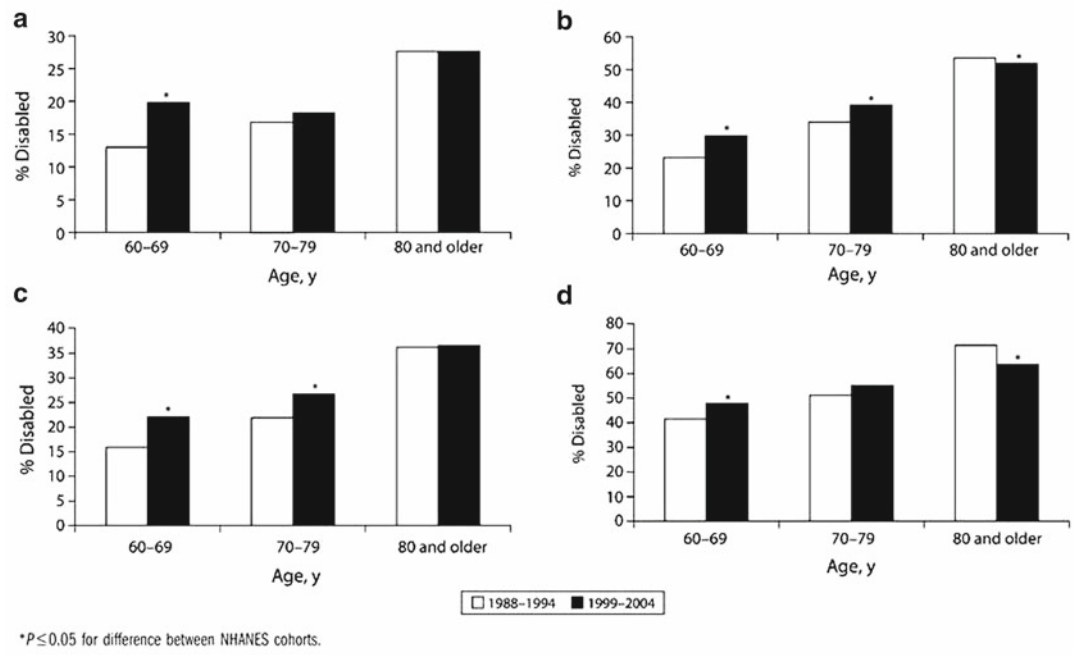

Fig. 7.11 Time trends by age group between National Health and Nutrition Examination Surveys (NHANES) in 1988–1994 and 1999–2004 [49]. (**a**) Prevalence of basic activities of daily living disability. (**b**) Prevalence of instrumental activities of daily living disability. (**c**) Prevalence of mobility disability (**d**) Prevalence of functional limitations

have their impact on disability improvement through changes in behavioral risk factors, reductions in the prevalence of several chronic diseases, utilization of medical care, improved cognition and other less well understood factors. Other proposed explanations for the decline in disability include changes in nutrition and public health at the time when these cohorts were young, improved health promotion and medical therapy in more recent cohorts, and better utilization of assistive devices and technology.

Several recent studies have offered evidence that these positive trends in disability prevalence decline may not be sustained in the future. In Fig. 7.11, data are shown from the NHANES study regarding prevalence rates of disability from the periods of 1988–1994 and 1999–2004 [49]. It appears that in the oldest subset (those ≥80 of age), the more recent cohort has identical rates for ADL and IADL disability and lower disability rates for mobility disability and functional limitations (e.g., difficulty stooping, crouching or kneeling; lifting or carrying 10 pounds; and standing from an armless chair). This is perhaps a vestige of this cohort doing better since mid-life. However, among the two younger age groups (60–69 and 70–79 years of age), the more recent cohort had higher disability rates for all of the measures, with most of them being statistically significant increases. This poorer picture for the "young old" in this national data set—which reflects recent increases in obesity and diabetes, both of which have major impacts on disability—may be a warning sign that in the future, the disability and health status of the older population may not be as good as in the current population. This argues strongly for the careful assessment of trends in the older population, with the institution of better strategies—in both disease prevention and therapy, as well as in improved behavioral risk factors—to reduce functional decline and disability in this rapidly growing segment of the population.

7.7 Summary

The assessment of physical functioning and disability is a component of nearly all epidemiological studies of older adults. There is a wide variety of measures to choose from and many decisions must be made when determining which assessments best fit a study that is being developed. Many aspects that are vital in making these choices have been discussed here. It is typically necessary to customize assessments for a particular study. Even the various large national studies that are supported by the US government often use different approaches to measuring disability. However, there are also advantages to having consistency in the way disability is measured. Having a small core of items that are asked in the same way on all studies would enable direct comparison of the populations being studied. A simple performance test, such as a gait speed test done in a standardized way, would also be an excellent assessment for comparing across studies. It would provide a simple measure of capacity that is free of the environmental challenges that differ across subsets of the population and have a strong impact on disability. Overall, there is evidence that self-report and performance measures complement each other and that both will add useful information in a comprehensive assessment.

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Comorbidity and Multimorbidity

8

Anne B. Newman

Abstract

Older adults often carry several chronic health conditions with varying degrees of severity and duration, and the combined effect can influence health outcomes. Conditions that co-occur with an index condition of interest are considered to be "comorbid" with the index condition, with the combination referred to as comorbidity. The term multimorbidity has recently been used to describe the totality of conditions. Methods for assessing comorbidity and understanding its impact are critical for the study of the epidemiology of aging. The presence of conditions in an individual can be based on self-reported diagnosis, administrative data or direct examination, each with its own strengths and limitations. Comorbid conditions are typically assessed as contributors to a health outcome, or as confounders or effect modifiers of a primary association. Some methods combine conditions into a single variable or index, including a simple tally or a weighted sum of conditions, which can be used to describe an individual's overall health status and compare individuals or groups for degree of disease burden. Regarding impact in older adults, comorbidity (both clinical and subclinical) is associated with greater disability. When analyzing comorbidity data, the analysis of each condition and their interactions can provide greater insight into the pathways of the associations involved.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Comorbidity • Multimorbidity • Health • Chronic health conditions • Disability • Mortality • Polypharmacy • Medical records • Subclinical disease

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Abbreviations

ADL	Activity of Daily Living
CES-D	Centers for the Epidemiologic Study of Depression

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COPD	Chronic Obstructive Pulmonary Disease
DRG	Diagnosis-Related Group
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
GI	Gastrointestinal
Health ABC	Health, Aging and Body Composition
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, Ninth Revision
LASA	Longitudinal Aging Study – Amsterdam
MI	Myocardial Infarction

8.1 Introduction

Older adults often carry one or more chronic health conditions that have varying degrees of severity and duration. The sum of multiple health conditions is conceptualized as a burden of disease, which indicates that it is the combined effect of these multiple problems that influences health outcomes. When conditions co-occur with an index condition of interest, the co-occurring conditions are considered be "comorbid" with the index condition. Sometimes investigators and clinicians will refer to the combination of the index condition and additional conditions as comorbidity. More recently, the term multimorbidity has been used to describe the totality of these conditions or the total disease burden.

Less than 25% of adults ≥65 years of age are free of diagnosed chronic health conditions, and about 16% of adults 65–79 years of age and 31% of adults ≥85 years of age have four or more chronic health conditions (Fig. 8.1) [1]. Given the impact of each condition on adverse outcomes, this high prevalence of multiple conditions cannot be ignored when studying older adults. In the analysis of health outcomes, it can be challenging to determine whether an index condition is independently related to morbidity or mortality when there are other conditions present that could also influence or confound the association of interest. When conducting clinical trials, there is a tendency to exclude individuals who have health conditions that could impact the treatment or outcomes. With 25% or fewer older adults having no conditions, the potential to reduce generalizability by exclusion is high. Methods for assessing chronic disease burden and understanding its impact are critical to the study of the epidemiology of aging.

The need to understand comorbidity is based in the principles of geriatric medicine. A fundamental principle is that geriatric conditions are usually multifactorial. Many complaints of older adults cannot be explained by a single condition but are often the result of the interplay between conditions. In older adults, there is rarely a simple direct relationship between a set of signs and symptoms and a single disease diagnosis. This is counter to the classic principle of diagnostic parsimony, which seeks a single unified diagnosis to explain a set of signs and symptoms. The relationship between a condition and an outcome in older adults is further complicated by the additional contributions of age-related changes, functional impairment and major psychosocial stressors [2]. These issues also have profound effects on the prescription for and evaluation of health services because a given patient may be prescribed medications that interact with—or be prescribed conflicting therapies for—a set of conditions [3]. Epidemiologic studies of aging need to recognize the multifactorial nature of health conditions, treatments and function in older populations. One key to doing this in any study of health outcomes in older adults is to assess the most common chronic conditions along with important common contextual factors in all studies.

Comorbidity and multimorbidity assessment have many uses in aging research. Additional health conditions are most often assessed as contributors to a health outcome or evaluated as confounders or effect modifiers [4]. The simple sum of conditions or a weighted sum of conditions can be used as an index to describe the overall health status of an individual and to compare individuals or groups for degree of disease burden. Clinical trials can use comorbidity assessment to enable comparison or stratification by groups with a similar disease burden and to help

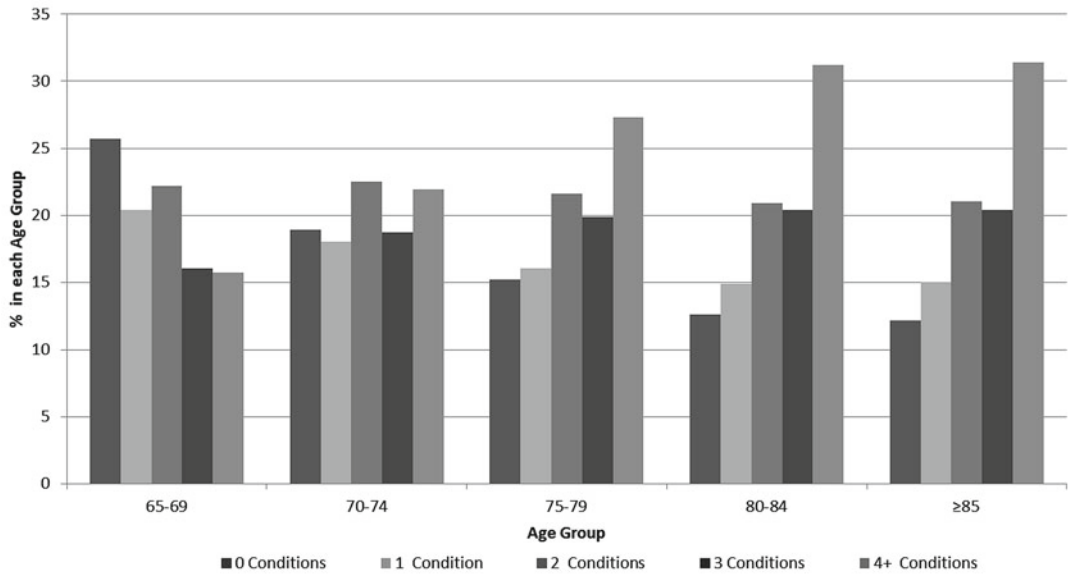

Fig. 8.1 Percentage of older adults who have chronic conditions within each age group [1]

us to understand the extent to which the study population represents a clinical patient population.

In this chapter, we will review methods for assessing and summarizing chronic health conditions. We will also review the relationship between comorbidity and the health outcomes of disability, mortality and frailty. Lastly, we will discuss analytic approaches for addressing comorbidity in geriatric research and address some methodological issues for the future.

8.2 Terminology

The term "comorbidity" has come to refer to the total burden of an individual's chronic disease. It is also sometimes used as a plural term, as in "comorbidities," to refer to a number of chronic conditions. The term was originally coined to refer to the "other" health conditions that can influence an "index" health condition [5]. Thus, comorbid conditions are the chronic health conditions which occur in addition to a condition of interest.

There are many important examples of how comorbidity can impact an association of primary interest. Diabetes is an important condition that can influence outcomes directly or through associated comorbid cardiovascular disease [6]. In the study of osteoporosis, several potential comorbid conditions (e.g., hyperthyroidism and vitamin D deficiency) are known to worsen osteoporosis directly, while others (e.g., orthostatic hypotension) can directly affect outcomes such as fracture and mortality. In a study of osteoporosis outcomes, such comorbid conditions must be assessed to determine whether they are causal factors or confounding factors. The analysis should first examine whether the comorbid conditions are associated with both the index condition and the outcome. If so, they may be potential confounders or mediators of a primary association of interest. Additionally, the potential direct effects of the co-morbid conditions on outcomes must be quantified to place the strength of the primary association in context.

More recently, aging research has adopted the term "multimorbidity" to refer to the group of conditions *in an individual* that result in a burden of disease [7]. The group of conditions can be analyzed individually or summarized in an index. Some work has been done to identify key clusters

of conditions. The term multimorbidity shifts the focus from an index disease to the individual who is carrying the burden of multiple disorders. In some studies of health outcomes in older adults, there might not be a single index condition that is the focus of study. Rather, the multiple conditions along with demographic and social factors are all assessed together for contributions to health. An individual who has more than one chronic condition can be more accurately described as having "multimorbidity" than "comorbidity." Nevertheless, many authors use the term "comorbidity" to refer to the co-occurrence of two or more conditions in an individual when there is no particular index health condition.

With the availability of non-invasive testing in epidemiologic studies, another category of comorbidity might be "subclinical" or "preclinical" disease. This concept has gained substantial momentum in the fields of cardiovascular epidemiology and osteoporosis, where non-invasive imaging has been used since the early 1990s. This will be further addressed below when clinical comorbidity is discussed in relation to frailty and to subclinical disease.

8.3 Assessment of Chronic Disease

To date, epidemiologic research has had no single approach for assessing chronic health conditions in older adults. When assessing such conditions, the first question that should be asked is, "Which conditions should be assessed?" Most assessments of comorbidity begin with a list of the most common chronic health conditions in older adults (Fig. 8.2). Some methodological studies have used a list of 50 or more candidate conditions, but most researchers will choose the 10–20 most common conditions for a baseline assessment. Some researchers include sensory impairments. While deafness and blindness are fairly uncommon, visual impairment and some hearing loss are very prevalent in older adults. Other researchers include testing for early disease that is conducted in the course of the study examination. One group of researchers in geriatric medicine has proposed that conditions be assessed according to impairments in physiologic systems [8]. Most researchers use clinical disease diagnoses rather than system impairments to define comorbidity in clinical research, but system impairments have been used for screening, risk assessment and etiologic studies [9].

8.3.1 Self-Reported Diagnoses and Validation

An assessment of comorbidity can be based on self-reported medical history. In this, a list of the most common or disabling conditions is created and assessed using simple self-report in an interview or self-administered questionnaire. The reliability of self-report can vary. Often, self-report is supplemented and validated through the use of medical records or by determining whether participants are taking medications that are appropriate for the condition. Early epidemiologic studies, such as the Framingham Heart Study, included a physical examination that was conducted by a physician who would also review the participant's medications and any non-invasive or laboratory blood testing. The study physician would then use this information to make a clinical judgment or diagnosis regarding key conditions. For example, a physician can diagnose heart disease on the basis of a Rose questionnaire for angina; a physical examination of the heart, lungs and peripheral circulation; a review of current medications and an electrocardiogram (ECG). The least reliable component of such an assessment is the physical examination, which often can only detect very extensive disease.

More recent studies have relied on a combination of participant self-report and the application of algorithms to validate self-report [11, 12], eliminating the physician examination and physician diagnosis. Sometimes a specific medication, blood test or other examination can be used to validate self-report in an algorithmic fashion. Diabetes is often defined as "present" if it is self-reported by the study participant and validated by a self–report of taking a specific corresponding drug for diabetes. Hypertension might be defined on the basis of a self-report of a diagnosis,

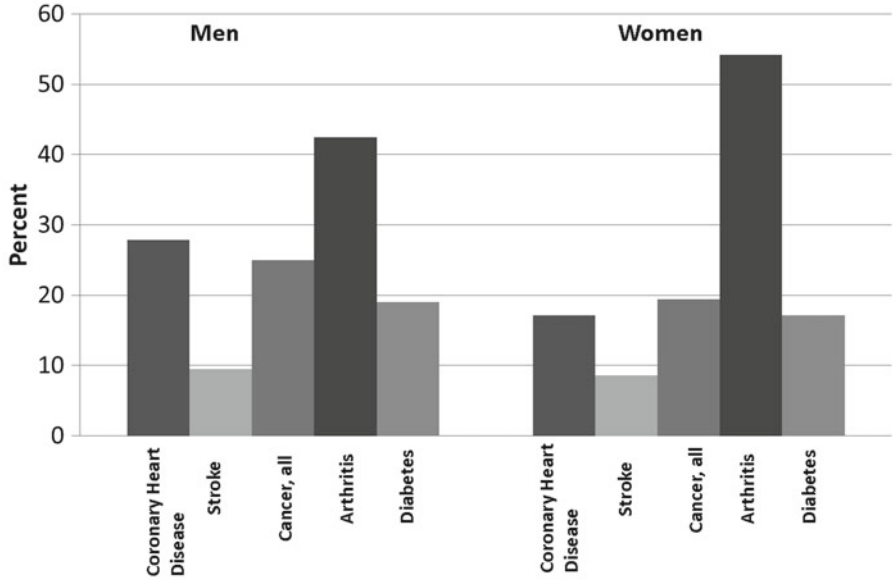

Fig. 8.2 Percentage of older men and women who have specific chronic conditions, age ≥65, US, 1999–2007 [10]

confirmed by appropriate medication use or by the presence of a measured high level of blood pressure during the examination.

As more testing is used in epidemiologic studies, care must be taken that it not be used to overdiagnose disease. If test results alone are used to diagnose a prevalent chronic condition within a study, disease rates will be higher than they are in real-world clinical practice because in clinical practice, testing is usually only initiated in response to symptoms of illness. Further, if testing is combined into a composite disease variable, the test itself cannot be evaluated for its independent predictive value. However, once a test has been shown to be predictive of a disease outcome, it may be adopted for screening and become incorporated into the definition of disease in clinical practice. This has been the case with osteoporosis, for which a diagnosis of disease is now made in clinical practice on the basis of a bone density value after a screening dual-energy x-ray absorptiometry (DXA) scan. In the cardiovascular field, some tests (e.g., ECG and ankle-brachial index) are widely used in screening and can themselves form the basis of a clinical diagnosis, while others (e.g., carotid ultrasound and coronary artery calcium scanning) remain controversial as screening tests but might be used to evaluate specific symptoms in some cases. If the study was to scan for coronary artery calcium, a higher rate of disease would be found than in clinical practice because in clinical practice, most tests are only done for symptomatic or high-risk cases.

For some diseases, self-report may lack sensitivity or specificity. In such cases, a participant self-report should be validated using an inpatient or outpatient medical records review. One well-documented example is cardiovascular disease, for which both under- and over-reporting are substantial. This phenomenon was examined extensively in the CHS study [13]. For myocardial infarction (MI), 75% of reported MIs in men and 60% of reported MIs in women were confirmed using either an old MI pattern on an ECG or using a medical record review. Under-reported events (false negatives) detected during the course of follow-up made up only 1–4% of incident events, but accounted for 10–30% of the true prevalent cases. This illustrates the limitation of self-report for cardiovascular disease and the importance of validating self-report.

Other conditions are also subject to self-report bias in epidemiologic studies. Chronic lung disease tends to be underreported compared to diagnosis via spirometric testing of lung function. In the Health, Aging and Body Composition (Health ABC) study, only 37% of participants who had airflow limitation and 56% of participants who had severe airflow limitation reported a diagnosis of lung disease [14]. The true prevalence is still controversial due to some disagreement on the level of change in spirometry that should be expected for age [15]. Furthermore, treatment for chronic obstructive pulmonary disease (COPD) is currently only symptomatic and not disease-modifying. Since the natural history and mortality are not improved by treatment, there is no reason for clinical practices to screen for cases using spirometry. Therefore, many studies of pulmonary conditions rely on self-report, which is specific but not sensitive for chronic lung disease.

There is less data on the validity of self-report for other conditions. Most of the work that has compared self-report to medical records has been in regard to the prospective evaluation of health outcomes. Cancer is usually more accurately reported, while questionnaire items on depression and other mental health issues may be denied for privacy concerns. At a minimum, prevalent diseases should be defined using self-report of diagnosed conditions along with a medication inventory, while the greatest precision in processing incident disease is through physician review of records and adjudication by committee [16].

The duration and severity of health conditions are also sometimes assessed by self-report, though this information is more difficult to obtain accurately without medical records. There is tremendous variability regarding the goals, methods, reliability and reproducibility of various approaches for defining disease severity in older adults [3]. Many methods apply functional criteria to define severity. This is particularly common for scales of angina severity [17] or osteoarthritis severity [18], for which limitations in exercise tolerance or the need for an assistive device attributed to the condition are used to define severity. Scales that ask for attribution of functional impairment to one condition can be problematic if there are multiple conditions that contribute to functional impairment because this would make a single attribution to the condition of interest illogical in the structure of the questioning when other conditions are contributing [19]. Some severity scales use measures of end organ damage. For example, the severity of hypertension can be defined according to proteinuria or left ventricular hypertrophy of the heart [20]. Other severity scales use clinical criteria of the pathophysiology of disease [21]. These various approaches to incorporating severity have not been applied systematically to the study of comorbidity across multiple chronic conditions.

8.3.2 Administrative Data

Administrative data, such as hospitalization data that uses the International Classification of Diseases (ICD) codes, can be used to assess the comorbid conditions of individuals in a cohort. Administrative data are useful for assembling very large populations [22]. A study that focuses on a patient population might use a database and/or medical record review as a starting point for case identification or for recruitment [23]. When using codes to define a population, the codes or terms for conditions must be defined and validated explicitly since terminology and coding can vary.

The rates of coded conditions may be greater than the actual rates of disease because coding practices are biased toward over-ascertainment for billing purposes. This was well documented as "DRG creep" in the era of prospective payment reform, where diagnosis-related groups or DRGs were found to be coded inaccurately 20.8% of the time, and these errors tended to favor the hospital and caused the case-mix index of severity to increase by 1.9% [24]. On the other hand, mild disease or asymptomatic disease may be under-ascertained by coding systems, which reduces sensitivity. Administrative data does not usually include information regarding duration or severity. Most importantly, the degree of misclassification using administrative data will

vary substantially by condition of interest, and thus will have a differential impact on data analysis. Many research studies favor specificity over sensitivity, but both are important to minimize misclassification.

Several examples of the accuracy of administrative data are informative. In a study of chronic kidney disease, ICD codes for a set of specific kidney disease diagnoses were compared to diagnoses for chart abstraction [25]. In this case, codes were very insensitive, with sensitivity varying from only 2.7% for diabetic nephropathy to 26.6% for a combined diagnosis of any kidney disease. However, the codes were very specific (>95%) and had high positive predictive values. Mild disease was most often missed. Thus, for chronic kidney disease, administrative codes are useful when specificity is desired, but would not be useful to screen for mild disease.

In a validation study for cardiovascular disease that compared hospital discharge codes to the gold standard of physician adjudication of medical records, agreement was higher for MI and stroke (kappa = 0.79–0.92) than it was for peripheral artery disease and congestive heart failure (kappa = 0.37–0.56). Thus it appears that MI and stroke can be more adequately ascertained using diagnostic codes. This also appears to be case with regard to codes for sudden cardiac death. In outpatient and emergency encounters, codes for sudden cardiac death had very good agreement with medical records [26]. These studies focused on the validation of cases and did not assess missed cases, favoring specificity over sensitivity.

Several studies have been conducted to determine combinations of information that can be used to improve the sensitivity or specificity of case ascertainment using administrative data. In a Veteran's Administration study of upper gastrointestinal (GI) bleeding, codes were insensitive, but an algorithm that combined diagnosis codes with medication use and a code for an upper GI procedure improved sensitivity to 73% [27]. Rheumatologic diagnoses are non-specific, but specificity can be improved when combined with treatment data regarding medications that are used for rheumatologic conditions [28, 29].

8.3.3 Direct Examination

Chronic health conditions can also be assessed using direct examination or interview-based assessments that have been validated against a clinical diagnosis. Dementia and depression are very difficult to assess adequately from medical records or administrative data. They are also difficult to ascertain by self-report, and thus they are most often assessed by direct examination using standardized interview-based testing. Dementia is probably more often recognized today than it was in the past, but it is still difficult to ascertain for many reasons. The cognitive impairment in early stages of dementia may not be recognized by the patient or family until it becomes more advanced, and it is often not acknowledged in the medical record. Patients who have frank dementia are unlikely to volunteer for research that is not explicitly targeted at dementia treatment, which partially explains why dementia tends to be underrepresented in epidemiologic studies. For these reasons, many clinical and field studies incorporate a cognitive assessment to screen for dementia into their baseline examination. Currently, studies in the United States most commonly use either the traditional 30-point Mini-Mental State Examination [30] or the modified 100-point version [31]. Both have cut points that have been validated against the clinical diagnosis of dementia and have been normed for different ethnic groups.

Depression is a common mood disorder that is exacerbated by poor health and disability. Self-reported diagnoses may be very specific, but there is substantial underreporting in older adults [32]. A history of depression may be underreported due to concerns about confidentiality or due to past under-diagnosis of depression. Medical records for mental health conditions are under strict regulations for release due to confidentiality. Several symptom scales have been developed for use in epidemiologic studies to complement patient health history. The Centers for the Epidemiologic Study of Depression (CES-D) scale was not specifically designed for older adults, but it has been well validated against clinical diagnosis across a range of ages, which

enables the comparison of scores and rates of high scores between older and younger populations [33]. Another commonly used scale, the Geriatric Depression Scale [34], has the advantages of simpler item scoring (yes vs. no compared to the ordinal scale of the CES-D) and a focus on the psychological as opposed to the somatic symptoms of depression. The items were chosen due to their specific relevance for older adults. Antidepressant medication use is non-specific for a depression diagnosis because many antidepressants are used for other problems such as neuropathy and other pain syndromes, sleep disorders and anxiety disorders. However, antidepressant medication use can be used to add specificity to self-reported diagnoses of depression and to account for changes in symptomatology.

8.4 Comorbidity Indices

An index for comorbidity provides a summary measure of disease burden on an ordinal scale. Such a scale can be a simple tally of the number of conditions or it could be based on items that are weighted for severity or weighted based on associations with mortality. Some indices are designed for clinical patient care, while others are designed for health service research or for research into the causes of disability. We will review the most frequently encountered indices in research, which have been more fully critiqued in several reviews [4, 35].

The most common approach to comorbidity assessment is to simply tally or count the total number of conditions. The choice of which conditions to include varies widely. Some studies include as few as five conditions [36] while others include more than 50 [4]. The choice of which to include may vary depending on the outcome of interest. For example, a given condition may differ in its associations with disability vs. associations with mortality risk. Arthritis is the condition most strongly associated with disability while cancer is most strongly associated with mortality, so the choice of these two conditions and the weighting will depend on whether disability or mortality is more important in the research question. Most indices have been validated against mortality; this would explain the exclusion of non-fatal but disabling conditions such as arthritis from many indices of comorbidity.

The resulting count of conditions forms an ordinal scale, though it might be analyzed as if it were a continuous variable. The scale will often be skewed to lower values, but it will have a long tail to the right as the number of conditions increases. A very healthy population may include many individuals who have no conditions or only one condition, and few individuals who have two or more conditions. However, typical older populations will have many more individuals who have three, four or five or more conditions. Depending on the population, scores often need to be collapsed into categorical groups (such as none vs. 1–2 vs. ≥3 conditions) for analysis. The advantages of this simple tally method include being easy to understand and easy to replicate. The method uses primarily self-reported data, and thus lends itself to epidemiologic studies more readily than do methods that require hospital records. The disadvantages include an assumption that all conditions have an equal contribution to the outcome or outcomes and that there is no overlap or interaction between conditions. Additionally, tally methods do not account for the duration or severity of the condition.

One of the best known indices for comorbidity is the Charlson index [37]. This index was developed for a study of mortality in a group of hospitalized patients in which the presence of other health conditions might confound an association with mortality. Conditions were abstracted from hospital records and weights were developed for each of 19 conditions based on associations with 1-year mortality rates. After weights were assigned to each condition, the scores were summed. A global rating of severity was also used to stratify participants, which showed that the index could discriminate risk within each stratum. The index remained predictive of mortality even after adjusting for demographics and the physicians' global assessment. Numerous studies that are based on hospital records have used this index. Its strengths include the weighting of conditions according to explicit criteria and

the index's validation in numerous settings as a predictor of mortality. The limitations include requiring access to hospital records along with a physician review of records to extract information about severity, treatment and prognosis. Additionally, the index was not designed to be used in community-dwelling older adults and has not been validated as a predictor of disability.

The Cumulative Illness Rating Scale is another comorbidity scale that was developed for hospitalized patients. It assesses 13 systems rather than diagnoses and weights them based on clinical judgment using a 0–5 scale according to whether there is a life-threatening impairment. This scale has been validated against autopsy and has been compared to chart review. It has been used on many different aging populations, including long-term-care patients. Because it requires a clinical assessment, its use has been limited to the inpatient setting and it does not translate well to the setting of an epidemiologic study.

The Duke Severity of Illness Scale was one of the first scales to be developed for the ambulatory care setting. It attempts to quantify severity in a standardized fashion, based on medical record review. The scale is very clinically oriented, incorporating symptoms, treatment and prognosis. It therefore requires clinician administration.

The Index of Coexistent Diseases is another index derived from medical records. It assesses two dimensions: severity for a list of 14 categories of chronic disease and functional impact caused by the particular condition. The index is similar to the Charlson index with regard to the severity dimension. Many investigators prefer to uncouple comorbidity assessment from disability assessment and to not assume attribution as this scale requires.

The Deyo index [22] was adapted from the Charlson index for use with an administrative database. Two indices were compared, one based on comorbidity ascertained over a year's time and another based on only an index hospitalization. Both were comparable and yielded expected associations with mortality, nursing home admission, length of stay and cost. Specific ICD-ninth revision (ICD-9) codes that correspond to clinical diagnoses were provided for use in future studies.

Several derivations of the Deyo index have been developed for use with administrative data, including modifications for later versions of ICD codes [38]. Over time, changes in health outcomes and in the natural history of some conditions could impact prior validation of these older indices. An updated index was constructed using administrative data from Canada, and a study validated the scale in France, Japan and New Zealand [39]. The study found that fewer (12 vs. 19) conditions were needed to accurately predict mortality and that the weights of the conditions shifted. Consistent with improvement in prognosis, the updated weights were lower for diabetes, renal disease and AIDS/HIV but were higher for congestive heart failure, dementia and liver disease. The study authors hypothesized that the increases in weights for these conditions could reflect the aging of the population and also the greater severity of disease in hospitalized patients.

Comorbidity has also been combined with data on physical function to create weighted predictive indices for both short-term and long-term mortality. One index was developed in hospitalized older adults based on six factors: male sex, activities of daily living (ADL) dependency, cancer, congestive heart failure, creatinine and low albumin, and was validated in a second cohort. Notably, diseases were not weighted and functional status was one of the most important predictors of mortality [40]. In the Health and Retirement Survey, Lee et al. [41] developed a combined index of morbidity and disability to predict 4-year mortality. Twelve variables, including six comorbid conditions and four functional variables, were weighted and the summary score was validated in another cohort. Together these studies emphasize that function and comorbidity provide complementary information to predict mortality.

8.5 Associations of Comorbidity and Comorbidity Clusters with Disability

Comorbidity is strongly associated with disability. Cross-sectionally, there is a clear dose-response relationship. There is a stepwise increase

in the proportion of individuals who have self-reported difficulty in ADLs according to the number of conditions [42]. Prospectively, the number of comorbid conditions also predicts future disability. In the Established Populations of the Epidemiologic Study of the Elderly, the increase in the risk of mobility loss in both men and women ranged from about 1.5 times greater for one condition to three times greater for ≥4 conditions [43].

In an Italian cohort with a mean age of 85 years, Cesari at al. [44] found a strong relationship between comorbidity and performance-based measures of physical function. About one-third of participants reported ≥3 chronic conditions. Those with comorbidity had a slower gait speed and a lower short portable performance battery score. In older adults, disability is most often due to chronic and progressive health conditions, thus disability itself is sometimes used as an indicator for the burden of comorbidity. Studies like this lend support to this concept, though as noted previously, disability and comorbidity can be complementary in their predictive value. Therefore, disability and comorbidity should not be considered as equivalent constructs.

Despite the interest in comorbidity and disability, relatively little work has been done to examine how combinations of diseases distribute within individuals or how they might interact. Based on a medical records review, Marengoni et al. [45] used several different approaches to determine how conditions grouped together within individuals. Most conditions occurred with at least one other comorbid condition. Heart failure occurred rarely without comorbidity, while dementia occurred with no other comorbid conditions about one-third of the time. Cluster analysis revealed five clusters, though often these clusters included diseases already known to be related (vascular grouping), known to be connected through a common risk factor (smoking for lung disease and heart disease) or the cluster included one disease and its consequences (diabetes and visual impairment). The clustering of dementia, depression and hip fracture suggested that individuals who have one of these conditions are at a higher risk for other conditions in the same cluster than they are for conditions outside of the cluster. This interesting approach to defining patterns of disease should be pursued to determine whether there are interactions between conditions that result in higher risk than would be expected for each condition individually.

Such an analysis was conducted in the Longitudinal Aging Study – Amsterdam (LASA), in which 2,497 adults were examined to determine the combined influence of multiple chronic diseases on physical functioning [35]. An index of comorbidity was examined, along with individual conditions and combinations of conditions. Overall, a greater decline in physical function was noted in individuals who had a higher number of conditions at the baseline examination. The odds ratio for one condition vs. no conditions was 1.58, and this increased to 4.05 for ≥3 conditions. The study found two important combinations of conditions: arthritis and diabetes or cancer, and stroke and lung disease or cancer. A negative interaction was also found in which the effect of diabetes was weaker than expected in the presence of stroke, cancer, heart disease or peripheral arterial disease. This finding is probably due to the overlap between diabetes and these conditions (Fig. 8.3) since diabetes is a strong risk factor for all vascular diseases, and obesity (which is common in those with diabetes) is a risk factor for several common cancers.

This last study illustrates an important limitation of comorbidity indices. Conditions are considered to be independent of each other, when in fact some conditions are more closely related than others. In the example above, diabetes would not be expected to add more risk when its risk has already been expressed through the onset of cardiovascular complication. Nevertheless, many indices do not take overlap into account, and instead count each condition as independent.

8.6 Subclinical Chronic Disease – A Physiologic Index of Comorbidity

Non-invasive testing that was developed for clinical diagnosis has been used in epidemiologic studies of asymptomatic individuals, and these studies have demonstrated that many diseases

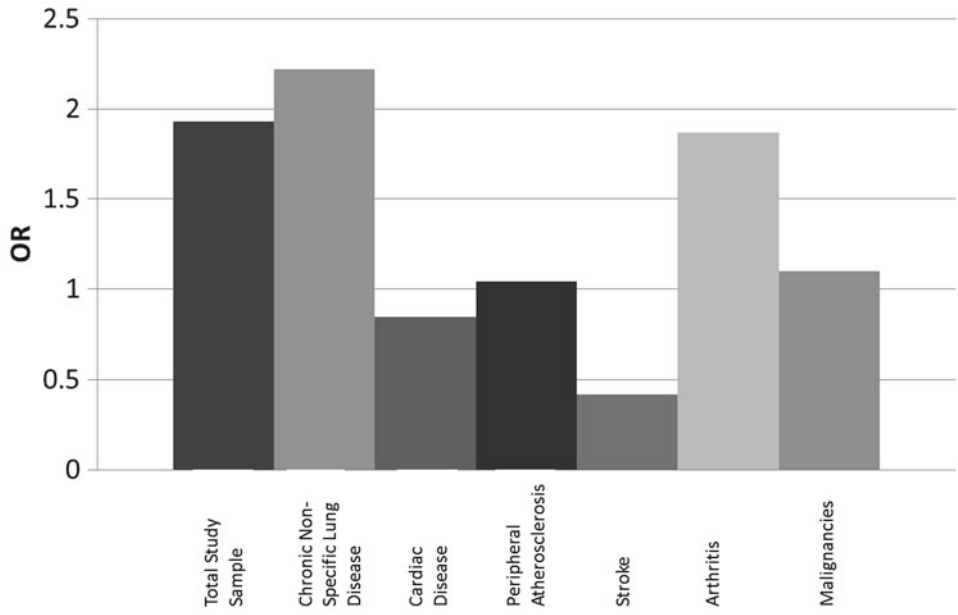

Fig. 8.3 Association of diabetes with decline in physical function by selected comorbid conditions [36]

can be detected many years before the onset of clinical symptoms. As previously discussed, individuals with established disease and with multiple diseases are at a very high risk for mortality and disability. What is less well recognized is that an undiagnosed individual can carry the same degree of disease on testing as an individual who has a diagnosed disease. Individuals who have a high degree of disease on testing are usually at a very high risk for clinical events, in spite of a lack of symptoms. Older adults who have no apparent clinical disease are still at a very high risk for poor health outcomes due, in part, to the extent of subclinical or undiagnosed disease. This phenomenon has been documented for several conditions, such as carotid artery disease, coronary artery disease and osteoporosis.

The Cardiovascular Health Study is notable for conducting fairly extensive non-invasive testing and imaging, not only of cardiovascular disease but also of other systems and conditions. Tests conducted over time included brain MRI, bone density scanning and spirometry. Using a set of five tests that were conducted at the same examination year, we were able to show that there is a continuum of abnormality in each of five systems (pulmonary, carotid, brain, kidney and metabolism [glucose]) [9]. When using these tests, there were very few individuals who had minimal disease in all five systems. We ranked each system as low (0), medium (1) or high (2), and summed the scores for the five systems on a 0–10 scale. We then compared those with minimal subclinical disease (0) to those with a high level of disease (10) and were able to show a 20-fold gradient in disease risk. A traditional comorbidity tally in this same group was able to identify those at high absolute risk, but could not distinguish those at average risk from those at very low risk with very minimal disease (Fig. 8.4). This physiologic index of comorbidity was able to explain about 40% of the effect of age on mortality, and as a single factor it was a stronger predictor of mortality than age itself. This study shows the potential for understanding disease burden and its impact at a subclinical level using non-invasive testing to define comorbidity.

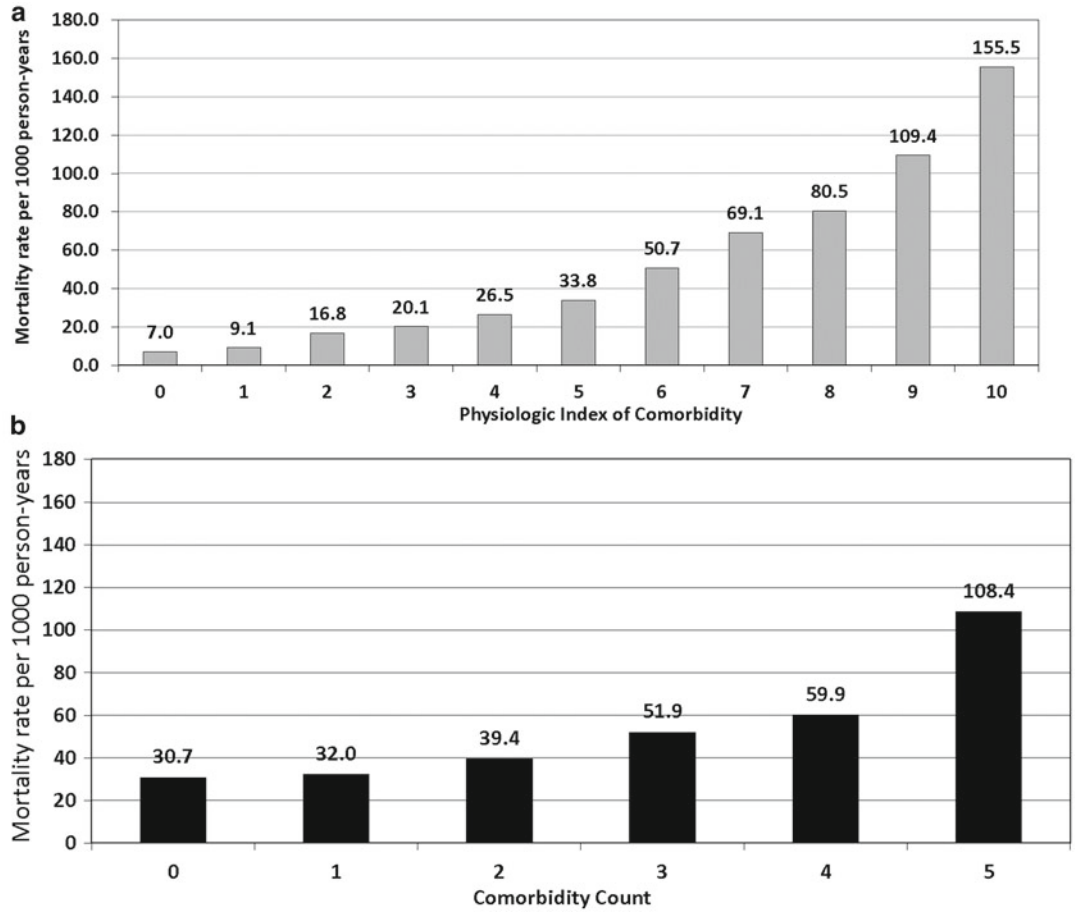

Fig. 8.4 Physiologic index of comorbidity [9]

8.7 Comorbidity and Frailty

Comorbidity is sometimes equated with the presence of frailty. Though they differ conceptually, they are overlapping constructs, just as comorbidity and disability overlap (Fig. 8.5) [46]. In the CHS study, frailty was defined as a clinical syndrome of vulnerability that is characterized by slow gait speed, low strength, low physical activity, low energy and weight loss. In a comparison of frailty to subclinical comorbidity in the CHS cohort, we were able to show that these two constructs are more closely associated than when only diagnosed disease is considered [47]. These studies reveal the importance of subclinical disease in explaining frailty.

8.8 Analytic Issues

There are several key issues to understand when analyzing comorbidity data. The main reason for using a comorbidity index is for analytic efficiency, especially when sample size and power are limited. If sample size allows, the analysis of each condition and their interactions can yield more insight into the pathways of the associations involved. Whether it is considered as a single variable or as individual conditions, comorbidity may be used in an analysis as an exposure, an outcome, a confounder or an effect modifier [48]. Because it is an imperfect measure of disease burden, some misclassification is to be expected.

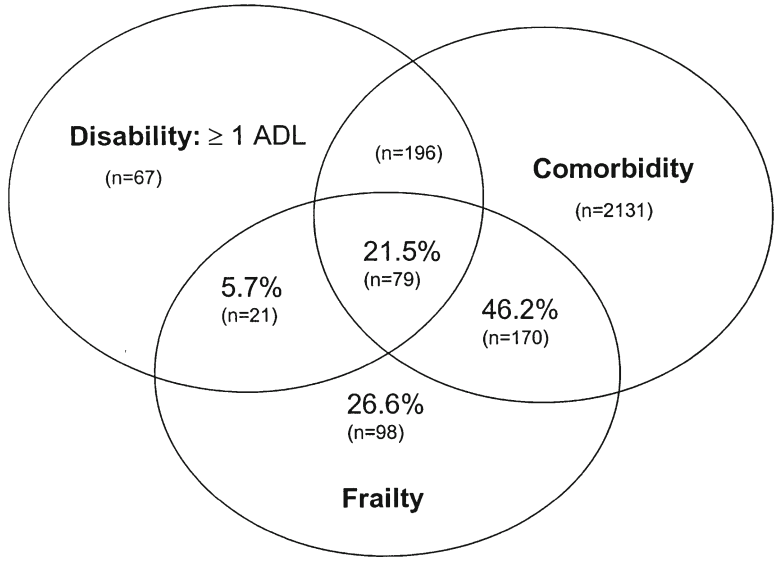

Fig. 8.5 Venn diagram displaying the extent of overlap of frailty with ADL disability and comorbidity (>2 diseases) [46] (Abbreviation: *ADL* activity of daily living). With permission Fried LP, et al. 2001, J Gerontol A Biol Sci Med Sci [46]

When comorbidity is examined as a confounder, it is likely that its effect is underestimated, and thus its relative risk would tend to be biased toward the null. The more common the condition, the greater its effect on confounding and the more important it is that the condition be measured as accurately as possible. Conversely, rare conditions usually have less impact as confounders, unless the effect is very strong.

It can be difficult to know how comorbidity is playing a role in a causal pathway because some conditions may precede, be concurrent with or postdate the outcome of interest in an analysis. A causal diagram should be drawn and consideration given to these temporal relationships when interpreting the analysis. Though the analysis of confounders and mediators may be mathematically equivalent, it may become apparent from considering the biological pathway that the comorbidity should be interpreted as a mediator rather than a confounder of the association of interest.

A modifier is a variable that impacts the strength of the association. In the case of comorbidity, it is possible that the association of interest might be quantitatively or qualitatively different in the presence or absence of comorbidity. When testing a therapy, there may be an effect in those with little comorbidity that is not seen in those with greater comorbidity. Due to misclassification, it is possible that an interaction may appear when not really present or it may be present but not be detectable.

Comorbidity can be considered as an exposure, and measurement error will usually bias associations toward the null. If errors in assessing comorbidity are correlated with the errors in assessing outcomes, it is possible that false correlations could be detected. This can be avoided by assessing exposure and outcome using different classification methods (e.g., self-report vs. record-based). When comorbidity is considered to be an outcome, it is recommended that it be used as a dichotomous or categorical variable. A high threshold should be adopted to increase specificity and decrease bias. In addition, comorbidity should be assessed independently of other variables in the study.

8.9 Summary

Over the past 25–30 years, the importance of comorbidity has become well established in the epidemiology of aging. A number of methods

are available for assessing comorbidity and understanding its impact. Studies have found that comorbidity (both clinical and subclinical) is associated with greater disability in older adults. The field would benefit from further methodical development and more detailed exploration into the co-occurrences and interactions between conditions. Key questions include:

1. Which conditions are critical to assess in an epidemiological study?
2. Which algorithms are best for combining data to define prevalent chronic health conditions?
3. To what extent should non-invasive testing be incorporated into defining prevalent diseases?
4. How do conditions cluster or co-occur in individuals?
5. Are there major interactions between conditions and what is the impact of morbidity and mortality?
6. How do interventions impact the comorbid conditions as well as the target condition?

More work in these areas will be useful for developing better preventive approaches in older adults. Given that fewer than 25% of older adults are free of any diagnosed chronic disease and fewer still will be found to be healthy if fully examined for subclinical disease, targeting any one condition is not likely to have a substantial impact on reducing morbidity and mortality. New approaches are needed that better define patterns and combinations of diseases, and methods for targeting multiple risk factors for multiple chronic conditions will be needed to make further progress in improving the health of older adults.

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Measurement of Social Factors in Aging Research

9

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Abstract

This chapter presents measurement and methodological issues regarding four social factors that are important in epidemiologic research on aging. These factors are socioeconomic status (income, education and occupation), living arrangement, caregiving status and widowhood. They were selected because they influence health outcomes in older adults. These factors may be dynamic over the life course, particularly during old age, which has implications for their measurement, study design, and interpretation of associations with health outcomes. In this chapter we also reviewed five general measurement and methodological issues that are common to these factors: consideration of the factor from a life-course perspective, cohort effects, influence of prior health status, changes in the factor over time, and choice of comparison groups. For each factor, we present data to illustrate its importance in epidemiologic studies of older populations, describe different approaches to its measurement and their advantages and limitations, summarize its associations with health outcomes, and discuss implications of measurement and methodological decisions. We also address specific methodologic issues such as study design, sampling, and confounding that are unique to individual factors.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Health outcomes • Care giving • Stress • Sociodemographic factors • Depression • Education

Abbreviations

ADL	Activities of Daily Living
IADL	Instrumental Activities of Daily Living
Il-6	Interleukin-6
LSOA	Longitudinal Study of Aging

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SES Socioeconomic Status
SOF Study of Osteoporotic Fractures
US United States

9.1 Introduction

Social factors are increasingly viewed as independent risk factors for physical and psychological health outcomes in older adults. This chapter will cover four social factors that are relevant to epidemiologic studies of older adults: socioeconomic status (income, education and occupation), living arrangement, caregiving status and widowhood. This chapter will address general measurement and methodological issues that apply to all of these factors, as well as specific issues that apply to individual factors. The sections on each factor will (1) address the importance of the factor for health outcomes in older adults; (2) describe ways that the factor is measured and their meanings; (3) summarize the factor's associations with health outcomes; and (4) discuss the implications of measurement and methodological considerations, with examples from selected studies.

9.2 General Measurement and Methodological Issues

The social factors reviewed in this chapter are complex and dynamic. All influence risk of many health outcomes, and in turn, are affected by current and prior health status. They interact with each other and may modify another factor's associations with health outcomes (e.g., caregiving appears to modify the short-term psychological effects of widowhood). Importantly, these factors may be thought of as life exposures. They change across the life course and, as a result, may have different effects on health outcomes in different age groups. Investigators must consider these aspects of social factors when deciding on study designs and measures for evaluating their impact on health outcomes. This chapter will review five considerations that investigators may face when measuring social factors: (1) social factors from a life-course perspective, (2) cohort effects, (3) the influence of prior health status, (4) changes in a factor over time, and (5) choice of comparison group.

9.2.1 Social Factors from a Life-Course Perspective

It has long been acknowledged that childhood social circumstances, such as poverty or the loss of a parent, affect health in adulthood. A life-course approach conceptualizes exposures from early life through late life as having cumulative, long-term and interrelated effects on physical and mental health outcomes. This approach posits that biological, physical and social exposures that individuals experience prenatally, during childhood and during young adulthood will have meaningful effects on their morbidity and mortality in later years.

Measuring the effects of social factors across the life course is inherently difficult in studies of aging because there are two temporal relationships between the social factor of interest and the health outcome: current and past. In most epidemiologic studies, current status is measured at the time of the interview, whether the factor is a sociodemographic variable such as income or a health measure such as perceived health status. However, current status does not necessarily capture the nuances of the relationship between a social factor and incident health outcomes. The past status of the factor may play a critical role in this pathway as well. The assessment at a single point in time may miss large deviations that occur during a person's lifetime.

Occupation provides an example of the contrast between a current assessment and a life-course approach. An older individual's current occupation may not be an accurate measure of the social, physical and psychosocial exposures that the individual has experienced throughout his or her employment. Older adults are more likely to be retired or to have changed to a less strenuous or demanding occupation in later life. An evaluation of current occupational status may miss the past physical and psychosocial stressors that influence current disease status. Several studies have suggested that the most accurate measure

of occupational exposure is not an individual's current occupation, but the longest-held occupation [1]. Alternatively, asking about "previous occupation" may be a more accurate measure than asking about "current occupation" since "previous occupation" is often aligned with an older adult's longest-held occupation.

Some challenges of measuring the life-course effects of social factors in older adults are inherent to the epidemiologic study design. Few studies are able to follow a cohort from conception or early life through to older age with repeated measures of the social factors and disease conditions that are relevant to older adults. Since eligibility criteria for epidemiologic studies of older adults usually target those who are well past the time when occupational exposures occurred, participant recall of the period spent in these occupations or of the types of exposures encountered in these occupations may be incomplete or inaccurate, which may lead to biased or missing data. This, in turn, may reduce the validity of associations between these factors and health outcomes. The work associated with the participant's occupation may also change over time (e.g., become more automated and less physically challenging). It is difficult to capture these changes in an epidemiologic study.

To overcome these challenges, investigators may use union records or other public documents (e.g., tax records, census data, birth certificates) in addition to the respondent's self-report. Another method is using life event history calendars that prompt participants to orient to particular personal events (e.g., the year they got married) or historic events (e.g., the election of a president) and report their social factor at those times. Following existing cohorts that have data collected at time points throughout adulthood would handle problems of inaccurate recall and also allow investigators to compare the effects of prior, current and long-term social factors on health outcomes as the cohort ages.

9.2.2 Cohort Effects

There are important biological, psychological, societal and environmental differences between groups that are related by time of birth. Cohort effects, brought about by environmental and societal changes over time, not only result in generational differences in physical and psychological health profiles, but also inform social factors. These effects are particularly pronounced in older age groups that have experienced many years of environmental and societal changes. Birth cohorts are an important consideration when studying older adults due to the variability in exposure status by generation. Individuals born during the same period are more likely to experience similar exposures than are those born in different periods. Moreover, the relationship between a social factor and health outcomes may differ across birth cohorts due to changes in the salience of that factor (e.g., the health disadvantage of low education), government policies on preventive care or other health-related factors.

In order to determine whether a phenomenon is the result of a cohort effect, the researcher must tease apart the effects of an individual's age at a particular time point, the time point when the measurement occurred, and the individual's birth cohort. Age effects are common to all individuals and are a natural result of the development and senescence that individuals experience. Period effects are due to population-wide exposures to environment and societal phenomena that arise at a particular point in time. A cohort effect can be thought of as a period effect that differs between age groups, or as the interaction between age and time. A cohort effect may be an effect modifier of the relationship between social factors and health outcomes.

Cohort effects are not the result of the year of birth, but rather of the unique situation that the individuals of the cohort were born into since the characteristics of social factors during a specific period may be different from those of other periods. One example of a social factor that has changed over time is educational attainment. Due to social and economic changes, the proportion of individuals who graduated from high school and college in the United States (US) has increased dramatically over the twentieth century. Of US adults born in the early part of the twentieth century, fewer than 25% attended college. By the time those born in the 1940s reached adulthood, almost 50% had attended college [2].

9.2.3 The Influence of Prior Health Status

Prior health status can influence the relationship of social factors to health outcomes in two ways. First, it may introduce a selection bias into a study. As with any epidemiologic investigation, the individuals who are included in a study sample may be systematically different from those who are not included. Non-participation has been shown to be related to age and to factors associated with age, such as poor health status [3]. Social factors, such as low socioeconomic status, are associated with higher rates of mortality at younger ages. Thus, adults who survive lifelong hardship and live to old age may be constitutionally heartier than those who do not survive. This selective survival of older adults who survived socioeconomic hardship may lead to underestimates of the associations between lifelong low socioeconomic status and health outcomes when compared to older adults of higher socioeconomic status. The increased mortality of those of low socioeconomic status may also lead to a smaller proportion of these individuals being included in epidemiologic studies of older adults compared to those of higher socioeconomic status.

The second way that prior health status can influence the relationship of social factors to health outcomes is that health status may influence social factors, such as living arrangement. Older adults whose health is declining or who suffer a fall or fracture may move to live with their adult children or move to a nursing home or assisted living facility. Thus, comparisons of current living arrangement with health outcomes may be confounded by prior health conditions (e.g., falls) that may not be assessed in a study.

9.2.4 Changes in a Factor Over Time

While some social factors (e.g., educational attainment) remain generally constant throughout adulthood and old age, others may change in later years or over the duration of a study. Income and occupation may vary throughout adulthood, but remain fairly stable in older age. Therefore, investigators must decide whether the exposure of interest is income or occupation at the beginning of the study period, or over the course of adulthood. In contrast, marital status and caregiving status are more likely to change over time in older adults than in younger adults. There appear to be different short- and long-term health effects of becoming widowed, and of beginning and ceasing caregiving. Thus, it is important to document the timing of these transitions; otherwise investigators may overlook their more severe, short-term impact on health.

9.2.5 Choice of Comparison Group

Choosing a relevant comparison group is vital for minimizing the possible confounding or bias of the association between some social factors and health outcomes. Some comparison groups may not truly reflect the "counterfactual experience" to the social factor of interest (i.e., provide the risk of the health outcome that the exposed group would have had if they were not exposed, all other things being equal). Comparison groups may combine the social factor with other factors, thus precluding the ability to isolate the effect of the social factor on health outcomes. This point is illustrated in studies that assess mortality or disease incidence in caregivers to a spouse with a condition (e.g., dementia) compared to married non-caregivers. The rationale for comparing these two groups is that the sampling design controls for marital status, so it does not confound the results. However, spouse caregivers have significantly more stress than do caregivers to other relatives and being married confers a health advantage to older adults. Thus, investigators observe higher rates of mortality in married caregivers versus married non-caregivers if there is no control for differences in stress level. When these studies adjust for stress levels, caregiving is no longer associated with poorer health outcomes [4].

The comparison group is also a consideration when studying the health effects of transitions in social factors, such as entering retirement or becoming widowed. It is important to compare participant health status prior to the transition to their health status following the transition.

However, predisposing health and psychosocial factors may differ in participants who experience these transitions compared to those who do not. Thus, to determine the impact of the transition on health, investigators should also measure health changes over the same period among participants who do not transition, and compare changes in these two groups.

9.3 Discussion of Specific Factors

9.3.1 Income

Annual household or individual income is regularly used as a measure in epidemiologic studies for two main reasons: income determines access to social and health resources and it is a marker of social status and poverty level. Income varies across older adults due to a variety of demographic factors. US Census data show a dramatic decrease over the years in the proportion of older adults whose annual income falls below the poverty level, from 35% in 1959 to 10% in 2007 [5]. Income levels in older adults vary by gender, age and race, so these demographic factors may be confounders of associations between income and health outcomes. Income is also subject to both forward- and reverse-causation with regard to health outcomes [6]; low income increases exposure to health risks while illness reduces earning capacity.

Income information is commonly collected via self-report, though recent studies have instead used area-wide indicators of income such as neighborhood and census-tract level data. Self-report measures may reflect either individual or household income. In these cases, respondents are generally asked to indicate a category that best represents their income level. If household income is reported, the number of persons living in that household is collected as well. In addition to personal and household income, individual-level income measures can include measures of existing wealth, net income or disposable income. Area-wide income measures may include, among others, measures of median household income, percentage of people below the poverty line, or the median value of owner-occupied housing units [7].

Lower income is consistently associated with an increased risk of health decline and mortality. Among all of the socioeconomic predictors of mortality, including education and occupation, income is the strongest predictor of mortality [8]. Lower income is also a robust indicator of poorer self-rated health. A study that utilized both US Census data and data from three population-based studies (the Coronary Artery Disease Risk Development in Young Adults Study, the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study) found correlations between several related income-based measures, including pre-tax income, individual monthly income, and household income without considering the number of household members [9]. These data suggest that a number of different individual- and area-level indicators of income will be sufficient when evaluating the association of income with health outcomes. Still, while area-level socioeconomic data predicts negative health outcomes such as depressive symptoms and self-rated health in older adults, individual-level data may play a stronger role in this relationship, especially over time [10].

Like most social factors, income exhibits cumulative effects over time, so its relationship with health outcomes may be more nuanced than a simple cross-sectional association. Income is sensitive to life events that occur most frequently in older adults, such as retirement, death of a household member and eligibility for social support services. Some studies have found no association between higher income at older ages and better health outcomes [11]. As such, current income may not be as valuable a predictor of current health status in the elderly since changes in income levels over the life course will significantly impact other social factors that, in turn, will affect health status [12].

There is evidence that income may be a better indicator of an individual's wealth, instead of an indicator of one's access to resources [13]. This is an important consideration in studies of older adults, who generally have lower income and greater wealth [8]. Wealth is the result of assets and economic reserves that are acquired over the life course, and it may be less likely to be affected by reverse-causation than is income [8].

The potential limitations of measuring income include non-response and incorrect response of self-reported measures, as well as incorrect classification of individual-level income when using area-level measures. The rates of non-response for self-reported income range from 10 to 25% [14], which is higher than the non-response to most other social factor measures. The sensitivity of income information contributes to these high rates of non-response, as do respondent characteristics such as age, health status and income level. Participant non-response to income measures significantly increases with age, which may reduce the validity of the associations between income and health outcomes [14]. The method of data collection also influences response rates of income measures. For example, telephone surveys elicit more complete responses on income than do mailed surveys, and less specific questions (e.g., asking the respondent to select a category of income level) have higher response rates than those that ask respondents to report their actual income [14].

Regarding the incorrect classification of individual-level income when using area-level measures, self-reported income is usually divided into categories of income ranges into which the respondent self-selects. While this may lead to a higher response rate than if respondents were asked to report a specific amount of income, there is no standard system of categorizing income ranges. Frequently, the ranges are based on the expected distribution of income in a study sample, and are further condensed into "lower" or "higher" income levels for analysis. The implication is that participants who fall into the "low" income group in some studies may fall into the "high" income group in others, making the association between a particular annual income amount and a health outcome difficult to compare across studies.

When household income is used instead of individual income, it is necessary to adjust for family size to allow for comparisons across households. Other indicators of low income (e.g., difficulty paying for necessities such as rent and heat) may be more useful than simply assessing monetary household income. Similarly, poverty and affluence indicators, based on relative household income in comparison to neighborhood income, can be created from household-level data coupled with census data. Economic data may also be gleaned from tax records and other relevant documents. While these sources may be the most reliable sources of income data, they are difficult to obtain [8, 12]. The major limitation of area-level data on income is the incorrect classification of individual-level income when using area-level measures. This is known as the ecological fallacy. Since there is generally variation in income level within a geographic region, assigning a single value to all persons who live in a specific area will misclassify some individuals. As a result, the associations between regional-level mean income and health outcomes may be different from the true associations based on individual-level income.

9.3.2 Education

Compared to the variable nature of income and occupation, educational attainment tends to be set early in the life course and reflects social and economic resources at younger ages. Education is a common marker of socioeconomic status because it is correlated with other social factors such as income and employment, and it is also associated with better health in cross-sectional and prospective studies [15]. Historically, educational attainment has been inversely associated with older age, but that gap is decreasing. Between 1965 and 2008, the proportion of older adults who were high school graduates rose from 24 to 77%, and the proportion who had graduated from college rose from 5 to 21% [5].

Educational attainment is usually measured on a continuous or ordinal scale, is not subject to inaccurate recall and has a high response rate [16]. Continuous measures capture the number of years of education, while ordinal measures group individuals by the type of education they have completed (i.e., grade school only, attended but did not graduate from high school, completed high school, attended college, completed college, post-graduate education). One consideration when using this method of measurement is that the number of years of education may not represent

quality of education, and quality of education is likely associated with other social factors, particularly socioeconomic status on the individual and neighborhood level and region of country.

Lower education is generally associated with poorer psychological and physical health outcomes. However, the effect of education on health status appears to differ across the life course and by demographic characteristics. Research has shown that while self-rated health declines with age, it declines more rapidly for those with lower levels of educational attainment [17].

There are cohort effects of education as well due to changes in the social and economic benefits of higher education over time [16]. Older generations are less well-educated than younger generations, so individuals of older generations may comprise a larger proportion of groups categorized as "less educated". In addition, cohort effects must be taken into account when examining the association between education and age [18]. As social norms have changed and advanced schooling has become more attainable, especially for women and minorities, a greater percentage of US adults has completed high school and obtained higher education. Thus, the cutpoints for "low" or "high" education will differ for populations of older adults who reached adulthood in the 1930s or 1940s compared to those who reached adulthood in the late twentieth century, and compared to those who are reaching adulthood today. Further, because fewer older adults have attained higher levels of education, there is potentially reduced variability of this social factor in the current older populations [19], and those who have attained advanced education may be systematically different from those who have not. The failure to take age and cohort into account when measuring and evaluating education level may result in confounding.

Educational attainment may also be subject to biases of selective survival. While the risk of morbidity and mortality increases with age for all education levels, the differential risk of incident chronic conditions and functional impairment across education levels is reduced at older ages [20]. Health differences by educational attainment tend to remain constant or increase slightly through younger old age, then begin decreasing among adults in their 70s. Still, selective survival may only describe part of this changing relationship between education and health outcomes. Older individuals may be more likely to have access to health services, such as Medicare, which can equalize the effects of educational attainment on morbidity and mortality.

9.3.3 Occupation

Occupational status in older adults is related to the physical and cognitive ability to work, as well as necessity, yet the effects of occupation on health outcomes reflect not only current occupational status but experience over the life course. US Census data show that a moderate proportion of older adults are currently employed: in 2008, 36% of men and 26% of women who were 65–69 years of age were currently employed, as were 15% of men and 8% of women who were 70 years of age or older [5]. Working conditions—including amount and intensity of physical labor, exposure to environmental toxins or dangerous conditions, and quality of social relationships—will necessarily inform an individual's health status both during and beyond the employment time period. Since individuals frequently work for decades over the life-course, the cumulative exposure to these conditions will have measurable effects on health in later life.

As a result of these varied exposures, occupation has an impact on an individual's health status beyond access to income and socioeconomic resources. Employment frequently dictates access to health resources, affects social networks and exposes workers to physical conditions that directly influence health such as contact with pesticides and solvents, manual labor, excessive heat or noise, and stressful working conditions [1, 21]. Research suggests that individuals who are in low-paid, manual labor occupations report lower self-rated health than those in high-paid, skilled work occupations. Decline in self-rated health with increasing age is faster for these low-paid manual workers [22].

Occupation is measured in a variety of ways, depending on the population being studied. It may be a dichotomous variable such as employed versus non-employed, or may be a more specific categorical variable that measures current occupation, previous occupation or longest-held occupation. If the validity of self-reported occupation is questioned, employment records may be used. In occupational epidemiology studies, job employment calendars are used to track the time an individual was exposed to different substances. An important consideration when studying older adults is that women of this generation frequently report their occupation as "housewife", and by implication, it is really their husband's employment status that will influence their socioeconomic status.

Like other socioeconomic factors, the effects of occupation are cumulative across the life course. While employment status and type of employment have short-term health effects, many work-related exposures can have long-term consequences that may appear even after changes in employment or retirement [1]. In addition, the longer the exposure to negative working conditions, the greater is the decline in health status. As such, cross-sectional analyses may not fully reflect the association between occupation and health outcomes. It is important to evaluate career paths, previous occupation or longest-held occupation rather than examining occupation at a single point in time [21].

Participation in the workforce and type of occupation differ by gender, though this can partially be explained by differences in education attainment, especially in older adults [12, 23]. Men are more likely to hold jobs that are physically demanding, while women are more likely to hold jobs that are cognitively demanding [24]. The more education a worker has, the less physical labor is required at their job [24].

Evaluating occupation in older adults is problematic due to the high rate of employment changes in older age and the strong relationship between health and employment. Older adults may change jobs due to declining health, choose to stop working because they have reached retirement age, or begin volunteer work after being out of the workforce for some time. Moreover, classifying adults who do unpaid volunteer work as "not employed" may lead to potential misclassification since these adults may accrue similar health benefits from volunteering as do those who continue to work for pay, but they may not report themselves as such. Societal factors, including the state of the economy, unemployment rate and personal wealth, will necessarily influence when and whether an older adult has the option of retiring. Individuals tend to stay in the work force if their financial situation is not secure. In addition, the effects of retirement on health are different depending on the type of job held. For example, individuals who had more complex jobs experience a higher rate of decline in cognitive performance after retirement than do those who had less complex jobs [23].

9.3.4 Living Arrangement

Living arrangement among community-dwelling older adults is inextricably linked with family structure, marital status, financial resources, and past or present health conditions. There are striking gender differences in living arrangement among older adults. In 2008, 72% of older men lived with a spouse, 19% lived alone and 7% lived with other relatives. In contrast, 42% of older women lived with a spouse, 40% lived alone and 17% lived with other relatives [5]. Living arrangements, particularly living alone, have been associated with increased risk of depression, some physical health outcomes and nursing home placement. In contrast, living with a spouse has been shown to be protective against these outcomes. Living in long-term care facilities rather than in the community is associated with having more physical and cognitive impairments. Those who live in long-term care facilities are also more likely to be women, simply because women live longer than men.

Living arrangement is typically measured by self-report of the number of individuals in a respondent's household and the respondent's familial relationship to each individual. Area-based indicators of living arrangement, such as census-tract information, have also been used in recent studies. As with other social factors, living situation is

subject to change over time. Not only are current living arrangements important in predicting health outcomes, but changes in living arrangements are important as well. Meaningful life changes that frequently occur in older adulthood (e.g., widowhood, change in economic status, health decline) may result in changes in living situation. These factors may be confounders of the association between current living arrangement and health outcomes. Thus, when conducting prospective studies, investigators should measure living situation at each interview point in order to accurately determine the temporal relationships between living situation—or change in living situation—and health outcomes.

Because an older adult's current living arrangement may be intertwined with other psychosocial factors that affect health outcomes (e.g., gender, marital status, social support, socioeconomic status), confounding by these factors is a concern in studies of health outcomes. For example, the health effects of living with others may be confounded by age or health conditions, as those who live with non-spouses are more likely to have characteristics that are associated with negative health outcomes such as increased age, more chronic diseases and a higher rate of disability [25].

Relationships between living arrangement and health outcomes in older adults appear to differ by gender and ethnicity. Recent research suggests that Hispanic ethnicity is a strong mediator of the association between living alone and depressive symptoms, as living alone is associated with higher levels of depression in Hispanics but not in non-Hispanics [26]. Women also experience different health effects from their living situation, and changes in their living situation, than do men. Women have poorer health and mortality outcomes when living with others or transitioning to living alone than do men [25].

There is a complex relationship between living situation and cognitive and physical health outcomes, particularly for those who live alone. Older adults who live alone are more likely to exhibit characteristics that predispose them to symptoms of depression and anxiety, such as having been widowed. Men who live alone tend to have less robust social support systems, but women who live alone tend to have stronger external support systems than do women who live with spouses or other people. Living alone is associated with faster rates of cognitive decline among elderly men, and this decline is greater for those who have been living alone for longer periods of time, even when controlling for confounders such as medical conditions, depression and functional limitations [27]. Older women who live alone tend to experience no negative health consequences as a result, except those who already have significant physical limitations [28].

Living alone may have effects on health status that are independent from low levels of social support. The association between living alone and negative health outcomes may be mediated by differences in social support networks beyond the number of, and relationships between, people living in a single household [26]. For example, even when adjusting for social and health conditions, women who live alone have less functional decline than do women who are married or live with non-spouse others [28].

Transitions into and out of a particular living situation also have a significant effect on health outcomes beyond the living situation itself. Older adults who transition from living with others to living alone experience a greater increase in depressive symptoms over time compared to those who consistently live alone or with others [27]. Research suggests that the relationship between living situation transitions and negative health outcomes differ by gender. Among adults ≥70 years of age who participated in the 6 years of follow-up in the Longitudinal Study of Aging (LSOA), women who transitioned from living with a spouse to living with a non-spouse had decreased survival compared to women who did not experience a similar transition, while men were not negatively affected by the transition to living with a non-spouse [25].

These characteristics of living arrangements in older adults have consequences for the interpretation of study results. Specifically, selective survival may also play a role in the better health outcomes of those who live alone. Older adults who have lived alone from middle to older age, or who survived a transition to living alone, may be

heartier than those who are in other living arrangements. Studies that evaluate the relationship between living situation, transitions in living situation and health outcomes may shed light on this association.

9.3.5 Caregiving Status

Caregivers are generally defined as individuals who provide unpaid assistance or supervision with basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs) to a person who cannot perform these activities independently due to cognitive, physical or psychological impairments. According to the National Alliance for Caregiving, in 2009 there were an estimated 43.5 million adult caregivers to adults ≥50 years of age in the United States [29]. This number is expected to increase given the growth of the older population and the concomitant rise in the prevalence of Alzheimer's disease and other chronic conditions that require assistance with daily tasks. Approximately 25% of caregivers report that they are engaged in caregiving activities for at least 40 h/week, and the average duration of caregiving is 5 years [29]. Furthermore, caregivers consistently report higher levels of stress and burden than do non-caregivers [30], and show more dysregulation in stress-related biomarkers such as Interleukin-6 (Il-6). Major public health concerns are that the chronic stress of caregiving may impair caregivers' psychological and physical health, and may also compromise the care provided to the care recipient.

There is no standardized definition of caregiving for research purposes. Some studies categorize persons as caregivers if they provide assistance with ADL/IADL tasks, while others require that the caregiver be the primary person who provides such help. Still other studies define caregivers on the basis of their relationship to a person with a particular disease (e.g., caregivers to a spouse with dementia), regardless of whether they assist with ADL/IADL tasks. Studies that use the criteria of assisting with ADL/IADL tasks to define "caregivers" typically define "non-caregivers" as individuals who do not assist anyone with ADL/IADL tasks [4, 31]. This ensures that the same criteria are used for categorizing both caregivers and non-caregivers. It also enables investigators in longitudinal studies to document study participants who become caregivers, and those who cease caregiving. However, studies that define "caregiver" based on the relationship to the care recipient have greater challenges in identifying a comparison group of non-caregivers, and in distinguishing whether the association between caregiving and health outcomes is really due to care-related activities or to the impact of living with someone with a degenerative illness.

Systematic reviews conclude that caregiving increases psychological distress, but that its effect on physical health outcomes and mortality is uncertain [30]. Cross-sectional studies that compared physical health in caregivers and non-caregivers indicate that caregivers report poorer self-rated health and have higher levels of inflammatory markers and other biomarkers. These results are largely based on studies that compared caregivers to a spouse with Alzheimer's disease or dementia to married non-caregivers, and thus they may be confounded by differences in levels of stress or social support between the caregivers and non-caregivers. Some prospective studies have found increased rates of health decline and mortality among caregivers [31, 32], while others have found no difference or decreased rates of these outcomes among caregivers [4, 33]. The inconsistencies in these study results likely reflect several methodological differences: studies that found increased rates of mortality among caregivers compared spouse caregivers to married non-caregivers. These studies did not differentiate caregiving from stress, and they seldom separated out levels of caregiving intensity. Studies that found no difference or lower rates of mortality among caregivers tended to adjust for stress level [4], and separated high-intensity from low-intensity caregivers based on the number of ADLs/IADLs that they performed for the care recipient [4, 33].

The importance of including separate measures of caregiving status and perceived stress is borne out in our study of the health effects of caregiving among older women who were enrolled into the Study of Osteoporotic Fractures (SOF).

In the study, both caregivers and non-caregivers who had high stress levels had elevated rates of mortality over the first 3 years of follow-up compared to non-caregivers with low stress levels, whereas caregivers as a group had lower rates of mortality over the 8-year follow-up period. Furthermore, caregivers who performed more caregiving tasks (high-intensity) had significantly better physical functioning and experienced less decline in functioning over 2 years than did non-caregivers or caregivers who performed fewer tasks (low-intensity). In this study and others, we found that non-caregivers who become caregivers over the study period have better initial health status than non-caregivers who remain as non-caregivers, and that individuals who remain as caregivers have better health status than those who stop caregiving. Moreover, caregivers who cease caregiving due to the death of their care recipient experience significant drops in stress and depressive symptoms over the year following the death of their care recipient. Thus, these results suggest that (1) the effects of caregiving on psychological and physical health are mainly due to stress; (2) that while caregiving has adverse consequences on psychological status, these effects diminish once the stresses of caregiving are over; and (3) that the relationship between caregiving intensity and better physical health may reflect the fact that better physical health enables older caregivers to take on more demanding caregiving tasks, rather than reflecting the effect of caregiving intensity on health.

These relationships between caregiving and physical health status that were observed in the SOF study have implications for conceptualizing the relationship between caregiving and physical health, as well as for the measurement of associations between caregiving and health outcomes, and the design of studies to investigate these associations. Conceptually, these results have led us to pose the Healthy Caregiver Effect [4, 33] to explain the relationship between caregiving and health outcomes. The Healthy Caregiver Effect postulates that older persons who are healthier are selected into the caregiver role, and that better health and the activity of caregiving tasks influence whether they continue caregiving. The physical activity of caregiving tasks may have health benefits that counteract the adverse effects of caregiving-related stress [34]. Thus, older caregivers may be fundamentally healthier than older non-caregivers, and this health advantage will influence associations between caregiving and health outcomes. For this reason, it is important to include three basic measures in studies that compare health outcomes in caregivers and non-caregivers: (1) a measure of stress that is applicable to both caregivers and non-caregivers; (2) a measure of overall physical activity that is also applicable to caregivers and non-caregivers, and that will capture the amount of activity expended in performing caregiving tasks as well as usual and leisure-time activity; and (3) a measure of caregiving intensity, such as number of ADLs/IADLs performed for the care recipient or the number of hours/day engaged in caregiving activities. These measures will allow researchers to adjust for the effects of levels of stress and physical activity that may be confounding associations between caregiving and health outcomes.

The measure of caregiving intensity will reveal whether adverse health outcomes differ in high- versus low-intensity caregivers, thereby giving insight into the mechanism by which caregiving affects health outcomes. Worse health outcomes in high- versus low-intensity caregivers would suggest a stress mechanism, whereas better health outcomes in high-versus low-intensity caregivers would suggest a Healthy Caregiver Effect mechanism. In addition, because caregiving status is so dynamic, it is recommended that caregiving status be updated for all participants (not simply caregivers) at each interview in a prospective study. This documentation will identify whether non-caregivers have become caregivers, and whether caregivers increased or decreased their caregiving activities or stopped caregiving, all of which may affect health outcomes.

In summary, prospective epidemiologic studies of caregiving on health outcomes have emerged during the past decade. Measurement and methodological factors may account, in part, for the inconsistent results of these studies. Future studies that account for these factors may give more

insight into the relationships between caregiving and physical health status.

9.3.6 Widowhood

Widowhood is considered to be one of the most stressful life events. Its incidence increases with age and it disproportionately affects older women. In 2008, widowers accounted for 7% of US men 65–74 years of age and 38% of men ≥85 years of age, whereas the proportion of widows rose from 25 to 76% among women in those same age groups [5]. Widowhood is associated with higher rates of depression and general psychological distress, although these results are not consistent across studies [35, 36]. Moreover, the psychological effects of widowhood appear to be worse for men than for women, and they tend to diminish with increased time since widowhood. Widowhood is also associated with increased mortality rates [37, 38]. The health effects of widowhood appear to be modified by whether or not the person was a caregiver to his or her spouse prior to the spouse's death. Thus, widowhood is an important social factor in epidemiologic studies of older adults due to its high prevalence and its relationship to adverse health outcomes. However, measurement and methodological challenges arise in determining how much of its health effects are due to the recent loss of a spouse, selection factors in those who remain widowed, shared risk factors with the deceased spouse, or preceding circumstances such as caregiving.

Widowhood is either measured cross-sectionally by asking respondents to report their current marital status, or prospectively in longitudinal studies that re-assess respondents' marital status at each follow-up interview. Some studies of the "widowhood effect" on mortality obtain data on marital status and vital status for both the respondent and the respondent's spouse from Medicare files [38] or census data [37]. Since respondents are seldom asked how long they have been widowed, studies based on cross-sectional assessments may underestimate the health effects of widowhood because they do not differentiate recently-widowed persons from long-term widows.

The "widowhood effect", or the excess mortality due to becoming widowed, is estimated to be 30–90% higher than the expected mortality rate in the first 3 months following widowhood and 15% higher thereafter [38]. Most studies on the widowhood effect have assessed all-cause mortality, and have lacked data that could pinpoint reasons for this effect. Recent studies suggest that the widowhood effect may vary according to the decedent's cause of death. For example, analyses of a large Medicare database found significantly higher mortality rates in widows regardless of their spouse's cause of death, with two exceptions: no excess mortality was observed for men or women whose spouse died of either Alzheimer's disease or Parkinson's disease [38]. Studies of the widowhood effect are limited because the effect is relatively modest, necessitating the use of very large databases to obtain statistically significant results. These databases lack information on lifestyle or health factors that could explain the underlying mechanism. Thus, it is unknown whether the widowhood effect reflects stress that is related to the spouse's death, poor health behaviors following the death, or other factors.

Gender differences in the psychological effects of widowhood are particularly influenced by how recently spousal loss occurred, as well as selection factors related to staying widowed versus re-marrying or dying. Reasons proposed for why studies might find higher levels of depression in widowed men than in widowed women include (1) men who are more resilient are more likely to remarry, resulting in men with poorer psychological functioning remaining widowed; (2) men have a greater risk of mortality following widowhood than women, so fewer men survive as widowers; (3) psychological distress decreases with time since widowhood and women stay widowed longer than men, so the average level of psychological distress for widows is lower than that for widowers; (4) married men report less depression than do married women, so the contrast in psychological well-being between married and

widowed men is greater than that between married and widowed women; (5) widowed women maintain more contacts with their family and friends, thereby providing psychological benefits that widowed men lack [36]; and (6) men have more problems coping with widowhood than women [35]. Indeed, there is evidence that recently-widowed older men and women have similar levels of depressive symptoms; the main difference is that older married men report significantly fewer depressive symptoms than do older married women [36].

However, cross-sectional studies that compare health status in widowed individuals to that in married individuals may not give as valid estimates of the health effects of widowhood as would prospective studies of changes in psychological or physical health status pre- to post-widowhood compared to changes in individuals who remain married over the same period. The latter study design minimizes potential bias due to factors related to remaining widowed and to the length of time since widowhood. In fact, different associations between widowhood and psychological and physical health indicators were found in cross-sectional analyses compared to prospective analyses of the Women's Health Initiative study [39]. Furthermore, prospective analyses revealed significantly greater impairment in social and psychological functioning among recent widows compared to continuously-married women, in contrast to the significant improvements found in these factors among longer-term widows and those who remarried compared to continuously-married women.

The health effects of widowhood may be entwined with those of caregiving, since the role of the caregiver often ends with the care recipient's death. Designing studies that simultaneously evaluate the health effects of widowhood and caregiving is a challenge. Ideally, the investigator would use a prospective design to compare the pre-widowhood to post-widowhood changes in health status in caregivers and non-caregivers (i.e., showing the effects of widowhood in each group), and also the changes in health status over the same period among spouse caregivers and married non-caregivers who do not become widowed. These comparison groups are important since caregivers report more stress and psychological distress than do non-caregivers. Evaluations of the effect of widowhood on psychological functioning must account for these pre-widowhood differences.

Most published studies compare caregivers pre- and post-widowhood to caregivers who continue to provide care to a spouse over the same period. The lack of comparison groups of non-caregivers who become widowed and non-caregivers who remain married precludes determining whether the caregiving experience exacerbated or reduced the health effects of widowhood. This distinction is important in that caregivers are thought to go through anticipatory grief while the care recipient is still alive. Two competing theories have been proposed for caregivers who become widowed. The "chronic stress" model proposes that the chronic stress of caregiving makes caregivers more susceptible to the adverse health effects of widowhood compared to their non-caregiver counterparts. In contrast, the "stress relief" model proposes that caregivers' health improves following widowhood because they are freed from the burden of caregiving and are thus less susceptible to the psychological effects of widowhood.

The single study that we found on the effects of widowhood in caregivers and non-caregivers showed a slight decrease in depression pre- to post-widowhood among high-strain caregivers compared to significantly increased depression from pre- to post-widowhood in non-caregivers, low-strain caregivers and caregivers who continued caregiving [40]. Using the Caregiver-SOF sample, we evaluated the 1-year change in depression, positive affect and perceived stress in caregivers to a spouse and married non-caregivers who became widowed versus caregivers to a spouse and married non-caregivers who did not become widowed (unpublished data). Among non-caregivers, those who became widowed had significant increases in stress and depressive symptoms and significant decreases in positive affect compared to those who did not become widowed.

In contrast, among caregivers, widowhood was associated with a significant decrease in stress, but was not associated with a significant change in depressive symptoms or positive affect. The results of these two studies provide support for a stress relief model of widowhood following caregiving. However, the critical aspect of each study is the ability to prospectively assess the effect of widowhood on psychological status in both caregivers and non-caregivers.

9.4 Summary

The tables below summarize the potential strengths and limitations of different sources of measures of sociodemographic factors in aging research, as well as measurement periods to capture the time-varying nature of these factors. As shown in Table 9.1, each of the sociodemographic factors that are addressed in this chapter may be measured in various ways. In general, these measures have high reliability (i.e., if assessed multiple times and by multiple methods, the response will be the same) and validity (i.e., the response is accurate). The exceptions are (1) self-reported income, due to the sensitivity of this information; (2) past living arrangement, if cognitive or physical health decline led to a change in living arrangements; and (3) status change in caregiving or widowhood over the course of a study period, because this information may be missed or misclassified if the respondent is providing care for multiple recipients, if the respondent stopped caregiving for one person and began caregiving for another person, or if the respondent got remarried between one interview assessment and the next assessment. In addition, different measures may result in biased associations between the social factor measured and health outcomes, ranging from non-response bias to misclassification, recall bias and the ecologic fallacy. Investigators must consider these strengths and limitations when deciding on which study design and measures to include in their study.

As presented in Tables 9.1 and 9.2, most of these sociodemographic factors are time-varying in older populations. Information on past status, as well as multiple assessments over a study period to document change in status, may be more effective than an assessment at a single point in time for revealing the most valid association between that factor and health outcomes. The time-varying aspect of these factors emphasizes the importance of longitudinal studies of aging and health.

This chapter focused on four social factors that influence health decline in older adults: socioeconomic factors (income, education and occupation), living arrangement, caregiver status, and widowhood. Older adults have poorer profiles with regard to these factors than do younger adults. Several themes emerged regarding the measurement and methods used to study these factors. First, these factors are dynamic over the life course, particularly during old age, and changes in these factors may not only increase the risk of health decline, but are often precipitated by adverse health events. Second, the measurement of social factors at a single point in time may not reveal the inter-relationships between these factors and health outcomes, such as the life-long influence of the factor on older adults' health or the short-term health effects of changes in a social factor over the study period. Third, there are a variety of ways to measure most of the factors reviewed in this chapter, and the particular measurement approach will affect the interpretation of the association between that factor and health outcomes. Furthermore, some measurement approaches may introduce confounding, or misclassification if participants are asked to report their status from earlier in life. Fourth, the evaluation of the health impact of transitions in a social factor may require comparing health status prior to the transition to that following the transition, as well as comparing health changes among individuals who do not transition over the same period. In summary, the investigator's research question, study design and health outcomes of interest determine the choice of measure for each social factor, which, in turn, influences the interpretation of the association between that factor and health outcomes.

Table 9.1 Sources of measures of sociodemographic factors in aging research, and their potential strengths and limitations

		Measurement considerations		Methodological strengths of measurement method		Potential methodological and pragmatic limitations of measurement method regarding associations with health outcomes				
Factor	Source	Measure of SES	Time-varying	Reliability	Validity	Non-response bias	Misclassification	Recall bias	Ecologic fallacy	Difficult to obtain
Income	Self-report, current status	*	*			*	*			
	Self-report, past status	*	*			*	*	*		
	Tax records	*	*	*	*					*
	Census-tract level data	*	*	*	*		*		*	
Education	Self-report	*		*	*					
	Census-tract level data	*		*	*		*		*	
Occupation	Self-report, current status	*	*	*	*		*			
	Self-report, past status	*	*	*			*	*		
	Union records	*	*	*	*					*
Living arrangement	Self-report, current status		*	*	*					
	Self-report, past status		*					*		
	Self-report, change in status		*	*	*					
	Census-tract level data		*	*	*		*		*	
Caregiving Status	Self-report, current status		*	*	*		*			
	Self-report, change in status		*				*	*		
Widowhood	Self-report, current status		*	*	*					
	Self-report, change in status		*	*			*	*		

Abbreviation: *SES* socioeconomic status

Table 9.2 Measurement of the current and time-varying nature of self-reported sociodemographic factors

Sociodemographic factor	Current status	Past status	Change in status during follow-up
Income	*	*	
Education	*		
Occupation	*	*	
Living arrangement	*	*	*
Caregiving status	*	*	*
Widowhood	*	*	*

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Lifecourse Epidemiology and Aging

10

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Abstract

Aging can be defined as deteriorative changes during postmaturational life that are associated with an increased risk of morbidity, disability and death. The process of human aging commences as early as conception with the inheritance of a specific genome, and does not cease until death. Environmental influences during intrauterine and early postnatal life modify gene expression with effects on phenotypes that persist into adulthood, and often result in a predisposition to age-related system decline. This developmental plasticity allows one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development. Thus, phenotypic alterations occur in response to environmental changes in just one generation. This plasticity has been shown to have specific effects on the musculoskeletal system. For example, lower weight at birth and at 1 year of age has been shown to be associated with a greater risk of osteoporosis and sarcopenia in later life. As an individual grows, the potential for plasticity reduces. Further research is required to obtain a full understanding of the lifecourse determinants of aging.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Lifecourse • Bone density • Development • Growth • Exposures • Outcomes • Risk factors • Prevention • Lifecourse • Birth cohort

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Abbreviations

BMC	bone mineral content
BMD	bone mineral density
DXA	Dual-energy X-ray absorptiometry

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10.1 Introduction

There is increased awareness that the process of human aging commences as early as conception with the inheritance of a specific genome, and it does not cease until death. Epidemiological studies have demonstrated that environmental influences during intrauterine and early postnatal life are able to modify gene expression, with corresponding changes in form and function which establish the later predisposition to age-related system decline. The biological process through which these changes in gene expression are established is known as 'developmental plasticity'. This process has been found to be ubiquitous throughout the animal world, and it provides the teleological mechanism whereby organisms of a given genotype can best adapt themselves to the environment that they are likely to meet once development is completed. This chapter considers the impact of developmental plasticity and other lifetime influences on aging. It also addresses the potential for translational public health strategies, using musculoskeletal aging as an example. In particular, the chapter considers in greater depth the epidemiological and mechanistic evidence for a developmental contribution to the aging of bone (osteoporosis) and muscle (sarcopenia).

Aging can be defined as deteriorative changes during post-maturational life that are associated with an increased risk of morbidity, disability and death. We usually describe aging within a population by using mortality statistics, and we describe it at the individual level in terms of chronology or biology. But why does aging occur at all? One school of thought is that aging arises as the culmination of multiple stochastic events. For example, oxygen free radicals significantly contribute to DNA damage. Also, long-lived macromolecules become modified over time by processes such as cross linking, which lead to changes in their structure and function [1]. The sequential loss of telomeric DNA with each somatic cell division results in telomere shortening. It has been proposed that when the telomere becomes critically short, the cell is no longer able to replicate and it enters senescence [2]. These theories are primarily concerned with molecular changes. Other theories describe aging at the systems level, and still others view aging as a whole-body process (Fig. 10.1).

Whichever theory is the most accurate, the question remains as to why we have not evolved to effectively repair this damage and prevent it from accumulating. The 'disposable soma theory' seeks to answer this question based on the premise that there is an implicit trade-off between the rate and effectiveness of reproduction and essential somatic (non-reproductive) processes such as maintenance and repair [3]. It implies that genes that increase the likelihood of procreation will be positively selected, even if they subsequently reduce the length of life. In a similar vein, the pleiotropic gene theory proposes that there are certain genes that have beneficial effects when expressed early in life, but have different, potentially detrimental effects when expressed in later life [4].

These theories are consistent with the evidence that aging is significantly influenced by genotype. Specific mutations in single genes can have a large positive effect on lifespan. Conversely, human progeroid syndromes (e.g., Werner syndrome) can cause premature aging. There is also an increasing recognition of the importance of gene-environment interactions [5], which will be discussed in more detail later in the chapter.

10.2 Lifetime Influences on Aging

10.2.1 Developmental Plasticity

There is a growing recognition that the rate and manner in which individuals age can be significantly influenced by extrinsic factors at multiple points throughout life. Numerous animal experiments have shown that hormones, undernutrition and other influences that affect development during critical periods of early life permanently determine the structure and function of the body's tissues and systems. This is known as 'programming' [6] and it relies on the principle of developmental plasticity. Programming is

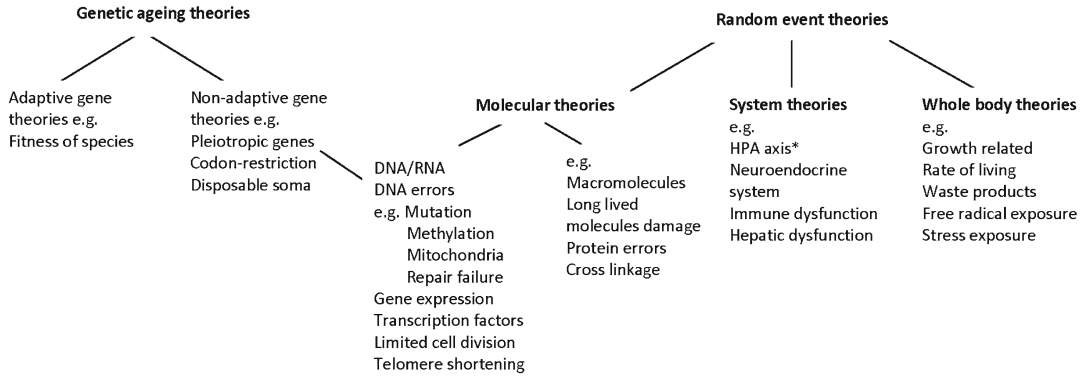

Fig. 10.1 Classification system for aging theories. **HPA axis* Hypothalamic pituitary adrenal axis

the ability of one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development.

Organ systems are most susceptible to programming during periods in which they are growing rapidly. During the embryonic period (the first 2 months of gestation), progenitor cells undergo extensive differentiation without rapid cell replication. The highest growth rates are observed during the following fetal period, and thus the organs are most susceptible to programming at this point. Growth slows in late gestation and continues to slow in childhood. This plasticity is lost later in life and the organism develops a fixed functional capacity.

Programming provides an evolutionary benefit, the ability to adapt to environmental changes in a relatively short span of time. Evolution in a species may take many thousands of years, but developmental plasticity allows phenotypic alterations to occur in response to environmental changes in the span of just one generation. This is possible because developmental plasticity does not require significant changes to the genotype. One example of this is the 'thrifty phenotype hypothesis', also known as the Barker hypothesis. This hypothesis proposes that when the supply of nutrients to a fetus is limited, the fetus will undergo adaptations which prepare it for life in an environment where resources are scarce. There is evidence that in some cases, these adaptations cause negative effects later in life. One study found that men and women in Hertfordshire, England who were of low birth weight or were thin at birth, and were therefore presumed to have been undernourished during intrauterine life, were found to be at increased risk for coronary heart disease, hypertension, non-insulin-dependent diabetes and hypercholesterolemia [7].

The lifecourse exposure response model of aging (Fig. 10.2) [8] illustrates how the aged phenotype develops from an initial genotype across the lifecourse as a result of intrinsic and extrinsic exposures and the individual's ability to respond in terms of regeneration, maintenance and repair.

10.2.2 Prenatal Life, Infancy and Childhood

Experiments on rats, mice, sheep and pigs have demonstrated that undernutrition can also slow fetal growth. Both protein and calorie restriction of a mother during pregnancy and lactation is associated with smaller offspring [9–12]. In general, the earlier in life that the undernutrition occurs, the more likely it is to have permanent effects on offspring body size [13]. Maternal diet restriction in rats resulted in progeny with not only permanent stunting of growth but also anaemia and a reduced resistance to hypothermia in later life [12]. Nutrition reduction in both the prenatal

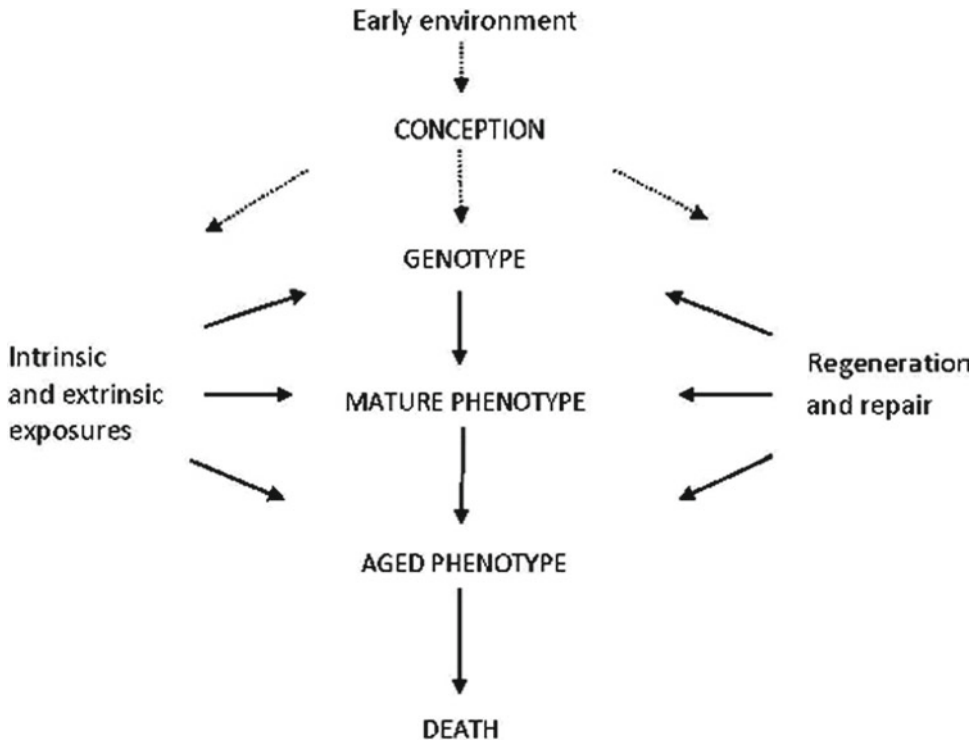

Fig. 10.2 Lifecourse model of aging and early environmental influences

and early postnatal period caused increased levels of age-associated enzymes in the liver and kidney [14]. An early diet that was restricted enough to cause growth retardation led to a permanent reduction in muscle mass [13, 15] and a decreased lifespan [16].

Information with regard to the effects of maternal nutrition on offspring in humans comes mainly from observational studies. The Dutch Hunger Winter occurred from 1944 to 1945, at the end of the Second World War. During this period, Dutch pregnant women received between 400 and 1,000 cal each day. Those exposed to the famine in later pregnancy produced lighter and shorter babies that had a reduced glucose tolerance in adulthood [17]. Women exposed in early gestation had babies with a more atherogenic lipid profile. A similar study design was used following the siege of Leningrad. However, in this case, intrauterine malnutrition was not associated with glucose intolerance, dyslipiaemia, hypertension, or cardiovascular disease in adulthood. The participants exposed to malnutrition did show evidence of endothelial dysfunction and a stronger influence of obesity on blood pressure [18]. Epidemiological studies, such as the Hertfordshire Ageing Study, have assessed the effects of early life markers on aging changes in different body systems, including the eyes, ears and skin [19]. It was found that poor growth in the first year was associated with increased lens opacity, worse hearing and thinner skin (Table 10.1), which suggests that early life factors can have effects on numerous facets of aging.

The aging effects of events in childhood have been less well investigated. Information on childhood lifestyle and anthropometry was available from Lord Boyd Orr's Carnegie survey on family diet and health, which was carried out in the United Kingdom between 1937 and 1939 [20]. When these children were followed up in later life, no factors were found to have a direct effect on all-cause mortality. Shorter leg length, a marker of adverse early diet, was found to be associated with an increased risk of adult coronary heart disease [21], and high energy intake in

Table 10.1 Associations between weight in early life and markers of aging in different body systems: Hertfordshire ageing study

Early weight		Mean lens Opacity score		Mean hearing Threshold		Mean Grip strength		Mean Skin thickness	
At birth									
Grams	**Pounds**	**LOCS III[a]**	**Number**	**dBA[a]**	**Number**	**Kilograms**	**Number**	**Millimeters**	**Number**
<2,500	<5.5	2.27	16	24.4	16	28.5	16	1.19	16
2,500–2,950	5.5–6.5	2.36	94	29.3	93	30.3	95	1.27	95
2,951–3,400	6.6–7.5	2.38	224	29.2	231	31.0	231	1.24	231
3,401–3,860	7.6–8.5	2.38	205	28.7	217	32.2	217	1.24	217
3,861–4,310	8.6–9.5	2.29	84	28.4	89	32.5	89	1.22	89
>4,310	>9.5	2.36	32	28.8	35	32.4	35	1.25	35
Multiple regression[b]		p=0.71		p=0.97		p=0.01		p=0.32	
At 1 year									
Kilograms	**Pounds**								
<8.16	<18.0	2.67	26	33.6	26	29.8	26	1.20	26
8.16–9.07	18.0–20.0	2.40	133	29.4	134	30.7	134	1.22	134
9.08–9.98	20.1–22.0	2.33	198	29.3	209	31.1	211	1.24	211
9.99–10.89	22.1–24.0	2.37	187	29.1	194	31.6	194	1.25	194
10.90–11.79	24.1–26.0	2.33	70	26.5	77	32.6	77	1.25	77
>11.79	>26	2.24	41	24.8	41	34.2	41	1.25	41
Multiple regression[b]		p=0.003		p=0.008		p=0.02		p=0.19	
All		2.36	655	28.8	681	31.5	683	1.24	683
Standard deviation		1.21		1.6		10.1		0.18	

[a]Logarithms used in analysis, therefore means geometric
[b]Adjusted for age, sex, current social class, social class at birth, and height

childhood was shown to lead to an increased risk of cancer [22]. Although some associations have been identified, further study in this area is required to fully elicit the level of importance that childhood influences have on aging.

10.2.3 Adulthood

In adulthood, the potential to change patterns of aging and resultant life-expectancy are more limited. In spite of this, several lifestyle choices do play a role. The decline in cardiovascular, metabolic and musculoskeletal function with age is likely to be mediated in part through a reduction in physical activity. Regular exercise in older adults has been shown to augment aerobic capacity, increase muscle strength, reduce blood pressure, lower plasma lipids, improve glucose tolerance and increase insulin sensitivity [23]. Regular exercise is therefore able to counteract several age-related changes. Both tobacco smoking and excessive alcohol consumption can lead to specific organ dysfunction, with deterioration in physical function. It could be argued that these changes would amount to disease rather than to an acceleration of the aging process; however, it is often difficult to distinguish the two.

An adult's diet can have significant affects on both morbidity and longevity. Excessive calorie intake is associated with a risk of obesity, hyperlipidemia, hypertension and diabetes, as well as the corresponding morbidity and mortality. However, little is known regarding the effects that selective energy restriction in adult life has

on human aging. Animal studies have shown that laboratory rats that are placed on energy-restricted diets after weaning will age slower and live longer than those without such restrictions. Possible mechanisms that have been proposed to underlie this finding are changes in stress hormones, changes in gene expression, altered glucose utilization, reduced glycation of macromolecules and decreased oxygen radical damage. Aging is known to be associated with the selective upregulation of the synthesis of proteins that are related to inflammation and oxidative stress [24]. There is observational evidence that links the lower intake of antioxidant vitamins with a large number of age-related diseases [25]. However, interventional studies have failed to show a benefit from supplementing these vitamins [26, 27].

10.3 A Lifecourse Approach to Musculoskeletal Aging

10.3.1 Bone

10.3.1.1 Osteoporosis

Bone mass is a composite measure that includes contributions from bone size and volumetric mineral density, and it is an established determinant of bone strength. An individual's bone mass in later life depends upon the peak attained during skeletal growth and the subsequent rate of bone loss. Osteoporosis is a skeletal disorder that is characterised by low bone mass and the microarchitectural deterioration of bone tissue, with a resultant increase in bone fragility and susceptibility to fracture [28, 29]. The risk of osteoporotic fracture also depends upon which forces are applied to the bone.

10.3.1.2 Fetal Life and Infancy

Animal models have directly shown the effects of maternal diet on the bones of offspring. The feeding of a low protein diet to pregnant rats produces offspring that exhibited a reduction in bone area and bone mineral content (BMC), with altered growth plate morphology in adulthood [30]. This regime was also found to delay the proliferation and differentiation of bone marrow stromal cells [31] as assessed by fibroblast colony formation at 4 and 8 weeks, which may represent an important candidate mechanism for the development of osteoporosis in later life.

The first epidemiological evidence that the risk of osteoporosis might be programmed during early life came from a study of 153 women born in Bath, England from 1968 to 1969 who were traced and studied at 21 years of age [32]. The study found statistically significant ($p<0.05$) associations between weight at 1 year and BMC at the lumbar spine and femoral neck, but not in bone density in these regions. These relationships were independent of adult weight and body mass index. The association between weight in infancy and adult bone mass was replicated in a second cohort of 238 men and 201 women, 60–75 years of age, who were born and still lived in Hertfordshire [33]. Weight at 1 year was significantly related to adult bone area and BMC at both the spine and hip.

More recently, the effects of prenatal and postnatal life on bone health in older age were investigated in a cohort of 966 patients [34]. Bone mineral content was found to be higher in patients who had a greater birth weight and those that had a greater weight at 1 year. A similar trend was seen with bone mineral density (BMD), but this only reached significance at the proximal femur in men. These data suggest that early life influences are likely to have a greater effect on bone size (estimated by BMC) rather than bone density (estimated by BMD). Studies from the United States, Australia and Scandinavia have found similar relationships.

Studies have shown that birth weight and weight in infancy are predictors of growth hormone [35] and cortisol [36] levels during late adult life. The levels of these two skeletally-active hormones were also found to be predictors of future bone loss rate [37]. One of the effects of programming could therefore be to predispose an individual to an accelerated rate of bone loss during later life through the modulation of the endocrine system.

Birth weight is a proxy for an adverse intrauterine environment, and several parental factors

could contribute to this with differing effects on the offspring's phenotype. The creation of a recent mother/offspring study cohort has enabled the study of these factors in detail [38]. The nutrition, body build and lifestyles of the mothers were characterised during early and late pregnancy, and samples of umbilical venous blood were obtained at birth. The body composition of 216 offspring was assessed using Dual-energy X-ray absorptiometry (DXA) at 9 years of age. Children born to mothers with sub-optimal vitamin D status, as assessed by serum 25-hydroxyvitamin D concentration, had significantly ($p<0.01$) reduced whole-body BMC at 9 years of age. This deficit remained significant even after adjustment for childhood weight and bone area. Those with lower ionised calcium concentrations in their umbilical venous serum showed a lower childhood bone mass ($r=0.19$, $p=0.02$). This data suggests that the placental capacity to maintain the materno-fetal calcium gradient is important in optimising the trajectory of postnatal skeletal growth, and it provides a potential target for interventions aimed at improving the skeletal health of future generations.

There has been a great deal of interest in the interaction between genes and the environment with regard to disease pathogenesis. Of note, one study has shown that the relationship between lumbar spine BMD and vitamin D receptor genotype varies according to birth weight. Among individuals in the lower third of birth weight, spine BMD was higher ($p=0.01$) among individuals of genotype "BB" (absence of the restriction site on both alleles) after adjustment for age, sex and weight at baseline. In contrast, spine BMD was reduced ($p=0.04$) in individuals of the same genotype who were in the highest third of the birth weight distribution [39]. Thus the relationship between genotype and phenotype is not linear, and it can be significantly affected by environmental factors.

10.3.1.3 Childhood and Adulthood

Growth begins to track shortly after birth, which is demonstrated in humans by the way children grow along centile curves. The rate of growth has become set, homeostatically controlled by feedback mechanisms. Recent longitudinal studies have confirmed that this tracking also applies to bone traits in children across the pubertal growth spurt [40]. Yet, despite this tracking, certain environmental factors in childhood can still affect bone health in later life. Data from a unique Finnish cohort has directly linked growth rates in childhood with the risk of later hip fracture [41]. After adjustment for age and sex, the study found that a low rate of childhood growth between 7 and 15 years of age (height, $p=0.006$; weight, $p=0.01$) was associated with a greater risk of hip fracture (Fig. 10.3). Hip fracture risk was also elevated ($p=0.05$) among adults who were born short, but who obtained average height by 7 years of age. This suggests that hip fracture risk might be particularly high among children in whom growth of the skeletal envelope is forced ahead of the capacity to mineralise, a phenomenon which is accelerated during pubertal growth.

For men and women of normal body weight, total skeletal mass peaks a few years after fusion of the long bone epiphyses. The exact age at which bone mineral accumulation reaches a plateau varies with skeletal region and with how bone mass is measured. Bone mass tends to also track throughout adult life and an individual at the high end of the population distribution at 30 years of age is likely to remain at that end at 70 years of age. However, this trajectory can be modulated by several factors that influence bone mass in adult life. These include body mass index, cigarette smoking, alcohol consumption, physical activity, dietary calcium intake, comorbidities, and drug use. In women, there is often a dramatic increase in the rate of bone loss following menopause due to a reduction in estrogen levels, which can be moderated by the use of hormone replacement therapy.

10.3.2 Muscle

10.3.2.1 Sarcopenia

Sarcopenia is a reduction in muscle mass and strength which usually occurs due to aging. Most epidemiological studies have focused on factors that influence the decline in later life, but the life-

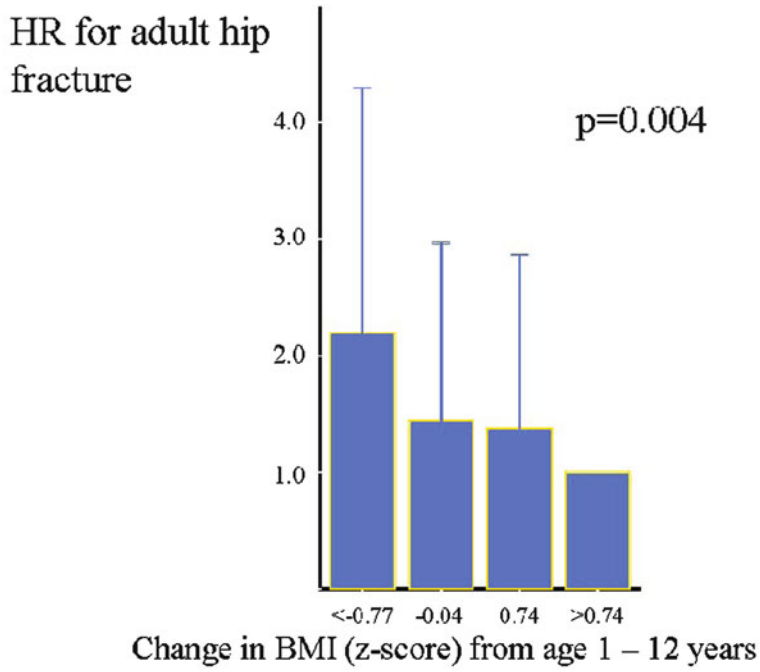

Fig. 10.3 Relationship between childhood growth and adult risk of hip fracture

course model of sarcopenia additionally focuses attention on the determinants of peak muscle mass and strength. Muscle mass increases throughout childhood, peaks in early adulthood and then gradually declines after 35–40 years of age [42]. Figure 10.4 illustrates that there is substantial variation in peak muscle mass between individuals, which is partly explained by genotype, age, gender, size and levels of physical activity.

The level of disability caused by sarcopenia will vary later in life depending on extrinsic factors such as how well the individual's environment is adapted to them. Although the focus of care in older adults is on preventing disability and maintaining independence, it should also be noted that a paucity of muscle will, in itself, predict a poorer prognosis. Low grip strength, as a surrogate marker for sarcopenia, has been found to be significantly associated with increased mortality from all causes in men (after adjustment for potential confounding factors including body composition) and with health-related quality of life in both men and women [44]. This further highlights the importance of sarcopenia as a public health issue in older adults.

10.3.2.2 Fetal Life and Infancy

The link between early life events and muscle strength in older adults was first elicited in the Hertfordshire Ageing Study, which examined a cohort of men and women born between 1920 and 1930 [19]. Lower birth weight and lower weight at 1 year were significantly associated with lower grip strength in later life, independent of adult size. This finding has been replicated in a younger Hertfordshire cohort born between 1931 and 1939, and in a national cohort of middle-aged men and women born in 1946 who participated in the United Kingdom's National Survey of Health and Development [45].

The relationship between early life factors and muscle mass was illustrated in a study of older men from the Hertfordshire cohort [46]. Both birth weight and weight at 1 year were positively associated with fat-free mass. Weight at 1 year, but not birth weight, was also associated with adult fat mass as estimated using anthropometry.

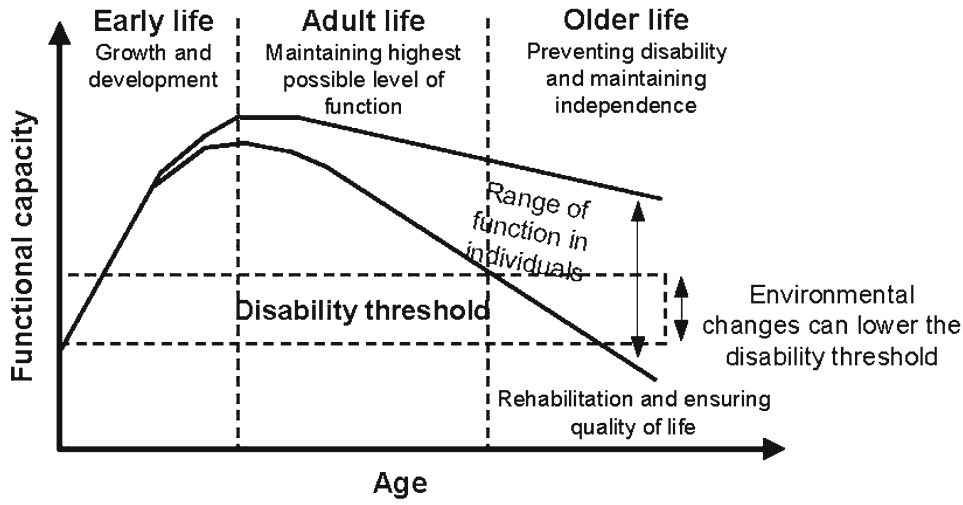

Fig. 10.4 A lifecourse perspective for the maintenance of functional capacity [43, 66]

Low birth weight has also been shown to be associated with lower muscle mass in older adults as measured by DXA [47] and Peripheral Quantitative Computed Tomography [48]. Together, these studies suggest that there is a significant component of sarcopenia severity in later life that is determined before birth and in early infancy. Part of this association is likely to be through the determination of peak muscle levels, as effects of birth weight have been shown on both peak muscle strength in young women 20–35 years of age [49] and muscle mass in young adults [50].

One of the critical determinants of muscle mass and strength is muscle fibre number and type. Although genetic factors appear to be the major influence on primary fibre number, environmental factors have a predominant effect on the growth and development of secondary fibres [51]. In pigs, a high maternal feed intake at specific points in early gestation induces the production of significantly more fibres in the offspring, with an increase in the proportion of secondary to primary fibres [52, 53]. There is also evidence in humans that skeletal muscle fibre composition is affected by the prenatal environment [54]. Individuals of low birth weight were found to have a higher proportion of type IIx fibres at the expense of type IIa fibres. There was also a tendency for the type I and IIa fibres to be larger in area, though this only reached statistical significance in the case of the latter. In the past, it was thought that muscle fibre number was set from birth and did not change. Recent evidence suggests that post-mitotic myonuclei lying within mature myofibres might be able to reform myoblasts or stem cells, and there is an increasing recognition of the role that satellite cells play in postnatal muscle growth and regeneration [55, 56].

10.3.2.3 Childhood and Adulthood

Muscle mass and strength vary considerably between individuals, and the largest influence appears to be muscle training. This can provide more dramatic results in younger adults, but it is uncertain whether this will translate into a lower risk of sarcopenia in later life. There is, however, consistent evidence that links the level of physical activity in later life with muscle mass and strength [57, 58]. In particular, resistance exercise training is the most effective intervention to ameliorate the loss of muscle mass and strength with age [59, 60]. It is recognised, however, that the development of sarcopenia in older adults is not solely due to reduced levels of physical activity, as some loss of muscle mass and strength is experienced even by elite athletes who maintain very high levels of exercise into later life [61].

Several conditions can be associated with the development of a myopathy. Some of these, such

as a statin-induced myopathy, would be separate from the aging process. However, the Hertfordshire Cohort Study [62] showed a graded association in older adults between increased glucose level, weaker muscle strength and impaired physical function. This was not only seen in individuals who had diabetes or impaired glucose tolerance, but also in those without either diagnosis. Since glucose levels tend to increase with age, this is likely to represent an age-related factor that contributes to muscle weakness in an older population rather than a separate disease.

10.4 Future Research Directions

The lifecourse model of aging can clearly be applied to both bone and muscle aging; however, it is by no means limited to these areas. It is, for example, beginning to be used for diseases such as osteoarthritis, the most common joint disorder worldwide. The prevalence of osteoarthritis increases with age and it can lead to physical and psychological distress, significantly reducing the quality of life [63].

When developing a lifecourse model of disease, information should be gathered regarding the effects of events from conception to death. An individual's genome often plays a role in determining how a pathological process will manifest, and osteoarthritis is no exception. Evidence from sibling studies suggests a genetic contribution to the development of osteoarthritis in both men and women [64].

Environmental factors begin to influence development shortly after conception, and there is particular interest in the period of intrauterine and early postnatal life. The evidence for this association most commonly originates from epidemiological studies that conventionally correlate the adult disease phenotype with early life records. In the case of osteoarthritis, a cohort study in the United Kingdom found that low birth weight in men was associated with an increased risk of developing clinical hand osteoarthritis by 53 years of age [65].

In some conditions, it is possible to closely follow fetal and early life development, and link these to traits in childhood that predispose to disease in later life. In this type of study, epigenetic changes that result in modifications to the phenotype can also be investigated, giving potentially valuable information regarding the underlying mechanism that predisposes to disease.

As the process of aging continues throughout life, it is important to study potential influences that occur through childhood and adulthood. In post-menopausal women, there is an accelerated age-related rise in osteoarthritis incidence that implies a possible role for sex hormones, such as estrogen deficiency, in the pathogenesis. There is some evidence that this effect can be reduced by the use of estrogen supplementation, but these results are inconsistent. One randomised, controlled trial of estrogen plus progestin vs. placebo found no significant different in knee osteoarthritis-related symptoms [66].

Whilst investigating the lifecourse approach to a disease, we must always consider the potential to develop public health strategies to influence the disease course. Interventions of this type may yield a small benefit for the individual, but have substantial benefits for the population as a whole.

10.5 Conclusion

There have been several attempts to explain why people age. Random event theories focus on the role of stochastic events over time at the molecular, system or whole-body level. Within individual cells, telomere shortening takes place with each mitotic division and may ultimately lead to cell senescence. The action of free radicals and the accumulation of DNA damage also play an important role in aging, which is counteracted by cellular repair processes. Genetic aging theories suggest that a compromise exists in which aging occurs to allow other processes to occur which improve the fitness of the organism.

An individual's genotype will, in part, determine how they age, but this effect can be significantly modified by environmental factors. Animal models have shown that early life events can lead to phenotypic changes that persist into

adulthood. This programming has been shown to have specific effects on the musculoskeletal system. Weight at birth and at 1 year have been shown to be associated with a greater risk of osteoporosis and sarcopenia in later life, which has significant implications on public health. As an individual grows, the potential for plasticity reduces and there is less scope to influence the pattern of aging. Our understanding of the lifecourse determinants of aging is still in its infancy, and further research in this area is required to gain a full appreciation.

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Using Epidemiology to Inform Community Health Programs and Policy

11

Steven M. Albert and Julie Donohue

Abstract

There's an increasing awareness of the need to bring together aging services research and research on the mechanisms of health and aging. The application of epidemiologic methods to aging services research requires an expansion of traditional epidemiology to include greater flexibility and methods, access to large administrative data sets that allow only partial control over selection bias in the identification of diagnostic groups and service episodes, and the incorporation of new measures that account for program access and reach. The use of traditional epidemiologic tools in aging services research is demonstrated by the increasing number of randomized controlled trials in this area. The ultimate goal of aging services research is to find methods for delivering effective medical and supportive care services to older adults which may enable them to continue living in the community. This may involve evaluating particular programs or assessing the implementation of evidence-based programs that were developed for different settings or populations. It may also involve assessing changes in national policy or attempts at quality assurance in hospitals and nursing homes. Such research is critical for the implementation of rational policy and it demonstrates the value of expanding epidemiologic tools into aging services research.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Community health • Health policy • Health programs • Physical function • Disability • Evaluation • Assessment • Intervention • Health planning • Health policy • Social security • Retirement

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Abbreviations

AAA	Area Agencies on Aging
ADAMS	Aging, Demographics, and Memory Study
AMI	Acute Myocardial Infarction
AoA	Administration on Aging
CCDE	Cash and Counseling Demonstration and Evaluation
CHS	Cardiovascular Health Study
CMS	Centers for Medicare and Medicaid Services
Health ABC	Health Aging and Body Composition Study
HMO	Health Maintenance Organization
HQA	Hospital Quality Alliance
HQID	Hospital Quality Incentive Demonstration
HRS	Health and Retirement Survey
ICD	International Classification of Diseases
IOM	Institute of Medicine
MCBS	Medicare Current Beneficiary Survey
NCOA	National Council on Aging
NDI	National Death Index
NEEP	Number of Events Prevented in a Population
PACE	Program for All-Inclusive Care
PCT	Pragmatic Clinical (or Controlled) Trial
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
SEER	Surveillance, Epidemiology, and End Results
SOF	Study of Osteoporotic Fractures
US	United States

11.1 Introduction

Academic investigators and policy makers have become increasingly aware of the need to bring together *aging services research* and *research on the mechanisms of health and aging*. While the research designs and analytic tools that have been developed in modern epidemiology are appropriate for aging services research (which can be considered a subset of health services or comparative effectiveness research), the tools of epidemiology also enable researchers to investigate aging services and related community interventions as exposures which may affect the risk of functional decline or other important health outcomes.

Epidemiology and efforts to improve aging services work together in a variety of ways. At its simplest, community health programs and policymakers implement important findings from epidemiologic studies, developing programs that seek to deliver health benefits that these studies have identified. For example, one way that findings regarding the benefit of flu vaccination (as established in cohort studies) have been successfully implemented are "Vote and VAX" programs that offer influenza vaccinations at polling places [1, 2]. In other cases, the research efforts of aging services are very much like other clinical epidemiologic investigations, with randomized designs and physiological or clinical indicators. An example is a community-based exercise program for people with arthritis, *Fit and Strong!*, which a randomized trial has shown to have benefit for pain, range of motion and mobility [3]. In yet other cases, only quasi-experiments are possible as a way to assure the fair comparison of groups that differ in aging services interventions. For these efforts, propensity score adjustment and other statistical adjustments may be required.

This chapter will show how epidemiology can inform aging services research, including policy analysis. After a brief discussion of the aging services sector, the chapter will review the methodology of aging services research, including the special design issues that must be considered when assessing aging services or policy changes, how epidemiologic research differs from evaluation or implementation science, and how policy analysts who are interested in aging services incorporate epidemiologic concepts into their work. We then turn to applications, highlighting the use of epidemiologic methods in policy analysis that is related to aging services. We focus on the assessment of quality of care and

federal incentives for better delivery of care, as well as recent changes in Medicare policy such as the introduction of the Part D prescription benefit.

11.2 The Need to Link Epidemiology and Aging Services Research

The need for a bridge between epidemiology and aging services research is clear from the Institute of Medicine (IOM) report, *Retooling for an Aging America* [4], which focused on the health care workforce that is available for the care of older adults (health care professionals, paraprofessional direct care workers and unpaid family caregivers). The panel rightly focused on the striking shortfall between the health care needs of the rapidly growing population of older adults and the healthcare workforce currently in place to meet these needs. We summarize a few of the findings from this report to reinforce the pressing need to link epidemiology and aging services research.

The IOM report makes clear the preeminence of older adults as consumers of medical and supportive care, which is consistent with the greater prevalence of disability and chronic disease in later life. Older adults account for about 12% of the United States (US) population, but account for 26% of physician office visits and 35% of hospital admissions. Older adults use 34% of prescriptions and are responsible for 38% of emergency medical service responses. All told, the 12% of the population that are older adults engages between one-third and one-half of the healthcare workforce. Demands on the long-term care workforce are even more extreme. About 90% of nursing-home residents are >65 years of age. In addition, over 60% of older adults with disabilities who reside in the community make use of at least one in-home or community-based long-term care service.

These medical and supportive care services are largely—though not exclusively—publicly financed. Together, Medicare and the federal share of Medicaid now make up 20% of the federal budget. Medicaid, which is a primary source of financing for long-term care services, has surpassed public education as the largest expenditure category in state budgets. Yet Medicare finances only about one-half of older adults' health care expenditures. Older adults spend approximately one-sixth of their income on health care, and supplemental sources of coverage play a major role in financing care for Medicare beneficiaries. Thus, it is important that epidemiology take up the challenge of assessing how these systems work and how they matter for health outcomes.

11.3 Community Health Programs and Policy: Overview of the Aging Services Sector

In assessing aging services, it is important to consider the providers of such services as well as the older adults who receive them. The previously-mentioned IOM report documented the inadequacy of the current education, training, practice and financing of public and private programs that are designed to meet the health care needs of older adults. The shortage of certified nursing assistants, home health care aides and other paraprofessional direct care workers is clear and documented in surveys that show poor working conditions, minimal training, little room for advancement and extraordinarily high turnover. Shortages in the professional health care workforce are also glaring. For example, the IOM reported that less than 1% of physician assistants, pharmacists and nurses receive specialty training in geriatrics. Projections of the demand for case management and for information and referral suggest that perhaps one-third of social workers should receive geriatrics training, yet only 4% currently do. Geriatric medicine is similarly under-resourced, with declining numbers of physicians taking advantage of available geriatric fellowships.

The IOM report also drew attention to the vital role that unpaid family, and paid and unpaid social network supports, play in aging services. Families call upon an alternative workforce, which aims to maximize the functioning of older adults by

helping to provide meals, transportation, home modification, social visiting, daily monitoring, house cleaning and medication management when families are unable to provide these services. These supports come from a loose network of nonprofit organizations and government agencies that often contract with nonprofits to deliver mandated services. The most central relevant US government agencies include the 665 Area Agencies on Aging (AAA), which function at the county level (or, in some cases, groups of counties), and also the nation's 3,000 local health departments. Departments of public welfare and other government entities may also provide funding or services.

Funding for aging services is fragmented. The older adult will have medical care costs covered by Medicare and other private insurance if available, or by medical assistance (Medicaid) if the individual meets income requirements. The US Centers for Medicare and Medicaid Services (CMS) coordinate this effort. Medicare is a national health insurance system with uniform standards. In contrast, Medicaid is a joint federal-state effort in which states have substantial latitude with regard to who is eligible and what will be covered. Over seven million older adults are low-income (about one in five American older adults) and are eligible for Medicaid, as are individuals who have aged with lifelong or longer-term disabilities. These individuals are dually eligible and covered by both Medicare and Medicaid.

Medicaid provides long-term care coverage for older adults (skilled nursing care, and in-home and community-based programs, through state-based waiver programs), while Medicare covers rehabilitative care, which may occur in homes (as in the case of services provided by visiting nurses or allied health clinicians) or in skilled nursing facilities (as in the case of subacute rehabilitation care). These Medicare services are linked to hospital episodes, are time-limited and are keyed to specific rehabilitation goals. Thus, Medicare covers medical care, but covers rehabilitation or longer-term maintenance only insofar as it is linked to hospital episodes. (Medicare's hospice benefit and end-stage renal disease program are exceptions). Medicaid covers long-term care, but only for individuals who meet mandated low-income criteria, which vary by state but are typically set at or below 100% of the federal poverty level.

Other services that are less explicitly linked to health fall out of the domain of the CMS and into aging services organized by the US Administration on Aging (AoA). Title III of the Older Americans Act includes funding for state units and county areas on aging (III-A, III-B), community services (such as senior centers, III-B), congregate and home-delivered meals (III-C) and the National Family Caregiver Support program (III-E). Newer efforts have added health promotion and disease prevention to this funding stream, pushing state departments of health and aging to collaborate in joint efforts.

The older adult who has health problems and disability, and who is unable to maintain a household independently, faces a complex array of supports and services. They may receive transportation support from a faith-based volunteer caregiver agency (such as the local branch of Interfaith Volunteer Caregivers), home modification services from a nonprofit agency under contract with the local AAA, cleaning and cooking services from yet another AAA vendor or perhaps a nonprofit multi-services agency funded by a local United Way or other philanthropy, clinical preventive services (such as immunization, falls prevention, cancer screening or chronic disease management) through a local health department initiative, and housing services and social work support from still other government agencies such as a local housing authority or public welfare department. The organizational relationships between these entities and complex funding streams would, of course, not be apparent to an older adult or a family; nor, at this point, are providers able to easily track duplication of services or develop ways to streamline delivery.

In recent years, the public health challenges of an aging society have become increasingly prominent, including those that stand apart from the need to deliver medical care and appropriate support to meet basic needs. Improving the health of older adults is a CDC priority, as indicated in the *Healthy People 2010* objectives to increase

life expectancy and reduce disability in old age. The CDC's Healthy Aging program, set within the National Center for Chronic Disease Prevention and Health Promotion, has developed a program of research and partnerships that begins with the premise that "poor health is not an inevitable consequence of aging" [5]. To this end, the CDC has increasingly joined forces with states to promote physical activity, better nutrition and tobacco cessation among older adults. More recent efforts support disease management in the case of diabetes, heart disease and arthritis, and seek to increase the uptake of the preventive services available through Medicare, such as immunization and cancer screening. The CDC's injury prevention program has begun to address falls prevention and the high rate of injury among older adults.

Although movement in this direction is welcome, much work remains to align the delivery of services with a broad-based healthy aging effort. New efforts address the charge made by then CDC director J. S. Marks to the US Senate in 2003: "To a certain extent, it is as if we have not fully engaged in applying public health practice to older populations…The aging network is looking to public health for science-based health promotion and disease prevention strategies that are tested and proven effective" [6]. In response, the CDC and its partners (e.g., the National Council on Aging [NCOA]) have recently developed guidelines for many evidence-based health promotion efforts [7].

In assessing these efforts, it is not enough to document the change in process measures such as providing services, increasing knowledge, attracting a clientele or changing the risk of an outcome. The central outcome for aging services interventions is to increase the opportunities for frail and vulnerable older adults to remain safely in their homes or in the least-restrictive community-based setting. Intermediate outcomes that support the preferred outcome include greater access to services, improvements in health, and greater use of prevention services. Since older adults overwhelmingly endorse the desire to age in their homes, and since communities also benefit when older adults remain in their homes, a central outcome of community programs and policies should be enabling older adults to age in their homes.

11.4 Epidemiology and the Methodology of Aging Services Research

11.4.1 What Special Design Issues Need to Be Considered When Assessing Aging Services Interventions?

Aging services research departs from traditional epidemiologic investigation in its greater emphasis on (1) effectiveness over efficacy, (2) the use of quasi-experiments when randomization is not possible, and (3) the greater use of administrative datasets. The key methodological innovation used in aging services research is the *pragmatic clinical (or controlled) trial* (PCT), which often blends these three areas of emphasis. The PCT seeks to assess the effect of interventions in the general population (e.g., eliminating restrictive inclusion–exclusion criteria) and uses existing service delivery systems to retrieve data or deliver interventions (with less control, therefore, over the implementation of interventions and less extensive data collection). Randomized controlled trials make internal validity paramount and usually focus on biological or clinical outcomes to assess mechanisms of disease or treatment. The PCT differs in asking whether the intervention will work in larger, more representative settings. Here the premium is on external validity, clinically significant outcomes, existing patient pools or program settings, scalable interventions, and less intensive assessment batteries [8]. With the focus on pragmatic trials, new measures of population impact for interventions are now available, such as the *number of events prevented in a population,* described below.

11.4.2 Effectiveness vs. Efficacy

The epidemiologic assessment of aging services interventions begins with the recognition that the effect sizes that have been established in randomized controlled trials will likely be lower in community settings. Randomized controlled trials

assess whether an intervention can work in a relatively small, homogenous set of study participants who have high fidelity to interventions that often require substantial resources (*efficacy*). In contrast, pragmatic trials assess whether these interventions work in real world settings, which have more heterogeneous populations and variation in the implementation of the intervention (*effectiveness*). A reduction in effect is inescapable given the wider range of older adults who will be targeted in the program, the variation in program resources and monitoring, and the greater difficulty in tracking outcomes.

This decline in effect size is evident in falls prevention efforts. While exercise and multifactorial interventions have shown that fall risk can be reduced by as much as one-third [9], these clinical interventions target highly selected risk groups and mobilize clinical resources that are not available in standard primary care or community program settings. For example, randomized trials of falls prevention interventions are usually limited to patients who were recruited in medical settings, or they require that participants meet specific risk factors for falling. Some trials only involve older adults who were recruited in long-term care settings, and many exclude older adults who have other comorbidities (e.g., cognitive impairment).

Assessments of community implementation of falls prevention programs indicate smaller effect sizes, though direct comparisons of similar interventions in the community setting have yet to be completed. The Connecticut Collaboration for Falls Prevention [10] compared differences in falls-related hospitalization in two regions to assess the effect of outreach to physicians, aging services providers and vulnerable older adults on falls-related hospitalization. The intervention led to a 9% reduction in falls-related hospitalization and an 11% reduction in overall medical service use related to falling, reductions that were maintained 2 years after the intervention. These effects are much lower than those established for clinical interventions. But the lower effect sizes still represent a huge impact in public health. The intervention prevented a total of 1,800 emergency department visits or hospitalizations, at a savings of $21 million. Notably, the intervention involved only educational outreach and it was geared mostly toward clinicians (who were, in fact, incompletely reached), thus suggesting scalability and good prospects for dissemination.

11.4.3 Experiments and Quasi-Experiments

A quasi-experiment is a comparison of groups in the absence of random assignment to an experimental condition. Campbell and Stanley [11] codified this array of designs and were able to recommend many ways to assess threats to the validity of these non-experimental studies. The biggest threat is always selection. Individuals who choose to be in a program differ from those who do not, sometimes in ways that we recognize and sometimes in ways that we do not. We can control for factors that we recognize using statistical adjustments or restrictions in analysis. Other differences, however, will not be controlled, and we risk misattributing an observed difference to an intervention when it may be due to some other factor that is correlated with participation in a program.

A case in point is influenza vaccination among older adults. In a multi-year study in a series of Health Maintenance Organizations (HMOs), Nichol et al. [12] compared community-dwelling older adults who received a flu vaccination to those who did not. They compared hospitalization and mortality in the two groups, replicating findings across the years, seasons and sites. Vaccination was associated with great health benefit, a 27% reduction in the risk of hospitalization for influenza or pneumonia, and a 48% reduction in all-cause mortality. These effects were consistent in stratified analyses (by age and medical risk group). Nichols et al. noted that the prevalence of medical conditions was significantly higher in individuals who received a vaccination, as would be expected given recommendations that high-risk older adults receive vaccination. Recognizing that unmeasured confounders might be responsible for the differences in outcome, they conducted a series of sensitivity analyses [13]. They simulated the presence of unmeasured

confounders, varying their prevalence in the population, and showed that even with such a confounder, the reduction in mortality associated with vaccination is robust. They concluded that, "in every non-randomized study on causal associations the robustness of the results with respect to unmeasured confounding can, and should, be assessed using sensitivity analyses" [10].

Sensitivity analyses are reassuring, since one would otherwise worry that individuals with chronic conditions who receive vaccination are also generally more likely to receive medical care and oversight as part of chronic disease management, and that this may be the source of the survival and hospitalization effect. Still, given the evidence of the health benefit of vaccination, it is not possible or ethically acceptable to conduct a randomized trial of flu vaccination. The quasi-experiment with sensitivity analysis is the best option. This challenge is typical of many health interventions and policy options in aging research.

An example in which randomization in aging services research was possible, though difficult, was the Cash and Counseling Demonstration and Evaluation (CCDE) [14]. The CCDE was an experiment in which older adults who were eligible for personal assistance care were offered an individualized budget or traditional Medicaid-covered services. Program participants "were free to choose the types and amounts of paid services and supports they judged best able to meet their disability-related personal assistance needs." [11] The study therefore compared consumer choice to agency-directed care.

This key trial revealed many important findings [15], including the following: participants typically hired relatives; seniors with control over in-home care reported less unmet needs, greater satisfaction with care and better quality of life; rates of adverse health events were similar in both conditions; participants' primary unpaid caregivers reported less physical, emotional and financial stress; program participants had higher Medicaid expenditures for personal care than did controls, but lower expenditures for other Medicaid services; and seniors in the usual care group received—on the whole—fewer services than were authorized.

The CCDE is a model for extending the reach of randomization in trials of aging services research. In fact, randomized designs should be considered for assessments of most policy and service interventions and may be possible with appropriate planning and partner involvement [16].

11.4.4 Administrative Datasets

For policy analysis and the large-scale assessment of service interventions, administrative databases are essential. A critical issue in using these datasets is recognition of their provenance. Often they are not designed for use in research. For example, CMS datasets are first and foremost maintained for the reimbursement and tracking of expenditures, not for research. A great deal of pre-processing is required for research use, and researchers need to work with agency personnel to assess the limitations of such data, which may not be obvious from code books and data dictionaries. A key challenge is identifying a population with a particular condition, as diagnoses obtained from claims data using the International Classification of Diseases (ICD) system may have limited sensitivity and specificity. For example, one might consider using prostatectomy, as recorded in Medicare claims, to establish the presence of prostate cancer. However, many patients with prostate cancer will not come to surgery, so other indicators of service use are required to identify this patient population. These clinical algorithms can become quite complex. More generally, epidemiologists and policy analysts will need to work with CMS data intermediaries, such as the Research Data Assistance Center [17], for certain data management functions.

A trickier challenge is extrapolating from these administrative datasets to the population of interest. It goes without saying that a Veterans Health Administration dataset only enables generalization to individuals who receive Veterans Administration services. For other datasets, such as commercial insurance or employer datasets, the reach of the data may be less clear. Even for Medicaid data, it can be difficult to establish reach because people may gain and lose

coverage in relatively short time-periods (so-called "churning") and because state Medicaid programs differ widely in their eligibility and coverage policies. Compiling a complete claims history for a sample of older adults is particularly difficult when using Medicare data, given the multiple sources of payment for health care that is delivered to Medicare beneficiaries (as discussed earlier). The appropriate use of administrative databases for aging services research is an evolving challenge as these databases become more available and more linked to other datasets.

An important addition to the aging services research armamentarium is large, nationally representative longitudinal cohorts that have been linked to Medicare claims data. These include the Health and Retirement Survey (HRS) (which has also been linked to pension data and lifetime earnings), the Medicare Current Beneficiary Survey (MCBS); the Cardiovascular Health Study (CHS); the Health Aging and Body Composition Study (Health ABC); the Study of Osteoporotic Fractures (SOF); and the Surveillance, Epidemiology, and End Results (SEER) program. Other key aging research cohorts have also been linked to Medicare claims, but few have been linked to Medicaid claims. Limiting claims to Medicare data will not give a complete picture of health services use for the 20% of older adults who receive services from both systems (see above). Also, the level of health encounter data will be less complete for the approximately 25% of older adults who participate in Medicare-sponsored HMOs (e.g., Medicare Advantage programs), Veterans Administration, or all-inclusive care programs (e.g., the Program for All-Inclusive Care [PACE]). More generally, due to capitated payment (lump sum payment for each member in the plan, adjusted for case mix and region), HMO's are not required to generate individual health encounter data, which is also a concern for health services research that involves non-aged populations.

The HRS biannually follows more than 26,000 Americans >50 years of age [18]. It was developed to examine labor force participation and health transitions in older adults, with a focus originally on predictors and outcomes associated with retirement. Extensions of the HRS include the Aging, Demographics, and Memory Study (ADAMS) which examined the prevalence of dementia [19], surveys of time use, and studies of economic decision-making related to health. Biologic samples are now being drawn from HRS participants. Also, HRS-type surveys, with National Institutes of Health support, have been launched in Europe, the Middle East and Asia.

The MCBS is an ongoing survey of a nationally representative sample of Medicare beneficiaries, including individuals who are disabled and institutionalized. The MCBS "is the only comprehensive source of information on the health status, health care use and expenditures, health insurance coverage, and socioeconomic and demographic characteristics of the entire spectrum of Medicare beneficiaries" [20].

The CHS is a population-based, longitudinal study of coronary heart disease and stroke in adults who are ≥65 years of age [21]. Access to Medicare claims in the cohort has enabled the investigators to explore medical costs and utilization profiles that are associated with the staging of cardiovascular disease and subclinical disease.

The purpose of Health ABC is to characterize change in body composition, identify clinical conditions involved in these changes, and examine the effect of these changes on functional impairment and disability. The study population consists of over 3,000 men and women who were 70–79 years of age at baseline [22]. The addition of Medicare claims data will enable the extension of the study into other areas. For example, it is possible that common conditions, such as falling or hip fracture, may have different medical care expenditures depending on the etiology of the conditions. These sorts of questions can only be answered using datasets that merge administrative claims and clinical indicators.

Public release data from the SOF study includes 6,000 variables that were collected over seven visits in a cohort of nearly 10,000 older women [23]. The merging of SOF clinical and epidemiologic indicators with Medicare claims has enabled investigators to examine key issues in health services research, such as the role of different chronic conditions in the decision to enroll or disenroll in Medicare Advantage (HMO) plans.

The SEER program is mainly designed to track cancer incidence in the US. It collects cancer incidence and survival data from population-based cancer registries that cover approximately 28% of the US population [24]. The merging of these data with Medicare claims offers an important resource for examining disparities in access to treatment and differences in outcome for older adults with cancer.

Data from an increasing number of longitudinal aging cohorts have also been merged with the National Death Index (NDI), which records information about death for all Americans. This approach enables investigators to use clinical and biomarker information they have collected in their studies to develop longer-term survival models.

Adding Medicare and Medicaid claims data to well-characterized clinical cohorts is very useful for both aging services and epidemiologic research. Epidemiologic data provides independent diagnostic information for cohort participants, which can then be used to assess service use, cost and outcomes for particular diagnostic groups that are recorded in Medicare claims. Examples of this approach include a study of the potential survival benefit associated with the receipt of personal assistance care [25] and studies of the increase in medical care costs that are associated with increasing severity of Alzheimer's disease [26–28].

11.4.5 Population Impact Numbers: Number of Events Prevented in a Population

A productive approach to estimating the population-level impact (or success) of public health interventions is the use of "impact numbers" [29–31]. Population impact measures provide estimates of absolute risk and benefit to a total population and take into account current practice, the uptake of interventions under different scenarios, intervention efficacy and program adherence. A key measure is the number of events prevented in a population (NEPP). Public source software is available for estimating population impact measures through the Population Health Decision Support & Simulation group at the University of Manchester [32]. To show the value of this approach, we return to the falls prevention example that was introduced earlier and estimate the number of preventable falls-related hospitalizations for a US state, using Pennsylvania as an example. Results are shown in Table 11.1.

Inputs for the simulation include the total Pennsylvania population >65 years of age in year 2009 (2010 US Census: 1.94 million), a 30% annual falls prevalence, and 5% annual falls-related hospitalization [33]. We also assume that 50% of older adults who participate in the intervention adhere to the intervention protocol. We varied three parameters:

- *Efficacy of the intervention:* as indicated by relative risk reductions of 10–30% in hospitalization for falls (reducing it from 5 to 3.5–4.5%). Reductions in relative risk of this magnitude were reported in the Connecticut Collaboration for Falls Prevention, described earlier.
- *Participant reach:* the proportion of older adults who participated in the intervention under the best practice scenario, ranging from 20 to 35%. The program reach to individuals at risk was 20% in a population-based intervention for physical activity among older adults (Belgium's *10,000 Steps* program [34]). In contrast, 45% of eligible participants were reached in the *Tai Chi-Moving for Better Balance* program, though this report was based on a small sample of six senior centers [35].
- *Current participation in falls prevention interventions:* ranging from 1 to 10%. We base current statewide participation on Pennsylvania's experience with *Healthy Steps for Older Adults*, a falls prevention program that reaches 1–5% of Pennsylvania's older adults each year. Similarly, only 5.9% of eligible employees participated in an insurance-sponsored weight management program that was offered to state employees [36].

The most favorable simulation suggests that nearly 1,500 falls-related hospitalizations could be prevented in Pennsylvania if current low rates of prevention efforts (1% of older adults participating) improved to reach about 35% of older

Table 11.1 Number of falls-related hospitalizations prevented (NEPP)

Intervention: Relative risk reduction (%)	Current program reach (%)	Program reach under best practice scenario (Older adults participating)	
		20%	35%
10	1	277	495
	5	218	437
	10	145	364
20	1	553	990
	5	437	873
	10	291	728
30	1	830	1,485
	5	655	1,310
	10	437	1,092

Abbreviation: NEEP number of events prevented in a population

adults and reduced the relative risk of hospitalization by 30%. While these 1,500 hospitalizations represent a reduction of only 1.6% of falls-related hospitalization in Pennsylvania, avoiding them would save a total of $29.2 million in medical care costs (with an average cost of $19,672 for hospitalization [33]), and $72.3 million in combined medical and work-loss costs. Under the least favorable scenario, about 275 hospitalizations would be prevented, with a savings of $2.8 million in medical care costs and $7.1 million in combined medical and work losses.

This approach gives the range of likely impact for an intervention introduced to a population. A virtue of this approach is its explicit assumptions and parameter estimates, as well as its incorporation of the intervention into a real-world setting of program delivery. A limitation is its dependence on reasonable parameter estimates for reach and intervention effects, which may not be available, and its uniform treatment of the population at risk.

11.4.6 How Does Epidemiologic Research in Aging Services Differ from Evaluation or Implementation Science?

An important advantage of the NEPP impact measure is its ability to integrate measures of effectiveness and delivery for an intervention. These combined measures are summarized in the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework [37, 38], which includes:

- *Reach:* The proportion of the target population (seniors, organizations, settings) that participates in the intervention;
- *Efficacy/Effectiveness*: The success rate of the intervention for older adults who participate;
- *Adoption:* The representativeness of organizations and settings that implement the intervention;
- *Implementation:* The fidelity to intervention, as indicated by the number of component elements delivered, with appropriate quality assurance;
- *Maintenance:* The extent to which intervention becomes part of routine practice, as indicated by site incorporation of interventions into operations, including budget, staff and space.

Figure 11.1 shows the hierarchical relationship of RE-AIM elements. The framework suggests a number of measures of public health impact. For example, individual-level impact can be calculated as (Reach * Effectiveness)/100, that is, effectiveness adjusted by how well an intervention was taken up in the target population. Likewise, the effect of long-term maintenance can be calculated as (individual completion * setting continuation)/100, expressing the likelihood that effective interventions require both

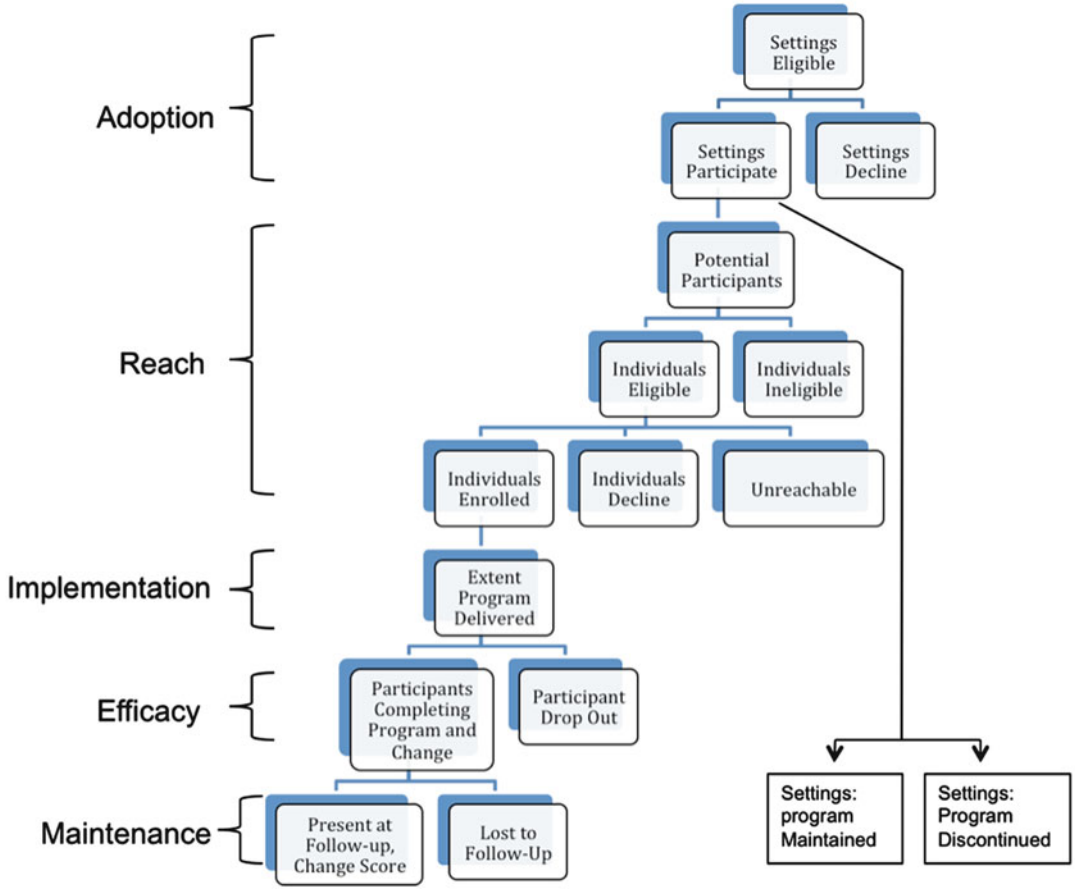

Fig. 11.1 Assessment of intervention impact and scalability (After Glasgow 2002 [27])

maintenance across settings and participation by individuals.

To give an illustration of the utility of the RE-AIM framework, note how estimates of effectiveness change when adjusted for the reach of an intervention. In a study of an Internet weight-loss intervention, participants in the intervention lost an average of 13 pounds compared to controls, which translated to an effect size of 0.44, a significant difference [36]. The researchers estimated that 32,878 out of 60,041 adults in a state agency were eligible for the intervention (based on a state obesity and overweight prevalence of 31 and 36%, respectively, and an imputation of the proportion of overweight adults with at least one comorbid condition, 61%, drawn from a national survey). The Internet intervention was successfully delivered to 1,952 members for a reach of 5.9%. The effectiveness adjusted for reach, or individual-level impact, was 2.4%, which shows substantial room for improvement in the delivery of the intervention for public health benefit.

The RE-AIM framework draws attention to evaluation indicators, but also to the challenges of implementation even in the case of interventions that have a strong evidence base. It may be necessary to tailor interventions to particular settings. These changes may threaten the fidelity of the program. Implementation science seeks to determine the range of these changes in particular settings, and to determine when such changes

irrevocably alter a program and essentially make it a new program in need of its own, new evidence base [39].

The focus on intervention indicators shows where traditional epidemiology and aging services research differ. In epidemiologic assessment, we ideally ensure implementation and fidelity of the intervention by exerting control over the experimental setting. Evaluation research and the PCT begin with the recognition that full control over implementation is unlikely. Hence, a variety of intermediate, or process, measures will need to be assessed to determine whether the intervention was, in fact, delivered and whether it affected outcomes. Returning again to the falls prevention example, Tinetti et al. [10] established the reach of their intervention in primary care, allied health, and long-term care settings. This was the primary indicator of whether the falls prevention intervention was delivered as intended. However, they were unable to determine how practitioners actually changed their falls assessment and referral practice as a result of the researchers' effort. Nonetheless, they were able to show a reduction in regional falls-related hospitalization.

The relationship between intervention elements, process indicators of whether an intervention was delivered as intended, and immediate and longer-term outcomes is typically shown in a logic model. The logic model is valuable for showing whether the absence of an effect is due to the lack of implementation of an intervention or a true failure of the intervention; that is, an error in the logic of the intervention.

11.5 Applications of Epidemiology to the Assessment of Policy in Aging Services

A major emphasis of Medicare policy in recent years has been to reduce the rate of growth in Medicare spending while improving the quality of care delivered to beneficiaries. We review contributions that aging services research has made to understanding sources of inefficiency in Medicare program spending, the impact of quality improvement initiatives in Medicare, and the effects of the new Medicare drug benefit on health care utilization.

11.5.1 Regional Variation in Health Care Service Use in Medicare: Evidence of Inefficiency

The need for cost containment in Medicare is great, as it is estimated that the hospital insurance trust fund will be insolvent in 2017. Medicare has grown to 12% of the federal budget and expenditures are growing at a rate much higher than the economy overall. This is due, in part, to demographic changes and the aging of the population, but it is mostly driven by technological innovation. Technological development in health care has brought gains in life expectancy and quality of life; however, there is considerable evidence of waste and inefficiency in the health care delivered to older adults.

The US spends far more per person on health care than is spent by other developed countries, 16% of gross domestic product compared to an average of 10% in Western Europe, Canada and Australia. Yet, life expectancy in the US lags behind these regions/countries [40].

Perhaps the most compelling evidence of inefficiency has come from health services research on regional variation using analyses of large claims datasets. The Dartmouth Institute for Health Policy has documented substantial variation in Medicare spending across 306 hospital referral regions in the US. As shown in Fig. 11.2, mean annual Medicare expenditures are more than two times higher in the hospital regions in the top quintile of spending ($9,224–$17,274) compared to those in the lowest quintile ($5,221–$7,122) [41]. Regions in the top quintile of Medicare spending have 50% more inpatient days, 36% more physician visits and 32% more MRIs per beneficiary than do regions in the bottom quintile of spending [42]. These differences persist even after adjusting for regional differences in health status and patient preferences.

Regional differences in the use of health care services appear to be driven by differences in the

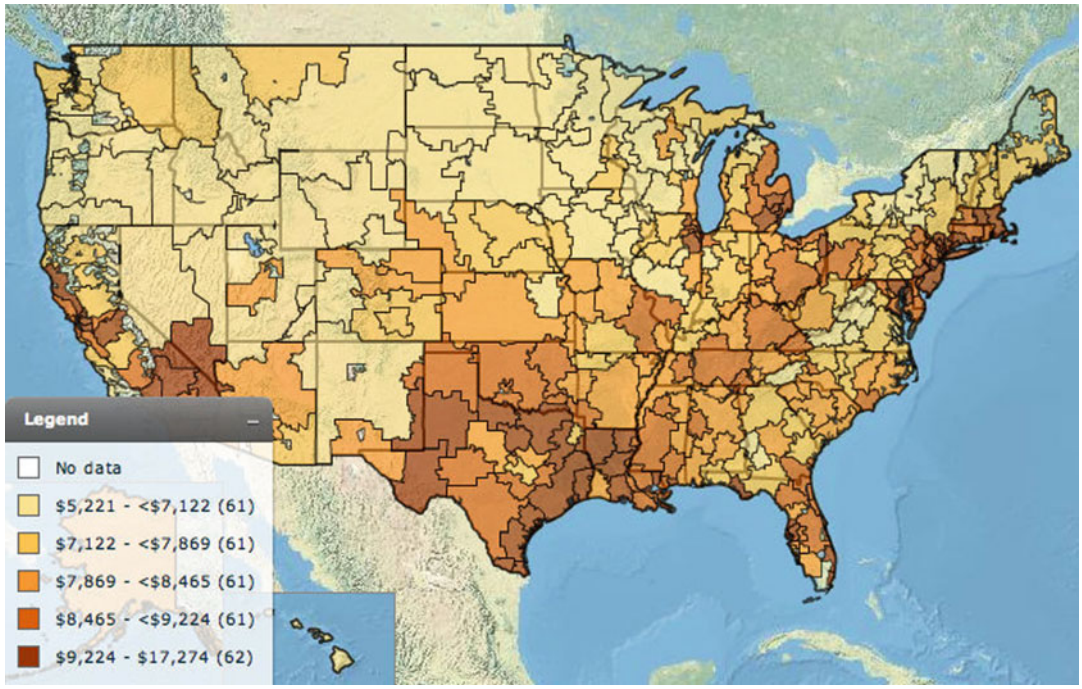

Fig. 11.2 Medicare reimbursements per enrollee, 2007 (Source: The Dartmouth Atlas of Health Care [46] http://www.dartmouthatlas.org/data/map.aspx?ind=124&ch=35%2c19&tf=10&loct=3)

supply of providers and technology. Incentives for the over-provision of care in Medicare are likely driven by fee-for-service reimbursement systems that pay hospitals for each admission and providers for each visit and/or procedure performed. Several studies have shown that this additional service use comes without commensurate gains in quality of care, or in health outcomes [43–46].

The sector with the greatest geographic variation is post-acute care (home health, skilled nursing facility, long-term care hospital, and inpatient rehabilitation facility). The metropolitan statistical area with the lowest spending on post-acute care spends an average of $60 per year per Medicare beneficiary compared to $450 in the area with the highest post-acute spending [47]. Post-acute care is therefore likely to be the target of policy interventions to standardize approaches to care and contain costs. In particular, CMS will experiment with new payment models that bundle or link payments for acute inpatient stays and post-acute care to encourage more efficient care delivery.

11.5.2 Quality Improvement in Medicare

In addition to efforts to control Medicare spending, policymakers seek to improve the quality of care delivered to beneficiaries. Although care has improved in some areas, it has worsened in others. For example, in-hospital mortality rates for pneumonia have declined, whereas 30-day mortality for pneumonia has increased slightly. Furthermore, many hospital admissions could be avoided through the better management of conditions, (e.g., chronic obstructive pulmonary disease and diabetes) in outpatient settings [48].

Two important approaches to improving the quality of inpatient care that is delivered to older adults have been the public reporting of hospital quality measures and pay-for-performance initiatives. In 2002, a consortium of organizations that represent hospitals launched the Hospital Quality Alliance (HQA), a national program to encourage hospitals to collect and report quality data. The program was meant to encourage hospitals that were performing poorly to implement

quality improvement initiatives. While participation was initially voluntary, the CMS subsequently made participation in the HQA a condition of hospitals receiving annual payment updates, and this requirement led to participation by 98% of hospitals. Hospitals began collecting and reporting data in 2003 on ten quality measures for three conditions: acute myocardial infarction (AMI), heart failure and pneumonia. These measures focused on processes of care; for example, whether or not older adults who were admitted for AMI received an aspirin and beta-blocker upon arrival.

In March of 2003, the CMS invited over 400 hospitals to participate in the Premier Hospital Quality Incentive Demonstration (HQID), a pay-for-performance initiative with the goal of determining whether economic incentives could be used to improve the quality of care delivered in hospitals. This program not only required hospitals to collect and report on quality measures (including the 10 used in the HQA plus 23 others), but also made bonus payments to top-performing hospitals, and in year 3 of the program, levied financial penalties against low-performing hospitals.

Epidemiologic methods have been used by health services researchers to evaluate the marginal impact of the HQID on hospital quality. Hospitals were not randomly assigned to participate in the program, but were invited by the CMS (and some declined). To adjust for secular trends in hospital quality, researchers matched hospitals that were exposed to the financial incentives with control hospitals that collected the same quality measures but did not participate in the pay-for-performance scheme [49]. Matching was based on hospital size, teaching status, region, location and ownership status. Over the 2-year study period, both the pay-for-performance hospitals and the control hospitals showed improvement in quality measures for all three conditions, but the magnitude of improvement was greater for the pay-for-performance hospitals. For example, control hospitals that participated in only the quality reporting initiative increased their vaccination rates for pneumonia by 19.1% from 2003 to 2005, whereas hospitals that participated in the pay-for-performance scheme increased their vaccination rates by 30% over the same time-period [49].

11.5.3 The Impact of Changes in Prescription Benefits

One of the most important changes to the Medicare program in recent years has been the creation of a prescription drug benefit (Part D) in January 2006. Prior to 2006, many older adults obtained drug coverage from private sources (e.g., retiree benefits, individually purchased Medigap plans) or, if they had incomes low enough to qualify them, public sources such as Medicaid. However, nearly 20% of beneficiaries had no source of insurance coverage for prescription drugs, and an additional 25% had limited coverage ($1,000 per year). The out-of-pocket burden of prescription drug costs was therefore high among older adults and led many, particularly those with low incomes, to skip doses or fail to fill prescriptions for essential medications [50]. Such cost-related non-adherence complicated the management of chronic diseases among older adults and was associated with the increased risk of emergency department use, hospitalization and mortality [51].

The Medicare Prescription Drug Improvement and Modernization Act of 2003 established Medicare Part D as a voluntary program (although beneficiaries face a late enrollment penalty if they fail to sign up when first eligible). Part D is administered by dozens of private insurance plans in each of 34 regions in the US. These plans differ with respect to the monthly premium they charge to beneficiaries, the list of drugs covered and the level of cost-sharing faced by beneficiaries. Medicare beneficiaries who are dually eligible for Medicaid, and who previously had their drugs paid for by state Medicaid programs, were automatically assigned to a Part D plan in their area. Other beneficiaries had to choose a plan in order to receive Part D benefits. Many who had private retiree benefits chose to remain in those plans as the coverage is often more generous than that offered under Part D.

In 2010, nearly 28 million beneficiaries (60%) were enrolled in Part D plans [52].

Part D has some unique features. First, the benefit design in Part D differs from drug benefits offered by other payers. The standard benefit calls for a $310 deductible, and 25% cost-sharing up to $2,840 in total annual drug costs (although plans are permitted to vary these aspects of benefit design and most choose to do so). Beyond $2,840 in total drug spending, Part D contains a gap in coverage (or "donut hole") within which beneficiaries must pay 100% of their drug costs. Older adults who have a high level of annual drug spending may then exceed the catastrophic coverage limit ($6,448 in 2011), beyond which the enrollee pays only 5% of drug costs. This benefit design structure was chosen to balance several competing policy goals: the desire to encourage beneficiaries with low drug spending to participate in the program, to offer protection to those who have catastrophically high drug costs, and to keep overall program costs low.

A second notable feature of Part D is its provision of very generous drug coverage to beneficiaries in the low-income subsidy program (individuals who have incomes less than 150% of the federal poverty level and have modest assets). Participants in the low-income subsidy program do not have to pay monthly Part D premiums, pay very low cost-sharing ($1–$5 per prescription) and do not face the coverage gap or donut hole. As of 2009, it was estimated that 12.5 million Medicare beneficiaries were eligible for this program, but nearly one-fifth (2.3 million) were not enrolled [52].

Some key challenges confront researchers who evaluate the impact of Part D on drug utilization and costs, and on health outcomes. The first is the lack of a nationally representative administrative dataset from which to construct measures of drug utilization both before and after Part D's implementation. One exception may be the MCBS, mentioned earlier. The MCBS collected validated self-report information on drug utilization before and after Part D. However, the sample size may be too small to study some drug classes, and claims data—which include the dates of prescription fills which are needed to construct measures of medication adherence—were not available prior to Part D. A second challenge to researchers who are examining the impact of Part D is that the voluntary nature of the program creates selection bias. Beneficiaries can choose whether or not to enroll in Part D, and these choices are likely influenced by characteristics that are related to key outcomes of interest. Prescription drug use is more persistent and therefore more predictable to consumers than the use of other health services, and may drive decisions to enroll in Part D as well as the choice of a particular Part D plan.

Quasi-experimental approaches to studying the impact of Part D seek to minimize the selection bias that is associated with enrollment into the benefit. For example, one set of studies has used data from a large Medicare Advantage plan with relatively stable enrollment that had various levels of pharmacy benefit before Part D's implementation. As noted earlier, approximately 25% of Medicare beneficiaries are enrolled in a Medicare Advantage or managed care plan. Before 2006, this particular plan had some members enrolled through their former employer, who offered generous pharmacy benefits. A second group enrolled in the plan as individual members and had either no drug coverage or quarterly caps on what the plan paid depending on the member's county of residence. On January 1, 2006, members who had no drug coverage or had limited benefits automatically received the Part D benefit if they stayed in the plan (and most did). This was the 'intervention' group that was exposed to Part D. Members with retiree drug coverage retained that coverage if they stayed in the plan (and most did). This second group served as the comparison group to adjust for secular trends in the outcomes of interest. Because the level of pharmacy benefits prior to Part D varied according to county of residence and whether or not the member was offered retiree benefits, selection bias was thought to be minimal.

Studies that use this quasi-experimental approach have reported a decrease in out-of-pocket costs for prescription drugs and a 74% increase in monthly prescription drug spending among those transitioning from no coverage

to Part D [53, 54]. In addition, adherence to pharmacotherapy for many chronic conditions improved with Part D [55, 56]. However, the use of potentially inappropriate medications such as antibiotics for acute respiratory infections also increased with Part D's introduction [57].

11.6 Conclusions

In this chapter we have shown ways that epidemiologic methods may be applied to aging services research. This effort requires an expansion of traditional epidemiology in a number of directions: greater flexibility in methods (use of quasi-experiments and PCTs); access to large administrative datasets that allow only partial control over selection bias and the identification of diagnostic groups and service episodes; and the incorporation of new measures that account for program access and reach (such as the RE-AIM framework). Still, traditional epidemiologic tools can be applied in aging services research, as shown in the increasing number of randomized controlled trials in this area.

The ultimate goal of aging services research is to determine how effective medical and supportive care services can best be delivered to older adults, with the goal of enabling older adults to continue living in the community despite disability, social isolation, chronic medical conditions, hospital episodes, polypharmacy and psychosocial vulnerability. This research may involve the evaluation of particular programs or the assessment of the implementation of evidence-based programs that have been developed for different settings or populations. It may also involve the assessment of changes in national policy, such as the new Medicare Part D prescription benefit, or of attempts to assure quality in hospitals and nursing homes through a mix of federal financial incentives and penalties. A growing body of research in these areas, which is critical for rational policy, shows the value of expanding epidemiologic tools in aging services research.

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Part II

Aging, Geriatric Syndromes and Common Conditions

Understanding the Aging Process Using Epidemiologic Approaches

12

Jason L. Sanders, Robert M. Boudreau, and Anne B. Newman

Abstract

Recent research has identified that aging and disease are not synonymous and that aging can be optimized. This has been demonstrated in animal models with genetic manipulation and caloric restriction that delay aging, morbidity and mortality. In these systems, mortality rate has been the primary marker of aging, but *in vivo* markers of aging are needed for human studies. Specifically, biomarkers of primary aging are needed as intermediate outcomes to understand the aging process and potential early benefits of preventive interventions. A useful approach for identifying and testing biomarkers of aging in epidemiologic studies includes demonstrating biologic plausibility that the marker describes a basic aging process, demonstrating the potential for translation from bench to bedside and to population, and subsequently assessing associations with important aging outcomes using optimal epidemiologic study designs and in accord with key statistical considerations. Biomarkers that putatively measure aspects of aging include interleukin-6, leukocyte telomere length, advanced glycation end products, insulin-like growth factor-1, dihydroepiandrostenedione sulfate and klotho. With these tools, epidemiologists will help uncover the secrets to living a healthy, long life and be integral to the design, implementation and assessment of interventions to promote healthy aging.

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Abbreviations

25(OH)D	25-Hydroxy Vitamin D
AGE	Advanced Glycation End Product
ApoE	Apolipoprotein E
CALERIE	Comprehensive Assessment of Long-term Effects of Reduced Intake of Energy
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHS	Cardiovascular Health Study
CI	Confidence Interval
CML	Carboxymethyl-lysine
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone Sulfate
DSST	Digit Symbol Substitution Test
ELISA	Enzyme-Linked Immunosorbent Assay
esRAGE	endogenous secretory Receptor for Advanced Glycation End Product
FGF	Fibroblast Growth Factor
GH	Growth Hormone
HDL	High-Density Lipoprotein
Health ABC	Health Aging and Body Composition
HGPS	Hutchinson-Gilford Progeria Syndrome
HR	Hazard Ratio
IGF	Insulin-like Growth Factor
IGFBP	Insulin-like Growth Factor Binding Proteins
IL-6	Interleukin-6
InCHIANTI	Invecchiari in Chianti Study
LDL	Low-Density Lipoprotein
LTL	Leukocyte Telomere Length
OR	Odds Ratio
PI3K	Phosphoinositol-3 Kinase
qPCR	Quantitative Polymerase Chain Reaction
RAGE	Receptor for Advanced Glycation End Product
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
sRAGE	soluble Receptor for Advanced Glycation End Product
TNF-alpha	Tumor Necrosis Factor Alpha
XP	Xeroderma Pigmentosum

12.1 Introduction

With the advent of deeper insights into the biology of the aging process, a new field is emerging: the epidemiology of the biology of aging. Many epidemiologic studies of aging have focused on a specific common, disabling chronic disease in older adults such as atherosclerosis, osteoporosis and Alzheimer's and other neurodegenerative diseases for which aging is a major, though poorly understood risk factor. These studies have been crucial in determining the factors that accelerate age-related diseases, and in intervening to prevent or delay them.

Aging can be recognized as a loss of physical functioning and an increasing vulnerability to mortality. After accounting for the accumulation of disease, there remains a component of disability and mortality risk that is not fully explained. Age itself remains a strong risk factor. Epidemiologic approaches have been useful for

elucidating the pathways that could explain the risk that age itself signifies. One approach uses non-invasive testing to identify early disease, showing that clinically diagnosed disease is just the tip of an iceberg of disease burden. Some changes that occur with aging, such as stiffening of the blood vessels and eye lenses, occur in the absence of disease and also impact function and survival [1]. Yet, even after considering these markers of undiagnosed disease and decline, age continues to be a strong and independent risk factor for functional loss and mortality. In addition to the changes of aging and disease, some of the loss of function and risk of death with aging can be attributed to disuse and inactivity as is often a consequence of disease, yet accounting for these secondary effects still does not explain the functional loss and vulnerability of older adults.

Another approach in epidemiology translates observations from model systems to human population studies. There are numerous examples of damage and repair systems that can influence aging and longevity when impaired in model systems. These basic processes have been shown to contribute to functional loss and mortality, either directly or through the acceleration of disease processes. This close relationship between aging and disease, and the influence of aging on age-related disease, make it difficult to define aging as a distinct process in epidemiologic studies. Thus, evidence of the acceleration of multiple age-related chronic diseases, age-related changes in function and mortality risk itself have been taken as evidence of aging *per se*.

In this chapter, we discuss some of the approaches that have been used to sort out biomarkers of aging in epidemiologic studies. We also review several epidemiologic studies of markers of the fundamental damage and repair processes that have been linked to aging in both basic and human studies.

12.2 Aging vs. Disease

Although it is uncertain whether a primary process of aging can be fully distinguished from the secondary process of disease, recent research has identified that aging and disease are not synonymous, and have subsequently identified that aging can be optimized. This has been most clearly demonstrated in animal models with genetic manipulation and caloric restriction that delay aging, morbidity and mortality. In these systems, mortality rate has been the primary marker of aging. In human studies, *in vivo* risk markers of aging are needed due to the longer human lifespan. Specifically, markers of primary aging are needed as intermediate outcomes to understand the aging process and potential early benefits of preventive interventions.

In spite of recent evidence that the rate of aging can be modified, aging remains an inevitable process. Herein, we define aging as a biological process that is universal, irreversible and deleterious. Its deleterious effects are recognized as a loss of or alteration in function and an increased vulnerability to death, thus these outcomes can be used in epidemiology studies to validate risk factors for aging. Age-related diseases are not universal in that they affect only some individuals and have risk factors other than age which are modifiable. Age-related diseases are possibly reversible (i.e., there are available preventive measures to remove risk factors and/or clinical treatments for overt disease), but they are still deleterious. Since age is a risk factor for disease, a biomarker of aging may well also predict disease, but it should do so independently of external risk factors (Fig. 12.1).

12.3 Working Definition of a Biomarker of Aging

In 1988, Baker and Sprott defined a biomarker of aging as, "a biological parameter of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age" [2]. This definition has stood the test of time, yet it deserves comment [3, 4]. First, the authors mentioned that biomarkers should be examined on both a one-by-one basis and as "multivariate composites." Researchers must consider the theoretical and practical limitations

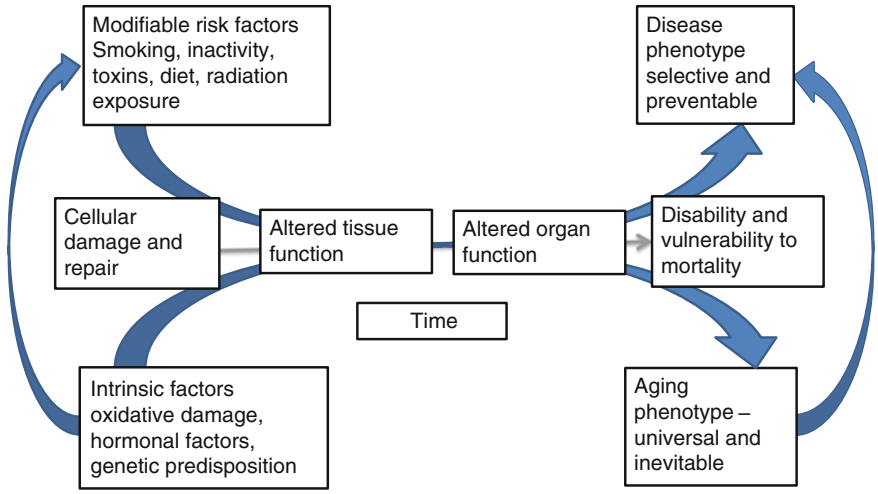

Fig. 12.1 Pathways that link aging and age-related disease

on which biomarkers can be combined and how biomarkers may be optimally combined to form a composite measurement. We will limit our discussion to individual markers of aging processes, though this would not preclude further study to develop composite indices.

Second, Baker and Sprott included the phrase "in the absence of disease." Age-related changes that occur regardless of disease include the thinning and wrinkling of skin and graying of hair; loss of visual accommodation, hearing sensitivity and smell; increased blood pressure; decreased maximal heart rate, kidney function, bone mineral density, muscle mass, peripheral nerve discrimination and thirst drive; impaired thermoregulation and immune function; intracellular accumulation of lipofuscin; cross-linking of collagen; and many others [5]. There are also aspects of aging and age-related disease which overlap [6]. It may be argued that a biomarker of aging is an indicator of primary aging (i.e., aging completely independent from disease, a process that is universal, irreversible and deleterious), an indicator of age-related chronic disease or an indicator of both. Preferably, a biomarker of aging would enable the monitoring of a basic aging process independent of disease. But due to the strong tie between aging and many chronic diseases and the increasing use of subclinical measurements which identify "disease" at earlier points in its course, it is expected that strong biomarkers of aging would interact with external risk factors to accelerate age-related disease.

Third, Baker and Sprott wrote that biomarkers should be used for prediction. This is logical, though we can explicitly add that if biomarkers were useful for prediction, they might serve as points of intervention for the prevention of unhealthy aging and/or disease.

Fourth, Baker and Sprott declared that biomarkers should predict "functional capability". Although there is no accepted definition of aging, it can be visualized as a progressive decline in the ability to function over time with increasing vulnerability to death, so this conceptualization seems an appropriate anchor for defining a biomarker of aging.

Fifth, Baker and Sprott asserted that a biomarker should predict functional capacity better than chronologic age. This idea stems from the observation that organisms of the same species with the same chronologic age exhibit heterogeneity in health, fitness and life expectancy [7], and that chronologic age is therefore a suboptimal predictor of health status. It must be noted that chronologic age remains the most robust predictor of future events, so prediction better than that of chronologic age is often difficult to achieve. In bench research, biomarkers may provide strong insight into the biology of aging without achieving

statistical dominance over chronologic age. Similarly, in epidemiologic studies, biomarkers may meaningfully increase predictive accuracy without being a stronger predictor than chronologic age. It is generally not accepted as a rule that biomarkers of aging must be stronger predictors than chronologic age in statistical models, but it is desirable that a biomarker of aging would attenuate the effect of age.

12.4 Identifying and Testing Potential Candidate Biomarkers of Aging

The selection of potential candidate biomarkers should be informed by a strong understanding of the basic biology of aging. Several key biologic pathways are robustly related to aging phenotypes and mortality, or can—when altered—produce longevity in animal models. To date, no criteria have been explicitly proposed for selecting potential candidate markers for epidemiologic studies of aging. In this section, we set forth an approach for identifying and testing biomarkers of aging in epidemiologic studies. This approach includes (1) demonstrating biologic plausibility that the marker describes a basic aging process; (2) demonstrating potential for translation from bench to bedside and to population, using non-invasive high throughput measurement with excellent reproducibility and validity; and (3) subsequently assessing associations with important aging outcomes using optimal epidemiologic study designs and (4) in accord with key statistical considerations.

12.4.1 Biological Plausibility

A biomarker should monitor a basic process that underlies aging. This basic process is likely conserved across species. Fulfillment of this criterion requires careful examination of the literature and one's own data. It is possible that species-specific biomarkers of aging exist, though the commonality of aging across species implies that a core set of processes are conserved and shared, and that identifying biomarkers of these processes will provide the most insight into the biology of aging. Basic processes include those that operate at the molecular, cellular, tissue, organ, organ system and whole organism levels. These can include alterations in the somatic genetic code (viral inclusions, errors of DNA replication and repair), transcriptional accessibility (epigenetic changes), transcriptional volume (mRNA content), translational volume (protein production), post-translational modification (glycation, oxidation, nitration, phosphorylation, racemerization, isomerization, ubiquitination), tissue histology and morphology (changes in tissue elasticity, lipofuscin accumulation, plaque formation), oxidative stress, inflammation, cellular senescence, organ function, and physical and cognitive function.

One of the most robust manipulations for inducing longevity is caloric restriction. Pathways that regard the sensing and response to nutrient availability in the environment can be manipulated in model systems to recapitulate caloric restriction [8]. The insulin signaling pathway is central to this well-conserved system. Animal models of longevity almost all involve the down-regulation of insulin-like growth factor (IGF). This provides strong support for examining IGF-1 as a probe of the integrity of the insulin signaling pathway in human studies of aging and longevity.

Oxidative damage plays a major role in damaging DNA, proteins and lipids and in producing an inflammatory response. Changes in these molecules may themselves be probed as indicators of oxidative damage. Precipitants of oxidative damage, such as non-enzymatic glycation, can also be directly assessed. The cumulative shortening of telomeres is thought to be due in part to oxidative DNA damage, thus telomere length can be assessed in part to probe the oxidative damage pathway.

A candidate biomarker should ideally act and be measurable in both humans and laboratory animals so that it can be tested in animals before being validated in humans. Observational and experimental studies in model systems are often simpler, cheaper and quicker than are similar

studies in humans, and they can be used to vet biomarkers in a semi-high-throughput fashion before expending resources on human studies. Even complex biomarkers, such as indicators of mobility and activity, have been measured in lower-order animals like the nematode *C. elegans* and rodents. Although some biomarkers will be specific to humans or act differently in humans, validation across species can uncover fundamental mechanisms that underlie aging and disease.

12.4.2 Translation to Large Human Population Studies

Once a candidate marker is proposed, it must be assessed for transferability to the population setting. This generally requires assessment in stored blood or via non-invasive imaging. Researchers should be able to test a candidate biomarker repeatedly and accurately without harming the tested individual. Ideally, researchers should also be able to measure the candidate biomarker inexpensively, efficiently and reproducibly. Because these samples are usually a finite resource, assays should require a minimal volume of sample and be accurate after cycles of sample thawing and refreezing. Fulfillment of these criteria maximizes the usefulness of the biomarker as a tool for research and clinical care. Nonetheless, if a biomarker provides meaningful data but its measurement is impractical, investigators should not dismiss it outright because future innovations may allow easy, cheap, safe and accurate measurement.

12.4.3 Epidemiologic Study Designs

Once a candidate marker is selected for study, there are several important study design issues to consider in determining whether a marker is associated with aging and important outcomes of the aging process. Most aging studies use a longitudinal cohort design that focuses on older adults (65 or 70 years of age and older) and examines baseline associations with prospective health outcomes [9]. Studies designed to examine specific disease outcomes will often include assessments of the consequences of the disease of interest, including total mortality as well as physical and cognitive function. Such cohorts can be studied for aging outcomes *per se*. Key aging outcomes to consider include the achievement of advanced old age itself, mortality risk, and decline vs. maintenance of physical functioning.

Markers of functional decline that are predictive of mortality can be assessed as intermediate outcomes. These include grip strength, gait speed, cognitive speed and other intermediate phenotypes. At least a portion of these age-related changes can occur in the absence of—and distinct from—age-associated chronic diseases. The analysis and interpretation of associations should carefully consider the temporal sequence of events and the potential for secondary declines subsequent to disease (Fig. 12.2).

Studies of age-related disease have demonstrated that there are changes that begin prior to age 65. Some of these changes have been described in life-course studies such as the Baltimore Longitudinal Study on Aging. Several aspects of aging declines, such as loss of muscle strength [10], exercise tolerance [11] and bone density [12] have been clearly documented to begin prior to age 40 or 50 and often seem to accelerate in later life. Studies of middle-aged adults will have few hard outcomes such as disease or mortality, but can inform us about aging biomarkers by assessing longitudinal change as intermediate aging outcomes.

There are several types of trajectories that can be seen with aging. The pattern will depend in part on whether the most important aspect is the starting value, the rate of decline or the age of decline onset. For example, the onset of decline in gait speed, a common measure of function in aging, might be delayed in healthier vs. less healthy older adults without a difference in the rate of decline (Fig. 12.3). For systolic blood pressure, the rate of rise might be slower in healthier older adults vs. the less healthy, and thus differ primarily in the slope or rate of age-related change. For cognitive decline, we hypothesized that the healthiest oldest adults may have started with higher values, and thus have higher absolute

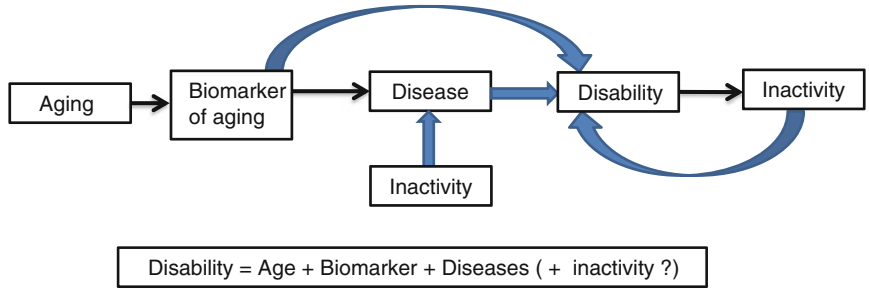

Fig. 12.2 Aging and disease consequences; an example of the potential for over-adjusting for inactivity in the analytic approach

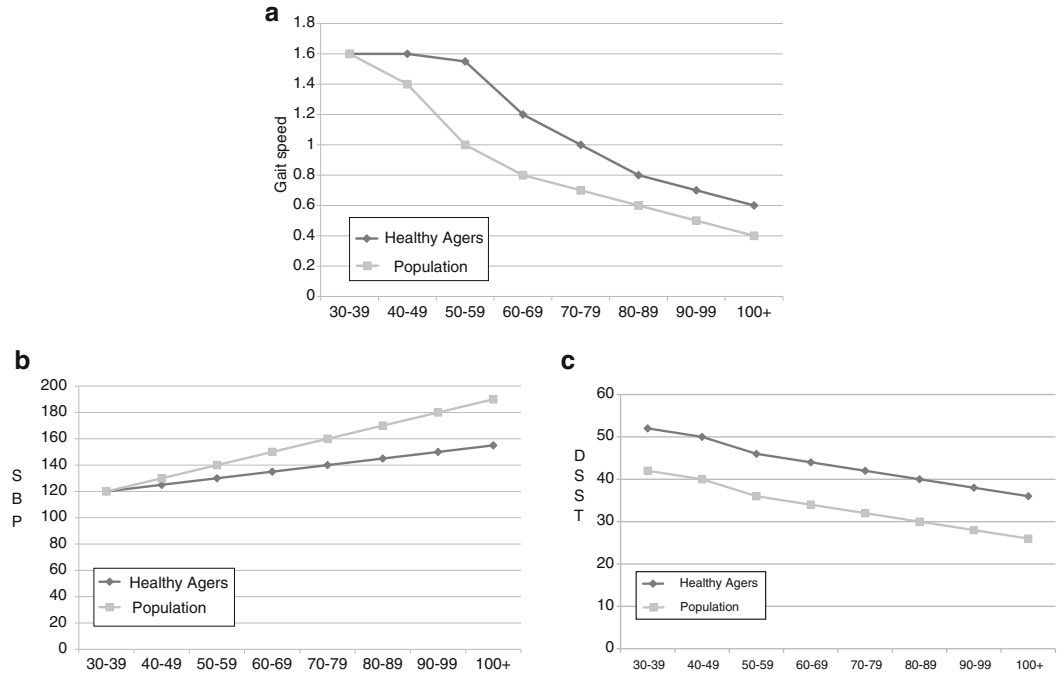

Fig. 12.3 Examples of trajectories of age-related change that represent different phenotypes: (**a**) delayed onset of decline (gait speed), (**b**) slower rate of change (SBP), or (**c**) higher peak function and greater reserve (DSST). *Abbreviations: DSST* digit symbol substitution test, *SBP* systolic blood pressure

function on a test such as the digit symbol substitution test (DSST). Therefore, the key factor in the trajectory might be the level of peak function obtained. We evaluated the associations of these factors with age in the Long Life Family Study and found patterns similar to those hypothesized [13]. The associations of aging biomarkers with longitudinal trajectories could well differ for different specific aspects of age-related change: age of decline onset, rate of age-related change or age of peak function. Additionally, we found that the variability of the trajectory can indicate another key aspect of physiologic change [14, 15]. Each of these aspects of trajectories should be characterized in a longitudinal analysis.

Another way to detect differences is by studying extreme populations such as centenarians or individuals with progeroid syndromes. More simply put, rather than compare individuals within a large general population, focus would instead be put on the outliers, those who are highly different from the average. Although data

derived from outliers may not be as generalizable, one often finds interesting associations at the extremes because there is a large difference between the mean of the general population and the mean of the outliers. Furthermore, gathering a small number of individuals who are at an extreme may create a more homogeneous phenotype, dampening the noise effect which can obscure associations and reduce statistical power.

At one end of the aging spectrum are individuals who age rapidly, who are often lumped into a group of progeroid syndromes. These syndromes, such as Werner's syndrome, Hutchinson-Gilford Progeria Syndrome (HGPS) and Xeroderma pigmentosum (XP), have characteristics which appear like accelerated aging. These syndromes also enable the probing of distinct molecular pathways due to their genetic origins. For example, in Werner's syndrome, which is caused by a mutation in the *WRN* gene, patients have a faulty $5' \rightarrow 3'$ DNA helicase and exonuclease. Interestingly, the molecular hallmark of Werner's syndrome is accelerated telomere attrition [16]. HGPS is characterized by a defect in lamin A (coded by *LMNA)*, a cytoskeletal protein which supports the nuclear envelope [17]. The defect causes accumulation of the protein around the nuclear envelope, the misshaping of the envelope, improper interaction between the envelope and adjacent chromatin, disordered nuclear function, and the inability of the cell to divide. HGPS patients have short stature, thinned skin, low-frequency conductive hearing loss, growth hormone deficiency, insulin resistance and many signs of cardiovascular aging including age-associated elevated blood pressure, reduced vascular compliance, decreased ankle–brachial indexes and adventitial thickening, but they usually show normal cognition [18]. HGPS patients die at an average age of 13 years from myocardial infarction or stroke due to massively accelerated arteriosclerosis. XP can manifest from one of many point mutations in genes that encode proteins that are involved in nucleotide excision repair [19, 20]. The genomic instability causes apoptosis and mutagenesis in many tissue types and clinically manifests as neurodegeneration (loss of neurons), endocrine dysfunction (loss of somatotrophic axis), photoaging of the skin and eyes, proliferation of cutaneous tumors, and hematopoetic failure (replicative senescence of hematopoetic stem cells). The drawbacks of using these syndromes to probe aging include the small numbers of available patients (limiting power) and differences in aspects of their presentation compared to "normal" aging. However, the syndromes can be replicated in model systems, particularly in rodents, which may enable the study of certain aspects of their biology in association with potential biomarkers.

At the other end of the aging spectrum are individuals who age slowly. These individuals have been described as exhibiting longevity, healthy aging or exceptional survival, among other terms which are not necessarily interchangeable. The opportunities to study the epidemiology of healthy aging are increasing rapidly [21]. The Long Life Family Study recruited nearly 5,000 individuals clustered in families with exceptional longevity (and their spouses) to participate in a study of the genetics of healthy aging. Compared to age-matched controls from population-based cohorts that were not selected for longevity, Long Life Family Study participants exhibited better health [13]. Centenarians have been gathered in the New England Centenarian Study. By virtue of living to be at least 97 years old, these adults exhibit exceptional longevity. A major limitation of these studies is the challenge of defining a comparison group. Given that a cohort-matched comparison group would be deceased, some have focused on the children of both centenarians and already-deceased individuals to provide this contrast [22].

Unique populations are also of interest to study. Seventh-Day Adventists, a self-selected cohort who adhere to strict dietary, social and religious customs, and the Okinawan Japanese, a geographically and ethnically defined cohort who also have a unique dietary, social and religious makeup, have been found to exhibit exceptional longevity compared to general population references [23–25]. Other populations of interest include long-lived individuals derived from general population cohorts, such as members of the Cardiovascular

Health Study (CHS) All Stars study. The CHS All Stars study re-recruited 1,677 participants of the CHS who were alive in 2005–2006 to assess cognitive and physical function [26]. With a mean age of 85 years, an age range of 77–102 years and nearly two decades of extensive phenotyping, the CHS All Stars could be a particularly interesting population within which to examine biomarkers. Another approach is pooling general population cohorts to achieve a sufficiently large sample of long-lived individuals, as was done in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. There are many opportunities to explore biomarkers among these extremes.

12.4.4 Statistical Considerations

Once the study design is set, key statistical criteria can support a measure as a biomarker of aging. First, a biomarker should be correlated with chronological age. It is unlikely that there will be much of an association with subsequent age-related changes if this fundamental association is not seen cross-sectionally. In other words, it should tell exactly where a person is in their total lifespan with regard to some measurable parameter of aging.

A second statistical criterion is that the marker should predict age-related outcomes independently of chronological age, and as or more strongly than does chronological age [2, 3, 27, 28]. Fulfillment of this criterion can be investigated in several ways. Using regression coefficients in a statistical model, the magnitude of the association of the biomarker with the outcome of interest can be directly compared to the magnitude of the association of chronologic age to the outcome. Ideally, when both are standardized, the coefficient of the biomarker is larger than the coefficient of age.

Another approach is to assess the magnitude of the standardized coefficient of the biomarker compared to the magnitude of the unstandardized coefficient of chronologic age in order to illustrate how many years of chronologic aging is depicted by a standard difference in biomarker levels when both are compared to an age-related outcome such as mortality risk or the loss of muscle strength. For example, if the coefficient of a biomarker on muscle mass was ten units per standard deviation (SD) of the biomarker and the coefficient of age on muscle mass was two units per year of age, then 1 SD in the biomarker can be expressed as being similar to the effect of 5 years of chronologic aging on muscle mass. Biomarkers that have more years of chronologic aging depicted by a standard difference in biomarker level are likely stronger biomarkers of aging.

One should always assess the ability of the biomarker to attenuate the statistical effect of age. In a statistical model, this can be achieved simply: one model is built including age as a covariate, and the next model is built including age and the biomarker. The degree to which the coefficient of age is attenuated by the addition of the biomarker provides evidence for how much the effect of chronologic age is explained by the biomarker. Greater attenuation suggests a stronger biomarker of aging. Significant attenuation—or more broadly, mediation—can be formally tested using mediation regression equations [29]. If longitudinal data is available, mediation can be identified using autoregressive models or latent growth modeling depending on assumptions of the relationship between changes in the mediator, independent variable and dependent variable.

Of note, continuous measurements may provide more statistical range and variance than categorical measurements. Subsequently, biomarkers that can be measured continuously may be able to account for more variance in a given outcome, so they may be more powerful predictors on this basis alone.

When testing a biomarker's predictive ability, it is important to consider what represents the "rate of aging". A rate implies change over time, so ideally the biomarker would be used to predict a change in a physiologic parameter over years. This introduces additional statistical nuance if measurements are derived from populations because person-specific (e.g., linear regression with random intercept) or population-average (e.g., generalized estimating equation) models can be fit to estimate the biomarker's ability to predict an outcome's change in an individual or

average change for the population, and each slope is interpreted differently. Rather than using a rate of change in an individual, a biomarker is more often used to predict a population's mortality or rate of death, or some intermediate representation of longevity such as high gait speed and cognitive function. Finally, when predicting an outcome, various statistical values can be used to illustrate the quality of prediction. Examples include the amount of variance in the outcome that is accounted for by a biomarker (e.g., using partial r^2 values) and the overall accuracy of prediction (e.g., using the area under the curve method to determine a concordance statistic).

12.5 Examples of Candidate Biomarkers of Aging in Epidemiologic Studies

Many biomarkers of aging have been posited (Table 12.1). They range from alterations in the genome (e.g., DNA methylation) to whole-body function (e.g., gait speed). It is important to consider the potential links between biomarkers at each level of organization. We will focus our discussion on factors that can be measured in stored blood, though biomarkers can also be measured at the level of organ and organism. Structural and functional changes, such as muscle strength, vascular stiffness, loss of lens accommodation and other changes in organ system function can be viewed as biomarkers of aging, and they link to frailty and disability as well as morality risk. Biomarkers at any level of organization frequently reflect several processes which may contribute to aging rather than a single process. Investigators must pay close attention to the sensitivity and specificity of biomarkers to illustrate particular processes and/or levels of organization, and must acknowledge the lack of specificity and sensitivity when appropriate. Below, we focus on examples of putative molecular biomarkers of aging which hold great promise for advancing the understanding of the biology of aging in epidemiologic studies. Table 12.2 summarizes how these particular markers reflect biologic plausibility, measurability and associations with key aging outcomes.

12.5.1 Inflammation: Interleukin-6 (IL-6)

Many theories of aging include inflammation as a central component. In an acute setting inflammation can be advantageous by promoting the death of infectious organisms and necessary wound healing. Chronic elevations of inflammatory markers are very common in older adults [30] and indicate immunomodulation of the inflammatory response to ongoing damage from multiple sources.

The biomarkers of inflammation that are most commonly used in epidemiologic studies of aging include IL-6, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-alpha) [30, 31]. IL-6 is a cytokine that is produced by immune cells, vascular endothelium, adipose tissue and muscle. It exhibits pro-inflammatory and anti-inflammatory behavior. CRP is an acute-phase protein that is produced by the liver in response to IL-6. CRP may illustrate liver function in addition to inflammation. TNF-alpha is also a cytokine and is mainly secreted by immune cells (macrophages, mast cells, lymphoid cells), with additional secretion from adipose tissue, muscle, fibroblasts, vascular endothelium and neurons. In the absence of disease, there is a steady age-related increase in these biomarkers, particularly IL-6 and TNF-alpha [30, 31]. The half-life of circulating IL-6 is short and some studies have examined their receptors or the total number of elevated markers to get a more stable estimate of exposure. The primary literature on these biomarkers and their relevance to aging and disease is extensive. In this section, we briefly discuss IL-6 because it exhibits the most consistent associations in older populations.

There are many potential causes for the age-related increase in IL-6, but specific risk factors remain poorly defined. Adipose tissue is an endocrine organ that produces cytokines and adipokines. In particular, visceral adipose tissue vs. subcutaneous adipose tissue may preferentially secrete IL-6 [32]. With the age-related shift in body composition toward visceral adiposity, this may account for 10–35% of circulating IL-6 [32, 33]. The Invecchiari in Chianti (InCHIANTI) study, Health, Aging and Body Composition

Table 12.1 Candidate biomarkers of aging under investigation in laboratory and epidemiologic research

Level of organization	Marker	Potentially measured aspect of aging	Potentially associated disease if low[a]	Potentially associated disease if high[a]
Genetic	DNA Acetylation	Transcriptional accessibility, epigenetic imprinting		
	DNA Methylation	Transcriptional accessibility, epigenetic imprinting		
	microRNA expression	Post-transcriptional regulation		
	Thymine dimer	DNA repair capacity, radiation exposure		Cancer, Xeroderma pigmentosum
	8-oxoguanine	DNA repair capacity, oxidation		Cancer
Molecular & Cellular	Interleukin-6	Inflammation, infection, oxidation		Cardiovascular disease, cancer, osteoporosis, diabetes, frailty, sarcopenia, infection, cognitive decline
	C-reactive protein	Inflammation, infection, oxidation, liver function	Liver disease	Cardiovascular disease, cancer, diabetes, frailty, sarcopenia, infection, cognitive decline
	Telomere length	Inflammation, oxidation, cellular senescence, oncogenic potential	Idiopathic pulmonary fibrosis, bone marrow failure syndrome, dyskeratosis congenita, Werner's syndrome	Cancer
	p16	Cellular senescence, oncogenic potential	Cancer	
	Dehydroepiandrosterone sulfate	Sex steroid hormone reserve		
	Insulin-like growth factor	Energy metabolism, growth	Growth insufficiency	
	Advanced glycation end products	Non-enzymatic glycation and oxidation of proteins, lipids, nucleic acids		Diabetes, cardiovascular disease, kidney disease, dementia
	Isoprostanes	Lipid peroxidation, oxidation		Neurodegeneration, coronary heart disease
	KLOTHO	Insulin sensitivity, Vitamin D regulation	Hyperphosphatemia, reduced bone mineralization, kidney disease	
	Lipofuscin	Fatty acid oxidation, lysosomal digestion, autophagy, protein recycling		Lipofuscinoses (neurodegeneration), liver disease, kidney disease
Tissue & Organ	Aortic calcification	Arteriosclerosis		Arteriosclerosis
	Pulse wave velocity	Arterial stiffness		Hypertension
	Forced expiratory volume	Pulmonary reserve, muscle strength	COPD	

(continued)

Table 12.1 (continued)

Level of organization	Marker	Potentially measured aspect of aging	Potentially associated disease if low[a]	Potentially associated disease if high[a]
	Brain volume	Cognitive reserve	Dementia	
	White matter hyperintensities	Integrity of white matter and subcortical tract connectivity		Hypertension, dementia
	Cystatin-C	Kidney function, inflammation		Kidney disease, osteoporosis, cardiovascular disease
	Nerve conduction amplitude, monofilament sensitivity	Peripheral nerve function	Peripheral neuropathy, diabetes	
	Lens transparency	Maintenance of protein conformation, oxidation	Cataract	
	Lean mass	Sarcopenia	Frailty	
Organismal function	Gait speed	Muscle function, peripheral and central nervous system function, cardiopulmonary fitness		
	Digit Symbol Substitution Test	Processing speed, visual-motor function	Dementia	
	Fatigue	Energy metabolism, cardiopulmonary fitness, mental wellbeing		
	Activities of daily living	Mental and physical health		
	Frailty	Energy, strength, mental wellbeing		

[a]Associations may be correlative and/or causal. Most data is derived from human studies, though data for some markers (e.g., KLOTHO) is predominantly from animal models
Abbreviation: COPD chronic obstructive pulmonary disease

Table 12.2 Candidate biomarkers and evidence for examining for association with aging in epidemiology studies

Biomarker	Biologic plausibility	Measurable in high throughput, precise, accurate assay	Associated with aging outcomes	Attenuates effect of chronological age on outcomes
IL-6	++	++	++	++
Leukocyte telomere length	++	+	+/–	+/–
AGE's	++	+	+	+
IGF-1	+	++	+/–	+
DHEAS	+	++	+/–	+/–
KLOTHO	+	+	+	+

+Association
++Strong, consistent associations
+/–Mixed positive and negative associations
Abbreviations: AGE advanced glycation end product, *DHEAS* dihydroepiandrostenedione sulfate, *IGF-1* insulin-like growth factor-1, *IL-6* interleukin-6

(Health ABC) study and Framingham Heart Study demonstrated associations between obesity and IL-6 [34–36]. Age-associated decline in sex hormones, particularly estrogen after menopause, is strongly associated with a subsequent increase in inflammation, especially IL-6 [37–41]. Smoking has long been recognized as a risk factor for inflammation [42]. Periodontal disease is associated with elevated IL-6, possibly due to regular exposure of the body to infectious microorganisms that are harbored in the oral cavity [43]. Regular physical activity is associated with lower IL-6, which illustrates a possible mechanism for some of the benefits of physical activity [44, 45].

A myriad of cross-sectional and longitudinal studies have found associations between higher IL-6 and negative health outcomes such as disability, age-related disease (cardiovascular disease, diabetes, cancer), loss of muscle mass (sarcopenia), frailty and death [30, 31]. In older individuals with higher IL-6 (generally the upper tertile or quartile), the risk of these outcomes is elevated approximately 1.5- to 4.0-fold compared to older individuals with lower IL-6 levels (lowest tertile or quartile). These associations appear to transcend age, sex, race, country of origin, socioeconomic status and many other social, behavioral and health variables. The large number and consistency of studies suggests a mechanistic relationship, but data are derived from observational studies, so causal inference cannot be drawn. Nonetheless, the data strongly point to a role for chronic inflammation, particularly IL-6, in aging and age-related disease.

12.5.2 Cellular Senescence and Oxidation: Telomere Length

Telomere length is currently one of the most contested biomarkers of aging. Telomeres are repeating nucleoprotein caps that flank nuclear DNA. With the replication of nuclear DNA during mitosis, telomere length progressively shortens because the replication machinery cannot copy the absolute ends of DNA, which is termed the end replication problem [46]. Most age-associated shortening occurs during rapid somatic expansion (i.e., growth from birth through puberty) [47, 48]. With critically short telomeres, the cell exits the cell cycle and becomes senescent [49, 50]. Subsequently, telomere length may reflect the growth rate or remaining replicative potential of a population of cells [48, 51]. It is important to note that this process protects against unbridled cellular division, which can lead to cancer. Telomere length also shortens with increasing oxidative stress [48, 52]. Single-stranded breaks in DNA that are caused by oxidative stress may be the major determinant of telomere shortening [52–55]. *In vitro*, oxidative stress increases the rate of telomere shortening by an order of magnitude [53, 55, 56]. The reduction of

oxidative stress decreases the rate of telomere shortening and postpones replicative senescence [57]. Thus, telomere length may reflect systemic oxidative burden.

In epidemiology, leukocyte telomere length (LTL) has been the most studied due to the availability of peripheral blood for analysis; data from other tissues is lacking. Shorter LTL has only been consistently associated with older age, male gender [58–70] and Caucasian race [66, 68, 71]. Associations between LTL and other markers of health status are equivocal and do not appear to be dependent on differences between study populations, measurement method or statistical adjustment. These include associations with smoking [58, 59, 65, 67, 68, 72, 73], alcohol consumption [58, 59, 74], physical activity [59, 63, 68, 69], socioeconomic status [75, 76], body mass index [58, 59, 65–68, 72, 73, 77], lipids [59, 67, 71, 77], markers of glucose metabolism [59, 64, 65, 67, 69, 77] and blood pressure [59, 60, 65, 67, 77]. LTL has been inconsistently associated with markers of subclinical cardiovascular disease, including carotid or femoral intima-media thickness [61, 65, 72, 78], ankle-brachial index [65], coronary artery calcium [79] and pulse wave velocity [60]. Despite these discrepancies, some have argued that there is a robust association with atherosclerosis [59, 61, 62, 64–66, 72, 80–84] because there is a plausible mechanism, namely that reduced telomere length reflects increased cellular senescence in hematopoietic stem cells, and by association in epithelial progenitor cells, which would then be less able to maintain the vascular wall in response to oxidative stress and plaque growth [85]. Alternatively, because oxidative stress and inflammation are associated with atherosclerosis and there are consistent associations between markers of oxidation and inflammation (e.g., IL-6, CRP, homocysteine, isoprostane urinary 8-epi-PGF2α) and shorter LTL [59, 64, 65, 69, 86], atherosclerosis and shorter LTL may be linked via these shared mechanisms.

Several age-related changes are not associated with LTL. Pulmonary function [74, 87] and bone mineral density [69, 70, 88], markers of specific tissues which decline in function and degrade in structure with age independent of disease, are likely not or only weakly associated with LTL. Self-reported physician diagnosis of cataract (Odds Ratio [OR], 0.95 per 1,000 bp LTL; 95% Confidence Interval [CI], 0.89–1.01) and incident cataract surgery (Hazard Ratio [HR], 1.02 per 1,000 bp LTL; 95% CI, 0.94–1.10) were not associated with LTL in the Health ABC Study, though older adults with highly transparent lenses—measured using objective means—had markedly longer LTL (5,700 bp) compared to older adults with any lens opacity (4,770 bp) (OR, 0.47; 95% CI, 0.22–1.02) [89]. Grip strength, a marker of physical function, has not been associated with LTL [74, 87, 90]. It is unclear whether LTL is associated with cognitive function or dementia [91–95]. Furthermore, LTL is likely not associated with the Apolipoprotein E (ApoE) genotype [95, 96]. Interestingly, LTL was strongly associated with an index of disease burden independent of atherosclerosis, which suggests that LTL may reflect shared mechanisms that lead to the development of age-related chronic disease in different tissues [97].

Telomere length has been used in several epidemiologic studies as a predictor of lifespan or death. Cawthon [98] first reported an association between shorter LTL and increased mortality in individuals ≥60 years of age (HR, 1.86; 95% CI, 1.22–2.83). In that study, increased mortality was specifically due to higher rates of death from heart disease (HR, 3.18; 95% CI, 1.36–7.45) and infectious disease (HR, 8.54; 95% CI, 1.52–47.9). Since that report was published, some other studies have found that shorter LTL is associated with increased mortality [99–103] and others have found no such association [65, 74, 104–106]. In most of these studies, statistical models have been minimally adjusted for potential confounders, typically only for age and occasionally for sex or race. Differences in measurement methods for LTL (Southern blot vs. quantitative polymerase chain reaction [qPCR]) may contribute to the inconsistency between studies. Furthermore, the variability in LTL in a population may decrease with increasing age [104, 105]. Because these studies were conducted in individuals who were on average >60 years of age, it is possible that they had reduced power to detect associations

between LTL and mortality. In sum, LTL appears to be weakly associated with overall mortality, and possibly more strongly associated with cardiovascular-disease-specific or infectious-disease-specific mortality.

Several longitudinal studies have been conducted to determine predictors of change in LTL over time [80, 101, 102, 107–110]. In these studies, time between samples of LTL ranged from 2.5 to 10 years. All except one [80] relied on qPCR to measure LTL. All found that baseline LTL was the strongest—and often the only—predictor of the subsequent LTL measurement, and several noted that 11–34% of the population increased in LTL during the time period [80, 102, 107, 109, 110]. In patients with stable coronary artery disease, Farzaneh-Far et al. [109] found that higher omega-3 fatty acid levels were associated with less decline in LTL, though this has not been corroborated.

Although studies of changes in LTL have the potential to provide the strongest evidence for what LTL may reflect in humans, those published to date have substantial methodologic flaws [111, 112]. In particular, the time between telomere measurements was short, which resulted in small changes in mean LTL during the follow-up period. If telomere attrition in late life is approximately 30–100 base pairs per year [111], 5 years of change would result in only 150–500 base pairs of shortening, which was generally observed in these longitudinal studies. Given that inter-individual variation in LTL is approximately 5,000–10,000 base pairs (depending on the mean age of the population) and most longitudinal studies of LTL change have used qPCR for measurement (which has a higher coefficient of variance) and had a small sample size, then given the degree of measurement variability, it is highly likely that these studies were underpowered to detect possible associations between change in LTL and outcomes. In fact, it is possible that the changes in LTL observed during the follow-up periods were partly or mostly artifacts from measurement error. Longitudinal studies with much longer follow-up times and larger sample sizes are necessary to convincingly determine predictors of change in LTL and what change in LTL might predict.

Salient questions which remain unanswered include: What is the normal rate of telomere shortening in a human population? What is the most relevant measure of shortening, average or shortest chromosome? What is the variance in telomere shortening? What risk factors accelerate telomere shortening and what protective factors ameliorate shortening? Is the rate of telomere shortening more predictive of specific age-associated outcomes or overall organismal aging measured using different constructs? If there truly is a dichotomy between aging and cancer, is telomere shortening the central regulator of this dichotomy?

Answering these questions requires the longitudinal measurement of telomere length—likely over decades—in well-characterized populations. This could position telomere length as a prime candidate for exploration using the growing subfield of lifecourse epidemiology. It would also behoove researchers to standardize measurement techniques while developing assays that have higher throughput and higher accuracy to facilitate comparisons across studies and pooling for meta-analysis. If possible, telomere length should also be sampled from non-hematopoietic tissues to learn whether the tissue source impacts the strength of associations. With these advancements, researchers will be able to more confidently assess telomere length as a biomarker of aging in humans.

12.5.3 Glycation: Advanced Glycation End Products

Advanced glycation end products (AGEs) are formed by the non-enzymatic glycation of proteins, lipids and nucleic acids. The formation of AGEs occurs more often throughout an organism when there is excess glucose in the body [113–115]. AGEs enter the body from endogenous production through glycation and oxidation and are consumed in the diet, with the highest concentrations of AGEs found in foods that are processed at high temperatures. It is unknown whether circulating AGE level is an accurate indicator of the amount of AGEs consumed in the diet, particularly

because AGE accumulation is related to kidney function [116]. Regardless, AGE levels appear to rise with increasing chronologic age [116].

AGEs are detrimental for two reasons. First, the structural alteration of molecules can inhibit their function or allow them to aggregate excessively. This is demonstrated by the association of serum AGEs with atherosclerosis and vascular stiffening by spurring collagen cross-linking in vessel walls [113, 115]. Second, AGEs signal through the receptor for advanced glycation end products (RAGE) to promote free radical formation, oxidation and inflammation [117]. In particular, these processes damage delicate tissues for which function depends on sensitive membranous structures, such as the renal glomerulus, peripheral nerves and retina. This partly explains the diabetic triad of nephropathy, neuropathy and retinopathy [115]. More broadly, signaling through RAGE leads to widespread damage and may promote cellular senescence due to an increased demand for tissue repair and the activation of immune cells. Subsequently, AGEs are envisioned as a direct biomarker of age-related molecular glycation and possibly an indirect biomarker of inflammation.

The epidemiologic study of AGEs is relatively new. Recent results from the Baltimore Longitudinal Study on Aging, Women's Health and Aging Studies and the InCHIANTI study illustrate that higher levels of serum carboxymethyllysine (CML), a dominant AGE in serum and tissues, is associated with greater mortality, slow walking speed, anemia, poor kidney function and increased aortic pulse wave velocity in older adults [118–123]. In the InCHIANTI study, endogenous secretory RAGE (esRAGE) was positively associated with higher IL-6 and lower IL-1 receptor antagonist, but not IL-1beta, TNF-alpha, IL-6 receptor, IL-18 or CRP [124]. esRAGE was associated with chronic kidney disease [125]. In older women, CML, but not soluble RAGE (sRAGE) or esRAGE, was associated with weaker hand grip strength [126]. This mirrored the finding that pentosidine, another dominant AGE, was increased significantly and by ~200% in muscle biopsies from older individuals compared to younger individuals, and that this increase tracked with worse muscle function [127]. In older Japanese men, higher levels of skin autofluorescence—a non-invasive marker of AGE accumulation in tissue—was associated with lower hand grip strength [128].

AGEs are also associated with hallmarks of brain aging. With normal aging, the brain accumulates amyloid plaques and neurofibrillary tangles. The development of these pathologic signs is accelerated in Alzheimer's disease. It is theorized that AGEs could contribute to cognitive decline by promoting molecular aggregation or tissue inflammation. Effects may come from direct damage to neural tissues or the cerebral vasculature. In laboratory studies, AGEs have been found bound to plaques and tangles in the brains of normal individuals, and to a greater extent in the brains of Alzheimer's disease patients [129, 130]. In a study of community-dwelling older adults without dementia, a greater concentration of urine pentosidine was associated with a greater decline in cognition over 9 years, independent of age, sex, race, education, hypertension, cardiovascular disease, estimated glomerular filtration rate, and diabetes [131]. It is unknown whether this association is causal or correlative. The recent development of targeted pharmacological interventions using AGE-inhibitors, RAGE-antagonists, RAGE-antibodies, sRAGE or RAGE-signaling inhibitors suggests that AGE levels may be modifiable. Future research might identify AGEs as both a biomarker of aging and a point of intervention to promote healthy aging.

12.5.4 Energy Homeostasis: Insulin-Like Growth Factor Pathway

Establishing energy homeostasis is critical for proper development and continued survival. The IGF-1/insulin pathway was the first pathway shown to influence aging and lifespan in animals [132]. In *C. elegans*, mutations that decrease the activity of the *daf-2* gene, which encodes a hormone receptor with activity similar to the insulin and IGF-1 receptors in humans, results in nearly double the normal healthspan and lifespan. Reduced signaling

of IGF-1 via genetic manipulation of the ligand(s), receptor(s) or receptor substrate(s) acting through insulin, IGF, the phosphoinositol-3 kinase (PI3K) system, AKT kinases and forkhead transcriptional factors produces greater longevity in nematodes, fruit flies and mice [133–136]. Caloric restriction also leads to a greater lifespan in rodent models, and a key change observed with caloric restriction is a decrease in IGF-1 levels [137]. Cross-sectional epidemiologic studies of community-dwelling older adults confirmed that they have lower IGF-1 levels compared to younger individuals [138–143], suggesting selective mortality due to lower IGF-1 with age, which is similar to the model systems. Taken together, these results lead to the hypothesis that decreased IGF-1 signaling may be a marker for longevity in humans.

The clinical picture of IGF-1 decline in humans complicates this hypothesis. In mammals, IGF-1 is closely linked to growth hormone (GH) in the GH/IGF-1 axis. GH released by the pituitary gland stimulates hepatic secretion of IGF-1, which suppresses GH in a negative feedback loop. GH also decreases with age. Thus, the population-level decline in mean IGF-1 level with age may partly reflect changes in the GH/IGF-1 axis. Because the symptoms of GH deficiency overlap with the phenotype of aging, including decreased muscle mass, increased fat mass, decreased bone mineral density and decreased well-being, there has been speculation that lower levels of IGF-1 in older adults—whether due to declining GH or not—may actually contribute to age-related morbidity and mortality rather than indicate or promote longevity [144]. This discrepancy between findings in animal models and humans has been termed "the IGF-1 paradox" [145].

Prospective data from epidemiological studies would provide the best evidence to sort out these paradoxical findings in humans. In the Framingham Heart Study, greater baseline IGF-1 was associated with lower mortality (HR for death, 0.70 per log10 increase in pg/mL; 95% CI, 0.49–0.99; $p=0.04$) [146]. Nonetheless, no association was detected between baseline IGF-1 level and mortality in the CHS [147], Women's Health and Aging Study [15], National Health and Nutrition Examination Survey [148], Rancho Bernardo Study [149] or Seven Countries Study [150]. Although the Framingham Heart Study also reported that each SD higher IGF-1 was associated with a 27% lower risk of congestive heart failure ($p<0.05$) [151], no association was found with incident heart failure or coronary disease in the CHS [152, 153]. IGF-1 was also not associated with gait speed, grip strength or incident ADL difficulty in the CHS [147], while studies in bone show links to several bone phenotypes [154, 155].

IGF binding proteins (IGFBPs), which modulate IGF-1 levels, have also been studied using epidemiological techniques. In the CHS, higher IGFBP-1 was associated with an increased risk of congestive heart failure (HR, 1.22 per SD; 95% CI, 1.07–1.39; $p<0.01$) [153], worse hand grip strength and gait speed, incident ADL difficulty (HR, 1.40 tertile 3 vs. tertile 1; 95% CI, 1.01–1.94; $p=0.04$), and potentially higher mortality (HR, 1.35 tertile 3 vs. tertile 1; 95% CI, 0.98–1.87; $p=0.05$) [147], but not with incident coronary disease [152]. Also in the CHS, higher IGFBP-3 was borderline associated with a lower risk of incident coronary disease (HR, 0.88 per SD; 95% CI, 0.78–1.00; $p=0.05$), but not with overall or cardiovascular disease mortality [147, 152]. Interestingly, the middle tertile of IGFBP-3 was associated with better grip strength than the other two tertiles ($p=0.03$), though IGFBP-3 was not associated with incident ADL difficulty.

Regarding experimental data from human trials, the Comprehensive Assessment of Long-term Effects of Reduced Intake of Energy (CALERIE) trial demonstrated that 6 months of 25% dietary caloric restriction in non-obese humans did not alter GH level, GH secretion or IGF-1 levels [156], though fasting insulin levels were reduced [157]. Studies of GH replacement in older adults have been largely disappointing and do not support a role for GH supplementation to reverse declining IGF-1 and aging-related changes [158–160]. It is possible that these trials and observational studies failed to demonstrate clinical benefit or significant associations with mortality because they were conducted under the assumption

that the hormonal setpoint (baseline value) was the most important factor contributing to adverse effects seen with aging rather than modulation of IGF-1 over time, which would be a more accurate depiction of energy homeostasis. Population-based linkage and genome-wide association studies have identified haplotypes and rare genetic variants in the *FOXO* gene—the homologue of the master control *daf-16* gene in *C. elegans* and a downstream effecter in the IGF-1 pathway—as being associated with longevity in populations across the globe [161–166], with some exception [167]. In sum, data from observational and experimental epidemiologic studies does not support an association between IGF-1 and human longevity, but genetic studies have identified a number of variants in the IGF-1 pathway that are positively associated with human longevity.

There are several reasons why IGF-1 results from animal models might not translate to humans. Most importantly, experiments in model systems are conducted under controlled environments where any advantage of higher IGF-1 levels in the context of environmental stress are not operative, which may result in the overestimation of the advantages of low IGF-1 levels. In addition, these model systems have homogeneous genetic backgrounds. In contrast, human studies are complicated by potential confounding from known and unknown genetic and environmental factors, vastly more heterogeneous genetic backgrounds, longer timescales and the inability to manipulate genes, which appear to influence 38–63% of IGF-1 levels in humans [168, 169]. Second, the IGF-1 and insulin pathways are not distinct in lower-order animals but are separate (though with overlap) in mammals. Although results from mice are relatively consistent with those derived from *C. elegans* and *Drosophila*, consistency with humans cannot be assumed [134]. For example, in humans, IGF-1 and insulin receptors have opposing actions depending on their location in the periphery or central nervous system [145]. Furthermore, suppression of the PI3K/AKT system (via less IGF-1) promotes longevity through the upregulation of FoxO, proteins while inhibition of the system (via more IGF-1) promotes senescence through the upregulation of NF-κB signaling [170]. This is a key aspect of the GH/IGF-1 axis, but it is unknown how the natural balance of these opposing pathways or how age-associated changes in this balance differ between lower-order animals and humans. Third, the GH/insulin/IGF-1 pathway exhibits pleiotropy in model systems, promoting growth during development (which may also prime an organism for successful aging) but contributing to aging later in life. Teasing apart this pleiotropy in humans is considerably more difficult, particularly due to the longer lifespan of humans.

The more complex IGF-1 and insulin signaling systems in mammals may make extrapolating results from lower-order systems unreliable. Epidemiologic studies demonstrate mostly negative associations between IGF-1 and mortality, cardiovascular disease and disability. Some positive associations have been noted between IGFBPs and these outcomes, though data are too sparse to draw firm conclusions. Future epidemiologic studies should measure components of the IGF-1 pathway at multiple time points to more accurately depict energy homeostasis, and use these measurements (baseline value, changing slope and variability around the slope) to predict aging-related outcomes.

12.5.5 Sex Hormones: Dehydroepiandrosterone Sulfate

Dehydroepiandrosterone (DHEA) is produced by the zona reticularis, the innermost layer of the adrenal cortex. 17β-hydroxysteroid dehydrogenase converts DHEA into estrogen and testosterone, most often in the ovaries and testes. Over 90% of estrogens in post-menopausal women and 30% of androgens in men are derived from DHEA [171]. DHEA is modified into DHEA sulfate (DHEAS) via a sulfotransferase in the adrenals and also the liver and small intestine. DHEAS is by far the major circulating sex steroid hormone and the level of circulating DHEAS is roughly 300 times higher than circulating DHEA [172]. Although DHEA exhibits nocturnal

pulsatility, DHEAS does not, possibly due to DHEA's >100-fold higher metabolic clearance rate. On average, DHEAS is 10–30% higher in men than in women. There is evidence from laboratory and clinical studies that DHEA directly dampens inflammation, preserves endothelial nitric oxide signaling, stimulates the central nervous system, maintains sexual function and alters body composition and bone integrity [173]. It is unknown whether DHEAS itself has strong biologic activity. Thus, DHEAS may simply serve as a resource pool for DHEA and its derivative sex steroid hormones.

DHEAS levels peak at birth and in the third decade of life and fall by 80–90% by 80 years of age, which partly explains the age-associated decline in estrogen and testosterone [172, 174, 175]. The cause of this age-associated decline is unknown, though we reported that in older adults in the CHS-All Stars study, cardiovascular disease, male gender and black race were associated with a greater DHEAS decline over 9 years [176]. The strong correlation between DHEAS level and age led to the hypothesis that DHEAS may be a possible cause of age-related pathologies [177]. Epidemiological data on an association between DHEAS and mortality are equivocal [177–180]. A report that both low and high DHEAS were associated with greater mortality in disabled older women (U-shaped association) suggests that a disordered neuro-endocrine axis in general may increase mortality rather than a unidirectional shift in hormone levels [181]. Most interesting are the results of a study by Cappola et al. [182] of DHEAS level, slope and variability in 950 participants of the CHS. In adjusted models that included all three components, a steep decline (HR, 1.75; 95% CI, 1.32–2.33) and extreme variability (HR, 1.89; 95% CI, 1.47–2.43) remained significant predictors of mortality, whereas the baseline DHEAS level was not predictive of mortality (HR, 0.97 per SD; 95% CI, 0.88–1.07). The effect of trajectory pattern was more pronounced in men than in women. Individuals who had both a steep decline and extreme variability in DHEAS levels had a significantly higher death rate than did those who had neither pattern (141 vs. 48 deaths per 1,000 person-years, $p < 0.001$). To date, this study is the most effective attempt to capture the natural hormonal rhythm using longitudinal epidemiologic data, and it is a fine example of the strength of repeated measures modeling.

Clinical trials of DHEA supplementation have been completed. Morales et al. [183] demonstrated that in men and women 40–70 years of age, DHEA treatment with the goal of returning DHEA to levels of those of younger individuals resulted in improved self-reported physical and psychological well-being in women. Nonetheless, the vast majority of data on DHEA supplementation reveals that it has little to no benefit for reversing age-associated changes. Currently, there is not enough evidence to recommend DHEA as a supplement to ameliorate aging [184, 185]. The only patients that DHEA does seem to benefit are those who have pathologic adrenal failure [186]. It remains unknown whether the age-associated decline in DHEAS is a cause or consequence of aging, and whether DHEAS decline plays a role in aging apart from the related decrease in its derivative sex steroid hormones.

12.5.6 Oxidative Stress and Metabolism: Klotho

In 1997, Kuro-o et al. [187] reported the creation of a homozygous transgenic mouse that exhibited human-like aging. Initially, Kuro-o et al. used transgenic insertion to create mice that overexpressed the rabbit type-I sodium-proton exchanger. Only 3 of 28 mice expressed the transgene. The investigators independently bred the 25 mice that did not express the transgene in an attempt to create mice homozygous for the allele. One of these mice exhibited human-like aging phenotypes in several tissues. The phenotypes included atherosclerosis, endothelial dysfunction, low bone mineral density, sarcopenia, skin atrophy, impaired cognition, pulmonary emphysema and shortened lifespan [187–189]. Interestingly, the mouse had lower insulin production but greater insulin sensitivity, which resulted in lower serum fasting glucose [190]. The mice developed until at least 2 weeks of age,

which indicated that the phenotype was not due to a failure in development but rather a homozygous expression of the transgene. Penetrance of the aging phenotypes was 100% and they only appeared in mice homozygous for the transgene.

The targeted gene is now named *klotho* after one of the three Greek Fates who spins the thread of life. Complementary experiments that introduced klotho have demonstrated beneficial effects. The increased expression of klotho protein has increased the lifespan of mice by approximately 20–30% [189, 191]. This gain in lifespan seems to be attributable in part to protection against endothelial dysfunction [192], reduction of oxidative stress [193], improvements in IGF-1 signaling [191] and maintenance of calcium homeostasis [194].

Klotho protein has two forms, membrane-bound (beta) and secreted (alpha). Each has a different function. Membrane-bound klotho is a co-receptor for fibroblast growth factor (FGF)-23, a hormone secreted by bone to spur phosphate excretion into urine [195]. Secreted klotho regulates nitric oxide production by the endothelium [188, 192], calcium homeostasis in the kidney [196, 197] and inhibition of intracellular insulin and IGF-1 signaling [191]. Klotho protein is present in human sera and cerebrospinal fluid [198]. Although it was previously not feasible to measure soluble klotho in human serum, an enzyme-linked immunosorbent assay (ELISA)-based method has recently become available [199]. Results from development of the ELISA method illustrated that soluble klotho ranged from 239 to 1,266 pg/mL (mean [SD]: 562 [146] pg/mL) in normal adults (>20 years of age, n = 142, males = 66) with a mean (SD) age of 61.1 (18.5) years. Klotho levels were not modified by gender or indices of mineral metabolism. In adults >20 years of age, klotho levels were inversely related to age ($r = -0.199$, $p = 0.017$) and creatinine levels ($r = -0.183$, $p = 0.03$); these linear correlations were much stronger over the entire age range of the sample (age: $r = -0.599$, $p < 0.001$; creatinine: $r = -0.538$, $p < 0.001$). Klotho levels in normal children (n = 39, males: 23, mean [SD] age: 7.1 [4.8] years) were significantly higher (mean [SD]: 952 [282] pg/mL) than those in adults (mean [SD]: 562 [146] pg/mL; $p < 0.001$).

Since publication of the ELISA method in 2010, soluble klotho has been measured in the InCHIANTI study. In these Italian adults >65 years of age, lower plasma klotho concentrations were associated with older age, lower calcium, lower high-density lipoprotein (HDL) cholesterol, high triglycerides and greater cognitive impairment (i.e., worse health in all parameters) [200]. There were no significant differences across tertiles of plasma klotho by sex, education, alcohol intake, current smoking, body mass index, physical activity, mean arterial pressure, 25-hydroxy vitamin D (25[OH]D), parathyroid hormone, total cholesterol, low-density lipoprotein (LDL) cholesterol or prevalence of chronic diseases. Participants in the lowest tertile of plasma klotho (<575 pg/mL) had an increased risk of death compared with participants in the highest tertile of plasma klotho (>763 pg/mL; HR, 1.78; 95% CI, 1.20–2.63), and this association was not modified by age [200]. Using a slightly larger sample of the InCHIANTI population, Semba et al. [201] demonstrated that higher klotho was associated with lower alcohol intake, current smoking and lower CRP, and for each SD greater log(klotho) level, the odds of prevalent cardiovascular disease were 15% lower (95% CI, 0.72–0.99). Finally, a threshold effect was detected in association with grip strength: plasma klotho was associated with grip strength (β Standard Error [SE], 1.20 [0.35] per SD of klotho; $p = 0.0009$) in adults with klotho <681 pg/mL, which indicates that low plasma klotho was a marker for poor grip strength [202]. Results from the InCHIANTI study are complemented by genetic variants of *klotho* being associated with coronary artery disease [203–205], stroke [206, 207] and longevity [207, 208] in humans. Confirmation of these results and the exploration of associations with other age-related phenotypes is necessary to advance klotho as a biomarker of aging. As one of the most interesting biomarkers found to date that has an ELISA-based method available for measurement, it would be wise to measure klotho in other established epidemiologic cohorts.

12.6 Conclusions

In the future, epidemiologists who study aging will employ a number of tools to more sensitively probe human biology. At the epicenter of the toolbox will be classical epidemiologic techniques employed in artful ways, such as studying extremes of the population. The longitudinal measurement of changes in biomarkers of aging is necessary to determine their trajectory and whether the absolute level of a biomarker, its change or its variability is most important for the maintenance of health throughout the lifespan. Better assays and imaging systems will enable researchers to more accurately and specifically quantify biomarkers of interest. High-throughput systems will allow epidemiologists to link large populations with deep phenotyping to variations in molecules and genes. Advancing statistical techniques, such as joint modeling, longitudinal trajectory latent class analysis, mixed modeling and lifecourse analysis, will shift our rudimentary representation of biology toward a more sophisticated representation. With these new tools, epidemiologists will help to uncover the secrets to living a long and healthy life, and they will be integral to the design, implementation and assessment of interventions to promote healthy aging.

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Genetics of Human Longevity and Healthy Aging

13

Joanne M. Murabito and Kathryn L. Lunetta

Abstract

Genetic factors contribute to human aging and longevity through the modulation of biologic pathways, but few longevity-gene associations have been replicated to date. Participants in prospective epidemiologic studies provide an opportunity to investigate the genetics of many age-related phenotypes, but large discovery and replication samples are needed for genetic discovery. Today's genome-wide genotyping of centenarians and participants in longitudinal cohort-based and family-based studies provide the opportunity to assemble these large samples, as does today's unprecedented collaboration among investigators in the United States, Europe and around the world. This collaboration will make it necessary to standardize the definitions of aging phenotypes, and to assess potential sources of bias and confounding when planning a study and interpreting results. To date, the vast majority of genetic association studies have used populations of European descent. It is essential that in the future, such studies examine other worldwide populations to determine whether gene and allelic effects are heterogeneous across various genetic and environmental backgrounds. The collaboration of international scientists may aid in the translation of genetic associations, and thus uncover the functions of gene variants in the biologic mechanisms that lead to human aging.

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13.1 Introduction

Genetic factors play an important role in human aging and longevity through the modulation of a variety of biologic pathways. To discover these genetic factors, it is critical to develop well-defined aging phenotypes. Prospective population-based and family-based cohort studies provide a unique resource with a breadth of data across adulthood that can be used for the development of aging phenotypes that go beyond longevity. Phenotypes with high heritability (the proportion of the total phenotypic variance that is due to genetic effects) are of higher priority for genetic study as they are more likely to yield multiple genetic associations. The presence of a genetic basis for age-related traits can be determined by conducting heritability analyses using data from family-based cohorts, such as the Framingham Heart Study (www.framingham-heartstudy.org) and the Long Life Family Study (https://dsgweb.wustl.edu/llfs/), and by examining familial clustering in special aging populations such as centenarians.

Several study designs are used for genetic association testing. Genome-wide association studies (GWAS) have proven highly successful for gene discovery in common complex traits. The large discovery and replication samples needed to identify novel genes in GWAS have led to unprecedented collaboration among investigators across the United States and Europe who are working with longitudinal cohort studies. New worldwide collaborations are currently being formed that will allow us to better understand the role of genetics in aging and longevity. Further, advances in technology now enable the sequencing of the protein-coding regions of the genome ("the exome") and of the whole genome with the goal of identifying the causal genetic variants that are associated with common medical conditions. Many cohort studies are participating in genotyping and sequencing efforts and are thus poised to contribute to the discovery of genes that are associated with important age-related conditions. They also have the potential to uncover insights into the basic mechanisms of aging.

Evidence from both animal and human studies suggest that genetic factors have an important contribution to aging and longevity through the modulation of diverse biologic pathways [1]. Genes that slow aging appear to influence multiple age-related changes and delay the onset of age-related diseases. Determining which genes influence human longevity through increasing susceptibility to diseases that lead to premature death, and which genes contribute to a long and healthy life by slowing the aging process, is a research area with immense challenges. New research tools for the discovery of genes that are associated with complex traits have been provided by the success of the International HapMap project in cataloging the common patterns of human DNA sequence variation [2], recent advances in genotyping and sequencing technologies, and the accompanying developments in bioinformatic and statistical methods. With the unprecedented collaboration among investigators of many nations, it is vital that the definitions of aging phenotypes be standardized across studies and that potential sources of bias and confounding be assessed when planning a study and interpreting results. Of particular importance in the genetic research of aging is validation of the age of long-lived individuals and evaluation of birth cohort effects. The pursuit of aging and longevity gene discovery is likely to yield many genes with modest effects, along with the interactions of genes with environmental and behavioral factors.

In this chapter, we discuss the critical process of defining aging and longevity phenotypes which can be used across epidemiologic studies that

participate in genetic analyses. The detailed examinations conducted on participants in prospective population-based and family-based cohort studies provide uniquely rich data that enable the development of aging phenotypes that expand and refine upon longevity *per se* to characterize aging across multiple aging domains including age-related disease, physical function, cognition and frailty. Given the higher priority of phenotypes with high heritability, we review the heritability of aging and longevity traits. Next, we describe several different study designs that are commonly used for genetic association testing. We then review important sources of bias and confounding in genetic association studies of aging that need to be considered when planning a study and interpreting study results. We conclude with a review of future directions in the study of genetics, including sequencing efforts that may identify low-frequency and rare genetic variants, and the study of epigenetics or heritable changes in gene expression that occur without a change in the DNA sequence.

13.2 Defining Longevity and Healthy Aging Phenotypes for Genetic Association Studies

Given the complexity of the aging process and the variation in the rate of aging observed among individuals, the definition of longevity and healthy aging phenotypes for genetic study poses many challenges. Table 13.1 provides a listing of potential longevity and aging traits for use in genetic association studies. We review these below.

Table 13.1 Longevity and aging phenotypes for genetic association testing

Extreme longevity
Survival ≥90 years of age
Centenarians (≥100 years of age)
Supercentenarians (≥110 years of age)
Centenarian sub-phenotypes: survivors, delayers, escapers
Offspring of centenarians, health status
Exceptional survival
Age at death
Age at disease onset
Disease-free survival
Survival to ≥85 years of age free of major illness and cognitive decline
Survival free of morbidity with intact cognitive and physical function
Alzheimer's disease, dementia
Frailty
Hand-grip strength
Walking speed
Slower aging
Low levels of cardiovascular risk factors
Biologic age including maintenance of cognition, muscle mass and strength, bone mineral density
Index of physiologic age
Biomarkers of aging
Immune function/inflammation
Oxidative stress
Heat shock proteins
Insulin/IGF-1 signaling
Hormones
Telomere length
Later age at menopause
Later age at last birth

13.2.1 Extreme Longevity

In 2001, the National Institute on Aging (NIA) convened a panel to identify a standard set of measurements to define *exceptional survival* [3]. The panel recommended measures across multiple domains and suggested that a minimum set of measures be used in all studies of exceptional survival, with more detailed sets of measures for studies of specific domains of aging. The NIA subsequently funded the Long Life Family Study, a multi-center cohort study of families clustered for longevity, with the aim of discovering environmental and genetic factors for exceptional survival [4]. Initial comparisons of probands and offspring of the Long Life Family Study cohort to participants in longitudinal cohort studies (the Cardiovascular Health Study [5] and the Framingham Heart Study) suggest that those in the Long Life Family Study cohort were less likely to have a number of age-related diseases, and more likely to have a favorable cardiovascular risk factor profile and better measures of physical function.

In Europe, the Leiden Longevity Study recruited families of long-lived individuals of European descent together with their offspring and partners

of offspring with the aim of identifying genes related to longevity [6]. Families were eligible if at least two long-lived siblings were alive (≥89 years of age for males, ≥91 years of age for females); <0.5% of the Dutch population was eligible at the time of recruitment. In middle-age, the offspring of the Leiden Longevity Study participants had more favorable metabolic parameters including lipids, glucose, insulin sensitivity and thyroid hormone metabolism, as well as less age-related disease compared to their partners [7–9].

These two family studies of long-lived individuals have identified several potential phenotypes for genetic analyses that may uncover genetic variants associated with exceptional survival. There is likely to be heterogeneity of factors that influence longevity across populations, which make it important to study factors within populations worldwide. To facilitate phenotype definition and the harmonization of data collection across studies, the National Human Genome Research Institute (NHGRI) provided funding to the Web-based PhenX toolkit (https://www.phenxtoolkit.org/) to provide consensus measures of phenotypes and exposure to investigators who are examining a range of phenotypes [10].

13.2.2 Age at Death

One of the most common aging phenotypes studied is *age at death*, often referred to as longevity. Age at death is heritable, easy to collect and readily available across studies. At the Framingham Heart Study, deaths are identified using multiple strategies including routine participant contact for a research examination, health history updates, surveillance at the local hospital, search of obituaries in the local newspaper and use of the National Death Index.

Two important demographics need to be considered when age at death is used as a longevity phenotype. First, women live longer than men and make up a larger proportion of the population at advanced age. Second, longevity has increased dramatically in the United States, with the life expectancy at birth increasing from 47.9 years to 75.3 years in men and from 50.7 years to 80.4 years in women from 1900 to 2007 [11, 12]. While surviving to 90 years of age was an uncommon occurrence at the turn of the twentieth century (~1.5% of men and 2.3% of women), the proportion of men and women who achieve this age has risen steadily across birth cohorts from 1900 to 2000 (Fig. 13.1). Survival to extreme old age (≥100 years of age) is also increasing but remains rare, especially among men since five of six centenarians are women [13, 14]. It is unknown whether some genetic factors that promote longevity differ in women compared to men.

A major disadvantage of using age at death as a phenotype is that it measures overall lifespan without any information on health and function, and thus it is a very heterogeneous phenotype. Even among individuals who achieve *extreme longevity*, only a minority achieves old age with their cognitive and physical functioning intact. One study examined the age at onset of ten common age-related diseases among centenarians and three phenotypes emerged: survivors, delayers and escapers. This suggests the possibility that different underlying pathways and genes lead to extreme longevity [15]. Survivors were those who reported an age-related illness prior to 80 years of age, delayers were those who reported an age-related illness after 80 years of age, and escapers were those who reached 100 years of age without experiencing any of the age-related illnesses. Clear gender differences in the three phenotypes were noted: men were more likely to be escapers of common morbidities while women were more likely to attain 100 years of age after surviving age-related illnesses. This observation raises the hypothesis that there may be different genetic and environmental factors involved in achieving extreme longevity for men versus women. Offspring of centenarians have more favorable cardiovascular risk factor levels and a greater delay in important age-related diseases compared to the offspring of those who died before reaching 100 years of age [16]. Hence, the health status of *offspring of centenarians* has been proposed as a longevity phenotype, with the spouses of those offspring serving as controls [17].

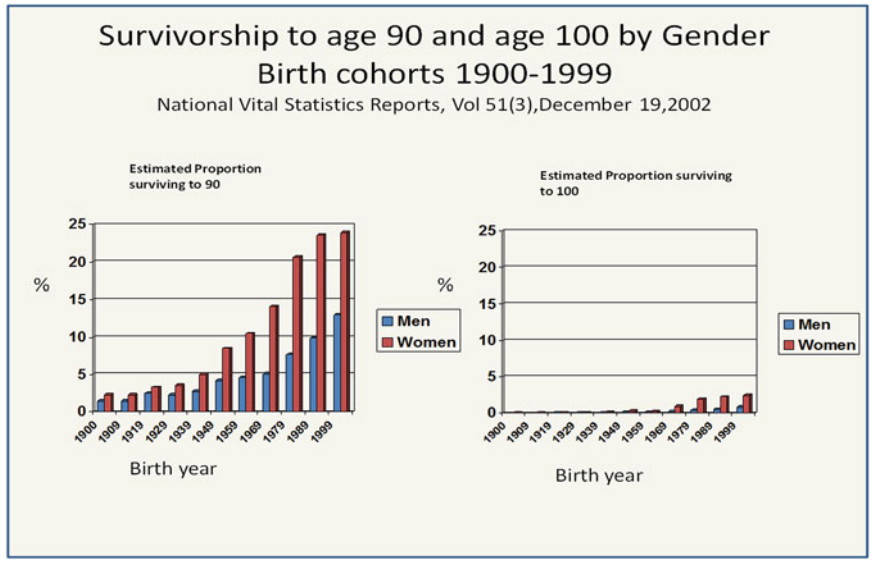

Fig. 13.1 Survival to age 90 and to age 100 by birth cohort and gender

13.2.3 Age at Disease Onset

Epidemiologic studies have made important contributions to the development of aging phenotypes for use in genetic association studies. Longitudinal cohort studies have collected an extensive and detailed set of measurements on study participants that are often repeated across adulthood using standardized protocols that include measures of multiple aging domains (age-related diseases and subclinical disease, cognition, physical function and frailty). Investigators working with these unique data have been able to examine the relevance of the developed phenotype in other populations and the significance of the phenotype in relation to functional decline and mortality. *Age at disease onset* or *disease-free survival* for a set of major age-related diseases (such as heart disease, stroke, diabetes, cancer, osteoporosis and dementia) may provide a better definition of healthy aging than longevity *per se*; however there is currently no consensus across studies regarding a standard set of diseases. In the investigation of non-genetic factors for healthy aging, investigators working with epidemiologic data have defined healthy survival as *survival free of morbidity with intact cognitive and physical function* [18, 19].

13.2.4 Frailty

Frailty is believed to be the result of a loss in physiologic reserve across multiple systems that occurs with aging. Using data from the Cardiovascular Health Study, Fried et al. [20] developed a frailty phenotype that includes criteria to reflect age-associated declines in physical activity, walking performance, balance, strength, endurance and lean body mass. This phenotype appears to be applicable across diverse populations [21] and is predictive of mortality [20]. Some components of the frailty phenotype, including *hand grip strength* and *walking speed*, are heritable [22, 23] and predict survival to old age [18].

13.2.5 Slower Aging

Several phenotypes have been proposed that may reflect a slower rate of aging. *Biologic age* is a measure of whether an individual appears to

function at a level typical for his or her chronological age or at a level much younger or older than his or her peers. Several different biomarkers have been proposed to define biologic age, including biomarkers reflective of the musculoskeletal system which were developed using participants of the Framingham Heart Study [24]. Among women who participated in the Study of Osteoporotic Fracture, those who *maintained bone mineral density* for up to 15 years experienced a lower risk of fracture, disability and mortality [25]. Similarly, older adults who *maintain cognitive function* into their eighth and ninth decade of life had lower risks of functional decline and death [26].

The avoidance of loss of function in other biologic processes may also serve as useful markers of successful aging. Newman et al. [27] used data obtained from participants in the Cardiovascular Health Study to develop an *index of physiologic age* which combines noninvasive assessment across multiple systems (cardiovascular, pulmonary, kidney, brain and metabolic). The index of physiologic age was a better predictor of mortality and disability than age itself. Matteini et al. [28] used data from the Long Life Family Study to construct *endophenotypes* using combinations of correlated physiologic parameters. Principle component analysis using measures of cognitive function, cardiovascular health, metabolic health, pulmonary health and physical function identified an endophenotype that is made up of pulmonary and physical function measures and is moderately heritable ($h^2 = 39\%$) [28].

13.2.6 Remaining Phenotypes

A number of *biomarkers* [29] may be additional phenotypes of aging, including the immune response/inflammation, oxidative stress, heat shock proteins, the insulin/IGF-1 signaling pathway and the hormonal axis [30]. Among women, later *age at natural menopause* or *older age at last pregnancy* may be a marker of slower aging. *Rate of change* phenotypes have been proposed; however, the challenges related to loss of sample size over time due to death or loss to follow-up of older participants may limit their usefulness [31].

13.3 Determining the Genetic Component to Longevity and Aging Phenotypes

If genes play an important role in human lifespan variation, then longevity should aggregate within families. Patterns of longevity within families can be examined to determine whether genetic factors contribute to human longevity. Family history information can be ascertained in several ways including simply asking study participants about the presence or absence of longevity in family members, obtaining more detailed information on the status of each family member, and using medical records and other data sources to confirm the lifespan of each family member. Once data are collected, statistical testing can then be performed to determine whether there is an association between family history and longevity.

13.3.1 Methods of Statistical Testing

13.3.1.1 Familial Clustering

For dichotomous traits, familial recurrence risk ratios can be calculated as follows:

$\lambda_R = K_R/K$, where K_R is the prevalence or risk of the trait among type R relatives of affected individuals and K is the prevalence or risk of the trait in the general population [32]. If genetic factors influence the disease under study, then the risk to close relatives of an affected individual will be greater than the risk in the general population. Usually, one can assume that the larger the recurrence risk ratio, the greater is the contribution of genetic factors to the phenotype under study, although ascertainment biases can influence the measure [33].

13.3.1.2 Heritability

For quantitative phenotypes, the calculation of heritability (h^2) provides an estimate of how much of the phenotypic variation in a quantitative phenotype is due to genetic factors. Estimates of heritability range from 0 (the absence of a genetic contribution) to one (variation in the phenotype is

entirely due to genetic factors). Although heritability is usually measured for quantitative traits, it can also be estimated for dichotomous traits by using a threshold model. In this, we assume that the liability (predisposition to the trait) is a quantitative measurement and that the trait is present only if the liability exceeds a threshold. The liability is a latent (unobserved) variable; we observe only whether or not an individual has crossed the threshold. For liability threshold models, heritability measures the correlation of the liability between relatives.

It should be noted that in addition to genetic factors, family members may have environmental and lifestyle factors in common that may contribute to trait susceptibility. Therefore, family studies cannot definitively determine the proportion of familial clustering due to genetics versus environment or behavior.

13.3.2 Familial Clustering and Heritability with Regard to Longevity and Aging Phenotypes

13.3.2.1 Extreme Longevity

Studies of centenarians offer compelling evidence of a familial component to *extreme longevity*. Using data from the New England Centenarian Study, Perls et al. [34] compared siblings of centenarians to siblings of a control group that was comprised of individuals from a similar birth cohort who died prior to 73 years of age. Compared to siblings of the controls, siblings of centenarians were about four times more likely to survive to ≥90 years of age. In a larger study of 444 primarily Caucasian centenarian families (which included more than 2,000 siblings of centenarians), male siblings of centenarians were at least 17 times more likely to attain 100 years of age and female siblings of centenarians were at least eight times more likely to attain 100 years of age compared to the general experience of their birth cohort [35]. The Okinawa Centenarian Study replicated these findings in a different ethnic group. Okinawa, Japan is a genetically and socially homogenous island with the highest prevalence of long-lived individuals in Japan and possibly the world [36]. Compared to their birth cohort, male siblings of Okinawan centenarians had a 5.4-fold greater likelihood and female siblings had a 2.6-fold greater likelihood of reaching 90 years of age [36].

To explore the influence of family history on longevity in the general population, Kerber et al. [29] examined large pedigrees in the Utah Population Database that included a cohort of 78,994 individuals born between 1870 and 1907, and who survived to at least 65 years of age. Individuals younger than 65 years of age were excluded to minimize any familial clustering of early mortality due to susceptibility to diseases that are known to have significant genetic determinants (e.g., premature coronary heart disease). The recurrence risk ratio (λs) for siblings of probands who achieved *extreme longevity* (defined as 95 years of age in males and 97 years of age in females) was 2.3 (95% confidence interval 2.1, 2.6).

Hjelmborg et al. [37] used data from the GenomeEUtwin project to also explore the effect of removing early deaths on the genetic contribution to longevity. In over 20,000 twins, the genetic contribution to lifespan was minimal prior to 60 years of age with relative recurrence risk ratios close to one for both monozygotic and dizygotic twins. However, starting at about 60 years of age, the relative recurrence risk increased with increasing survived age in both men and women. In women, recurrence risks similar to men occurred at a 5- to 10-year older age. As expected, recurrence risk ratios for monozygotic twins were greater than for dizygotic twins (at 90+ years of age, the recurrence risk was 3.6 and 1.9 in monozygotic and dizygotic male twins, and 2.2 and 1.4 in monozygotic and dizygotic female twins, respectively).

13.3.2.2 Age at Death

The heritability of longevity (*age at death*) has been estimated using large population-based twin registries. Most estimates from Scandinavian twins range between 20 and 30%, which suggests a significant but modest genetic contribution to

lifespan [38–40]. There were no gender or birth cohort differences in the observed heritability estimates; however, the birth cohorts spanned 1870–1890, which was prior to the marked improvement in life expectancy in the twentieth century. Two studies on population-based samples that used large extended families estimated heritability and age of death to be slightly lower at 15–25% [29, 41]. However, one of these studies examined a founder population [41] (descendents of a specific member of the Old Order Amish) and thus longevity may differ in non-Amish populations. The second report [29] was estimated from Utah genealogies that included individuals affiliated with the Church of Jesus Christ of Latter-day Saints. This religious affiliation is associated with longevity, which raises the concern that genetic differences as well as environmental and behavioral differences may be present in this group. One male twin study [42] examined the heritability of a healthy-aging phenotype defined as surviving to 70 years of age free of coronary disease, stroke, diabetes and prostate cancer. The study reported that over 50% of the variance for liability to healthy aging was genetic [42].

The Framingham Heart Study is a multigenerational longitudinal cohort study that was initiated in 1948 and is ongoing today. The study provides an opportunity to examine heritability of age at death in a general population sample without concern for founder effects or potential confounding by religious affiliation. The distribution of age at death in the sample is reflective of the general population (original cohort participants mean age at death: 78.2 years, range 32.9–105.1 years; offspring participants mean age at death: 68.2 years, range 17.1–95.9 years). Among 10,333 participants from the original cohort and offspring cohort who had age data, 6,272 were deceased and 4,061 were censored at the age of last contact. Using a variance components model, heritability of age at death was estimated to be 0.16 ($p = 0.006$), which is consistent with previous reports. Framingham Heart Study data also supports the presence of a genetic contribution to disease-free survival (defined as survival to the index age free of cardiovascular disease, cancer, diabetes and dementia). The heritability of liability to morbidity-free survival at ≥65, ≥75 and ≥85 years of age was significant but modest at 0.21–0.25.

Using the Framingham Heart Study sample, we aimed to determine whether genetic influences on lifespan increased with the achievement of older ages, as suggested by twin data, by examining age at death as a dichotomous trait above or below a pre-specified age cutpoint (65, 75 and 85 years of age) using a liability threshold model [43] adjusting for sex and birth year. Living individuals who had not yet achieved the pre-specified age were excluded. Heritability of age at death was substantial (~0.40) for age at death dichotomized at ≥65 years of age (Table 13.2).

We examined heritability separately in women and men to explore reports of a higher relative recurrence risk for survival to advanced age in males compared to females [44]. Heritability was approximately constant in the combined male and female sample for survival to ≥65, ≥75 or ≥85 years of age. However, heritability appears to decrease for age at death ≥75 to ≥85 years in women, while in men heritability increased from 0.31 for age at death ≥65 years to 0.50 for age at death ≥85 years (Table 13.2). Hence, genetic factors may play a more important role for longevity in men in the Framingham Heart Study sample. Similar observations have been made by other investigators [44]. Confirmation of these findings in independent samples is needed.

To our knowledge, there has been only one study of lifespan heritability in individuals of Hispanic and African-American ancestry. The Washington Height-Inwood Columbia Aging Project [45], conducted in New York City, identified Medicare and Medicaid beneficiaries ≥65 years of age and conducted detailed family history interviews that included current age and age at death of first-degree relatives. Heritability estimates were calculated for *lifespan* by restricting the analysis to deceased relatives, and for *survival* by combining age at death for deceased relatives and current age for living relatives. Genetic contribution to lifespan varied across ethnicities from 26% in individuals of European ancestry to 29% in Caribbean Hispanics to 4% in African-Americans, whereas the genetic

Table 13.2 Heritability of survival in Framingham heart study families: liability threshold model

	Number of relative pairs					
Phenotype	Total number	Parent-offspring	Sibling	h^2	SE	p-value
Full sample						
Survival ≥65 years	8,059	4,413	3,124	0.36	0.07	4.19×10^{-10}
Survival ≥75 years	6,725	2,772	2,283	0.35	0.04	1.53×10^{-13}
Survival ≥85 years	5,863	1,769	1,630	0.40	0.07	8.98×10^{-10}
Men						
Survival ≥65 years	3,893	983	736	0.31	0.03	1.00×10^{-3}
Survival ≥75 years	3,274	606	530	0.49	0.09	1.00×10^{-7}
Survival ≥85 years	2,916	427	396	0.50	0.17	5.05×10^{-4}
Women						
Survival ≥65 years	5,069	1,226	881	0.41	0.13	4.73×10^{-4}
Survival ≥75 years	4,304	777	652	0.46	0.10	1.50×10^{-6}
Survival ≥85 years	3,779	457	469	0.20	0.11	0.03

contribution to survival was similar across ethnicities (15–19%). When the heritability analysis was restricted to sibships to minimize environmental differences between the parent-proband generations, the heritability estimates were higher and continued to be similar across ethnicities (34–38%). Further work is needed to determine the presence of and reasons for differences in contribution of genetic factors to lifespan in individuals of different racial and ethnic backgrounds.

13.3.2.3 Remaining Phenotypes

In contrast to the significant but modest heritability estimates associated with age at death (~15–30%), the heritability of other aging phenotypes suggests a much larger contribution of genetic factors to the variability in the trait. The heritability of reproductive aging phenotypes, (age at menarche and age at natural menopause) is at least 50%, which suggests that half of the variance in the timing of these key reproductive events is attributable to genetic factors [46, 47]. In contrast, the heritability of bone mineral density ranges from about 50 to nearly 70% [48]. The heritability of Alzheimer's Disease is even higher (>70%) and does not differ by sex, which suggests that the same genetic factors affect both women and men [49]. Hence, the discovery of genes related to longevity may be more challenging than the discovery of genes related to other aging phenotypes with higher heritability.

13.4 Study Designs Used to Identify Genetic Associations for Human Longevity and Aging Phenotypes

13.4.1 Rare Disorders of Premature Aging: Progeroid Syndromes

Understanding the molecular basis for rare diseases of premature aging or progeroid syndromes may provide important insights into the biological mechanisms that underlie the normal aging process. Scientists participating in the Progeria Research Foundation Genetics Consortium (www.progeriaresearch.org) identified the gene responsible for Hutchinson-Gilford Progeria syndrome (HGPS) in 2002 [50]. HGPS is an extremely rare sporadic autosomal dominant syndrome that is caused by mutations in the lamin A/C (*LMNA*) gene and leads to death from cardiovascular causes by 7–20 years of age. Detailed phenotyping of 15 children revealed accelerated aging across multiple body systems [51]. A small histological study that compared cardiovascular tissues from two children with HGPS who died of myocardial infarction to a

cross-section of 29 individuals who ranged in age from 1 month to 97 years demonstrated the presence of progerin in the vascular tissue of individuals without progeria, a presence that increased with advancing age [52]. Furthermore, several potential biologic mechanisms that underlie HGPS have been hypothesized to contribute to normal aging, such as increased DNA damage and defective repair, cell cycle abnormalities and cellular senescence, and diminished stem cell proliferation [53]. Additional progeroid syndromes are currently being studied.

13.4.2 Genetic Linkage

Linkage analysis is a statistical technique used within families to localize genes that influence a specific trait on the human genome. Studies that examine dichotomous traits should sample families so that multiple affected individuals are present. Genes located close to one another on a chromosome tend to be inherited together. Linkage analysis looks for cosegregation of the trait of interest with known genetic markers. Linkage studies have low power for complex traits which are believed to be influenced by many genes with small effects. Linkage studies are also hampered by their inability to narrow the interval harboring a gene beyond chromosomal regions containing tens to thousands of genes.

A genome-wide linkage scan conducted in 137 sibships discovered a region on chromosome 4 that is significantly linked to extreme longevity [54]. A second small study of male siblings found that the same region on chromosome 4 is significantly linked to a healthy aging phenotype, which suggests that extreme longevity and healthy aging may share underlying genetic determinants [55]. A fine-mapping association study of a part of this region containing about 50 genes identified a microsomal transfer protein (*MTP*) gene that is important in lipoprotein synthesis to be associated with longevity [56]. However, the *MTP* gene association and the chromosome 4 linkage finding were not replicated in subsequent studies of long-lived individuals [57–59]. A meta-analysis of association studies of the *MTP* haplotype and longevity suggests that population stratification in the original report's control sample may explain the potentially false-positive association near the linkage peak [58]. Population stratification or the presence of subpopulations of different ethnic backgrounds can confound genetic associations and lead to false-positive results.

The Genetics of Healthy Aging (GEHA) project is a large collaboration of investigators from 11 European countries (in 15 geographic areas) and China with the goal of collecting DNA and health status information on a large sample of long-lived sibling pairs (n = 2,650, age ≥90) and younger ethnically-matched controls (n = 2,650, mean age 60–65) to perform linkage analysis and follow-up association studies [60]. This effort represents the largest family-based multi-national genetic study of longevity to date.

13.4.3 Candidate Gene Association Studies

Candidate gene association studies select genes for investigation based on known or postulated biologic function. This approach relies on *a priori* knowledge of the genes relevant to the phenotype and may be biased by pre-conceived hypotheses regarding which genes might be important. Thus, the approach may fail to discover genetic associations if a gene that influences the phenotype is not included in the list of genes to be studied. Unlike linkage studies, candidate gene association studies can be conducted in samples of unrelated individuals, eliminating the need for family data. The Human Ageing Genomic Resources is an online tool for biogerontologists that includes a database of genes that are potentially associated with aging in humans, and a list of genes tested for association with human longevity and genes related to aging in model organisms [61, 62].

Candidate genes in a variety of biologic pathways have been associated with human longevity, but most have not been replicated. The exceptions are *ApoE* [63] and several single nucleotide polymorphisms (SNPs) in *FOXO3a* [64]. The *ApoE* gene is involved in lipid metabolism and has three isoforms called epsilon 2, epsilon 3 and epsilon 4 *(E2, E3 and E4)*. Epidemiologic studies

Table 13.3 Web-based resources for human genetic association studies

Name	Web site
Aging and longevity phenotype definitions	
Exceptional survival, 2001 NIA panel recommendations	http://www.nia.nih.gov/ResearchInformation/ConferencesAndMeetings/NIAPanel.htm
PhenX toolkits (consensus measures of phenotypes and exposures)	https://www.phenxtoolkit.org
Publically accessible databases	
dbGAP (repository of genotypes and phenotypes)	http://www.ncbi.nlm.nih.gov/gap
Genetic Association Database (GAD)	http://geneticassociationdb.nih.gov
Human Genome Epidemiology Network (HuGENet)	http://www.cdc.gov/genomics/hugenet/
Human ageing genomic resources	http://genomics.senescence.org
Genetic consortia	
Longevity consortium	http://www.longevityconsortium.org
CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology)	http://web.chargeconsortium.com/ http://depts.washington.edu/chargeco/wiki/Main_Page
Genetics of Healthy Aging (GEHA)	http://www.geha.unibo.it/default.asp
Gene Environment Association Studies (GENEVA) and Genes and Environment Initiative (GEI)	http://www.genevastudy.org/
Population Architecture using Genomics and Epidemiology (PAGE)	http://www.pagestudy.org

have reported that the *E4* isoform is associated with elevated cholesterol, cardiovascular disease, age-related cognitive decline and dementia, while the *E2* isoform is protective for Alzheimer's disease. *Apo E4* is the major genetic risk factor for late-onset Alzheimer's Disease. In a case-control study, the *Apo E4* allele was found less frequently in centenarians than in adults 20–70 years of age [65]. Thus, *ApoE* may influence human longevity by decreasing risk for age-related disease and premature atherosclerosis.

FOXO3a functions in the human insulin/IGF-1 signaling pathway, a basic pathway that has been conserved throughout evolution and is important to lifespan extension in model organisms. *FOXO3a* was first reported to be significantly associated with extreme longevity in a candidate gene study conducted on male centenarians of Japanese descent. In that study, *FOXO3a* was also associated with several phenotypes of healthy aging that included less age-related disease, better self-rated health and high levels of physical function. The association between longevity and *FOXO3a* has been replicated in a Southern Italian Centenarian Study [66], a German Centenarian Study [67] and a Han Chinese Centenarian Study [68]. The Han Chinese Study also found an association between *FOXO1a* and longevity in female centenarians, which suggests that genetic factors may be influenced by gender.

13.4.4 Genome-Wide Association Studies

GWAS test genetic variants across the entire genome for association with a phenotype. GWAS are considered to be hypothesis-free in the sense that the association tests are not limited to a subset of genes or regions that are selected in advance due to prior hypotheses about what genes should influence the trait. Sample sizes for GWAS typically include thousands of individuals. GWAS test hundreds of thousands to millions of SNPs across the genome for association with the phenotype of interest. Large discovery samples and access to independent samples for the replication of novel genetic signals are needed to limit the potential for both false-positive and false-negative associations.

The GWAS approach has proven highly successful for the discovery of novel genes and pathways that are involved in many common human diseases and phenotypes (Table 13.3). A catalog of published GWAS results is available at

http://www.genome.gov/gwastudies. Several Web-based resources are available to support genetic association investigations. The NIH funds the Genetic Association Database (http://geneticassociationdb.nih.gov), a public repository of summary data from published GWAS and candidate gene studies of common disease. The Center for Disease Control maintains the Human Genome Epidemiology Network (HuGENet) (http://www.cdc.gov/genomics/hugenet/) to establish collaborations among groups who are working on population-based genetic research and to speed the translation of genetic findings into opportunities for prevention and public health. To facilitate scientific investigation, the National Center for Biotechnology Information (NCBI) maintains a public repository of genotypes and phenotypes (dbGAP) from richly-characterized studies with dense genotyping that can be accessed by investigators who are interested in conducting genetic association studies (http://www.ncbi.nlm.nih.gov/gap).

The GWAS approach was first used to investigate longevity and aging traits as part of the Framingham 100 K project. The study [69, 70] genotyped 1,345 Framingham Heart Study participants from the largest 310 families, many biologically related, using the 100 K Affymetrix GeneChip [71]. The study found modest associations between longevity (defined as age at death) and SNPs in or near *FOXO1a*, a gene implicated in lifespan in animal models. Other important candidate genes were also noted, but these associations did not reach genome-wide statistical significance. Results from the Framingham 100 K investigation must be considered hypothesis-generating and need to be replicated before the true positive associations can be identified. The Framingham 100 K experiment was limited by its small sample size and by limited coverage of the genome compared to today's standards.

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium formed in 2008 to facilitate large-scale genetic studies and replication opportunities among population-based longitudinal cohort studies in the United States and Europe [72]. The Aging and Longevity working group within the CHARGE consortium continues to grow. At the time of this writing, the working group includes 15 cohorts and >30,000 older participants with genome-wide genotyping. The success of the working group is dependent on several key factors. First, investigators with expertise in aging and a working knowledge of the study data are needed to contribute to phenotype development, harmonization and prioritization. Next, multidisciplinary collaborative teams comprised of investigators across studies are essential to create an appropriate analysis plan, conduct the study-specific GWAS and conduct the meta-analyses of GWAS data. Finally, well-characterized longitudinal cohorts that include large numbers of older individuals are critical to ensure adequate power to detect genetic variants with small effects.

The CHARGE Aging and Longevity working group conducted a meta-analysis of GWAS results from four cohort studies of longevity, which was defined as survival to ≥90 years of age [73]. The scientific collaboration enabled the assembly of one of the largest samples of long-lived individuals with genome-wide genotyping available to date (1,836 individuals achieved longevity) and enabled the identification of a comparison group drawn from the same cohort studies. The comparison group included only deceased participants to ensure that no individual in this group achieved longevity. The meta-analysis included only participants of European ancestry to minimize bias due to population structure. Since the various cohort studies used different dense genotyping platforms, statistical genotype imputation techniques were employed to enable all studies to test nearly 2.5 million SNPs with the longevity phenotype. The CHARGE investigation detected 273 SNP associations for longevity that achieved $p<0.0001$, but none of the associations achieved genome-wide significance ($p<5\times10^{-8}$).

In the next stage of the discovery analysis, two additional studies included [73]. These were identified through the Longevity Consortium, which is funded by the NIA (http://www.longevityconsortium.org/). The Longevity Consortium brings together an inter-disciplinary group of sci-

entists who are studying the genetics of aging, including investigators from population-based longitudinal cohort studies, studies of special populations such as centenarians, and laboratory-based scientists who are examining animal models of aging. Among the 24 strongest independent SNP associations in the CHARGE meta-analysis, 16 SNPs were successfully genotyped in the two independent studies and one SNP near *MINPP1* (a highly conserved gene that is involved in cellular proliferation) was associated with longevity with $p = 6.8 \times 10^{-7}$ in the combined stage 1 and stage 2 discovery sample. The minor (less frequent) allele was associated with lower odds of achieving longevity (odds ratio 0.8). Additional associations of interest in the stage 1 discovery analysis included SNPs in a longevity assurance gene (*LASS3*) and *PAPPA2*, but neither association was strengthened by the addition of the stage 2 discovery samples. *PAPPA* is an attractive candidate gene due to its association with lifespan extension in the mouse [74]. In the future, the use of larger sample sizes, more extreme phenotypes (e.g., centenarians) or more specific aging phenotypes (e.g., disease-free survival) may improve the power to detect age-related genetic variation and lend support to these initial findings.

A GWAS that was conducted in 801 centenarians from the New England Centenarian Study and 926 controls identified 70 genome-wide significant SNPs and replicated 33 SNP associations in a smaller independent sample of centenarians and controls [75]. This suggests that many genetic variants from a variety of biologic pathways contribute to the achievement of exceptional longevity. The genes identified among the replicated SNP associations included genes associated with age-related disease such as Alzheimer's disease (*TOMM40/ApoE*) and biologic mechanisms linked to aging such as insulin signaling (*GIP, RAPGEF4*), growth factor and hormonal regulation (*PLCB3*), stress response (*MAV3, IL7, ANKRD55*) and chromosome stability (*HJURP*) [75]. In that study, centenarians were genotyped using two different genotyping platforms (the majority of samples were analyzed using the Illumina 370 CNV chip and a small number of samples were genotyped using the Illumina 610-Quad array). If it is not appropriately accounted for in the analysis, using different genotyping chips can lead to "bias" and false-positive associations. A number of scientists have raised these concerns with regard to this study [76, 77]. Updated results from this GWAS are pending but the authors have since published a retraction after discovering technical errors in the genotyping array and inadequate quality control procedures that resulted in false-positive SNP-associations.[78] The Utah Population Database cohort found that individuals with a family history of longevity had lower mortality for most age-related diseases, including coronary disease, stroke and diabetes, but not cancer [79] and studies of offspring of centenarians demonstrated lower rates of all-cause, cardiovascular and cancer mortality [80]. Therefore, researchers hypothesized that these observations may be due to the absence of disease-susceptibility alleles. They tested the hypothesis by examining whether long-lived individuals who participated in the Leiden Longevity Study and the Leiden 85 Plus Study had lower numbers (compared to a younger comparison group) of 30 alleles that had been discovered through GWAS to be associated with coronary disease, cancer, and type 2 diabetes [81]. Interestingly, the long-lived individuals and younger comparison group both carried the same number of risk alleles, which suggests that survival to old-age is not determined by the absence of risk alleles for these age-related diseases.

GWAS have uncovered important clues to biologic pathways that underlie many common conditions, including age-related diseases such as Alzheimer's Disease and osteoporosis. However, the majority of GWAS to date have been conducted in white populations of European ancestry, with few large-scale genetic studies being conducted with individuals of other races/ethnicities. GWAS in non-white populations throughout the world are crucial to determine whether gene and allelic effects are homogenous across genetic and environmental backgrounds. In some cases, such studies would also provide improved localization of genetic effects. Allele

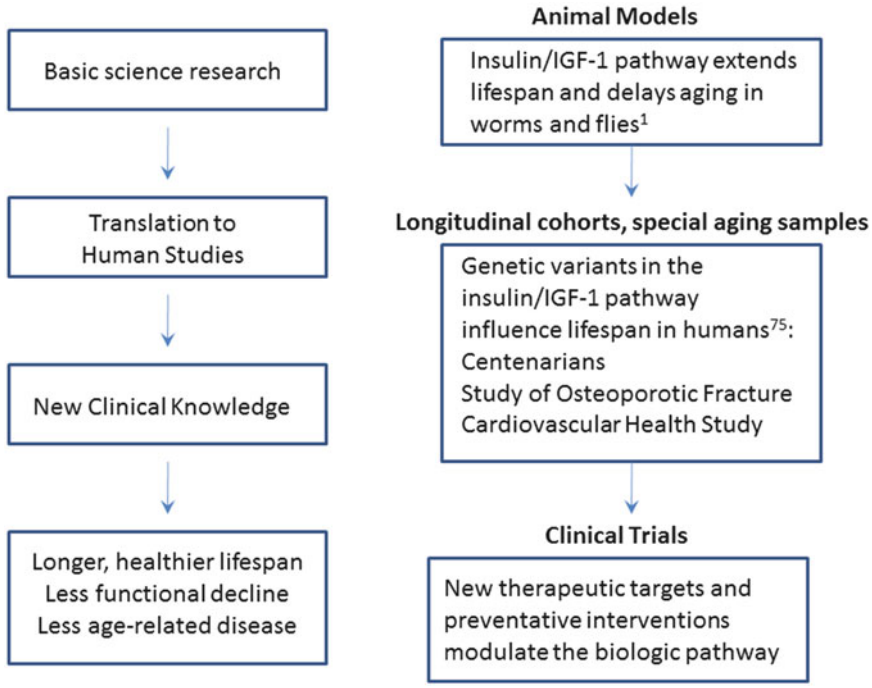

Fig. 13.2 Translation of basic science discoveries to human studies

frequency differences between global populations or in population genetic drift may result in higher allele frequencies in different populations with regard to some low-frequency alleles found in populations of European ancestry. Thus, GWAS conducted in diverse populations can result in improved power for gene discovery, especially for the low-frequency alleles in European populations [82].

While GWAS should continue to play an important role in identifying the genes and pathways that underlie age-related traits, association analyses are only the first step in determining the causal genetic variant and the associated function of the variant. GWAS results cannot distinguish whether the identified genetic variant is the causal mutation or is in linkage disequilibrium with the causal variant. Further, many GWAS associations are with SNPs that lie in chromosomal regions that lack known genes or function. Functional experiments are usually needed to determine the genetic variant's mechanism in causation of the disease or phenotype. Collaboration with scientists who work with animal models of aging may provide further mechanistic insights into the human GWAS associations.

Epidemiologic studies may also help to speed the translation of basic science findings to human studies (Fig. 13.2). For example, the first pathway that was shown to extend lifespan and influence aging in animals was the insulin/IGF-1 pathway [1]. To investigate whether genetic variation in this pathway influences human aging, about 300 genetic variants in 30 genes in the pathway were genotyped in older women who participated in the Study of Osteoporotic Fracture, and replication studies of genetic variants associated with longevity were conducted in the Cardiovascular Health Study and an Ashkenazi Jewish Centenarian Study [83]. Using data from the longitudinal cohort studies and study of centenarians, investigators were able to demonstrate that genes in the insulin/IGF-1 pathway are also associated with human lifespan.

13.5 Potential Sources of Bias and Confounding in Aging and Longevity Genetics

13.5.1 Self-Reported Age

Several sources of bias and confounding need to be considered in evaluating genetic association studies of longevity and aging phenotypes. Misclassification of long-lived individuals can reduce a study's power and bias its results toward the null hypothesis. Therefore, the *validation of self-reported age* is critical, especially for studies of extreme longevity (centenarians, supercentenarians [≥110 years of age]). The NIA panel on exceptional survival in humans recommended age validation using birth certificates or other documents, with consideration given to additional corroborating documents of proof of age at different points across the lifecycle (census records, school records, marriage certificate, employment records and death certificate)[3].

13.5.2 Definition of the Trait Under Investigation

Misclassification may also occur without a *clear definition of the longevity and healthy aging trait* that is under investigation. The harmonization of phenotypic data across collaborating studies is often a slow process, but it is a vital one. Data sharing and collaboration across multiple studies will be required to obtain the large discovery samples and independent replication samples needed to identify small effects.

13.5.3 Birth Cohort Effects

It is critical to consider *birth cohort effects* in studies of longevity [84]. The presence of a major infectious disease (such as the 1918 influenza pandemic) or war during a birth cohort's lifespan may significantly impact an individual's opportunity to achieve a long and healthy life. In addition to exposures, medical treatments and preventative strategies have changed dramatically across birth cohorts and may influence an individual's opportunity for survival. Figure 13.3 shows a timeline of events that could impact one's chances of survival which occurred over the lifetime of individuals who achieved centenarian status in 1990. Despite attempts to account for birth cohort in the CHARGE meta-analysis of longevity discussed earlier in the chapter, there was limited overlap regarding birth year between the long-lived group and the comparison group [73].

13.5.4 Other Factors

Additional *environmental and behavioral factors* unrelated to genetics may modify the genetic associations with longevity and healthy aging (e.g., cigarette smoking, alcohol use, physical activity). Longitudinal cohort studies that include older participants have the advantage of the prospective collection of exposure information across the lifespan so that the genetic association studies can account for potentially-confounding environmental and behavioral factors. *Population stratification* (also called population admixture or population structure) occurs when the study sample is composed of multiple subgroups of different ethnicity or geographic origin which, in turn, results in variation in the allele frequency and phenotype distribution between subgroups. Genetic association studies may then falsely identify the subgroup-associated genes as the genes influencing longevity. *Genotyping errors* are also an important cause of false-positive associations, especially when they occur differentially between longevity cases and controls.

13.6 Gene-Gene (G × G) and Gene-Environment (G × E) Interactions

Genetic associations may be modified by other genes or environmental factors. To our knowledge, few published reports have examined gene-gene or gene-environment interactions with respect to aging and longevity phenotypes in

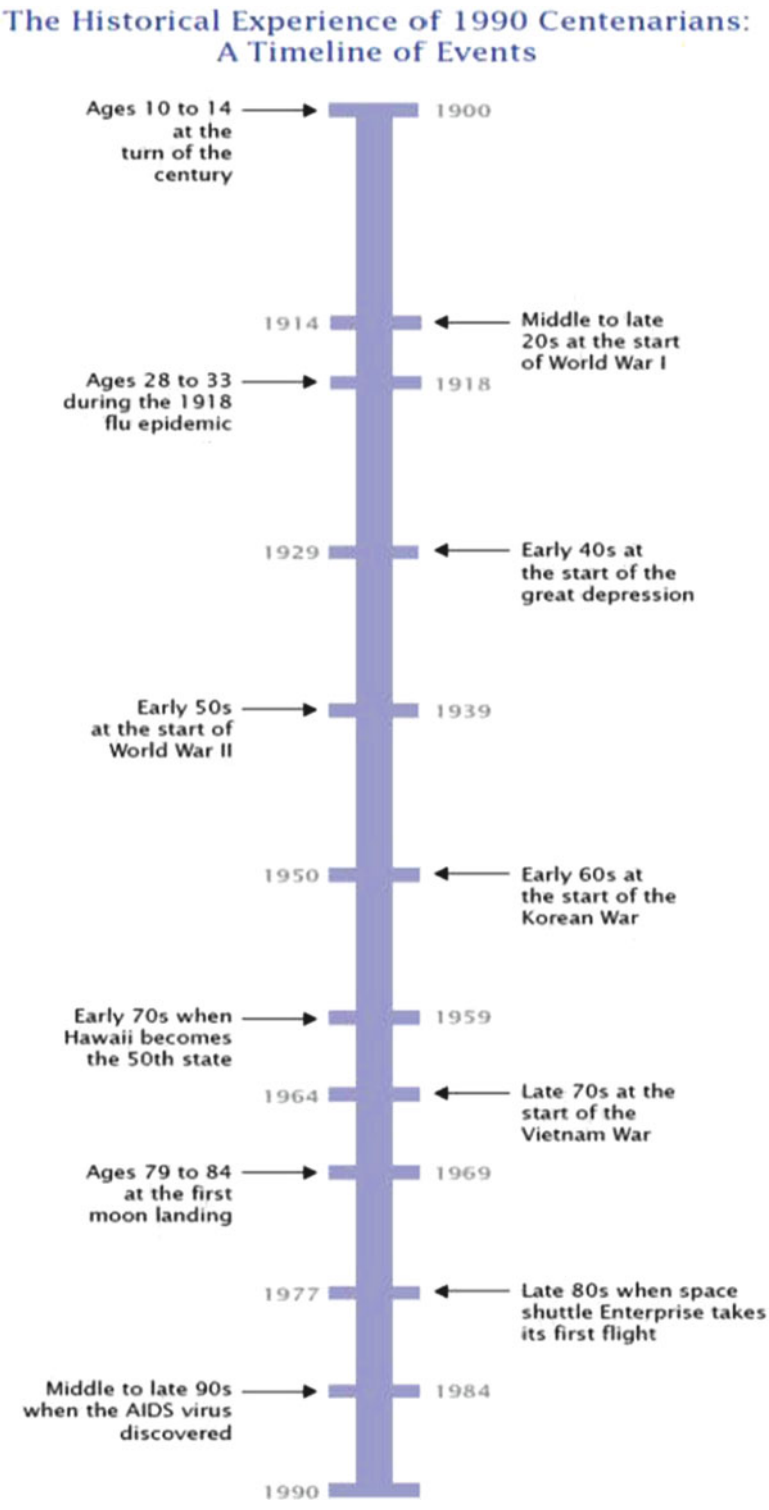

Fig. 13.3 A timeline of events for centenarians in 1990 (Krach and Velkoff [14])

humans. Zeng et al. [85] examined a Han Chinese sample that consisted of 760 centenarians and 1,060 middle-aged controls to study the interaction between genotypes in the *FOXO1A* and *FOXO3A* genes (G × G) and interactions between these genotypes and social-behavioral factors (G × E) on survival to advanced age. In that report, the 10-year follow-up of participants to 92–110 years of age demonstrated positive effects of *FOXO3A* on survival, G × G interactions between *FOXO1A-209* and *FOXO3A-310* or *FOXO3A-292* that decrease survival ($p<0.05$), and G × E interactions between *FOXO1A-209* and regular exercise that increase survival ($p<0.05$). However, some caution is warranted as the findings have not yet been replicated in an independent sample and the biologic mechanisms underlying the findings are unknown.

The NIH has sponsored initiatives to examine how non-genetic factors interact with genes to effect health. The Genes, Environment Association Studies (GENEVA) consortium includes a genetics and exposure component and aims to identify modifications in gene-phenotype associations that are related to environmental exposures. The Population Architecture Using Genomics and Epidemiology (PAGE) study (https://www.pagestudy.org/) will examine how genetic variants identified through GWASs are related to an individual's biologic characteristics (e.g., weight, blood sugar) and will explore how non-genetic factors (e.g., diet) influence genetic factors and ultimately health. Knowledge gained from these initiatives may provide insights into pathways that lead to longevity, or to new analytic tools that can be used for aging and longevity research.

13.7 Future Directions in Genetic Research

13.7.1 Next-Generation Sequencing

Advances in technology now permit the complete sequencing of all protein-coding portions of the genome (the "exome"). The ability to sequence the whole genome of individuals quickly and efficiently is not far in the future. Sequencing represents an opportunity to detect rare genetic variants that are unlikely to be discovered using the GWAS or candidate gene approaches, which focus on common genetic variations (minor allele frequencies of >5%). Furthermore, whole-genome or whole exome sequencing will enable the discovery of functional variants.

The NHGRI and the National Heart Lung and Blood Institute funded the Exome Project (http://www.nhlbi.nih.gov/resources/exome.htm) with the goal of unraveling genes that contribute to heart, lung and blood disorders. This innovative technology and the analytic tools under development will extend to the study of aging and longevity phenotypes. The sequencing of centenarian genomes may uncover rare genetic variants that underlie human extreme longevity and provide insights into the basic mechanisms of aging. Exome sequencing has already been successfully used to discover the gene responsible for Miller's syndrome, a rare Mendelian disorder of previously unknown etiology [86].

13.7.2 Epigenetics

Epigenetics refers to changes in gene expression that may be inherited and occur as a result of molecular mechanisms that do not change the primary DNA sequence [87]. Epigenetic mechanisms are believed to influence phenotypes and are affected by development, the environment, nutrition, drugs and aging. One of the best-studied epigenetic mechanisms is called DNA methylation. Usually, methylation in a genomic region results in the suppression of nearby genes. A study of global DNA methylation in an Icelandic cohort and a family-based Utah cohort demonstrated changes in methylation over time as well as familial clustering of methylation changes [88]. It has been hypothesized that changes in DNA methylation that occur with aging can alter normal gene expression and, in turn, contribute to functional decline and the development of age-related disease [89]. Additional

epigenetic mechanisms include alterations in chromatin, called histone modifications, which can make DNA more accessible to transcription and noncoding RNAs that can inhibit gene expression. DNA methylation sites and histone modifications can be identified using genome-wide analysis with microarrays (ChIP-chip) or next generation sequencing (ChIP-Seq). These new technologies may be used in longitudinal cohort studies in the future to uncover the role of epigenetics in human aging and longevity, and the contribution of epigenetic changes to age-related disease.

13.8 Conclusions

Genetic factors undoubtedly contribute to human aging and longevity. The search for longevity genes remains challenging. To date, few replicated longevity-gene associations have been discovered. The richly-characterized participants in prospective epidemiologic studies provide a unique opportunity to investigate the genetics of many age-related phenotypes including age-related diseases, physical function, frailty and cognition. Longevity and healthy aging traits are heterogeneous, and thus require the standardization of phenotype definitions and thoughtful study design that includes the consideration of birth cohort effects. The genome-wide genotyping of centenarians and participants in longitudinal cohort studies and family-based studies, along with unprecedented collaboration among investigators in the United States, Europe and worldwide, provide the opportunity for assembling the large discovery and replication samples needed for genetic discovery.

It is vital that genetic association studies be expanded beyond samples of European ancestry to worldwide populations in order to determine whether gene and allelic effects are heterogenous across different genetic and environmental backgrounds. Existing consortia that include scientists from population-based and laboratory-based arenas may speed the translation of genetic association results to uncover the functions of the identified genetic variants, and ultimately the biologic mechanisms that lead to human aging.

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Aging, Infection and Immunity

14

Sachin S. Kale, Namita Ahuja, and Sachin Yende

Abstract

Older adults are at high risk for developing an infection. Once an infection occurs, older adults experience high short- and long-term morbidity and mortality. A number of risk factors (e.g., living in a long-term care facility, chronic disease, malnutrition, age-related immune dysfunction, polypharmacy, difficulty in accessing health care, increased use of prosthetic devices and medical instrumentation) place older adults at high risk for increased susceptibility to infection, and older adults tend to have poor outcomes from infection. Common clinical infections in older adults include pneumonia, urinary tract infections, sepsis, gastroenteritis and viral infections. Serious infection in older adults can result in an increased risk of adverse events well beyond the patient's hospital stay. Acute infections may worsen chronic diseases in older adults, which may in turn put the older adult at a greater risk of serious infection. Altering modifiable risk factors (e.g., inactivity, malnutrition) may reduce the risk of infection in older adults. Vaccination remains an important strategy to prevent infections despite their variable efficacy in older adults.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Infection • Immunity • Pneumonia • Sepsis • Inflammation • Intensive care • Pulmonary function • Vaccinations • Influenza

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Abbreviations

APC	Antigen Presenting Cells
ASB	Asymptomatic Bacteriuria
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control
CMS	Centers of Medicare and Medicaid Services
DC	Dendritic Cell

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H	Hemagglutinin
H2	Histamine
IL	Interleukin
LPS	Lipopolysaccharide
LTCF	Long-Term Care Facilities
MRSA	Methicillin-Resistant *Staphylococcus aureus*
N	Neuraminidase
NK	Natural Killer cells
PHN	Postherpetic Neuralgia
RSV	Respiratory Syncytial Virus
TCR	T Cell Receptor
TLR	Toll-Like Receptor
US	United States
UTI	Urinary Tract Infection
VCV	Varicella Zoster Virus
VRE	Vancomycin-resistant enterococci (VRE)

14.1 Introduction

The term "infectious disease" is broadly defined as any infectious process that produces a clinical response in its host. Studies have found that the epidemiology of infectious diseases in older adults, defined here as those ≥65 years of age, is different than that of their younger peers. Older adults tend to be more susceptible to acquiring infectious diseases, have worse outcomes once infection occurs, are less able to effectively resolve the immune response during recovery and are less likely to respond to vaccination. In the United States (US) alone, the number of individuals >65 years of age is expected to double between 2000 and 2030. Given the aging demographic in the US and worldwide, it is increasingly important to understand the mechanisms that underlie age-related differences in susceptibility and outcomes of infection, as well as to design interventions targeted to older adults.

In this chapter we will begin by examining the significance and special characteristics of infections in older adults. Next we will explore the mechanisms and risk factors that increase susceptibility to infection in older adults, including age-related changes of the immune system. We will review these issues in the context of infections that are common in older adults. Finally, we will discuss the long-term impact of infection in older adults and the importance of vaccines in preventing infections.

14.2 Public Health Significance

Epidemiologic studies show that older adults are more susceptible to a number of infections. For example, the prevalence of community-acquired pneumonia (CAP) increases exponentially after the age of 65, and older adults are up to three times more likely to have pneumonia than are their younger peers [1]. The most common infections in the older adult population include lower respiratory tract infections (e.g., pneumonia, influenza), urinary tract infections (UTIs), skin/soft tissue infections (e.g., cellulitis) and severe sepsis (Fig. 14.1) [2].

Infection in older adults is currently responsible for roughly 12%, 14% and 19% of all hospital admissions in those 65–74 years of age, 75–84 years of age, and ≥85 years of age, respectively [2]. The rate of hospitalization due to infectious disease is highest among the very old (those >85 years of age), nearly double that for individuals 75–84 years of age and nearly three times higher than for those 65–74 years of age [3]. Older adults are also at a higher risk of acquiring an infection once hospitalized [4].

Infection in older adults is associated with higher mortality. In the US, lower respiratory tract infections and septicemia are the 7th and 10th leading causes of death, respectively, in the older population. In patients hospitalized with CAP, 90-day mortality for those ≥65 years of age and those ≥85 years of age were five-fold higher and seven-fold higher, respectively, than for those <65 years of age [5]. Older adults who have tuberculosis, a UTI or bacterial meningitis have approximately ten-fold, five-fold and three-fold higher mortality, respectively, compared to younger adults who have the same infection [6].

Infectious diseases in older adults are associated with tremendous economic costs. In 2001,

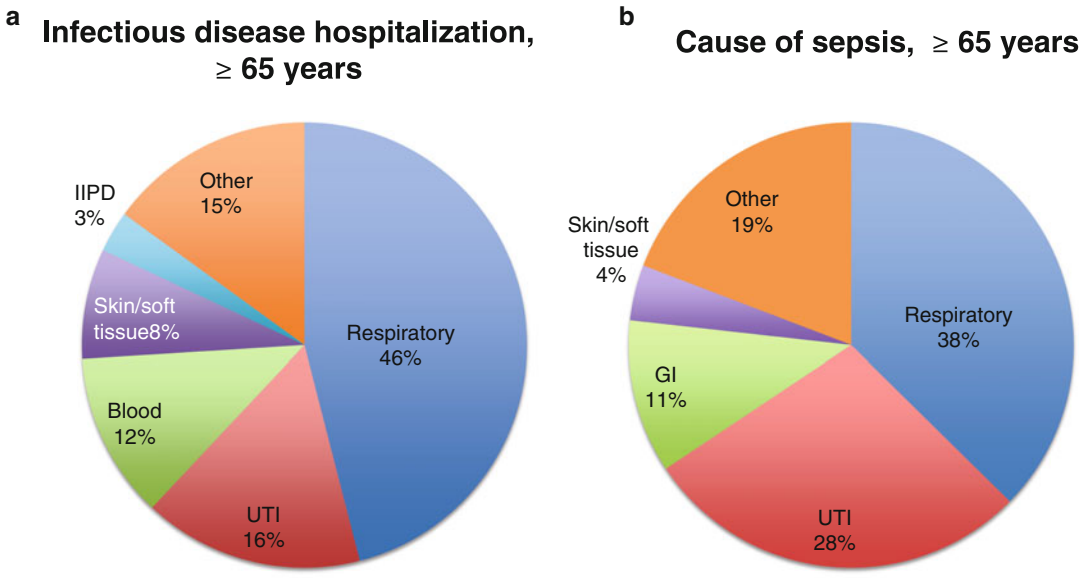

Fig. 14.1 (**a**) Proportion of infectious disease hospitalizations according to infectious disease group among patients 65 years and older in the United States (Adapted with permission from Curns et al. [2]). (**b**) Proportion of sources of infection among sepsis patients 65 years and older in the United States (Adapted with permission from Martin et al. [41]). Abbreviations, *IIPD* infections and inflammatory reactions to prosthetic devices, *UTI* Urinary tract infection, includes kidney and bladder infections, *GI* gastrointestinal tract

four of the top 20 diagnosis-related groups paid for by Medicare were due to infectious disease [7]. Approximately $16.7 billion per year is spent on costs that are associated with severe sepsis, a serious complication of infection, with over 80% of these dollars going toward the care of patients ≥65 years of age [8]. Furthermore, between 1998 and 2004, the costs associated with infectious disease hospitalizations increased by 45% among those ≥65 years of age and accounted for $204.2 billion [9]. As the number of older adults living in the US rises, the total costs associated with their care will continue to rise.

14.3 Key Clinical Issues

14.3.1 Infections in Long-Term Care Facilities

Older adult residents of long-term care facilities (LTCFs) are among the most vulnerable to infectious diseases. LTCFs include nursing homes and assisted living centers where non-acute health care is provided to patients who are unable to function independently. Residents of LTCFs tend to have a higher burden of chronic disease and are more likely to be immunocompromised than age-matched individuals who live in the community. There are a growing number of older adult residents in LTCFs, due in part to aging demographics and in part to an increasing trend toward the shifting of non-acutely-ill patients from the hospital to other care facilities. It has been estimated that over 40% of adults >65 years will stay at an LTCF at some point in their lifetime [10].

Infections in LTCFs are common and are responsible for a substantial proportion of resident transfers to hospitals. The three most common infections in LTCFs are urinary tract, respiratory, and skin and soft tissue infections [11]. The incidence of infection ranges from 1.8 to 13.5 episodes per 1,000 resident-care days, resulting in 1.6–3.8 million infections per year [12]. LTCF-acquired infection is associated with

high mortality. One study found that the 3-week mortality is as high as 10% among nursing home residents who have an infection [13]. The costs of hospitalization from an infection originating from an LTCF have been estimated to exceed $1 billion per year [12].

The increased infection risk at LTCFs is due both to the patient population and the environment. As we will explore below, residents of LTCFs have several risk factors for infection, including an increased prevalence of chronic diseases, immunocompromised states, indwelling catheters and functional impairment. Living in a closed environment with other chronically ill individuals and frequent contact with caregivers who can transfer disease also increases the risk of outbreaks of infectious diseases such as gastroenteritis and influenza. The frequent use of antimicrobial agents in LTCFs has led to the spread of antimicrobial-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [11].

As of September 2009, all infections that occur in LTCFs must be reported to the Centers of Medicare and Medicaid Services (CMS). Infection control programs in LTCFs are now required by the CMS to reduce the spread of infection. Integral to these programs are protocols that mandate frequent handwashing by caregivers, isolation precautions for infected individuals, and the use of immunizations.

14.3.2 Risk Factors for Infection

Older adults have many risk factors that contribute to the increased incidence and higher severity of infection. These risk factors include: living in an LTCF, chronic diseases, malnutrition, age-related immune dysfunction, polypharmacy, difficulty in accessing health care, and an increased use of prosthetic devices and medical instrumentation (Fig. 14.2). It is important to note that these risk factors can act synergistically to magnify the risk of infection.

Although the presence of chronic disease is a risk factor for infection across all ages, it plays an important role in older adults due to its higher prevalence and severity. The US Centers for Disease Control (CDC) estimates that approximately 80% of older adults have at least one chronic disease, and 50% have two or more chronic diseases. Common chronic diseases include diabetes mellitus, chronic obstructive pulmonary disease, chronic heart disease, chronic kidney disease and cancer. In studies of individuals who are hospitalized with infection, an increasing burden of chronic disease is routinely associated with an increased susceptibility to infection and worse outcome.

Chronic disease can increase the risk of infection in several ways. First, certain chronic diseases are associated with increased susceptibility to specific pathogens, such as the relationship between diabetes and skin infection by *Staphylococcus sp.* Second, individuals who have long-standing chronic diseases often have decreased organ reserve and are thus more prone to organ failure during infection. It has also been proposed that several chronic diseases (e.g., diabetes, hematologic malignancies) can alter immune function.

Importantly, medical therapy itself can be a risk factor for infection in older adults. Frequent hospitalizations among older adults place them at higher risk for hospital-acquired (nosocomial) infections than their younger peers. Polypharmacy is another important risk factor for older adults, as they are more likely to take multiple medications and to be susceptible to side effects. Many commonly used medications (e.g., anti-inflammatory agents, steroids, histamine [H2] blockers) have been described as potentially suppressing immune response. Additionally, the prevalence of prosthetic devices (e.g., heart valves, artificial hip and knee joints) in older adults is a risk factor for foreign body infection [14].

Older adults may engage in behaviors that increase the risk of infection. Smoking is a well known risk factor for pneumonia and the risk increases with the number of years a person has

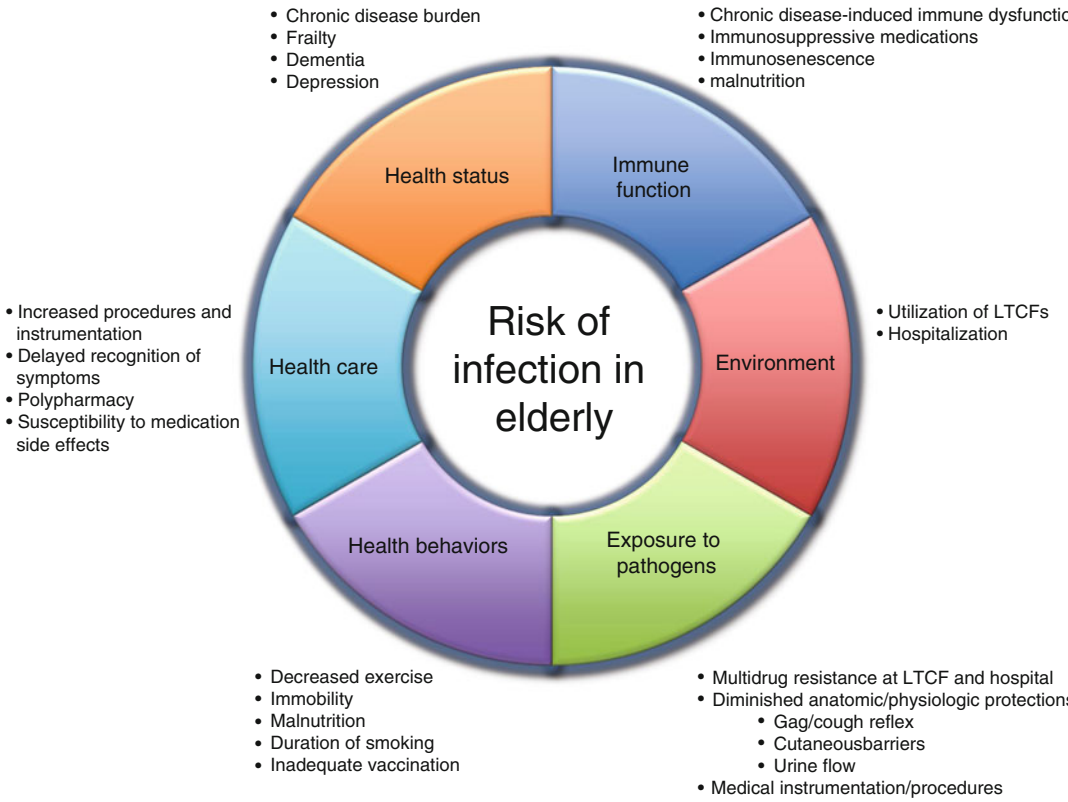

Fig. 14.2 Conceptual model of the broad determinants and risk factors for infection in older adults. Abbreviations, *LTCF* long-term care facility [41]

smoked, making the deleterious effects of smoking prominent in older adults. Older adults are also less likely to exercise and be active, due in part to frailty. Although a definitive link between diminished physical activity and susceptibility to infection has not been shown, exercise may have beneficial effects on the immune system and help to prevent infections.

Another risk factor is poor nutrition. Nearly 50% of hospitalized older adults with infection have a nutritional deficit [15]. The primary cause of malnutrition is decreased nutrient intake. Frail older adult patients often have a decreased appetite secondary to dementia, illness or medication side effects. They may also have an impaired ability to feed themselves or be unable to properly chew or swallow. Age-related atrophy of the salivary glands can decrease the absorption of important nutrients such as calcium and iron. Infection itself may cause or worsen malnutrition due to high metabolic demand or reduced dietary intake. Promoting healthy behaviors in older adults is an important public health measure and is advocated for in the *Healthy People 2010* guidelines.

Before microbes interact with the immune system, they must get past a broad array of anatomic and physiologic defenses. Unfortunately, many of these defense barriers decay with age, increasing the likelihood of pathogen invasion. For example, skin and mucous membranes become thinner and drier with age, increasing the risk of ulcerations [16]. The blunting of protective reflexes in the airway and decreased mucociliary clearance predisposes older adults to pneumonia. Decreased urinary flow and urinary

stasis in older adults can provide a nidus for UTI. Chemical defenses such gastric acidity also decline in older adults due to both physiological and medication side effects, which can increase susceptibility to gastrointestinal infection [17].

14.3.3 Immunosenescence

Immunosenescence is the age-related, progressive alteration of the immune system. It contributes to increased susceptibility to infection in old age and increased mortality due to infection. Immunosenescent changes may accelerate the progress of several chronic conditions and may also contribute to the decreased efficacy of vaccination in older adults. It is unclear why some people have more senescent immune systems than do others, but factors such as genetics, environment and chronic disease burden likely play a role. However, it is important to note that even healthy older adults without chronic diseases have some immune defects [18]. The study of immunosenescence is mired in controversy because much of the work has been done in murine models and these results may not always translate to humans. Studies in humans have also come under scrutiny due to small sample sizes and variable study groups that make it difficult to compare results across studies.

14.3.4 Innate Immunity

The innate immune system plays a vital role in resistance to infectious disease. Components of the innate immune system's response form the first line of defense in the recognition and destruction of pathogens and are characterized by their rapid action, lack of immunologic memory, and their function as antigen presenting cells (APCs) which activate the adaptive immune system. The principle cellular components of the innate immune system include neutrophils, monocytes/macrophages, natural killer (NK) cells and dendritic cells. These cells are able to recognize pathogens through the use of toll-like receptors (TLRs), which are evolutionarily conserved molecules that are expressed on the cell surface of pathogens, such as lipopolysaccharide (LPS) or bacterial flagellin. The activation of the TLRs leads to the destruction of the pathogen and the release of inflammatory cytokines, which recruit nearby immune cells and help to activate the adaptive immune response. Although the cells of the innate immune system have traditionally been thought to be spared from the effects of immunosenescence, recent evidence reveals several age-related changes in the function of the innate immune system.

Neutrophils are the predominant phagocytes circulating in the blood and help to clear bacterial and fungal infections. They are recruited to the site of infection by a chemotactic gradient. Neutrophils have a short half-life, but their lifespan is prolonged when primed by endotoxins and other mediators that are involved in immune response [19]. Although the overall number of neutrophils and their chemotactic ability remains intact in old age, studies of aged neutrophils show a decreased response to priming and an increased rate of apoptosis [19]. Studies have also shown a decreased phagocytic ability in neutrophils, especially with regard to bacteria that are coated with opsonins (e.g., *Escherichia coli, Staphylococcus aureus*) [20].

Monocytes are derived from hematopoetic stem cells and they circulate in the blood and spleen, only differentiating into macrophages once they have entered the tissue. Macrophages function as phagocytes of microbes and are important APCs that initiate the inflammatory response. Although the absolute number of monocytes and macrophages remains stable in older adults, studies of macrophages have shown a decreased phagocytic function and intracellular killing ability in older adults, which may contribute to a decreased ability to clear infection [20]. Furthermore, older macrophages appear to have decreased TLR-1 and TLR-4 surface expression and a diminished expression of intracellular proteins that are involved in the TLR signal transduction pathway. Age-related defects in TLR activation are likely related to the reduced sensitivity to LPS antigens and diminished cytokine expression that is seen in the macrophages of older adults.

Dendritic cells (DCs) phagocytize and transport antigens to lymph nodes in order to activate the T and B lymphocytes of the adaptive immune system. Thus DC cells play an important role in the cross-talk between the innate and adaptive immune systems. Studies on the effect of aging on DCs have yielded varied results [21]. In general, the antigen-presenting function of DCs appears to be well preserved in healthy older adults. However, decreased cytokine expression was observed in the DCs of aged mice that were infected with Herpes Simplex Virus-2, which may suggest an impaired ability to combat viral infections in older age [22]. Decreased inflammatory response has also been seen in experimentally-induced DCs from older adults, though further studies are needed to validate this finding in the clinical setting [21].

NK cells are cytotoxic cells that are important for host defense against viral infections and the detection of certain malignancies. NK cells are able to directly kill pathogens by releasing perforin and granzymes, which induce apoptosis in the target cells. While the effects of age on NK cell function are still under debate, two age-related changes in NK cells have been suggested. First, on a per-cell basis, NK cell cytotoxicity appears to be diminished in older adults [20]. However, the number of circulating NK cells in older adults is increased, thus mitigating the effect of the decreased cytotoxicity. Second, there appears to be an age-related decrease in cytokine expression in activated NK cells, which could diminish the NK cell-driven activation of the adaptive immune response [21]. This latter effect is not likely mitigated by the increase in NK cells.

14.3.5 Adaptive Immunity

Adaptive immunity differs from innate immunity in its ability to adapt its immune response to previously-encountered pathogens. The predominant cells of the adaptive immune system are T cells and B cells. T cells, or thymus-derived lymphocytes, participate in the activation of immune cells and the cell-mediated destruction of infected cells. B cells are bone-marrow-derived lymphocytes that produce antibodies that recognize and attack foreign antigens. Both classes of lymphocytes are activated by encountering antigens that are initially displayed by the APCs of the innate immune system.

Age-related changes in the adaptive immune system begin shortly after birth. The thymus, a lymphoid organ that is responsible for the maturation and differentiation of CD4 and CD8 T cells, begins involution during infancy and accelerates during adolescence. Thymic involution is characterized by a reduction in the size of the thymus and the encroachment of fat into the cortex and medulla. By 70 years of age, the majority of the thymus has undergone fatty infiltration, which results in almost no thymic output [23]. As a consequence of this involution, the number and diversity of circulating naïve T cells decreases with age. The remaining naïve T cells have numerous other deficits as well, including a restricted T cell receptor (TCR) repertoire, impaired interleukin (IL)-2 cytokine production, and impaired expansion into effector cells. This decreased thymic production is compensated for in older adults by an increase in the basal proliferation of T cells in the periphery and the shifting of the T cell composition toward memory cells. This provides the aging immune system with a relatively intact capacity to defend against previously recognized pathogens. However, as the ratio of naïve T cells to memory T cells declines, there is a diminishment in the repertoire of immune cells that are capable of responding to challenges from novel antigens [24].

The phenomenon of replicative senescence is another characteristic of T cell aging [23]. Replicative senescence is the age-related shortening of telomere length and the impairment of cell division. Normally, the binding of the TCR to a novel antigen causes clonal expansion of the activated T cell into effector and memory T cells. Upon resolution of the immune response, the majority of recently-activated T cells undergo apoptosis. Some memory cells survive and enter the T cell pool, thereby ensuring the ability to mount a rapid response during a future encounter with the pathogen. However, clonal expansion is diminished in older age, with T cells unable to

replicate as avidly upon binding with an antigen [23]. This diminished proliferative capacity hinders the ability of older adults to generate sufficient memory response upon exposure to a neoantigen.

Age-related changes also occur in the B cell pool, with a decreased ratio of peripheral naïve B cells to memory B cells. Similar to the change in T cell repertoire, the consequence of this composition shift is an impaired ability to respond to new antigens but a maintained ability to respond to previously-encountered pathogens. There is also a shift in the composition of circulating immunoglobulins with aging. The immunoglobulins of older age are primarily T-cell-independent, low-affinity, polyspecific antibodies. These immunoglobulins have an increased autoantibody reactivity and are implicated in the increased incidence of autoimmune disease in older adults.

The diminished ability of T cells and B cells to generate an immune response to new antigens with age is supported by epidemiologic studies that have shown that older adults are often the first to be affected by new or emerging pathogens, such as the West Nile Virus [25]. T cell and B cell immunosenescence also has clear implications on vaccine efficacy in older adults, with those at the extremes of age being most affected [24]. For example, seroprotection against influenza is only 29–46% in those >75 years of age, compared to 41–58% in those 60–74 years of age [26]. Nonetheless, older adults are still able to mount a response to neoantigens, and vaccination is a vital preventative measure in older adults.

14.3.6 Cytokine Dysregulation and Chronic Inflammation

Cytokines are chemical messengers that are released principally by the immune system to coordinate the migration and activation of immune cells. Studies of age-related cytokine regulation have often yielded contradictory results, likely secondary to differences across studies regarding study population and testing techniques. Nonetheless, the majority of studies suggest that aging is associated with a dysregulated cytokine response, in particular an increase in pro-inflammatory cytokine IL-6 [27]. This phenomenon has been referred to as "inflam-ageing", and chronically-elevated IL-6 has been correlated with chronic disease and functional decline in older adults.

The reasons for chronic inflammation in older adults are not well understood. Age-related T cell cytokine expression appears to change in older age to a "type 2" response, which favors the expression of pro-inflammatory mediators. Anti-inflammatory cytokines, such as IL-10, do not appear to compensate for the increase in inflammatory cytokines [28]. Although many chronic diseases (e.g., diabetes) are associated with increased inflammation, older adults who do not have any chronic diseases also have elevated inflammatory mediators compared to younger adults. Chronic subclinical viral infections (e.g., cytomegalovirus) have also been hypothesized to contribute to increased inflammation in older adults. In this scenario, older adult have an increased prevalence of subclinical viral infections that act to persistently stimulate inflammatory response.

Older adults tend to have more prolonged inflammatory responses to infection than do younger adults. This may be due to an inability to clear infection or an inability to appropriately resolve the inflammatory response. A recent study of patients who were hospitalized with CAP found that despite having a similar inflammatory profile upon hospital admission, older adults had higher IL-6 levels at hospital discharge than did their younger peers [5].

The increased inflammatory profile of older adults has been linked to an increased susceptibility to infection, perhaps through increased bacterial adherence [29]. Chronic inflammation has also been linked to several chronic diseases of older age, including sarcopenia, frailty, dementia and cardiovascular disease [27].

14.3.7 Altered Clinical Presentation

Infections in older adults often present differently than they do in younger patients. For example,

fever—the predominant sign of infection—may be absent or diminished in older adults 20–30% of the time [30]. Decreased fever response is thought to be due to an altered immune response to infections, the presence of coexisting chronic diseases and the effects of potential concurrent medications. Importantly, the inability of the individual to communicate or difficulty in obtaining an accurate temperature in older adults due to noncompliance may also be reasons for the observed lack of fever in older adults. The inability to recognize the signs and symptoms of infection in older adults may delay diagnosis and appropriate treatment. Similarly, other symptoms of infection (e.g., tachyarrythmias) may be absent due to the use of beta-blockers or calcium channel blockers. Classic symptoms (e.g., the cough or dyspnea that are associated with pneumonia) may not occur and uncommon presentations (e.g., delirium, altered mental status, loss of balance, decreased oral intake) may occur. Thus, a high clinical suspicion for infection should be maintained in the care of older adults.

14.4 Common Clinical Infections

Pneumonia, UTIs, sepsis, gastroenteritis and viral infections are common in older adults. Key clinical issues for individual infections are described below.

14.4.1 Pneumonia

Pneumonia is an inflammatory condition in the lung that is often due to an infection by bacteria, viruses or fungi. Although pneumonia occurs in people of all ages, it has traditionally been considered a disease of older adults. It is estimated of hospitalized patients who are >85 years of age, one in twenty have pneumonia [3]. The annual incidence of pneumonia in older adults is from 25 to 44 cases/1,000 individuals among non-institutionalized patients, which is approximately fourfold higher than in those <65 years of age [1]. Among those living in an LTCF, the incidence increases to 33–114 cases/1,000 individuals.

The microbial etiology of pneumonia is an important consideration in the treatment and prognosis of pneumonia. Unfortunately, in approximately half of patients who are clinically and radiographically diagnosed with pneumonia, an etiological agent cannot be found using traditional culture techniques such as sputum and blood cultures [31]. The predominant microorganism in both community-acquired and hospital-acquired pneumonia in the elderly is *Streptococcus pneumonia* [1]. Hospital-acquired pneumonias are more likely to be due to Gram negative infections such as *Pseudomonas aeruginosa* and *Staphylococcus aureus.* Atypical organisms, such as *Chylamydia pneumoniae, Chylamydia psittaci* and *Mycoplasma pneumoniae* are common causes of CAP and are more likely to occur in younger adult patients than in older adult patients. Non-bacterial organisms (e.g., influenza, respiratory syncytial virus [RSV]) are also an important cause of pneumonia in older adults. Gram negative pneumonia occurs more often in chronically ill patients and is associated with nursing home residence and decreased functional status [1].

An important contributor to pneumonia in older adults is the aspiration of oropharyngeal secretions. The aspiration of secretions can transfer pathogenic organisms that colonize the upper airway. Older adults have many risk factors for aspiration. First, aging is associated with disordered oropharyngeal movements, which can lead to the decreased clearance of airway secretions and an increased risk of aspiration. Second, tube feedings, which are more often used in older adult patients, may also increase the risk of aspiration by weakening the ability of the lower esophageal sphincter to prevent the reflux of gastric contents into the lungs via the esophagus [32]. Third, the prevalence of stroke is higher in the elderly and about one third of stroke patients acquire pneumonia, making it the 3rd most frequent cause of death in the first month after a stroke [33]. Fourth, many medications (e.g., antidepressants, antihypertensives antipscyhotics) that are commonly used in older adults can reduce salivation, which can lead to the overgrowth of bacteria in the oropharynx. Fifth, poor oral

hygiene is more likely to occur in older adults and can also increase the risk of pathogenic oropharnyngeal colonization. Appropriate dental care can reduce the risk of aspiration pneumonia in older adults [1]. Finally, dementia can lead to reduced awareness when swallowing and increase the risk of aspiration events.

14.4.2 Urinary Tract Infection

A UTI is defined as the presence of bacteria or yeast in the urine ($\geq 10^5$ colony forming units/ml) with symptoms of fever, dysuria, frequency, flank pain or hesitation. UTIs can be classified as either lower (confined to the bladder) or upper (e.g., pyelonephritis). A frequent route of infection is presumed to be from the gastrointestinal tract, and, in women, the vaginal cavity. After lower respiratory infections, UTIs are the most common cause of infectious disease hospitalization in older adults and the most common infection in hospitalized older adults [2]. Symptomatic UTI occurs in 0.1–2.4 cases per 1,000 resident days [34]. Although UTI infections are more common in younger women than in younger men, the sex differences in prevalence diminish in older age.

Eliciting symptoms from older adult patients who have advanced chronic disease can be difficult and is a barrier to accurate diagnosis. For example, patients who have advanced dementia may be unable to report symptoms. Patients who have advanced diabetes may have frequent urination or urinary incontinence at baseline, making the onset of UTI less noticeable. Diagnosis in patients who have indwelling catheters is also difficult. Often, the presenting symptom of a UTI in an older adult is a change in mental status.

Escherichia coli (E. coli) is the most frequent pathogen across all age groups and occurs in 80% of cases [35]. *E. coli* is the most common organism isolated in women, whereas *E. coli* and *Proteus mirabilis* occur in equal proportions in men [36]. Polymicrobial bacteriuria is also commonly identified, more often in LTCF residents. LTCF residents are also much more likely to have a UTI caused by multidrug-resistant bacteria.

Older adults have several risk factors that contribute to a UTI. Common risk factors in both men and women include dementia, incontinence of the bladder or bowel, urinary retention and the use of indwelling urinary catheters. The increased incidence in men is driven by urethral obstruction secondary to prostatic hypertrophy. Risk factors in women include being postmenopausal and the presence of a cystocele.

Bacteriuria without any symptoms (asymptomatic bacteriuria [ASB]) is common in older adults, does not lead to adverse outcomes and does not necessitate antibiotic therapy. The prevalence of ASB increases with age. While relatively rare in young adults, women 65–90 years of age have a reported prevalence of 6–16%, and men in the same age range have a prevalence of 5–21% [37]. High chronic disease burden and living in a nursing home are risk factors for ASB, and ASB is almost universal among institutionalized residents who have long-term indwelling catheters [38]. The unnecessary treatment of ASB has contributed to the growth of drug-resistant strains of UTI by altering the urinary tract's natural microbial flora [34]. Recommendations for the prevention of UTIs in long-term care facilities include the management of incontinence, the avoidance of long-term indwelling catheters, and surveillance for symptomatic infection [36].

14.4.3 Sepsis

Sepsis is a syndrome of systemic inflammatory response due to documented or presumed infection. While the terms infection and sepsis are often used interchangeably, sepsis refers to the presence of at least two of the systemic inflammation syndrome criteria (fever or hypothermia, tachycardia, increased respiratory rate and elevated leukocyte count) in the presence of infection. Most patients who are hospitalized for infection also meet the criteria for sepsis. Sepsis can be further complicated by organ failure; this is called severe sepsis. The presence of severe sepsis is a grave prognostic indicator. Compared to sepsis, severe sepsis has higher mortality and

is the most common cause of death in the non-coronary intensive care unit [39].

Severe sepsis affects nearly 750,000 individuals per year in the US [8]. The incidence of severe sepsis increases exponentially with age, with a mean age of 63.8 years, and with those ≥65 years of age having a 13-fold increase in frequency [8, 40]. In the US, the annual incidence of severe sepsis in individuals ≥85 years of age is 26 cases per 1,000 individuals. Furthermore, the incidence rate of sepsis among those >65 years of age increased from 1979 to 2002, in part due to better recognition of the disease [41]. Case fatality rates of sepsis are reported to be from 20 to 40%, and are responsible for nearly 20% of all in-hospital deaths [40].

Given that sepsis is largely a clinical diagnosis, the blunted clinical responses that are typically seen in older adult patients mean that sepsis is not always properly diagnosed. Older adult septic patients may remain afebrile or may not exhibit leukocytosis, but may be more likely to exhibit tachypnea and altered mentation [42]. The challenge of diagnosing sepsis in older adults was shown in a recent study of older adult patients who were hospitalized with bacteremia, in which only about 15% were correctly diagnosed with sepsis [43].

14.4.4 Skin/Soft Tissue Infection

Skin and soft tissue infections are common in older adults. In one study of nursing home residents, skin infections accounted for 35% of reported infections [44]. The most frequent skin and soft tissue infections in older adults include erysipelas/cellulitis, necrotizing fasciitis and infected ulcers. Traditionally, skin infection is confirmed by taking swab of the wound surface and sending it for microbial analysis. *S. aureus* and Beta *Streptococcus sp.* are the most common cutaneous pathogens that cause skin infection. There are several risk factors that may precipitate skin and soft tissue infection in older adults. As the skin ages, it becomes thinner and drier, thereby increasing the likelihood of tears and erosions. Wounds are less able to heal because the aging skin receives a decreased blood flow. Chronic medical conditions such as diabetes mellitus and vasculopathies, as well as malnutrition, can further reduce wound healing.

Erysipelas and cellulitis are acute infections of the dermis and upper subcutaneous tissue that can rapidly spread over a large area. The infected skin is bright red, edematous, and tender in a unilateral distribution. Serious complications include tissue necrosis and cavernous sinus thrombosis. It is not always possible to distinguish clinically between erysipelas and cellulitis. Erysipelas is a superficial skin infection that involves cutaneous lymphatic vessels and it is most often caused by Group A *Streptococci*. Erysipelas most often involves the face and legs, and it is accompanied by systemic symptoms such as fever and chills, which may be muted in older adults. Cellulitis is a more serious infection and is associated with diffuse erythema, pain, swelling and systemic symptoms. Cellulitis most often occurs in the legs and most cases are caused by Beta-hemolytic *Streptococci* or *Staphylococci* [45]. These organisms often gain entry through breaks in the skin

14.4.5 Pasteurella Multocida or Polymicrobial Organisms

Necrotizing fasciitis is a life-threatening infection that causes a rapidly-evolving deep tissue necrosis that often requires surgical debridement. Although initial symptoms appear disproportionate to clinical findings, pain is eventually minimal or absent as cutaneous sensation is lost. Physical inspection may reveal dark, malodorous exudate and gas formation. The etiology is often polymicrobial, though about 10% are due to *Streptococci* [45]. Risk factors for necrotizing fasciitis include trauma, surgery, malignancy, peripheral vascular insufficiency, alcoholism and diabetes.

Infected ulcers are the most commonly encountered skin infections in older adults. They occur most often in patients who have diabetes and those with impaired mobility. They occur in 10% of nursing home patients [46]. The presence of an ulcer increases the risk of cellulitis,

osteomyelitis, bacteremia and sepsis. The etiology is most often polymicrobial, although frequent isolates include *E. coli, P. mirabilis*, and Pseudomonas. It is important to note that the majority of pressure ulcers can be prevented. The strongest risk factors for pressure ulcers are limited mobility and poor nutrition. The inability to shift body weight leads to prolonged exposure to pressure and to tissue damage. Bed-bound patients are most likely to get ulcers over bony prominences, particularly the sacrum and heels which correspond to pressure points. Chair-bound patients are often at risk for ulcers on the ischial tuberosities. Several studies indicate that the critical period of applied pressure, before irreversible tissue damage is likely to occur, is within 1–2 h [47]. Therefore, many hospital and health care facilities mandate that staff rotate incapacitated patients at least every 2 h to help prevent ulcer formation. Moisture from urinary or fecal incontinence can increase the risk of pressure ulcers five-fold and can be a source of bacterial contamination [47].

14.4.6 Gastrointestinal Infections

Norovirus is responsible for 23 million cases of viral gastroenteritis annually in the US, and major outbreaks are common in both LTCFs and hospitals. The virus has multiple modes of transmission, including the fecal-oral route and by inhalation of vomitus. Viral shedding can continue for 72 h to 28 days, and viral particles can survive on surfaces for up to 2 weeks. Treatment includes supportive care, and infected patients should be isolated.

Colitis due to *Clostridium difficile* is a common infection in LTCFs and hospitals, due in large part to the widespread use of antibiotics. Antibiotic usage is an important risk factor since antibiotics can clear out the natural microbial fauna of the colon and thus allow *C. difficile* to emerge. *C. difficile* infections may occur as late as 3 months after initiating antibiotics. Alcohol-based hand sanitizers are insufficient to eradicated *C. difficile* spores, and thus handwashing with soap and water is crucial for preventing the spread of the disease.

14.4.7 Viral Infections

Although many viral infections are more common among older adults, we will focus on influenza and varicella zoster virus. Influenza is a leading cause of mortality in older adults. The incidence of varicella zoster and post-herpetic neuralgia is a major cause of morbidity in older adults, and incidence increases dramatically with age.

Although influenza is a relatively common and self-limited virus in younger adults, it is one of the ten major causes of death in older adults. Influenza viruses are classified as either A, B or C based upon the composition of internal proteins. The virus can undergo rapid antigenic changes of its surface proteins hemagglutinin (H) and neuraminidase (N), leading to annual epidemics and the potential of a pandemic. Peak influenza activity in the US occurs from December through March. The classic presentation of influenza consists of the abrupt onset of fever, chills, headache and myalgias. However, this presentation may be altered in the frail and immunocompromised.

Although attack rates of influenza are highest in children, mortality from most strains of influenza rise dramatically with age. Nearly 90% of influenza-related deaths occur in adults ≥65 years of age [24]. Influenza-related deaths most often result due to pneumonia from the virus itself, secondary to bacterial pneumonias, or due to the exacerbation of underlying cardiovascular and respiratory conditions. In recent years, a subtype of influenza A (H1N1) has reached global pandemic levels. Unlike other strains of influenza, H1N1 appears to be particularly lethal in younger adults. The reasons for the relatively decreased severity of H1N1 infection in older adults are unclear, though serologic studies suggest that a higher proportion of older adults may have a preexisting immunity to H1N1, possibly from previous exposure [48].

Varicella zoster virus (VZV), also known as shingles, is a painful vesicular rash that is caused by the reactivation of latent varicella (chickenpox). It can be complicated by postherpetic neuralgia (PHN), which is defined as pain that lasts after the rash has subsided. Approximately one million incidents of VZV occur annually in the

US [49]. The lifetime incidence of VZV is approximately 25% in the general population and 50% among those >85 years of age [50]. Older adults have a three to four-fold increased incidence of VZV compared to younger adults, and the incidence increases drastically after 50 years of age.

Older age is the major risk factor for developing VZV, as well as postherpetic neuralgia complications. Other important risk factors include immune suppression, which is often due to disease or a drug side effect. The frequency of VZV in immunocompromised individuals is reported to be 20–100 times greater than similarly-aged immunocompetent individuals [50]. Other common risk factors for the development of VZV are White race, psychological stress and trauma [51].

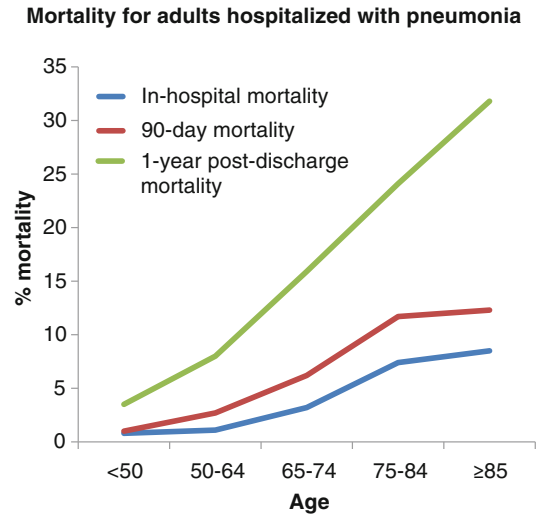

Fig. 14.3 Mortality rate from a prospective cohort study of adults hospitalized with community-acquired pneumonia. In-hospital and 90-day mortality measured from day of hospital admission. 1-year post-discharge mortality measured from day of hospital discharge

14.5 Long-Term Outcomes of Infection

Although the traditional focus of care in patients who have infectious disease has been to reduce short-term morbidity and mortality, in recent years interest has increased with regard to understanding the impact of infection on long-term outcomes. Studies that have examined long-term outcomes in older adults who have serious infection suggest an increased risk of adverse events that persists well beyond the hospital stay. In a study of more than 150,000 older adult Medicare recipients who were hospitalized with CAP, one in three patients who survived hospitalization for CAP died within the following year [52]. As with the risk of serious infection, the risk of 1-year mortality in survivors of CAP hospitalization is highest in the very old. In a prospective cohort study of adults who were hospitalized with pneumonia, those ≥85 years of age had a 1.3-fold and two-fold greater risk of 1-year post-discharge mortality than did those 75–84 years of age and 65–74 years of age, respectively (Fig. 14.3) [5].

While it is commonly perceived that serious infection occurs in older participants who have chronic health conditions and that these conditions contribute to higher mortality even after recovery from acute illness, several studies show that higher long-term mortality is independent of baseline functional and health status [53, 54]. These studies suggest that pathophysiological processes initiated during infection may lead to higher long-term mortality. For example, recent studies suggest that the immune response activated during an acute infection may remain upregulated during recovery and is associated with higher long-term mortality, particularly due to cardiovascular disease. Higher circulating levels of inflammatory and coagulation markers were observed at hospital discharge when patients appeared to have clinically recovered from infection and were associated with increased subsequent mortality [5, 55]. Higher long-term mortality among older adults could be due to age-related dysregulation of immune response resolution. For instance, older adults are more likely to have a delayed resolution of immune response, as evidenced by a three-fold increased IL-6 concentration at discharge that is associated with increased risk of death over 3 months [56].

Adverse long-term outcomes are not limited to increased mortality risk. Acute infections may worsen chronic diseases and the relationship between acute infection and chronic illness is bidirectional. The increased burden of chronic health

Table 14.1 Recommended vaccinations in older adults

	Pneumococcal Pneumonia	Influenza	Varicella Zoster	Tetanus
Indication in elderly	≥65 years	≥50 years	≥60 years	If previously unvaccinated OR with contaminated wound and >5 years since last dose
Recommended interval to next dose	One time revaccination dose if age of first dose ≤65 years	Annually		Booster every 10 years
Clinical effectiveness in elderly	Effective in preventing invasive pneumococcal disease, but not in preventing pneumonia [59]	60% effective in reducing hospitalization and 80% effective in reducing mortality due to influenza in adults ≥60 years living in a LTCF [60]	Incidence of varicella zoster reduced by 64% in those 60–69 years and 38% in those ≥70 years. Incidence of PHN reduced by 66% in both age groups [61]	Effectiveness well established
Cost effective	Yes [62]	Yes	Varies substantially with patient age and often exceeds $100,000 per quality-adjusted life year saved [63]	Tetanus is a very rare but deadly infection, making cost-effectiveness difficult to asses
Notes	Pneumococcal polysaccharide vaccine contains 23 purified capsular antigens, which represent 90% of serotypes that cause invasive pneumococcal disease in US	Having ≥1 vaccination over previous 4 years confers greater protection against influenza virus than 1st time immunization	Found to work across all age strata and in individuals with chronic diseases [64]	>90% of persons who contract tetanus in U.S. are not up to date on tetanus vaccination. Tetanus toxoid combined with diptheria toxoid adult vaccinations (Td)

conditions increases the risk of infection and sepsis, and survivors of infection may develop a higher burden of chronic disease. For example, individuals who have renal disease are at a higher risk for serious infection. An episode of serious infection can lead to renal failure, which may worsen outcomes of the acute illness and eventually lead individuals to require chronic dialysis. Similarly, it has been shown that infection with influenza is associated with an increased risk of cardiovascular disease [57], whereas reducing influenza risk through vaccination in older adults is associated with reductions in hospitalizations for cardiac disease and stroke [58]. These examples underscore the complex relationship between infection and underlying chronic disease, where comorbid conditions are both a risk factor and are modified by the infectious event. The worsening of chronic illness following infection is, in turn, a risk factor for subsequent acute illness, thereby initiating a spiral of events that can ultimately lead to death.

14.6 Vaccination

Across all age groups, vaccinations are among the most effective means of preventing morbidity and mortality due to infectious disease across all age groups. In older adults, the CDC currently recommends vaccinations against influenza, pneumococcal disease, varicella-zoster and tetanus (Table 14.1). Additional vaccines are recommended for travelers on a country-by-country basis, and include vaccinations for hepatitis A and yellow fever. For further information regarding travel-related vaccinations, please refer to the CDC Web site at http://www.cdc.gov/travel.

Despite the benefit of vaccines in older adults, vaccination rates remain low. In 2008, 67% of non-institutionalized adults who were >65 years of age were vaccinated, well below the *Healthy People 2010* goal of 90% coverage. Strategies to improve vaccination rates among older adults include patient reminder/recall systems, home visits and standing orders to allow vaccine administration by non-physician medical personnel [59]. Immunization against influenza for healthcare workers, especially those working in LTCFs, is recommended to reduce person-to-person transmission.

Unfortunately, because successful vaccination depends on a robust immune response, the efficacy of vaccines wanes in older adults. Efficacy is likely even lower in the oldest older adults along with other risk factors for immune suppression, such as high chronic disease burden or frailty. Despite these limitations, vaccinations strategies are critically important in older adults [60, 65]. Research is underway to find ways to boost vaccine responses in older adults. These novel approaches include inoculating patients with a higher antigen dose and augmenting vaccines with TLR agonists [61].

14.7 Conclusion

Despite improvements in therapy and hygiene, infection remains an important cause of chronic disability and mortality in older adults. Infections are associated with poor short-term and long-term outcomes in this population. Older adults have many risk factors that place them at high risk for increased susceptibility to infection and have poor outcomes of infection. Our current understanding of the underlying mechanisms is limited. Altering modifiable risk factors, such as inactivity and malnutrition, and the use of vaccination may reduce the burden of infectious diseases in the older adult population.

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Nutritional Epidemiology in Aging

15

Stephen B. Kritchevsky and Denise K. Houston

Abstract

Epidemiologists have attempted to identify nutritional factors associated with the preservation of health and function in older adults. A number of methods are available for identifying patterns of dietary intake that are associated with health, including identifying the intake of specific nutrients; factor or cluster analysis to identify foods co-consumed in a given population; studies of *a priori* dietary patterns based on prevailing hypotheses regarding the role of nutrients in disease prevention; and a combined method that identifies food patterns that explain variation in a set of intermediate response variables, then examines the association between the dietary pattern and the disease outcome of interest. Methods of assessing usual dietary intake include methodologies that fall into two broad strategies: interview/questionnaire-based and biomarkers of nutritional exposure. The reliability and validity of recalled nutritional data in older adults is a concern; methods that combine recall-based dietary data with biomarkers of nutritional exposure can be used to help improve the validity of recalled nutritional data. A number of nutrients have been hypothesized to affect age-related disability processes, including omega-3 fatty acids, protein, vitamin D, calcium, B vitamins and dietary antioxidants. While the identification of specific nutrients that slow age-related changes has met with limited success, dietary patterns that are associated with general good health and low levels of chronic disease have been identified.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
ALA	α-linolenic Acid
AMD	Age-related Macular Degeneration
AREDS	Age-Related Eye Disease Study
ASA24™	Automated Self-administered 24-hour Dietary Recall
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic Acid
EAR	Estimated Average Requirement
EPA	Eicosapentaenoic Acid
FA	Fatty Acid
FFQ	Food Frequency Questionnaire
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
NHANES	National Health and Nutrition Examination Survey
PLP	Plasma pyridoxal 5-phosphate
PUFA	Polyunsaturated Fatty Acid
RDA	Recommended Dietary Allowance
RIA	Radioimmune Assay
RMR	Resting Metabolic Rate
TEF	Thermic Effect of Food
US	United States
USDA	United States Department of Agriculture
WHAS	Women's Health and Aging Study

15.1 Introduction

The importance of nutrition to the maintenance of health and the prevention of disease is well recognized. However, nutritional concerns vary by the stages of life. In clinical geriatrics, nutritional concerns have centered around high-risk groups and, in particular, around the causes and consequences of unintentional weight loss. As a consequence of age-related changes in physiology, many older adults are at risk for vitamin and mineral deficiencies. In addition, it is becoming increasingly recognized that for many nutrients, marginal but not clinically deficient nutritional status can be associated with poor health and function. Also under investigation is the role of nutritional factors in the onset and natural history of conditions of specific interest to an aging population, such as frailty or dementia. Readers interested in the clinical nutrition of older adults are referred to other excellent texts (see, for examples, references [1, 2]). Nutritional epidemiology is a wide-ranging and complex discipline, so while this chapter presents an overview of the relevant methodological issues, it focuses on the special considerations involved in applying these techniques in older populations and summarizes the current understanding of the role of better-studied nutrients in the preservation of physical and cognitive function.

15.2 Nutrition in the Aging Context

Aging *per se* has important implications for the nutritional status of older adults. The requirement for energy from food is determined by one's energy expenditure, which can be partitioned into three components: (1) resting metabolic rate (RMR), (2) the thermic effect of food (TEF) and (3) energy expenditure from physical activity. RMR describes the amount of energy utilized at rest to support the functions vital for life. RMR's share of total energy is usually between 60 and 80%, depending on energy expenditure from

physical activity. An individual's RMR is strongly related with fat-free mass, which includes the mass of organs, blood, muscle and bone. Fat-free mass declines from mid-adulthood and consequently, energy requirements decline with age. TEF describes the proportion of energy expenditure that is used for the processing and storage of ingested food. TEF can be measured directly, but is usually estimated to be 10% of the total energy intake. The TEF is also lower in older adults. The remainder of total energy expenditure is accounted for by the energy expenditure from physical activity. This also appears to decline in older adults.

The net effect of the age-related changes in energy expenditure is that there is a progressively lower requirement for energy with age. If these declining needs are not matched with reduced intake, weight gain occurs. However, the intake of vitamins and minerals from food is associated with the total amount of food ingested. If vitamin and mineral intake is already marginal, it may fall to sub-optimal levels as total food intake declines with age.

In addition to the age-related physiological changes described above, there are a number of other age-related changes that can affect the nutritional status of the older adult (Table 15.1). Many older persons experience changes in their sense of taste and smell, which can be caused either by essential changes in the sense organs or by change brought on by disease or medications. Food ingestion and mastication can be impaired by a number of factors, including tooth loss, poorly fitting dentures, xerostoma (dry mouth) and swallowing difficulties. Disease states and chronic inflammation can decrease appetite, and physical and cognitive impairments can lead to difficulties in obtaining and preparing food. Eating behaviors occur in a social context, so a change in living situation or the death of a spouse can lead to changes in the types and amounts of food eaten. Reduced economic resources can also affect the amounts and variety of foods consumed.

Due to these age-related factors, older populations are much more heterogeneous than are middle-aged and young adult populations. Epidemiologists must carefully consider this heterogeneity because the same factors that affect patterns of food intake are often associated with outcomes of interest in older populations, which may make it difficult to distinguish cause from effect.

Table 15.1 Factors potentially affecting dietary intake in older adults

Types of factors	Factors
Age-related factors	Decreased lean body mass
	Changes in smell and taste
	Dyspepsia
	Changes in gastrointestinal function
Disease/function Related factors	Poor dentition/chewing pain
	Xerostoma/swallowing difficulties
	Impaired ability to obtain and prepare food
	Diseases affecting appetite
	Medications/polypharmacy
	Prescribed diets
Psychosocial factors	Alcohol/substance abuse
	Reduced income
	Bereavement/depression
	Changing social situations/ isolation
	Decreased physical activity

15.3 Conceptual Issues in Nutritional Epidemiology

15.3.1 Diets, Foods and Nutrients

Nutritional epidemiologists seek to identify patterns of dietary intake that are associated with health. This goal is complicated by the fact that the food supply includes thousands of foods, beverages and dietary supplements, which contain tens of thousands of different chemical constituents. Two strategies are used to deal with this complexity: (1) a reductionist approach that examines a particular compound or class of compounds across many foods, and (2) a pattern-based approach that identifies patterns of food consumption.

In the reductionist approach, exposures are essential nutrients (e.g., vitamins/minerals),

Table 15.2 Selected dietary patterns used in nutritional epidemiology

Dietary pattern	Description
A priori	
Healthy Eating Index (HEI) 2005	Measures the degree to which an individual's diet conforms to the Dietary Guidelines for Americans based on adherence to serving recommendations for fruit; whole fruit; total vegetables; dark green and orange vegetables and legumes; total grains; whole grains; milk; meat and beans; and non-hydrogenated vegetable oils and oils in fish, nuts and seeds; while moderating intake of saturated fat; sodium; and calories from solid fats, alcoholic beverages, and added sugars
Mediterranean diet	Emphasizes the consumption of fruits and vegetables, legumes, grains, fish, nuts, and monounsaturated fat while limiting dairy products and red meat
Dietary Approaches to Stop Hypertension (DASH) diet	Emphasizes fruits and vegetables, low-fat dairy products, grains, especially whole grains, legumes, lean meats, fish and poultry, and nuts
A posteriori or data driven diet patterns	
Factor analysis	Reduces the number of dietary variables by finding factors that are composed of correlated dietary variables using principal components analysis (e.g., a 'prudent' pattern consisting of lower fat but higher fruit, vegetable, and whole grain intake and a 'Western' pattern made up of higher fat, meat, and refined grain intake)
Cluster analysis	Places individuals into distinct non-overlapping groups on the basis of their dietary intake
Reduced rank regression	Identifies food patterns that explain as much variation as possible in a set of intermediate response variables, such as disease-related nutrients or biomarkers. Once the dietary pattern is derived, the association between the dietary pattern and the outcome of interest is examined

major sources of energy (i.e., protein, carbohydrate and fat), non-essential food constituents that are hypothesized to have specific biochemical properties that affect health (e.g., ethanol, carotenoids, isoflavonoids), or toxins and contaminants (e.g., aflatoxin, pesticides). The reductionist approach has several attractions. Examining the dietary exposure to a specific chemical fits comfortably into accepted frameworks of exposure-disease evaluation. The substances of interest can be studied in animal models, which can help to identify biological mechanisms of action that support claims of biological plausibility. Epidemiological relationships that are identified can be verified, hypothetically, in clinical trials.

The argument against the reductionist approach is that people eat foods, not nutrients. A diet that is high in vitamin C, for example, is not a diet low in vitamin C to which vitamin C has been added. Therefore, trying to isolate and evaluate particular nutrients may be difficult to do, and thus the results can be misleading. From a public health perspective, it is easier to promote the consumption of foods than the consumption of individual nutrients.

There are a number of dietary pattern-based strategies that have emerged as an alternative to studying individual nutrients (Table 15.2) [3]. One strategy uses statistical data-reduction techniques, such as factor or cluster analysis, to identify foods that tend to be co-consumed in a given population. Both factor and cluster analyses require decisions to be made at several steps, including what individual foods should be aggregated into food groups, how many factors or clusters should be retained, and how identified factors or clusters should be interpreted (e.g., prudent or Western diet patterns). The limitations of both factor and cluster analysis approaches are that they may not be reproducible across studies due to differences in dietary variables and in analytic decisions made, and the patterns derived may not readily lend themselves to translation into dietary recommendations.

Alternatively, investigators can identify *a priori* dietary patterns based on prevailing

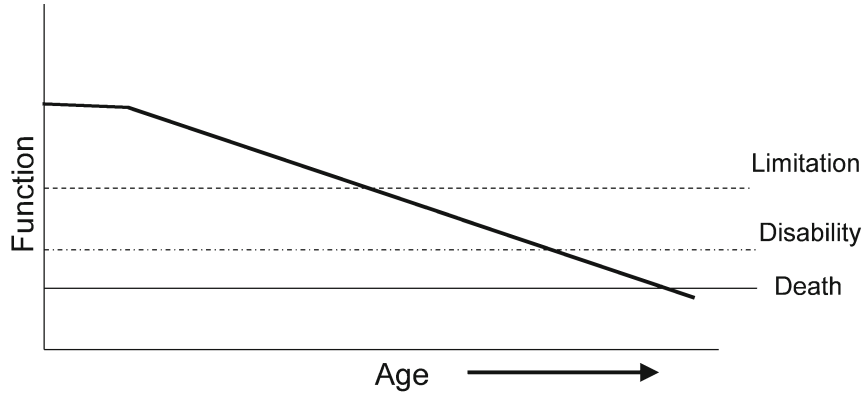

Fig. 15.1 The time course of physiologic change and on the onset of functional limitations and disability

hypotheses regarding the role of nutrients in disease prevention, like a Mediterranean diet pattern; the Dietary Approaches to Stop Hypertension (DASH) diet pattern; or a pattern based on dietary recommendations such as the Healthy Eating Index, which is based on the United States Department of Agriculture's (USDA's) Dietary Guidelines for Americans. Individuals are scored according to how closely their diet conforms to the pattern of interest.

A relatively new method of creating dietary patterns has emerged that combines hypothesis-driven and data-driven methods. This method, using reduced rank regression, identifies food patterns that explain as much variation as possible in a set of intermediate response variables such as disease-related nutrients or disease biomarkers. Once the dietary pattern is derived, the association between the dietary pattern and the disease outcome of interest is examined. An advantage of this approach, as opposed to strictly empirical or data-driven approaches, is that the derived dietary pattern incorporates information on hypothesized biological pathways of disease risk.

Regardless of how dietary patterns are derived, more healthful dietary patterns have, in general, been associated with better nutritional and disease biomarkers and a relatively lower risk of functional limitation, cognitive impairment, major chronic disease and mortality [4]. A number of human clinical trials have been successful in evaluating interventions based on dietary patterns (e.g., DASH diet). The reductionist and pattern-based approaches are complementary, providing different kinds of information for different scientific and public health contexts.

15.3.2 The Timing of Exposure and Outcome

A *sine qua non* of a causal relationship is that the putative cause must precede the effect. This is not straightforward where disability outcomes are concerned. Figure 15.1 provides a schematic representation of the relationship between diminishing function over time and the onset of limitation and disability. Declines in strength start in mid-adulthood, but this decline is only called an event for epidemiological purposes after it reaches a magnitude that affects function in daily life. Similarly, cognitive decline may be evident 8–10 years in advance of the onset of diagnosed Alzheimer's disease. The progressive nature of both physical and cognitive disability implies that nutritional assessments done at the time of clinical onset are relevant only to the extent to which they reflect intake when the disease process started (as with Alzheimer's) or during the span of time in which the underlying physiologic changes are occurring (as with strength). Moreover, disability is often precipitated by acute disease events. When these diseases or their treatments affect overall nutritional status or appetite, the affected individuals will often be observed to have inadequate intakes of a variety of dietary constituents.

Given the progressive nature of disability onset, longitudinal designs are preferred for the study of dietary exposures. Even though the underlying disease processes may take decades to evolve, patterns of dietary intake are relatively stable during much of adulthood. So, as long as diet is not assessed during times of active underlying illness or advanced disease, the measurements obtained should be related to the exposure period of interest. In data analysis, one can examine the diet-disease relationships in persons with stable weight, or who have not been recently hospitalized or are free from nutrition-related disease (e.g., type 2 diabetes). Events occurring early during the follow-up period can be omitted to account for the presence of undetected disease at the time of the dietary exposure measurement. These kinds of sensitivity analyses provide reassurance that results are not being driven by the influence of clinical or subclinical disease on dietary intake.

15.4 Strategies for Assessing Nutritional Exposures

Sound nutritional epidemiology depends on the accurate and unbiased assessment of usual dietary intake. Several methodologies have been developed to achieve this goal (Table 15.3). These methodologies fall into two broad strategies: interview/questionnaire-based and biomarkers of nutritional exposure. These approaches are often used together since they can provide complementary information.

15.4.1 The 24-h Recall

One commonly used interview-based technique is the 24-h recall. As the name suggests, this method involves a trained interviewer eliciting from the participant all foods and beverages consumed over the previous 24-h period. The interviewer also collects information on amounts and preparation techniques. When necessary, the interviewer can explore the composition of mixed dishes such as soups and stews. Once this data is collected, the foods are linked to databases which provide the amounts of the nutrients consumed. This process is repeated for each consumed item. The total nutrient intake is then based on summing individual nutrient content across all items consumed.

While intake is relatively stable over the long-term, diets are characterized by rather large day-to-day variation. Therefore, a single 24-h recall is insufficient to characterize typical nutrient intake. The number of recalls required to characterize usual intake will depend on the nutrient of interest. In general, it takes more recall days to characterize the intake of nutrients that are found in high quantities in foods which are eaten relatively infrequently. Willett [5] has summarized the number of recalls needed to characterize individual nutrient intake to within 20% of the true value. After statistically adjusting for total calories, 4 days are required to characterize total fat intake, but 36 days are required for cholesterol intake and 106 days are required for vitamin A intake.

The 24-h recall method has several epidemiological applications. It provides a comprehensive and, at least conceptually, unbiased picture of what foods are being consumed in a given population and what foods contribute to the population's intake of the key nutrients of interest. Since all foods and their amounts are collected, the 24-h recall provides data on absolute levels of nutrient intake. However, despite the relatively short time period covered by the recall, errors in recall are common regarding both the inclusion of unconsumed items and the omission of items consumed. Participants can be assisted in providing better information through in-depth probing, visual aids and training to provide better data. Studies that use 24-h recall methods often collect data on random days over a given time period to capture both weekday and weekend consumption. The primary weakness of the 24-h recall is that it can be resource-intensive. The associated costs make it difficult to use as a primary data collection methodology in very large epidemiologic studies. The National Cancer Institute developed an internet-based self-administered 24-h recall method—the Automated Self-administered 24-hour Dietary Recall (ASA24™)—which may address the cost

Table 15.3 Comparison of dietary assessment methods commonly used in epidemiologic research

Characteristics	24-h recall	Food frequency questionnaire	Food records
Study burden & time	~30 min per interview; extensive data entry and coding	~45–60 min as an interview; less as a self-administered questionnaire; minimal coding and data entry	Interview time for instruction (~30 min); extensive data coding and entry
Participant burden & time	~30 min interview	~45–60 min as interview; <45 min as self-administered questionnaire	Extensive participant burden; ~20–60 min/day
Reference time period of measured intake	One day intake	Usual intake over a specified period in the past (e.g., past year)	Current intake over a specified time period (3–7 days)
Type of food intake data captured	Meals and snacks: food items, amount consumed, and preparation methods	Frequency of consumption for lists of foods, approximate amounts if semi-quantitative	Meals and snacks: food items, amount consumed, and preparation methods
Advantages	Low participant burden for a single recall	Low participant burden	Detail about type of food, preparation methods, and portion sizes recorded
	Few restrictions for use; can be used in low literacy populations	Represents usual, long-term intake	
		Minimal data entry with use of machine readable questionnaire	Comprehensive coverage of foods and beverages
	Does not rely on generic memory		Does not rely on memory
	Comprehensive coverage of foods and beverages		Provides estimates of absolute intake
	Provides estimates of absolute intake		
Limitations	Extensive coding and data entry required	Participant required to think in terms of lists not meals	Coding and data entry are labor-intensive
			Participant may change behavior due to intrusiveness
	Accuracy depends on degree of probing	Not all foods are listed	
		Food preparation methods are generally missing	Requires respondent literacy
	Single 24-h recall does not reflect usual intake	Food lists for one population may not be useful in another	Generalizability may be compromised due to low response rate related to participant burden
		Provides relative ranking of nutrient intake not absolute quantities	Does not reflect habitual intake
Issues for Older Populations	Results unreliable in memory impaired	Long FFQs can be difficult to complete in persons with impaired vision/hand function.	Difficult to complete for persons with impaired vision/hand function
		Results unreliable in memory impaired.	
		Participants may fatigue during administration	

Abbreviations: *FFQ* food frequency questionnaire

concerns. While this development lowers the investigator's burden, the relatively large participant burden may remain depending upon the nutrients targeted in the study.

15.4.2 The Food Record

Participants can also be asked to record all foods ingested over a given period of time. While this method does not depend as much upon participant memory as does the 24-h recall, the quality of the data does depend upon the willingness and ability of the participant to provide complete and accurate data. In addition, food choices may be influenced by the expectation of recording intake. Post-data collection processing is also as extensive as with the 24-h recall approach. Because the food record only covers a relatively small number of consecutive days, it is not suited to characterize long-term intake.

15.4.3 The Food Frequency Questionnaire

Humans tend to rely on two strategies for recalling the frequency of events: (1) trying to remember every instance of a behavior over a given period, and (2) estimating a rate at which a behavior is performed and then applying that rate over the period of interest. This second method, sometimes referred to as the event decomposition method, seems to lead to more accurate estimates than does the recall of individual events, and it is the basis of the food frequency questionnaire (FFQ). In the FFQ, the participant is asked to provide an estimate of the frequency of consumption for each item in a list of foods. In some FFQ versions—so-called semi-quantitative FFQs—the participant also estimates the typical serving size.

The first step in the construction of the FFQ is the compilation of the list of foods to be included. A key concept in FFQ design is that the food list is not selected to account for *all* intake of a given nutrient, but rather targets foods that discriminate high and low consumers of a given nutrient. This is done because the number of foods required to account for a high proportion of total intake of all relevant nutrients would lead to a food list that is prohibitively long. Thus, FFQ data are not suited to provide information on absolute nutrient intakes. Rather, the FFQ is designed to accurately distinguish relatively high consumers from low consumers. Therefore, foods are selected based on the identification of those food items that best account for the variability of nutrient intake. For example, in a study of 1,742 women in the United States (US), Willett [5] found that 96% of the variance in this population's vitamin C consumption was accounted for by the use of nutritional supplements and just five foods, and 85% of cholesterol consumption was accounted for by 13 foods. The information used to make these calculations and the resulting food list is based on 24-h recall or on food record data that ideally would be collected in the same population in which the questionnaire will be used. Depending on the goals of the study, the food list can be of varying lengths. General purpose FFQs typically have between 100 and 120 items. Additional items may be included to provide greater resolution for particular nutrients of interest or to account for regional or ethnic specific foods. After the food list has been finalized, investigators assign response categories for each food item. The participant is asked to estimate how frequently a food is consumed over a specified time-frame. Portion sizes are assigned based on the mean serving size as determined from the 24-h recalls. The response categories typically cover a range of intake frequencies that make sense for the food being assessed. Each food is associated with a vector of nutrient amounts for a serving size of the food. This vector is multiplied by the frequency of consumption to provide an estimated intake of nutrients for that food item. These estimates are then summed over all of the food items included in the questionnaire.

The attraction of the FFQ is its low burden for both the investigator and the participant, thus making very large nutritional epidemiological surveys feasible. In older populations or populations unaccustomed to filling out surveys of this type, the food list can be administered by an interviewer and visual aids can also be used.

The weaknesses of the FFQ are that there will be some individuals who consume foods that are not included on the food list but which are also important sources of key nutrients. This can present an additional challenge for studies in diverse populations. With an ever-changing food supply, the food lists can become outdated. Also, the FFQ employs many imputations (e.g., what constitutes a serving size or what a mixed dish contains) that can lead to the misclassification of an individual's dietary exposure.

The intake of some nutrients cannot be reliably estimated from questionnaires. The nutrient contents of foods are derived from both US government databases and determinations made by research laboratories. The nutrient content of foods can depend upon growing conditions and processing. For example, the selenium content of grains depends upon the selenium content of the soil, which shows a high level of geographical variability. Thus, it would not be possible to quantify intake just from knowing the intake of particular foods.

15.4.4 Biomarkers of Nutritional Exposures

For many nutrients, biochemical markers can be used to quantify nutrient intake (Table 15.4). Biomarkers are measured in biologic tissues such as blood, urine or fat. Biomarkers can be direct measures of the nutrient of interest, a measure of a metabolite of the nutrient, or a measure of other enzymes or metabolites for which levels are determined by the level of the nutrient. Total energy expenditure can be measured by the doubly-labeled water method. In this method, a participant is asked to consume a known quantity of water in which one of the hydrogen atoms is deuterium and the oxygen is the stable isotope O^{16}. The body's production of CO_2 is then calculated by measuring the relative disappearance of these isotopes over time, providing a physiologic estimate of total energy expenditure over the time period. Dietary protein can be measured by tracking urinary nitrogen excretion, usually over a 24-h period. Serum levels of fat-soluble substances like β-carotene or α-tocopherol can be used to measure the intake of foods that contain these substances. Vitamin B_{12} can be measured directly in serum, but since it is water soluble, its half-life is relatively short. However, methylmalonic acid, a substance in B_{12}'s metabolic pathway rises when B_{12} levels are insufficient, and, therefore, it is sometimes used as a functional marker of B_{12} deficiency. Not all nutrients have acceptable biomarkers. For example, there is no biomarker for Vitamin A (retinol). Vitamin A can be accurately measured in the blood, but blood levels of the vitamin are tightly regulated and buffered by liver stores, so serum levels do not reflect dietary intake except in situations of prolonged deficiency.

The advantage of biomarkers is that they provide an assessment of nutritional exposure that does not depend upon the accuracy of human recall. Furthermore, since they are measured in human tissues, they are to some extent a measure of the tissue exposure to the nutrient, a factor that can only be surmised with self-reported intake data. However, the interpretation of biomarkers is complicated by several factors. The level of a biomarker in tissue depends not only on the ingestion of a nutrient but also on the efficiency of its absorption, its distribution into various tissue compartments and its subsequent metabolism and excretion. In many cases, biomarker levels are correlated with other serum constituents. For example, the carotenoids are transported in the serum largely on lipoprotein particles. Therefore, the serum levels also depend upon the levels of serum cholesterol, a fact which complicates the interpretation of studies of carotenoids and coronary heart disease. In addition, many nutritional biomarkers are also sensitive to inflammatory stimuli (e.g., albumin, ceruoplasmin, transferrin). Thus, low levels of these markers may indicate the presence of an active inflammatory process rather than a low dietary intake. Hypothetically, any of these factors that affect tissue biomarker levels could themselves be related to a disease or condition of interest, so biomarker-disease relationships must be interpreted cautiously.

Recall-based dietary data and biomarkers are frequently combined. A level of biomarker indicates the intake of the measured substance, but it

Table 15.4 Selected biomarkers of nutritional intake

Nutrient	Tissue	Method	Approximate median correlation with FFQ derived intake estimates	Comments
Docosahexaenoic Acid/ eicosapentaenoic acid (omega-3 fatty acids)	Red blood cells/ adipose	HPLC	0.5	
Protein	Urine	Kjeldahl technique	0.3–0.4	Correlations after adjusting for total protein intake
Vitamin B_6	Plasma	Direct measurement of PLP	0.3–0.4	Long-term vitamin B_6 status is commonly measured by plasma PLP
Vitamin B_{12}	Serum/plasma	RIA	0.3–0.4	Measurement of functional biomarkers methylmalonic acid or total homocysteine increase sensitivity for detecting poor B_{12} status
Folate	Serum/red blood cells	Microbiologic, competitive binding	0.4–0.5	Serum for short-term intake; RBC for long term intake
β-Carotene	Serum/plasma	HPLC	0.2–0.3	Transported on lipoproteins, adjust for total cholesterol
Vitamin C	Plasma/leukocytes	HPLC	0.3	Higher when accounting for supplement use
Vitamin D	Serum/plasma	25(OH)D by RIA, HPLC, LC-MS	Insufficient data	25(OH)D measures vitamin D intake and cutaneous vitamin D production
Vitamin E	Serum/plasma	HPLC	0.3–0.4	Transported on lipoproteins, adjust for total cholesterol

Derived from Willett [5] and other published sources
Abbreviations: *25(OH)D* 25-hydroxyvitamin D, *FFQ* food frequency questionnaire, *HPLC* high performance liquid chromatography, *LC-MS* liquid chromatography-mass spectrometry, *PLP* plasma pyridoxal 5-phosphate, *RIA* radioimmune assay

is also an indicator of a pattern of dietary intake that is rich in the measured indicator. As such, when analyzing biomarker data, it is still necessary to adjust for other aspects of correlated dietary patterns as potential confounders. In addition, biomarkers can be used to calculate adjustments to increase the validity of the analysis of recalled dietary data. To reduce costs, measurements for this purpose can be conducted in subsets of participants.

15.5 The Reliability and Validity of Nutritional Data in Older Adults

Maximizing the reliability and validity of dietary data is an abiding challenge of nutritional epidemiology. Reliability (the extent to which two measurements in the same person agree) has been frequently studied and is typically in the moderate to good range. Reliability of nutrient comparisons is improved by accounting for the use of dietary supplements where appropriate and by statistical adjustment for total caloric intake (see below). Validity (the extent to which the study measure reflects the true value) is difficult to assess because a true 'gold standard' measure often does not exist. As a result, validity is often inferred by inter-measure comparisons such as comparing FFQ results to multiple 24-h recalls, food records or nutritional biomarkers [5].

Several investigators have reported that measures of reliability and validity of nutritional data collected from community-dwelling older adults is similar to that in middle-aged populations. Conceptually, it makes sense that short-term memory problems would impact recall-based methodologies, but only a few investigators have explicitly evaluated the validity of dietary data in persons with impaired cognition. In the Health ABC study, poorer performance on a measure of general cognitive ability was associated with a greater likelihood of reporting impossibly high/low total energy intakes with an interviewer-administered FFQ [6]. Bowman et al. [7] found that memory deficits were associated with better FFQ reliability but reduced validity compared to cognitively intact older adults. Proxies are used in aging research to obtain data for cognitively impaired or acutely ill individuals. In the best of situations, there is modest agreement between index participants and proxies, and thus the use of proxies introduces additional variability and risk of bias to the characterization of nutritional exposures [5]. In the future, mobile technology—which can provide opportunities to collect dietary information by collecting visual recordings of food consumed at each meal—may help to increase the validity of intake data even in cognitively impaired populations.

15.5.1 Accounting for Imperfect Measurement

Due to the inherent variability of nutritional measures, problems of bias secondary to misclassification are to be expected. This can lead to a distortion of the true association between the nutrient and the outcome. If the misclassification of a continuous measure is non-differential—that is, the error is unrelated to the outcome of interest—then this error would tend to cause observed associations to understate the true association. However, once the variable is categorized or when other nutrition-related variables are included in models as covariates, the direction of bias can be difficult to determine. If appropriate validation data are available for the nutrient of interest, it can be used to correct the nutrient-disease association for the effects of misclassification error.

15.6 Analysis of Nutritional Data

For the most part, nutritional exposures are approached much like other epidemiological exposures, though there are some differences. Analyses of individual nutrients must almost always account for total energy intake. The tissue "dose" of a nutrient depends to some extent on body size, and since total energy intake is highly correlated with the lean component of body size, this adjustment helps to deal with this issue. Just as important, individuals reporting dietary intake

may have a tendency to systematically under- or over-report intake to varying degrees. The adjustment for total energy intake helps to account for this, and a number of studies have shown that the adjustment for total calories improves the validity of self-reported nutritional data. Most analysts will also exclude participants with very high or very low reported total energy intakes as this can be an indication of poor data quality.

The adjustment for total energy intake can be done in one of two ways. Total energy intake can be included as a covariate in a multivariable model along with the nutrients of interest. One can also fit a linear model of the following form: nutrient of interest = intercept + β(total calories) + error. The resulting nutrient residual (actual nutrient intake minus predicted intake from the model) provides an intake value that accounts for total intake. The residual method is preferred when one intends to calculate disease risks by categories of nutrient intake.

15.6.1 What Kinds of Dose-Response Relationships Should Be Expected for Nutritional Exposures?

The presence of a dose-response relationship is considered to be evidence in support of a causal relationship between an exposure and a disease. One must be cautious in applying this kind of 'toxicological' thinking to nutritional exposures as many counter-examples exist. Selenium and vitamin A are essential nutrients, but both are toxic if taken in too-high amounts. The relationship of alcohol consumption and health outcomes is among one of the most studied in all of nutritional epidemiology. The literature consistently indicates a "u-shaped" relationship, such that those with moderate alcohol consumption (1.0–2.0 drinks/day for men, 0.5–1.0 drink/day for women) have lower mortality than do either non-drinkers or heavier drinkers. For many essential nutrients, there are no proven benefits to health beyond the amount required to prevent deficiency. In the epidemiologic context, this would imply that threshold effects should be observed in studies of these nutrients. Thus, in well-nourished populations, it is possible that no association would be seen at all. In view of these examples, the lack of a linear dose-response relationship in a diet-disease relationship should not be interpreted in the same way as the lack of dose-response in other epidemiological contexts.

Even when a dose-response relationship is observed, one must be careful when extrapolating. If a diet that includes a moderate amount of a nutrient is associated with better health outcomes, it does not necessarily mean that a diet manipulated to provide extremely high amounts of the nutrient will be superior. For example, smokers with high serum β-carotene levels are less likely to develop lung cancer, but supplementing smokers with high doses of β-carotene that achieve serum levels much higher than those observed in non-smokers is associated with increased cancer mortality.

15.6.2 Dietary Supplements

Many dietary substances of epidemiological interest can also be consumed in the form of dietary supplements. Data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) found that nearly 50% of older US adults report taking a multivitamin/multimineral supplement in the past 30 days (Table 15.5) [8]. The amounts of nutrients found in supplements can vary greatly between products and the formulation of a given branded product can change over time. How one approaches the use of supplements depends on the nutrient of interest. For some nutrients, such as vitamin D, supplements may make up a majority of the intake for those individuals taking them, and thus it makes sense to include vitamin D supplement users as a separate category that is assumed to have the highest exposure. For other nutrients, such as vitamin C, the solution is not so clear cut.

In general, it is advisable to adjust for supplement use in analyses because the behaviors and attitudes that lead to the use of supplements may themselves be related to the outcomes of interest. Also, when the dietary supplements contribute to

Table 15.5 Prevalence of vitamin and mineral containing supplement use in the past month in the U.S. population aged >70 years: 2003–2006

Supplement	Prevalence (%)
Multivitamin/multimineral	46
Vitamins B_6 & B_{12}	36
Vitamin C	41
Vitamin D[a]	51
Vitamin E	40
Calcium[a] (women only)	60
Iron	16
Zinc	36
Selenium	32

Adapted from Bailey et al. [8]; and Gahche et al. [9]
[a]Age >60 years

intake in the range of normal consumption, it can be informative to stratify the analysis by supplement use. Uncertainties regarding the frequency of use and the amounts in a given supplement will introduce additional sources of misclassification, a non-issue in non-supplement users.

15.7 Specific Nutrients of Interest

Outcomes of geriatric interest—including falls, fractures and physical and cognitive disability—occur both through age-related and disease-related pathways. Stroke, vascular disease, obesity, diabetes and hypertension are all associated with outcomes of geriatric interest. Each of these disease processes has a substantial nutritional component. There are many excellent reviews available elsewhere for disease-specific associations. The remainder of this chapter focuses on a few of the better-studied nutrients that have been hypothesized to affect age-related disability processes, while directly acknowledging that it may not always be possible to separate disease-related pathways from non-disease-related pathways.

15.7.1 Omega-3 Fatty Acids

Polyunsaturated fatty acids (PUFAs) are dietary fatty acids (FAs) with more than one double bond that are essential to human health. PUFAs are divided into omega-6 FAs and omega-3 FAs, depending upon their chemical structure. Omega-6 FAs are found in high concentrations in seed oils that are commonly used in the food supply. Omega-3 FAs are found in high concentrations in fatty fish and some seed oils (e.g., soybean, canola and flax seed). The predominant omega-3 FA in foods of plant origin is α-linolenic acid (ALA), while the predominant FAs in the oils of fatty fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The latter two are more biologically active, and while the human body can synthesize EPA and DHA from ALA, the efficiency of this conversion is relatively low. Both omega-6 and omega-3 FAs are precursors for signaling molecules called prostaglandins, but the omega-6 FAs are associated with pro-inflammatory compounds while omega-3 FAs are associated with anti-inflammatory compounds. DHA is important in brain development and neuronal function, and there are *in vitro* data showing that DHA can reduce Alzheimer's disease-related inflammatory changes. A number of epidemiologic studies of Alzheimer's disease and cognition have examined these nutrients, with cohort studies tending to show a benefit for higher omega-3 intake. The USDA's 2010 Dietary Guidelines for Americans recommends eating 8 oz of seafood per week to provide a daily average of 250 mg of EPA/DHA; supplements typically contain 1,000 mg. An important genetic determinant of dementia risk is APOE allele status, and several studies have found that the greatest evidence for omega 3 FA benefit is in participants who are non-carriers of the APO ε4 allele [10].

15.7.2 Protein

Changes in body composition occur with advancing age. Of particular concern is the age-related loss of skeletal muscle (i.e., sarcopenia) and the resulting decline in physical function. Although a number of underlying mechanisms contribute to age-related declines in skeletal muscle, inadequate dietary protein intake may accelerate this

process [11]. The recommended dietary allowance (RDA) for protein intake in adults is based on short-term nitrogen balance studies and is currently set at 0.8 g per kg of body weight per day [12]. Although nitrogen balance may be achieved at the current RDA for protein, it has been suggested that a moderate increase in protein intake (up to ~1.5 g per kg of body weight per day) may be necessary to maximize muscle protein synthesis and reduce the loss of muscle mass that occurs with advancing age [11]. However, renal function must be considered with protein intakes of ≥2.0 g per kg of body weight per day.

High biological value proteins, such as protein from animal sources—which contain all the essential amino acids—appear to determine the rate of muscle protein synthesis [11]. Many older adults are at risk of consuming inadequate animal protein due to age-associated factors including cost, difficulty chewing, fear of consuming too much fat or cholesterol, and perceived intolerance to certain foods. In NHANES 2003–2004, approximately 9% of women and less than 3% of men ≥71 years of age consumed less than the estimated average requirement (EAR; 0.66 g per kg of body weight per day) based on ideal body weight [13].

Few longitudinal studies have investigated the association between protein intake and changes in body composition and physical function among older adults. In the Health ABC study, protein intake was associated with 3-year change in both total and appendicular muscle mass among older adults, with those in the highest quintile of protein intake (median intake ~1.1 g per kg of body weight per day) losing ~40% less total and appendicular muscle mass compared to those in the lowest quintile of protein intake (median intake ~0.7 g per kg of body weight per day) [14]. Furthermore, in the Women's Health Initiative Observational Study [15], the odds of frailty over 3 years were ~35% lower among older women for every 20% increase in protein intake (in g per kg of body weight per day). Dietary protein has also been shown to influence bone metabolism, with higher protein intakes associated with higher bone mineral density and decreased risk of fractures [16]. Although some studies have shown an adverse effect of high protein on bone health, the adverse association appears to be strongest among individuals with low calcium intake, which suggests that calcium intake may influence the impact of dietary protein on the skeleton.

15.7.3 Vitamin D

In the past two decades, it has become evident that the role of vitamin D extends beyond calcium homeostasis and bone health.

Vitamin D may decrease the risk of many chronic conditions including autoimmune and infectious diseases, cardiovascular disease and common cancers [17]. Vitamin D is taken up by most tissues in the body. There is a growing list of tissues that show 1-α-hydroxylase activity and are thus able to synthesize the active form of the vitamin, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), from 25-hydroxyvitamin D (25[OH]D), the primary circulating form. This suggests an autocrine or paracrine role in a variety of tissues [18]. Vitamin D receptors have also been identified in more than 30 different tissues including muscle, osteoblasts, activated T and B lymphocytes, and most organs in the body including the brain, heart and prostate [18].

Many older adults are at risk for low vitamin D status due to low intakes of vitamin D-rich foods (such as vitamin D fortified milk and fatty fish), as well as reduced exposure to UVB radiation due to decreased outdoor activity along with the decreased ability of the skin to synthesize vitamin D. The RDA for vitamin D is 600 IU/day for adults 50–70 years of age and 800 IU/day for adults ≥71 years of age [19]. Serum 25(OH)D is the preferred indicator of vitamin D exposure, reflecting vitamin D consumed in both food and supplements and vitamin D produced cutaneously [17]. Of concern is the considerable variability in the measurement of serum 25(OH)D due to different assay methodology, laboratory experience and differences between assays in recognizing the vitamin D_3 and D_2 form equally [20]. Experts have suggested that the optimal serum 25-hydroxyvitamin D concentration for health outcomes other than bone is ≥30 ng/mL (≥75 nmol/L) [21];

however, the Institute of Medicine's 2011 report considers 20 ng/mL (50 nmol/L) as adequate for bone and overall health in healthy individuals [19]. In NHANES 2000–2004, approximately one-third of men and women ≥70 years of age were vitamin D insufficient (serum 25(OH)D <20 ng/mL [<50 nmol/L]) [22]. Serum $1,25(OH)_2D$ is generally not a good indicator of vitamin D status because serum concentrations are tightly regulated by parathyroid hormone, calcium and phosphate, and $1,25(OH)_2D$ has a short half-life.

Vitamin D metabolites affect muscle metabolism through their effects on calcium transport, uptake of inorganic phosphate for the production of energy-rich phosphate compounds, and protein synthesis in muscle cells [23]. In older adults, low serum 25(OH)D concentrations have been associated with muscle weakness, poor physical performance and falls [23, 24]. Neuroprotective benefits of vitamin D have been observed in animal and *in vitro* models, and human observational studies have shown evidence of the role of vitamin D in both global and specific areas of cognitive function [25]. Low serum 25(OH)D concentrations have been implicated in co-morbid conditions such as cardiovascular disease, diabetes, hypertension and osteoarthritis [17], conditions that are also directly related to the development of limitations in physical and cognitive function. Low serum 25(OH)D concentrations have also been associated with increased overall mortality as well as cardiovascular and cancer mortality, and vitamin D supplementation is associated with decreased mortality risk [26]. Despite these intriguing epidemiologic findings, the Institute of Medicine concluded that definitive conclusions could not be made with regard to the efficacy of vitamin D beyond bone health and fractures.

15.7.4 Calcium

Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling, hormonal secretion and maintenance of bone health. Approximately 99% of the body's calcium supply is stored in the bones and teeth, with the remaining 1% found in blood, muscle and intercellular fluids. Serum calcium is tightly regulated, with the calcium stored in bone serving as a reservoir to maintain constant concentrations of calcium in blood, muscle and intercellular fluids; thus, serum calcium is not a good indicator of calcium status. 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), along with parathyroid hormone, plays a critical role in regulating circulating calcium concentrations through $1,25(OH)_2D$'s role in intestinal calcium absorption and bone and renal calcium resorption.

Calcium is naturally-occurring in some foods (e.g., dairy products) and is added to others, and it is available in supplements and some medications (e.g., antacids). The current RDA for calcium is 1,000 mg/day in men and 1,200 mg/day in women 50–70 years of age, and 1,200 mg/day in men and women ≥71 years of age [19]. Approximately 30% of the calcium consumed from diet, supplements and medications is absorbed, with absorption efficiency inversely related to the amount of calcium consumed [19]. In NHANES 2003–2006, over half of older adults consumed a calcium-containing supplement; however, only 31% of men and 39% of women ≥71 years of age met the RDA from diet and supplements combined [27].

Secondary hyperparathyroidism can occur among older adults who have a low calcium intake in addition to a low vitamin D concentration, resulting in increased bone resorption and suppression of bone formation leading to osteomalacia (inadequate mineralization of the bone matrix) and osteoporosis (reduced bone mass). Randomized controlled trials have shown that calcium supplementation, along with vitamin D, increases bone mineral density and reduces non-vertebral and hip fractures, particularly among institutionalized older adults [19]. Although observational studies show that calcium and/or dairy food intake may protect against cardiovascular disease—possibly by decreasing the intestinal absorption of lipids and increasing lipid excretion, thus lowering cholesterol levels—it has recently been suggested that calcium supplements (without vitamin D) may increase the risk of cardiovascular disease [19].

15.7.5 B Vitamins

The B vitamins folate (folic acid is the synthetic form found in fortified foods and supplements) and vitamins B_6 and B_{12} serve as cofactors in one-carbon metabolism. The active form of folate, tetrahydrofolate, is a cofactor for many enzymes that are involved in the metabolism of amino acids and nucleotides. The metabolically active form of vitamin B_6, pyridoxal phosphate, is a cofactor in a number of enzymes that are involved in the metabolism of amino acids, and is also required for the utilization of glycogen to release glucose for the maintenance of normal blood glucose concentrations. Vitamin B_{12} is a cofactor for the enzymes methionine synthase and L-methylmalonyl-CoA mutase, which catalyze the conversion of homocysteine to methionine and L-methylmalonyl-CoA to succinyl-CoA, respectively. Deficiencies of either folate or vitamin B_{12} can result in megaloblastic anemia. A deficiency of folate, vitamin B_6 or vitamin B_{12} can increase blood levels of homocysteine. Prolonged vitamin B_{12} deficiency can result in neurological disorders such as peripheral neuropathy, memory loss and dementia.

Red blood cell folate measures long-term folate intake, while serum folate reflects recent folate intake. Long-term vitamin B_6 status is commonly measured by plasma pyridoxal 5-phosphate. Vitamin B_{12} status is usually determined using serum or plasma vitamin B_{12}. However, methylmalonic acid and homocysteine levels have been shown to be more sensitive in the diagnosis of vitamin B_{12} deficiency than the measurement of circulating vitamin B_{12} concentrations alone. In vitamin B_{12} deficiency, both methylmalonic acid and homocysteine levels will be high; however, in folate deficiency, only homocysteine levels will be high.

In 1998, the US Food and Drug Administration required that folic acid be added to all enriched breads, cereals, flours, corn meal, pasta products, rice and other cereal grain products sold in the US. Since the advent of folic acid fortification, both serum and red blood cell folate concentrations have increased, with the prevalence of low folate status less than 5% in older adults [28]. However, there is concern that high folate intakes could mask vitamin B_{12} deficiency in older adults. Low vitamin B_{12} concentrations are common in older adults (~15–20%), primarily as the result of atrophic gastritis and a decrease in gastric acid, which reduces the absorption of protein-bound vitamin B_{12} such as that found in animal products [29]. Thus, older adults should consume vitamin B_{12} in the crystalline form, such as in fortified foods or in a dietary supplement, which does not require gastric acid or enzymes for initial digestion. For adults ≥51 years of age, the RDA for folate is 400 mcg/day, for vitamin B_6 is 1.7 mg/day in men and 1.5 mg/day in women, and for vitamin B_{12} is 2.4 mcg/day [30].

Elevated circulating homocysteine concentrations have been implicated as a modifiable risk factor for cardiovascular disease, cognitive decline and fractures. Since low folate, vitamin B_6 or vitamin B_{12} can increase homocysteine concentrations, low intake of these B vitamins may increase the risk of cardiovascular disease [31]. Although observational studies have found elevated homocysteine concentrations, low dietary and circulating folate, and low vitamin B_6 and B_{12} intakes and concentrations to be associated with cardiovascular outcomes, randomized controlled trials of supplemental B vitamins have not shown a benefit on cardiovascular outcomes [32]. Observational studies have found elevated homocysteine concentrations, as well as low dietary and circulating folate, vitamin B_6 and B_{12} intakes and concentrations, to be associated with impaired cognition and cognitive decline [33]. However, the few randomized controlled trials of folate, vitamin B_6 or B_{12}—alone or in combination—have not shown improved cognitive function [34].

15.7.6 Dietary Antioxidants

One of the predominant theories to explain aging is based on the observation that the process of respiration generates chemically reactive by-products called free radicals which can interact with cellular machinery in harmful ways, often through oxidation reactions. The body has several enzymatic systems which have evolved to

Table 15.6 Summary of selected dietary antioxidants

Putative antioxidant	Major dietary sources	RDA[a]
Carotenoids		
α-Carotene	Pumpkin, carrot, yellow squash	None established
β-Carotene	Carrot, pumpkin, dark green leafy greens, sweet potato	None established
β-Cryptoxanthin	Pumpkin, papaya, sweet red peppers, citrus	None established
Lutein/Zeaxanthin	Dark green leafy vegetables, peas, broccoli, corn	None established
Lycopene	Tomato, tomato products, watermelon	None established
Tocopherols		
α-Tocopherol	Nuts, seed oils	15 mg/day
γ-Tocopherol	Soybean, corn and canola oils	None established
Vitamin C	Citrus, berries, broccoli, sweat red pepper	75 mg/day women, 90 mg/day men
Selenium	Seafood, meat, whole wheat products	55 mcg/day

Source: Food and Nutrition Board, Institute of Medicine [35]
[a]Recommended daily allowance for adults >70 years

detoxify these free-radicals, including copper/zinc superoxide dismutase, manganese superoxide dismutase, catalase, glutathione, glutathione peroxidase, glutathione peroxidases and glutathione *S*-transferase. A number of dietary constituents also have antioxidant properties, including vitamin E (α-tocopherol) and related compounds, vitamin C, and the carotenoids (Table 15.6). The carotenoids are a group of lipophilic compounds found primarily in fruits and vegetables. They provide orange and yellow colors to many foods. Serum levels are often used as a biomarker of fruit and vegetable intake. Some of the carotenoids can be metabolized into vitamin A (α-carotene, β-carotene, β-cryptoxanthin). Selenium is of interest due to its essential role in the glutathione system, the activity of which increases with increasing selenium intake. Despite having been identified as dietary antioxidants, it has generally been unclear whether these compounds have a functional effect on the aging-process through antioxidant-mediated mechanisms. Moreover, there is some evidence that cell-based enzymatic antioxidant systems are regulated by the oxidative burden, so the increase in dietary antioxidants may lead to reduced enzymatic detoxification capacity.

There are longitudinal data that suggest that most of the commonly studied dietary antioxidants are associated with a reduced risk of mobility limitation and both cognitive and physical disability. However, the pattern of associations has not been entirely consistent. For example, in the Women's Health and Aging Study (WHAS) I, low selenium—but not total carotenoids—was associated with a 47% higher 3-year risk of disability in activities of daily living ($p<0.001$) in a cohort of already-functionally-impaired women [36]. But in the Invecchiare in Chianti (InChianti) study, high total plasma carotenoids were associated with a 49% reduction in the development of severe walking disability ($p=0.01$) [37]. Part of this inconsistency is due to the examination of nutrition at different stages of the disability pathway. Selenium was associated with mortality in InChianti, and carotenoids with declining walking speed in the WHAS I study cohort.

Of the antioxidants commonly studied, there is little data available regarding vitamin C. Serum vitamin C status is difficult to assess because specimens must be collected with this specifically in mind. Vitamin C and E supplement use have both been related to decreased dementia risk, but again the evidence varies from study to study [38].

The eye is a target of age-related degenerative processes. Cataracts or clouding of the lens are observed in the great majority of individuals >75 years of age. Cataracts have been a target of antioxidant research because the process of

cataract formation is driven in part through oxidative cross-linking of the crystalline proteins in the lens and because the lens is acellular. In theory, circulating antioxidants could have an important role in cataract prevention. Epidemiologic studies have found inverse associations with many putative antioxidants, but the studies have been inconsistent and randomized clinical trials have failed to show a benefit of high-dose antioxidant supplementation in well-nourished older populations [39].

Age-related macular degeneration (AMD) leads to loss in the center of the visual field due to damage to the retina, and it is a leading cause of blindness in the US. Two of the commonly measured carotenoids—lutein and zeaxanthin—are found at high concentrations in the macula of the eye. Low levels of retinal lutein are associated with a higher risk of macular degeneration. The Age-Related Eye Disease Study (AREDS) evaluated nutrient supplement combinations to prevent the progression of AMD-related pathology, though none of the supplements contained lutein [40]. The supplement combination that showed the greatest benefit included 500 mg of vitamin C, 400 IU of vitamin E, 15 mg of β-carotene, 80 mg of zinc as zinc oxide, and 2 mg of copper as cupric oxide. It is important to note that the amounts of these nutrients are beyond that which can be reasonably consumed from food.

15.8 Conclusion

The functional health of older persons presents special epidemiological challenges due to the long natural history of functional decline and the heterogeneity of the older population. Nutrition undoubtedly plays a role in both the onset and pace of these changes. While studies have had limited success in the identification of specific nutrients that slow the age-related physiologic changes that impact health and function, the literature suggests that maintaining an adequate intake of both micronutrients and protein is important to maintain health and function in the later stages of life.

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Body Composition and Aging

16

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Abstract

Body composition in older adults can be assessed using simple, convenient but less precise anthropometric methods to assess (regional) body fat and skeletal muscle, or more elaborate, precise and costly methods such as computed tomography and magnetic resonance imaging. Body weight and body fat percentage generally increase with aging due to an accumulation of body fat and a decline in skeletal muscle mass. Body weight and fatness plateau at age 75–80 years, followed by a gradual decline. However, individual weight patterns may differ and the periods of weight loss and weight (re)gain common in old age may affect body composition. Body fat redistributes with aging, with decreasing subcutaneous and appendicular fat and increasing visceral and ectopic fat. Skeletal muscle mass declines with aging, a process called sarcopenia. Obesity in old age is associated with a higher risk of mobility limitations, disability and mortality. A higher waist circumference and more visceral fat increase these risks, independent of overall body fatness, as do involuntary weight loss and weight cycling. The role of low skeletal muscle mass in the development of mobility limitations and disability remains controversial, but it is much smaller than the role of high body fat. Low muscle mass does not seem to increase mortality risk in older adults.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Body Composition • Fat mass • Lean mass • Muscle mass • Sarcopenia • Sarcopenic obesity • Physical function • Mobility • Strength • Appendicular lean mass • Body fat distribution

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Abbreviations

ADL	Activity of Daily Living
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
DXA	Dual-energy X-ray Absorptiometry
HR	Hazard Ratio
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
SD	Standard Deviation
WHO	World Health Organization

16.1 Introduction

Body composition is considered to be an important determinant of health and functioning in old age. A large variety of methods are available for assessing body composition in older adults, including anthropometry, bioelectrical impedance, densitometry, dual-energy x-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI). Some methods are more suitable for application in older adults than are others, and methods differ with regard to price, availability, radiation exposure, precision (validity) and accuracy (reproducibility). The first section of this chapter will provide an overview of methods that are most frequently applied and discuss their ability to assess adiposity, body fat distribution and skeletal muscle mass.

The next section will provide an overview of the age-related changes in body composition, specifically addressing the changes in overall adiposity, fat distribution (including visceral fat and fat infiltration into the muscle) and skeletal muscle in old age. This section will also describe prospective studies that used repeated assessments of body composition to monitor change over time. Care was taken to include the results of studies that used precise and accurate methodology to assess body composition.

The final section will describe the associations of adiposity, fat distribution and skeletal muscle with mortality and with mobility limitations and disability in older adults. This will include describing the results of the limited number of prospective studies that have investigated change in body composition in relation to these outcomes.

16.2 Measurement of Body Composition

16.2.1 Anthropometry

Anthropometric measures are the simplest and cheapest methods for assessing body composition in older adults. They include measures of body height; body weight; skinfold thicknesses; and circumferences of the waist, hip, arm or calf. The measurement of body weight and body height enables the calculation of the body mass index (BMI, body weight [in kg] divided by body height [in meters] squared). When body height cannot be measured, knee height or arm span can be used as alternative measures from which body height can be estimated [1]. The BMI provides a crude indication of the level of overweight or underweight in older adults. The BMI cut points applied to assess overweight and underweight in older adults often differ from the World Health Organization (WHO) cut points, though there is no consensus regarding the preferred cut points. The cut points applied in older adults vary between >25 and >28 kg/m^2 to assess overweight and between <18.5 and <22 kg/m^2 to assess underweight [2, 3]. The BMI is positively correlated with body fat percentage in older adults on a group level, but provides limited information on body composition at the individual level [4, 5].

Waist circumference has been used as an indicator of body fatness and especially abdominal body fat [6]. However, in older adults, waist circumference tends to better reflect total body fatness than it does abdominal fat [7]. There are recent indications that the cut points for high-risk waist circumference as endorsed by the WHO (>102 cm for men and >88 cm for women) should be higher for adults who are ≥70 years of age, both men (>100–106 cm) and women (>99 cm) [8]. The use of the waist-hip ratio, calculated as the waist circumference divided by hip circumference, is no longer endorsed by the American Heart Association [9].

Mid-upper arm circumference and calf circumference have been used as indicators of skeletal muscle mass in older adults. Arm circumference together with the triceps or biceps skinfold enables the calculation of mid-upper arm muscle area. However, these measures are rather weakly correlated with skeletal muscle mass from DXA or with muscle area from MRI, and they should therefore be considered crude indicators of body composition [10–12]. A low arm circumference (<25 cm) or calf circumference (<31 cm) has also been used as a marker of under-nutrition in older adults [13, 14]. Recent studies show that a low arm circumference better reflects thinness and under-nutrition in older adults then does a low BMI [13, 15].

Skinfold thickness (in mm) can be measured using a skinfold caliper to assess subcutaneous fat. Using prediction equations, body fat percentage can be predicted from the sum of two or four skinfolds [16]. Only prediction equations that have been specifically developed for older adults should be used in older adults because general equations will underestimate body fat percentage in older adults due to the redistribution of body fat and the accumulation of body fat in the abdomen with aging [17]. Body composition estimates from skinfold measurement should be carefully interpreted on an individual level due to individual prediction error and the high intra- and inter-observer variability of the skinfold thickness assessment.

16.2.2 Bioelectrical Impedance

The bioelectrical impedance method is a simple and non-invasive method for estimating body composition. The method is based on the fact that body water (with soluble electrolytes) is a good conductor of an electric current while adipose tissue is not. For this method, two electrodes are attached to the hand as well as to the foot, and body resistance to the provided current is measured. Since body height influences the measured resistance, a resistance index is usually calculated (height^2/resistance). A prediction equation is then used to predict body composition from this resistance index.

Prediction equations have been developed to predict total body water, fat-free mass, fat mass, percentage of body fat and appendicular skeletal muscle mass [18–21]. Depending on the equation, information may also be needed regarding age, sex, body weight or other anthropometric variables. Thus, body composition components such as muscle mass cannot be directly measured by the bioelectrical impedance method, but instead are estimated using a prediction equation. The validity of the method strongly depends on the prediction equation that is used [22]. The equations are population-specific and to reduce bias, they should be developed for older adults or the specific patient group under study [23]. The prediction of body composition can also be affected by the amount and distribution of total body water. Prior to obtaining measurements of bioelectrical resistance, it is required that the participant rest in the horizontal position for about 5–10 min. In addition, the equations may be inaccurate if the individual has any degree of water retention. This has been a particular problem in the prediction of body composition in renal dialysis patients, in whom shifts of body water are important. Lastly, because a prediction equation needs to be used, body composition prediction errors can be unacceptably large for an individual older adult [24].

16.2.3 Densitometry

Densitometric methods include underwater-weighing and air-displacement plethysmography (a technique popularized by a proprietary product called the BodPod). Both methods assess body volume, which together with body weight (as measured by a regular scale) enables the calculation of body density. From body density, the amount of fat mass and fat-free mass can be estimated using the Siri's or Brozek formula [25, 26]. These formulas are based on the assumption that the density of fat mass (0.900 g/l) and the density of fat-free mass (1.100 g/l) are constant. Body composition as assessed by densitometric methods may be biased in specific older adults in whom this assumption is unlikely to be met, such as in those who have severe osteoporosis, edema

or dehydration [27]. While the underwater-weighing method has been frequently used in older adults, the method is less suitable for frail older adults compared to air-displacement plethysmography.

16.2.4 Dual-Energy X-Ray Absorptiometry

DXA was originally developed to measure bone mineral density, but it has gained popularity as a method for assessing whole-body and regional soft-tissue composition (fat mass and lean mass). Because the method assesses three body-composition components (bone, fat and lean), it is considered by many as the gold standard for body composition assessment. It is important to realize that while the bone mineral content may be measured directly, the calculation of lean and fat mass are based on equations that have improved over time. Two frequently-used regional body composition measures obtained from DXA include trunk fat (using either the complete trunk or an area between two specific lumbar vertebrae as an indicator of abdominal fat [28]) and appendicular skeletal muscle mass (the non-fat, non-bone mass of the arms and legs [29, 30]). Reference values for body composition in older adults assessed by DXA are available from the National Health and Nutrition Examination Survey 1999–2004 [31].

16.2.5 Computed Tomography and Magnetic Resonance Imaging

CT and MRI are used to produce cross-sectional images of the body from which tissue areas can be assessed in cm^2, though whole-compartment imaging can be used to produce entire compartment measurements of lean or adipose tissue. An image at the abdomen (usually at the L4-L5 level) provides information on fat distribution by separating subcutaneous adipose tissue area from visceral adipose tissue area using the muscle wall of the abdomen as the separator. A single slice at the mid-thigh is frequently used to assess muscle cross-sectional area, subcutaneous adipose tissue area and intermuscular adipose tissue area (cm^2). CT and MRI are also used to assess ectopic fat, which is adipose tissue that is stored in non-adipose tissue compartments such as the liver and muscle [32]. Adipose tissue in muscle can be separated into the larger pools of marbling adipose, which can be summed as cm^2 and which represents intermuscular fat. The assessment of muscle density using CT, also called the attenuation of the muscle, is a measure of both the extramyocellular adipose in the perimysium space and intramyocellular adipose. This measure provides a reliable and valid measure of the fatty degeneration of muscle tissue [33]. Magnetic resonance spectroscopy (MRS) enables the measurement of the molecular composition of a tissue, including the lipid content [34]. It can also separate intramyocellular from extramyocellular adipose, though careful positioning of the participant is important. A main advantage of MRI over CT is the lack of radiation exposure, which enables a whole-body measurement protocol that involves multiple slices across the body to assess whole-body tissue volumes [35]. However, at this time, only CT enables calculation of the attenuation coefficient in muscle.

A potential issue with measurements using CT and MRI is that while they are relatively easy to obtain, they require the application of special analysis programs in a separate step. There are multiple programs available for use with CT or MRI images and it is important to assess which program provides the features that are necessary for the body composition components of interest.

16.2.6 Overview of Methods

The body composition methods discussed above all have their advantages and disadvantages with regard to the assessment of body composition compartments in older adults and their applicability to older adults. See the following tables for an overview of the characteristics of each method and their capability to assess body fat, fat distribution (Table 16.1) and muscle mass (Table 16.2).

Table 16.1 Overview of body composition methods for assessing adiposity and regional fat depots in older adults

Method	Frequently used measures	Body fat compartment			Low cost	Availability	Radiation exposure	Precision	Accuracy
		Visceral fat	Inter-/intramuscular fat	Whole body fat					
Anthropometry	Body mass index	+	+	++	+++	+++	+++	+	++
	Skinfold thickness	+	+	++	+++	+++	+++	+	+
	Waist circumference	++	+	++	+++	+++	+++	+	+
	Arm circumference	+	+	+	+++	+++	+++	+	++
	Predicted fat mass	+	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted fat mass	+	+	++	+++	+++	+++	+	+++
Densitometry	Body density	+	+	+++	++	++	+++	++	+++
Dual-energy X-ray absorptiometry	Total body scan	++	+	+++	++	++	++	+++	+++
Computed tomography	Abdominal image	+++	++	+	+	+	+	+++	++
	Mid-thigh image	+	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Abdominal image	+++	++	+	+	+	+++	+++	++
	Mid-thigh image	+	+++	+	+	+	+++	+++	+++
	Total body multi-image	+++	+++	+++	+	+	+++	+++	++

Note: +++ indicates a very positive feature of the method, while + indicates a less positive feature

Table 16.2 Overview of body composition methods for assessing whole body and regional skeletal muscle in older adults

		Skeletal muscle compartment						
Method	Frequently used measures	Regional muscle	Whole body muscle	Low cost	Availability	Radiation exposure	Precision	Accuracy
Anthropometry	Arm circumference	++	+	+++	+++	+++	+	+
	Calf circumference	++	+	+++	+++	+++	+	+
	Predicted ASMM	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted FFM	+	+	+++	+++	+++	+	+++
	Predicted ASMM	++	++	+++	+++	+++	+	+++
Densitometry	Body density	+	+	++	++	+++	+	+++
Dual-energy X-ray absorptiometry	Whole body scan	+++	++	++	++	++	(+)++	+++
Computed tomography	Mid-thigh image	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Mid-thigh image	+++	+	+	+	+++	+++	+++
	Total body multi image	+++	+++	+	+	+++	+++	++

Abbreviations: ASMM appendicular skeletal muscle mass, *FFM* fat-free mass
Note: +++ indicates a very positive feature of the method, while + indicates a less positive feature

16.3 Changes in Body Composition with Age

16.3.1 Overall Adiposity

Body weight and BMI generally increase from young adulthood until 70–80 years of age when a plateau is reached, and this plateau is followed by a gradual decline [36]. As body height decreases with aging, the BMI will increase even if the person is weight-stable over time. Due to this height loss, the BMI in old age may be overestimated. Such overestimation is most predominant in women who are ≥85 years of age, leading to an overestimation by 0.9 (standard deviation [SD], 0.7) kg/m^2 [37]. Individual trajectories of body weight and BMI are very heterogeneous in older adults and repeated weight change episodes (weight cycling) are common [38, 39]. Also, studies report different BMI trajectories over time between survivors and non-survivors; survivors having a continuing increase in BMI over time while non-survivors have a more stable BMI or decline in BMI [40].

The percentage of body fat in men and woman increases until ≈80 years of age, and after that the percentage seems to level off. The increase is due to an increase in body fat as well as a decrease in lean mass; a decrease in fat mass is observed after 80 years of age [41]. Even in weight-stable older adults, an increase in fat mass and body fat percentage with aging can be observed due to the loss of skeletal muscle mass [42, 43]. Due to the obesity epidemic in the Western world, later birth cohorts of older adults have a higher BMI and higher body fat percentage compared to earlier birth cohorts [41, 44, 45]. Research suggests that the different birth cohorts follow the same body fat pattern with aging [41] and that the adiposity differences between the cohorts continue into the last year prior to death [45].

The amount of fat mass in old age and the body weight changes that are experienced in old age may also impact the subsequent age-related changes in body composition. For example, higher body fatness in old age has been associated with an accelerated loss of muscle mass [46]. Also, significantly more lean mass is lost during weight loss than is gained during weight gain, particularly in older men [47]. These examples illustrate the dynamics of body weight and adiposity in old age and the individual variation in their age-related change.

16.3.2 Body Fat Distribution

The distribution of body fat changes with age, including a general reduction in appendicular fat (mainly subcutaneous fat) and an increase in trunk fat (mainly abdominal fat). Prospective data show a reduction in skinfold thickness with aging, which is indicative of the decrease in subcutaneous fat [48]. The decrease in subcutaneous adipose tissue has also been confirmed using CT data of the mid-thigh as well as whole-body MRI [49, 50]. The increase in abdominal fat has been observed through anthropometric methods such as waist circumference [48], and through imaging methods such as CT and MRI with which an age-related increase in visceral fat can be observed at the waist level [49, 51].

Apart from the redistribution of body fat, an increasing fat infiltration into non-fat tissues can also be observed in old age. The changes in ectopic fat have been mostly studied in aging muscle. Based on whole-body MRI data in older women, the total amount of intermuscular adipose tissue in the body was estimated to be 1.08 kg [49]. This adipose tissue and the total-body visceral adipose tissue mass (1.87 kg) comprise a substantial adipose tissue store. With aging, the amount of intermuscular adipose tissue increases rather steeply: +9.7% per year in older men and +5.8 to +6.5% per year in older women [49, 50]. The increase in intermuscular adipose tissue is most pronounced in those who experience an increase in body weight, but it increases even in those who experience weight loss [50].

16.3.3 Skeletal Muscle Mass

Using potassium counting data, Forbes and Reina [52] were among the first to report prospective

data that showed an age-related decrease in lean body mass. The reported decline was −0.41 kg per year in 13 men and women who were 22–48 years of age. In 1997, the age-related loss of muscle mass was termed sarcopenia, from the Greek words *sarx* (flesh) and *penia* (loss) [53]. However, most researchers today operationalize sarcopenia as the presence of a low skeletal muscle mass. As yet, no consensus has been reached with regard to the specific cut point for low skeletal muscle mass in older adults [54].

More recent prospective studies have precisely measured the decline in skeletal muscle mass in older adults, specifically the decline in appendicular skeletal muscle mass using DXA [42, 46, 49, 55], the decline in total body skeletal muscle mass using 24-h urinary creatinine excretion [56] and the decline in muscle cross-sectional area using CT [50, 57] (Table 16.3). These studies provide a precise estimate of skeletal muscle mass loss because other lean tissues, such as the visceral organs and bone, are not included in the muscle assessment. From these studies, the relative annual decline in skeletal muscle mass is estimated to be between −0.64 and −1.29% per year for older men and between −0.53 and −0.84% per year for older women (Fig. 16.1). In older adults, the absolute as well as the relative decline of skeletal muscle mass with aging is larger in men than in women.

The combination of low muscle mass together with excess body fat has been termed sarcopenic obesity [58, 59]. Due to the increase in body fat and the loss of muscle mass with age, older adults are at a higher risk of developing sarcopenic obesity.

16.4 Associations of Body Composition with Mobility, Disability and Mortality

16.4.1 Overall Adiposity

16.4.1.1 Associations of Adiposity with Mobility and Disability

Prospective studies have consistently shown that obesity in older adults, as determined by a high BMI, is strongly associated with a future decline in functional performance and the new development of disability [60, 61]. For example, a 6.5-year follow-up of 2,982 black and white individuals 70–79 years of age showed that a BMI ≥30 kg/m^2 was associated with a 60% increased risk for self-reported mobility limitations [62]. The increased risk was consistently observed in obese older adults regardless of their level of physical activity [62], which indicates that obesity is an important determinant of functional status and not an indicator of physical inactivity. It is unclear whether being overweight but not obese (a BMI between 25.0 and 29.9 kg/m^2) in old age poses an increased risk of functional problems. A recent study among 406 participants who were 70–89 years of age showed that overweight individuals had approximately half the risk of developing major mobility disability then did those who had normal weight (BMI <25 kg/m^2) or those who were obese (BMI ≥30 kg/m^2) [63]. Prospective studies using bioelectrical impedance or DXA to accurately assess body fatness confirm that higher levels of body fatness increase the risk for mobility limitations and disability in older men and women [60, 61, 64–67].

Functional status in old age is not determined only by the level of adiposity in old age, but also by the lifetime history of being overweight or obese. Men and women 70–79 years of age who have been overweight or obese since age 25 are almost three times more likely to develop mobility limitations compared to those who maintained a normal weight throughout life [68]. In contrast, risk for new mobility limitations was only 1.7 times higher for those who had a normal weight at young age and became overweight or obese in old age. Thus, a longer exposure to being overweight or obese seems to increase the risk for functional decline in old age [69].

Another important determinant of functional status in old age is weight change. Several prospective studies suggest that weight gain in older age is associated with a decline in functional status [70, 71]. For example, among 2,910 Italians ≥65 years of age, a weight gain of ≥5% since age 50 was associated with an increased risk for limitations of activities of daily living (ADLs) [71]. However, a 7-year weight gain pattern among

Table 16.3 Characteristics of prospective studies that investigated age-related change in skeletal muscle in older men and women

Reference	Numnber and Sex	Age mean (SD) or range (years)	Mean follow-up time (years)	Body composition method	Muscle measurement	Mean annual decline in skeletal muscle (%)
Frontera et al. [57]	12 men	71.1 (5.4)	8.9	CT	Mid-thigh total anterior muscle cross-sectional area	–0.64
Delmonico et al. [50]	813 men	70–79	5	CT	Mid-thigh muscle cross -sectional area	–0.98
	865 women					–0.64
Song et al. [49]	26 women	75.5 (5.1)	2.04	DXA	Leg skeletal muscle mass	–0.84
Koster et al. [46]	1,129 men	70–90	5	DXA	Leg skeletal muscle mass	–0.84
	1,178 women					–0.71
Gallagher et al. [42]	24 men	60–90	4.7	DXA	Appendicular skeletal muscle mass	–0.80
	54 women					–0.61
Fantin et al. [55]	62 men	71.6 (2.2)	5.5	DXA	Appendicular skeletal muscle mass	–1.11
	97 women	71.4 (2.2)				–0.60
Hughes et al. [56]	52 men	60.4 (7.9)	9.7	24-h urinary creatinine excretion	Total body skeletal muscle mass	–1.29
	68 women	60.4 (7.4)				–0.53

Abbreviations: CT computed tomography, *DXA* dual-energy x-ray absorptiometry, *SD* standard deviation

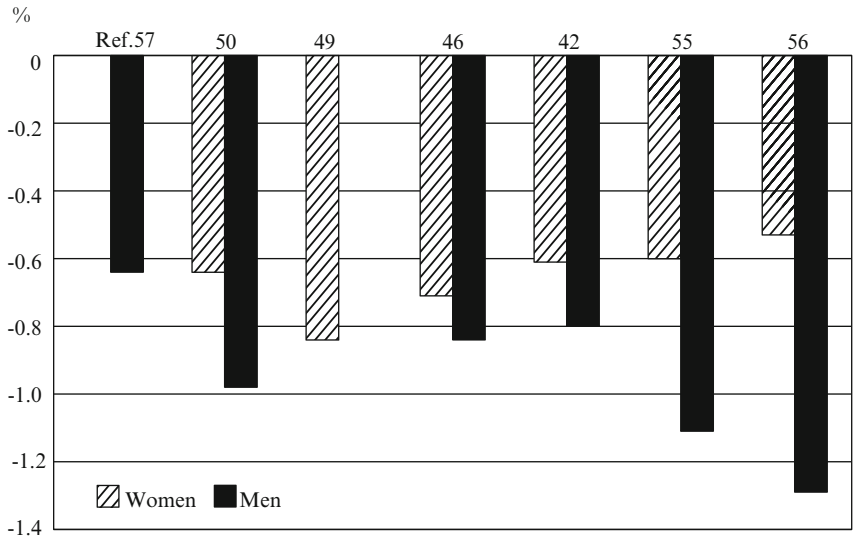

Fig. 16.1 Mean annual decline (%) in skeletal muscle mass in older men and women from prospective studies that used precise methodology

men and women ≥65 years of age did not increase the risk of ADL disability and mobility difficulty compared to a stable weight pattern [39].

Weight cycling and weight loss have consistently been associated with a higher risk of ADL and mobility disability in older adults [39, 60, 72]. The results of these observational studies, where most reported weight changes were unintentional [73], contrast with the results of recent intervention studies that show a clear improvement in physical performance and self-reported functional limitations in obese older adults after intentional weight loss by dietary restriction [74]. The American Society for Nutrition has acknowledged the functional benefits of intentional weight loss in obese older adults [75]; however, further research is needed to optimize weight loss strategies for obese older adults and to examine their long-term benefits.

16.4.1.2 Associations of Adiposity with Mortality

In general, observational studies have shown a U-shaped or J-shaped association between BMI and mortality for older adults [76]. A low BMI (underweight or thinness) increases the risk of death; though in these observational studies, the possibility cannot be excluded that underlying illnesses such as cancer or lung disease may have caused the increased mortality rate. The literature is less consistent with regard to the mortality risk associated with being overweight (BMI 25–29.9 kg/m^2) or obese (BMI 30+ kg/m^2) in old age. Some studies report an increased mortality risk for obese older adults only, while some studies report an increased mortality risk in overweight older adults. Strikingly, some observational studies even report a protective effect of obesity on mortality in older adults [77]. However, many of these studies did not exclude potential bias due to smoking behaviour and chronic disease, or they used the lowest BMI group (consisting of underweight and generally sicker, older adults who have a high mortality risk) as the reference category. These study limitations may increase the likelihood of observing a protective effect of obesity on mortality.

In a well-conducted study that eliminated potential biases and used a group with a BMI of 23.5–24.9 kg/m^2 as the reference group, being either overweight or obese increased the risk of mortality. A J-shaped association between BMI and 10-year mortality was observed in healthy men and women who had never smoked and were 50–71 years of age at baseline [78]. Even after

careful adjustment for fitness as assessed by a maximal treadmill exercise test, a J-shaped association between BMI and mortality was observed in individuals who were ≥60 years of age [79]. Based on a meta-analysis of the association between BMI and mortality in older adults that was conducted in 2007, it was concluded that being overweight did not increase mortality risk (hazard ratio [HR], 1.00; 95% confidence intervals [CI], 0.97–1.03), but being obese did increase mortality risk in older adults (HR, 1.10; 95% CI, 1.06–1.13) [76]. A recent study among healthy, non-smoking Adventists 75–99 years of age showed that a BMI >22.3 kg/m^2 in men and >27.4 kg/m^2 in women was associated with an increased mortality risk during 29 years of follow-up [80], which shows a clear distinction in the level of excess body weight between men and women from which mortality risk starts to increase.

In several studies that were conducted in the oldest older adults only, no association was observed between obesity and mortality risk and no protective impact of obesity was observed [81, 82]. The possibility cannot be excluded that the relationship between obesity and mortality differs with age or that obesity in very old age may be protective, though larger studies are needed to confirm these findings. Overall, there seems to be a general consensus that obesity in old age is associated with a higher mortality risk, with the potential exception of obesity in very old individuals, but no consensus has been reached regarding the level of being overweight at which this risk starts to increase.

Most studies that have investigated the association between adiposity and mortality used the BMI to assess adiposity. However, as discussed earlier, BMI is only a crude indicator of body fatness. Even so, only a few studies have used precise assessments of body fat mass or body fat percentage in older adults to examine their relationship with mortality. Those that have done so have also observed inconsistent results: higher body fat increased mortality risk [83, 84], decreased mortality risk [3], or was not associated with mortality risk [79, 85] in late middle-aged and older adults.

Body weight change is also an important predictor of mortality risk in older adults. In particular, weight loss and weight cycling among adults who are ≥65 years of age have been shown to increase mortality risk [39, 86–89]. Weight loss and fat mass loss increased mortality risk in ambulatory men 65–93 years of age [89]. A long-term follow-up of obese knee osteoarthritis patients who had intentionally lost weight by participating in a weight-loss trial 7 years earlier showed a 50% lower mortality rate in those who had lost weight [90]. These results suggest that unintentional weight loss—and/or the underlying disease(s)—but not intentional weight loss may increase mortality risk in older adults. Unfortunately, most of the observational studies mentioned above made no distinction between intentional vs. unintentional weight loss. Body weight gain has not been found to be associated with higher mortality risk in older adults [39, 87]. However, a study that used accurate body composition methodology showed that older men who gained ≥5% fat mass over a 4.6-year follow-up had a higher mortality risk compared to men who had a stable fat mass [89]. Because weight gain can consist of increases in fat mass as well as in muscle mass, future studies need to assess the actual changes in these body composition components to investigate their relative influence on mortality risk.

16.4.2 Body Fat Distribution

16.4.2.1 Association of Body Fat Distribution with Mobility and Disability

Several cross-sectional studies conducted in older men and women, but not all such studies [91], have shown that a higher waist circumference is associated with mobility limitations and limitations in (instrumental) ADLs [92, 93]. A study among 904 older adults showed that higher waist circumference, but not higher trunk fat as assessed by DXA, was associated with mobility performance [94]. The results of these cross-sectional studies have been confirmed using a prospective design. A high-risk waist circumference (>102 cm

in men and >88 cm in women) at baseline was associated with a higher incidence of mobility limitations and a greater increase in functional limitations and mobility limitations over time [62, 95]. The risk was especially increased in older adults who had a low level of physical activity [62]. Two other prospective studies showed a relationship between higher waist circumference and greater 2-year incident mobility disability or functional limitations at 9-year follow-up, findings that remain significant even after adjustment for BMI [96, 97]. Waist circumference has been found to be more strongly associated with a greater 5-year incidence of mobility disability and ADL disability than has BMI [98]. In contrast to the consistent results of these prospective studies that used a baseline assessment of waist circumference, the single study that assessed 5.5-year change in waist circumference showed that it was not associated with change in self-reported disability [55].

A lower density of thigh muscle as assessed by CT (indicative of greater fat infiltration into the muscle) was associated with lower knee extensor strength and higher risk of incident mobility limitations in men and women 70–79 years of age [66, 99].

16.4.2.2 Associations of Body Fat Distribution with Mortality

High waist circumference in old age is a predictor of mortality [84, 100, 101]. Even after adjustment for BMI [101, 102] or body fat measured using bioelectrical impedance [84], higher waist circumference remains an independent determinant of mortality risk in older adults. An increased mortality risk has been observed especially among individuals who have a high waist circumference but a normal BMI [101]. However, in men and women who were ≥60 years of age, the positive association between waist circumference and mortality disappeared after adjustment for cardiorespiratory fitness [79]. There are suggestions that in older adults, a high waist circumference may be a stronger predictor of mortality then is a high BMI, particularly in men [103]. Men ≥55 years of age who never smoked and were in the highest quintile of waist circumference (>101 cm) were 1.6 times more likely to die within 5.4 years compared to those with a waist circumference between 86 and 90 cm. However, men in the highest quintile of BMI (>27.9 kg/m^2) had no increased risk compared to those with a BMI between 23.1 and 24.6 kg/m^2 [103]. In contrast to the above studies, some studies have shown a protective effect of a higher waist circumference in adults 65–102 years of age [77]. A higher waist circumference was protective in men who were ≥90 years of age but not in women, though the association in men disappeared after adjustment for BMI [82].

Studies not based on anthropometric data confirm the deleterious impact of abdominal fat on mortality in older adults. In men and women ≥65 years of age, a J-shaped association was observed between relative truncal fat (the ratio of truncal fat/total body fat as assessed by DXA) and 5-year mortality [3]. In a smaller study, visceral fat as determined by CT was associated with greater 2.2-year mortality in 291 men (mean age 56 years), even after adjustment for waist circumference [104]. Overall, the evidence thus far suggests that higher levels of abdominal fat, independent of total adiposity, are associated with higher mortality risk in older men and women.

With regard to other fat deposits, a study among 934 older Italians showed that a higher density of calf muscle tissue (as assessed by peripheral quantitative CT and indicative of lower fat infiltration into the muscle) was not associated with 6-year mortality risk [85]. To our knowledge, no other studies have yet investigated the relationship between inter- or intramuscular fat and mortality risk in older adults.

16.4.3 Skeletal Muscle Mass

16.4.3.1 Associations of Skeletal Muscle Mass with Mobility and Disability

It has been hypothesized that low skeletal muscle mass in old age is associated with functional decline in older adults [53]. Using previously developed definitions of sarcopenia, several studies have indeed shown that sarcopenia is associated with poorer functional status [105–107] or

5-year functional decline [108, 109] in older adults. Strikingly, two studies have found a high muscle mass to be also associated with poorer functional status or greater functional decline [104, 109]; this is possibly due to the role of excess body fat, which is associated with greater muscle mass but poor functional status. This shows the importance of adjusting for body fatness when studying the relationship between skeletal muscle mass and functional status in old age [107, 108]. More recent studies have shown that low skeletal muscle mass is not associated with, or only weakly associated with, functional status [110–114] and that low skeletal muscle mass is not associated with future decline in functional status [66, 67]. These studies made careful adjustment for both body fat and body height. It is important to note that all of these studies showed a strong negative impact of high body fat mass on functional status in older men and women, even after additional adjustment for physical activity level. This suggests that excess body fat is a far more important determinant of functional status in old age than is low skeletal muscle mass.

The concept of sarcopenic obesity was launched in 2004 with a paper that showed that compared to older adults with no sarcopenia and normal fat levels, older adults who were sarcopenic (based on a cut-off point for appendicular skeletal muscle mass divided by body height squared) and who had a high percentage of body fat had a twofold higher risk of developing instrumental ADL disability [115]. However, more recent cross-sectional studies failed to show that a combination of low muscle mass and high body fat mass is more detrimental to functional status than is having a high body fat mass only [116, 117]. In fact, most studies have found that sarcopenia alone does not increase the risk of poor functional status [113, 116–118]. A recent study conducted in French women showed that compared to those who were obese only, those who were sarcopenic obese (defined as having a body fat percentage >40% and a skeletal muscle index <5.45 kg/m^2) tended to have a higher risk for having difficulty going down stairs [113]. However, this association was not observed for the other six physical function items that were included in the study. Based on the current literature, we cannot conclude that the combination of sarcopenia and obesity is more detrimental for physical functioning than is obesity alone. Furthermore, no evidence is available on whether the risks associated with sarcopenic obesity are higher than the summed individual risks of sarcopenia and obesity.

Although observational studies have not shown a clear association between *low* muscle mass and functional status, there are some indications that a greater *loss* of skeletal muscle mass in old age might increase disability risk. In 159 older men and women who were followed for 5.5 years, the loss of appendicular muscle mass and leg muscle mass (as assessed by DXA) was associated with a worsening in disability score [55]. Change in appendicular skeletal muscle mass over 5 years had a weak, positive association with change in physical performance measures [109]. It remains unclear whether the decline in functional status was caused by the actual decrease in skeletal muscle mass or by the involuntary loss of body weight which strongly determines loss of muscle mass [119] and decline in functional status in old age. In addition, a recent intervention study showed that after voluntary weight loss, the improvement in functional performance was more related to the loss of fat tissue at the abdomen and the thigh compared to the change in muscle tissue [120].

16.4.3.2 Associations of Skeletal Muscle Mass with Mortality

Only three prospective studies have used accurate and precise methodology to assess skeletal muscle mass for the examination of the relationship between muscle mass and mortality in older adults. Data from the Health, Aging and Body Composition Study showed that leg skeletal muscle mass (assessed by DXA) was not associated with 4.9-year mortality risk in men and women who were 70–79 years of age [121]. Low mid-thigh muscle cross-sectional area (as assessed by CT) was associated with mortality in men (HR, 1.26; 95% CI, 1.02–1.55), but this association was not observed in women (HR, 0.94; 95% CI, 0.61–

1.35). The InChianti study found that calf muscle area (as assessed by peripheral quantitative CT) was not associated with 6-year mortality among 934 older adults who were ≥65 years of age [85]. In this study, sarcopenic obesity was also not associated with an increased mortality risk. And lastly, data from 3,153 Chinese men and women who were ≥65 years of age showed that older adults with sarcopenia had a similar 5-year mortality risk to those without sarcopenia [109]. These studies consistently show that low muscle mass is not associated with an increased mortality risk.

A recent study investigated the association between change in muscle mass with aging and mortality risk. Loss of appendicular muscle mass (as assessed by DXA) during a 4.6-year follow-up was associated with increased mortality risk in 4,331 men who were 65–93 years of age [89]. Since the loss of skeletal muscle mass in older adults is highly correlated with the loss of body weight [119], the possibility cannot be excluded that the increased mortality was actually caused by the experienced weight loss and the underlying causes of this loss, including disease.

16.5 Summary

This chapter has provided an overview of the literature regarding methods for assessing body composition in older adults. Care should be taken to select the optimal body composition method—with regard to accuracy and precision—to measure the body composition component of interest and with regard to the setting and characteristics of the study participants or patients. Age-related changes in body composition are substantial, and until the age of 75–80 years they predispose to the development of sarcopenic obesity. After this age, a general decline in body weight is observed, consisting of declines in both body fat and skeletal muscle mass. It should be recognized that body composition and its changes in old age are heavily influenced by changes in body weight.

Studies have repeatedly shown that obesity in old age increases the risk of mobility limitations, disability and mortality. A higher waist circumference and more visceral fat also increase these risks (independent of overall body fatness), as do involuntary weight loss and weight cycling. The role of low skeletal muscle mass in the development of mobility limitations and disability remains controversial, but it is much smaller than is the role of high body fat. Low muscle mass does not seem to increase mortality risk in older adults.

Future studies should focus on the change in body composition as assessed by precise methodologies and using repeated assessment over time. Studies should also focus on how these body composition changes relate to healthy aging. Based on these studies, potential interventions can be developed to positively modify body composition in old age to enhance healthy aging.

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Epidemiology of Falls and Mobility Disorders

17

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Abstract

Falls and mobility disorders are common in older adults and have multiple serious consequences that include injury, disability and even death. Inconsistencies among data sources with regard to terminology and study methods create challenges in interpreting the literature on this subject. Nevertheless, the field now has an extensive knowledge base regarding risk factors, screening and preventive interventions. Since the needs of older adults vary greatly by setting (e.g., community, hospital and long-term care), so must public health services. Mobility disorders frequently overlap with falls and problems with balance. Thus, public health approaches should integrate the screening and management of falls, balance disorders and mobility problems.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Falls • Mobility Disorders • Gait Disorders • Fractures • Physical Performance • Gait speed • Balance • Disability • Self-report • Prevention • Risk factors • Injury

Abbreviations

FDA	Food and Drug Administration
LIFE-M	Lifestyle Interventions and Independence for Elders – Main
LIFE-P	Lifestyle Interventions and Independence for Elders – Pilot
SPPB	Short Physical Performance Battery
US	United States

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17.1 Introduction

Falls and mobility disorders are common in older adults and have serious consequences for individuals, families, communities and society. This chapter is intended to serve the public health community, including educators, researchers, policy makers and providers who are based in community service organizations. We will provide an overview of the current terminology related to falls and mobility, then review the frequency and consequences of falls and mobility disorders in the various settings in which older adults live. We will then present concepts and data regarding established and emerging risk factors before addressing public health approaches to screening and prevention. Finally, we will explore gaps in knowledge and explore the research agenda for the future, including critical methodological challenges that must be addressed. Our approach assumes that, in order to promote function and reduce harm from falls and mobility disorders, practitioners and investigators with public health and biomedical perspectives must interact and collaborate.

17.2 Terminology

17.2.1 Falls

Data on falls in older adults are often difficult to interpret because there are no universally accepted terms and definitions. We do not even have full agreement on what is meant by a fall event, much less on what defines an injurious fall, faller or recurrent faller. Since the 1980s, a fall event has been considered to require an "involuntary descent to a lower level", but controversy remains regarding whether all fall events should be included or whether some types of fall events should not be counted (Table 17.1). Some authorities exclude falls that are considered to be not relevant because they are due to "overwhelming intrinsic or extrinsic factors that would cause a healthy person to fall"; examples might include being hit by a car (extrinsic) or passing out (intrinsic). Others feel that falls associated with loss of consciousness should be included because they may be a common cause of falls in older adults [1].

While a person can be defined as a faller if at least one fall has occurred, there is no clear agreement regarding the length of the observation period. A recent report derived from a multinational effort [1] suggests using a period of 1 year, but many studies, especially those in healthcare settings, use time periods based on a patient's length of stay in the hospital, nursing home or rehabilitation ward. Length of stay varies in most healthcare settings, so the unit of analysis often involves a fall rate per unit of time, accounting for volume of admissions. An example would be falls per 1,000 bed-days. Obviously, a single person might contribute several falls, and the number of individuals who occupy a single bed over a period of time can vary widely.

Many other issues of terminology are even less clear. For example, what is a recurrent faller? This is often defined as having more than one fall over a time period such as 1 year, but definitions may differ when observing those with high fall rates (e.g., individuals with stroke or Parkinson's disease) who may have multiple falls in a single day. Another example is the term "injurious fall". While falls cause many types of injuries, some are harder to confirm than others. For this reason, the leaders of the above-mentioned multinational effort suggest that for large studies, injurious falls should be limited to those associated with radiologically-confirmed limb or limb girdle fractures. Others have defined a range of injuries to be applied to the definition, from bruises and cuts to sprains, fractures, head injuries and death. Injurious falls are sometimes defined as those that result in the use of medical care (e.g., the emergency department, hospital or physician's office). Fear of falling, discussed in more detail below, is also hard to define and can occur whether or not a person has fallen. Definitions of fear of falling vary widely from a positive response on a single-item query to a score on one of several scales [2].

The approach used to detect fall events is also critical for interpreting evidence. Older adults can

Table 17.1 Terminology

Term	Definition
Fall	An event in which a person descends unintentionally to the ground or other lower level
Faller	An individual who has had a fall over some period of time
Recurrent faller	An individual who has had more than one fall over some period of time
Fall injury	Harm from a fall
Fear of falling	Lack of confidence in the ability to remain upright while moving through the environment
Mobility disability	Limitations in the ability to move independently in the environment
Community mobility disability	Limitations in the ability to move independently outside the home
Serious mobility disability	Limitations in the ability to move around inside the home or other living setting
Severe mobility disability	Inability to walk

be asked about falls either retrospectively or prospectively. Since prior falls are easily forgotten over time, prospective systems are considered to be more reliable. Most prospective systems start with an orientation to the definition, accompanied by diaries, calendars and/or post cards. These are supplemented as needed by telephone reminders. More recently, modern communications technology has made it possible to use automated telephone systems for monitoring. Falls can also be reported by others, such as caregivers in the home or staff in healthcare settings. In some healthcare settings, video monitoring can be used to detect falls. Many healthcare settings have created safety monitoring reporting systems that allow fall data to be tracked and evaluated in an ongoing fashion. Falls can also be detected through healthcare or insurance billing records, but many older adults do not report falls to their doctors and the billing codes for falls are used in an inconsistent fashion. New wearable digital devices use a variety of accelerometers and gyroscopes to track sudden changes in position that might indicate a fall.

17.2.2 Mobility Disorders

Mobility is the capacity to move around independently in the environment. Typical human mobility is bipedal (depending on just the two lower limbs) and is defined primarily by the ability to walk. Problems with mobility have been termed "dysmobility" or "mobility disability", which include several levels of severity (Table 17.1). Dysmobility is most typically considered to be present if there are limitations or difficulty with walking. Serious or in-home mobility disability could be considered to be present if there are limitations in the capacity to get around inside the home or other living settings. Community mobility disability could be considered to be present if there is difficulty getting around outside the home, or in the neighborhood or community. An even more severe form of mobility disability is important in hospitals and long-term care settings: the inability to walk at all. In non-ambulatory individuals, the capacity to transfer from bed to chair or toilet, and the capacity to independently move a wheelchair, is critical for some degree of independence.

Mobility disability can be detected by self-report, professional report or by physical performance tests [3] (Table 17.2). Self-report can be based on single items that query difficulty or dependence in walking, or on questionnaires that focus on lower-extremity function. Another approach to detecting mobility by self report is to ask about life space, which reflects the frequency and extent of ability to travel around the environment [4]. Several professional assessments, such as the Barthel Index or Functional Independence Measure, are commonly used in rehabilitation and home health settings to characterize mobility disability. Reports can also include the use of mobility assistive devices such as canes, walkers and wheelchairs. Physical performance measures

Table 17.2 Approaches to detection of falls and mobility disorders

Approach	Examples
Falls	
Retrospective self-report	Survey questions about fall history
Prospective self-report	Diaries, calendars
Observer report	Nursing home and hospital adverse event reports
Physical performance tests	Timed up and go, functional reach, tandem stands
QuickScreen physical assessment	Vision, sensation, tandem stand, stepping, sit to stand
Wearable electronic monitoring	Accelerometers, gyroscopes
Environmental electronic monitoring	Video cameras, floor sensors
Medical information systems	Billing codes, discharge diagnoses, nursing home minimum data set
Mobility disability	
Single-item self-report	Items in functional status measures on overall mobility
Self-report by questionnaire	Multiple item scales with overall scores
Professional report	Scales used in rehabilitation
Physical performance: 400 m walk	Time to walk 400 m
Physical performance: 6 min walk	Distance walked in 6 min
Physical performance: SPPB	Score on three mobility tasks (walking speed, chair rise and 3 balance positions)
Physical performance: walking speed	Time to walk a short distance such as 4, 6 or 10 m reported in meters per second

have also been used to detect mobility disability. One definition of mobility disability that is based on performance is the inability to walk 400 m. In the rehabilitation of conditions such as stroke, a walking speed of 0.4 m/s is considered important for mobility within the home, and 0.8 m/s for community mobility. A Short Physical Performance Battery (SPPB) score of ≤9 is considered evidence of limited mobility, and a score of ≤6 evidence of more serious mobility disability [5]. More recently, accelerometers and global positioning devices are being employed to detect activity levels and infer mobility capacity.

The timing and duration of mobility disability can vary, which can influence reports of incidence and prevalence. Mobility disability onset can be gradual or acute, sometimes termed progressive or catastrophic [6]. Once it has occurred, it is not necessarily a chronic condition, but can rather be intermittent with periods of decline and recovery. Therefore, mobility disability is now considered a dynamic rather than a static state [7]. A period of mobility disability might last from days to a lifetime. Persistent mobility disability can be considered to be present if it has lasted at least 6 months.

Given the heterogeneity of definitions, time frames and detection methods for falls and mobility disorders, evidence should be examined carefully for how the condition of interest was defined and detected. Variability among studies may be explained at least in part by differences in how they approach these issues.

17.3 Consequences

17.3.1 Falls

The consequences of falls are far-reaching. Falls are the fifth leading cause of death in older adults and the leading cause of accidental death and unintentional injuries in individuals ≥65 years of age [7, 8]. About 22–60% of falls result in injury and 10–15% in serious injury, which includes all types of fractures as well as other major health threats such as head injury [8, 9]. Falls are a major contributor to the over one-half million hip fractures that occur each year in the United States (US). Other fractures of the upper and lower extremities and pelvis are often related to falls. Falls are a major source of head injury, and

head-injury-related falls account for almost half of all deaths from falls [10]. While less medically serious, joint dislocations, sprains, bruises and lacerations may require medical management and cause significant discomfort. Regardless of the type of injury, about 25% of individuals who fall require medical attention. Falls contribute to 14–40% of emergency department visits in older adults [8, 11]. One-third to two-fifths of emergency department visits for fall-related fractures or internal organ injuries require long-term care admission either directly or following hospitalization. The risk of hospitalization increases proportionally with the number of falls. An individual who has a single fall has a one-in-five chance of hospitalization, which doubles with subsequent falls. Falls are the leading cause of accidents in the acute-care setting [11] and increase the probability of admission to a nursing home [12].

Psychological and behavioral consequences of falls include fear of falling, reduced activity, social isolation and loss of functional independence. Falls evoke significant anxiety and fear, causing social isolation and functional decline with subsequent cognitive deterioration, depression and reduced quality of life [8, 9]. The "post fall syndrome," characterized by decreased activity, physical deconditioning, gait dysfunction and reduced balance and coordination, increases the risk for future falls, loss of independence, disability and ultimately nursing home admission.

The economic cost of falls to society has direct and indirect components. In the US, direct costs for all fall-related injuries in the 1990s was estimated to be near $20 billion annually or over $7,000 per injured faller [10, 13]. Major sources of costs were hospitalization and nursing home care. With the expected growth in the older adult proportion of the population throughout the world, fall-related costs are projected to increase three-fold in the coming decades. Although injurious falls clearly lead to high healthcare costs, non-injurious falls are also expensive, with an increased risk of nursing home admission and ancillary home services. In one study, community-dwelling individuals who had one or multiple non-injurious falls over a 3 year time period were three to five times as likely to be admitted to a nursing home compared to individuals who did not fall. [12]. Despite lack of injury, these fallers had longer hospital stays, higher overall hospital costs and were three times more likely to be admitted into a nursing home compared to non-fallers. Indirect costs of falls may include loss of income when an employed family member reduces their work role to care for an older adult faller. Other indirect expenses may include the need for home modifications.

Epidemiological studies have largely been performed in first-world countries, with most reporting generally similar types and rates, or consequences [8]. In 1999, the estimated cost of falls in the United Kingdom was almost one billion pounds per year, and the estimated cost in Australia was $333 million Australian dollars. Internationally, fall-related costs are estimated to consume 0.85–1.5% of the GDP [9].

17.3.2 Mobility Disorders

Similar to falling, the loss of mobility leads to functional limitations, the need for human help, social isolation and increased healthcare costs [3]. Poor performance on mobility tests predicts future self-care difficulty and mobility disability. Among community-dwelling older adults >70 years of age who have no baseline self-care disability and no higher level of self-reported difficulty in the ability to walk one-half mile and climb stairs, the baseline short physical performance score was a powerful predictor of incident disability in both activities of daily living and higher-level mobility disability [5]. Mobility self report and performance have been shown to predict disability and mortality in older populations from numerous countries and cultures worldwide.

A slow walking speed is associated with an increased risk of disability, hospitalization and death. For example, in a 75-year-old man, the probability of surviving 10 years ranges from less than 20% to over 80% depending on walking speed [14]. Poor mobility performance also predicts healthcare utilization, including hospitalization and nursing home placement [15, 16]. In a

population-based study of nondisabled older adults, a poor baseline physical performance score doubled the risk of hospitalization and was associated with more days in the hospital over a four–year period, and the risk was independent of baseline health status. Hospitalization was especially related to such geriatric conditions as dementia, pressure ulcer, hip fractures, other fracture, pneumonia and dehydration.

Poor mobility could be considered a core risk factor for multiple geriatric syndromes, including incontinence, delirium, falls and functional decline [17]. In contrast, good mobility is an independent predictor of recovery of independence after a period of disability [7]. Abnormalities of gait and slow gait speed have been found to precede the onset of cognitive decline and dementia, especially vascular dementia [15, 18].

Severe mobility disability, especially being limited to bed, is a dangerous condition. Becoming bedbound induces rapid and deleterious changes in bone, muscle, heart, circulation, lung, skin, blood, bowel, kidney, nutrition and metabolism [3]. This loss can be remarkably fast and severe; muscle strength can decline by 1–5% per day of enforced bed rest. Skin breakdown and pressure ulcers start to occur after only hours of persistent and unrelieved pressure. Thus, even temporary and brief periods of bed rest—as commonly occur during hospitalization—combined with acute illness and aging greatly increase the risk of death, disability and institutionalization.

17.4 Descriptive Epidemiology

17.4.1 Falls

Fall rates vary greatly depending upon age and setting. From 20 to 40% of community-dwelling older adults ≥65 years of age fall each year [8, 9]. Rates increase with age and can exceed 50% in those >85 years of age. About one-quarter of fallers have more than one fall over a year. Women are more likely to be fallers than men. Individuals of Asian descent may have lower rates than Caucasians, while some reports suggest higher rates in African-Americans and Hispanics. Socioeconomic factors such as low income, limited education and worse housing conditions also increase the risk for falls. Fall rates appear to increase seasonally with winter weather. Many falls occur within the home, in the bedroom or in the bathroom. Fall rates increase markedly in settings that serve older adults who have disability. In home health settings, up to one-third of older adults will fall during an episode of service, while the rates can be even higher in rehabilitation settings. Fall rates in nursing homes and hospitals tend to be reported as events per 1,000 bed-days. Across several studies based in long-term care, fall rates ranged from 600 to 2,900 per 1,000 bed days, while in general hospitals that serve all types of patients of all ages, fall rates range from 4 to 14 per 1,000 bed days [19].

17.4.2 Mobility Disorders

Rates of mobility disability vary greatly by setting and definitions. In the community, about 5% of older adults ≥65 years of age need help with transfers in and out of a chair or bed, while about 7.5% need help to get around within the home [3]. In long-term care settings, almost four out of five older adults need help with transfers or with getting around within the facility. Mobility disability increases dramatically with age; mobility problems within the home increase from 5% at age 65 to 30% at age 85. Women have higher rates of mobility disability than do men, and nonwhites have higher rates than do whites. In-home mobility disability can have a gradual or acute onset. Over half of all in-home mobility disability has a gradual onset, and the proportion increases with age and in the presence of multiple chronic conditions.

About 13% of community-dwelling older adults report difficulty with mobility outside the home, with rates increasing with advancing age. Interestingly, rates vary geographically, with higher rates in the southern US compared to other regions. Again, rates are higher with women than with men. As opposed to community fall rates, which seem to be somewhat constant over recent decades, rates of mobility problems outside the home may be decreasing over time.

17.5 Classic and Emerging Risk Factors

17.5.1 Classic Risk Factors for Falls

The literature regarding risk factors for falls has now been accumulating for over 20 years, and hundreds of factors have been identified. The field now offers numerous summaries of the frequency and impact of these risk factors [8, 9]. Risk factors for fall injuries are largely the same as for all falls, though injury risk is also influenced by factors such as osteoporosis and prior injury. Risk factor identification faces a wide range of methodological challenges that influence the ability to interpret the evidence. These methodological issues are described in more detail in Sect. 17.7.

17.5.1.1 Mobility and Balance as Core Indicators of Fall Risk

The greatest risk factors for falls are a history of falling and evidence of problems with balance and mobility. As with many other adverse events (e.g., myocardial infarction or hip fracture), having experienced the event once increases the risk of further events. The fall is probably not directly causing more falls, but rather is a powerful summary indicator of the presence of multiple risk factors. Most falls are a direct consequence of problems with balance and mobility, and in this sense many risk factors for falls work through their effect on balance and mobility [20, 21]. Interestingly, the relationship between risk of falling and the severity of mobility and balance disorders is not linear. Rather, the curve is shaped like an upside-down U; low at both ends and high in the middle (Fig. 17.1). Individuals who cannot independently move their bodies are unlikely to fall unless they are dropped and individuals who have a very high capacity for mobility and balance are sufficiently skilled to avoid many falls. Thus, fall rates appear to be highest in individuals who are mobile and unsteady, and fall rates are lower in individuals who are either not mobile or are mobile and have good balance.

17.5.1.2 Factors That Contribute to Poor Mobility and Balance

There are numerous causes and risk factors for poor balance and mobility. Multiple body systems are needed to remain upright while moving, which is one way to describe what we mean by balance [22]. Balance is influenced by three main domains: sensory systems, central nervous system integration and effector outputs that carry out instructions from the brain. Sensory systems that affect balance and have been shown to be risk factors for falls include low vision, peripheral neuropathy and vestibular disorders. There are several aspects of vision that are important for monitoring the environment, including acuity, peripheral vision, depth perception and dark adaptation. Some studies have found that the use of bifocal lenses can increase fall risk because the focal length is either fixed for reading or distance but not for monitoring the ground.

Multiple brain processes are important for balance. Any cardiovascular condition that affects perfusion of the brain can contribute to falls. Thus, studies have found that orthostatic hypotension, certain cardiac arrhythmias and some kinds of cardiac valve disease might affect brain perfusion and contribute to falls. Alterations in alertness, attention and reaction time are risk factors for falls. Thus falls risk is increased in individuals who have cognitive impairment, especially in non-memory cognitive functions called "executive functions" that involve planning, sequencing, judgment and visual spatial abilities.

Medications can have strong effects on key cognitive functions such as reaction time and attention. The highest risk categories of medications are psychoactive formulations such as sedatives, anti-anxiety and antipsychotic agents and analgesics [23, 24]. The brain is also responsible for a variety of automatic reactions, called postural responses or righting reflexes, which are evoked when a person is beginning to lose their balance. These reactions are lost in conditions such as Parkinson's disease and some types of dementia, which are associated with a high risk of falling. Effector factors that can influence balance and mobility include joint function, musculoskeletal pain, muscle strength and endurance.

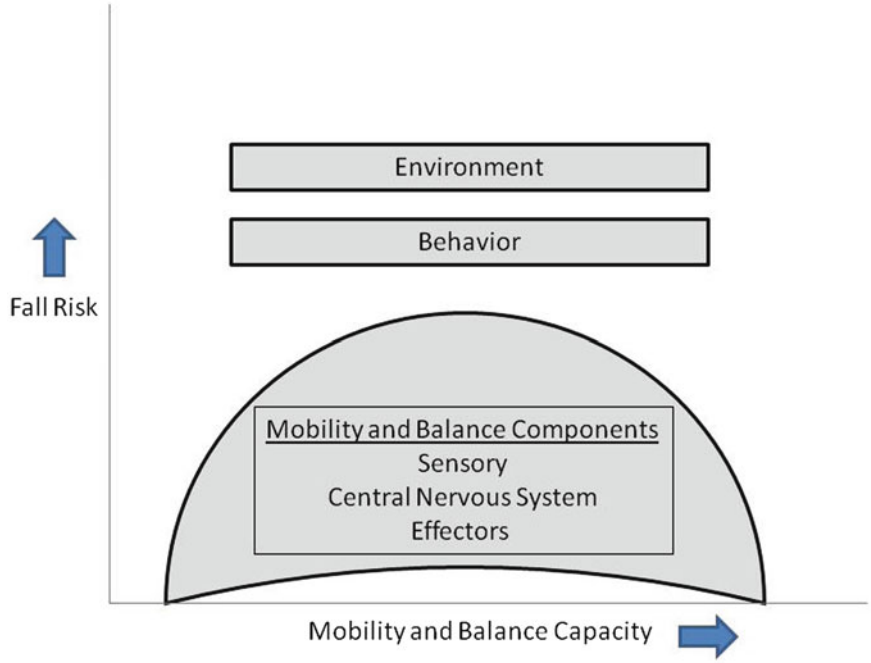

Fig. 17.1 Sample model of fall risk

Some studies have found that the use of certain types of footwear, especially loose slippers or high-heeled shoes, may increase fall risk [25].

Each of these factors can be assessed using measures that can be performed in the field (Table 17.3). Lord et al. [8] developed a package of tests—the Physiological Profile Assessment—which assesses many of these factors. There is also a short form called the QuickScreen (Tables 17.2 and 17.3).

Many of these physiological systems provide supplemental and compensatory resources to each other. Thus, individuals who have limited vision may be adept at avoiding falls if their other sensory systems and cognitive functions are intact. Balance worsens and fall risk increases as impairments accumulate and potential compensatory strategies become more limited.

17.5.1.3 Behavioral Factors That Affect Fall Risk

Cognitive impairment and depression increase fall risk. In addition, there appear to be personality factors that affect risk. Some older adults may choose to avoid falls at any cost and so voluntarily restrict activity, which might reduce fall events but also unintentionally worsens deconditioning and social isolation. Some may be unwilling to depend on others and so persistently engage in a range of activities that increase the risk of falls. This conflict within the individual could be considered a type of "risk preference" or personal decision-making that weighs conflicts between safety and autonomy [21]. Fear of falling can become a serious problem in some older adults who become terrified to move and may become completely unable to walk. At times, fear of falling can increase fall risk if the individual reacts to fear by becoming rigid and unable to react when beginning to lose their balance. There are multiple assessment tools to assess balance confidence and fear of falling [2]. Problems with judgment and risk-taking probably affect fall risk most in individuals who have problems with mobility and balance.

17.5.1.4 Environmental Factors

Environmental risk factors within the home include loose carpet, poor lighting, slippery floors, variable stair step heights and depths, lack of handrails, raised doorsills, unstable furniture,

Table 17.3 Body systems that contribute to balance and mobility

System	Screening tests
Sensory	
Vision	Acuity at short, medium and longer distances, depth and fields by confrontation
Vestibular	Difficult to test clinically
Somatosensation	Filaments, vibratory sense
Central Processing	
Brain perfusion	Orthostatic blood pressure
Attention and alertness	Reaction time, dual tasks, timed rapid alternating movements
Automatic postural reflexes	Righting reflex
Effector systems	
Bones and joints	Range of motion
Strength	Isometric strength with dynamometers
Endurance	Long distance walk or step ups
Combined: physiologic profile assessment [8]	Includes visual acuity, visual contrast sensitivity, depth perception, tactile sensitivity vibration sense, proprioception, isometric lower extremity strength, reaction time, postural sway, maximal forward and backward lean, coordinated stability

tripping hazards and assistive devices that are in poor repair [8]. Community environments also present hazards such as irregular sidewalks, sloping ramps with insufficient friction and poorly marked stairways and curbs. The ability to cope with environmental challenges decreases as balance and mobility decrease, so even small environmental problems can exacerbate fall risk in vulnerable older adults.

17.5.2 Novel and Emerging Risk Factors for Falls

Recent research has focused on other important and previously unrecognized potential risk factors, and especially on the detection of more subtle subclinical abnormalities that contribute to falls. We summarize the findings to date below.

17.5.2.1 Dual Task Performance and Subclinical Deficits in Cognition and Gait

While typical balance assessments are performed under simple conditions with unobstructed walkways and full attention to the task, many falls occur in more complex environments under conditions where the individual must simultaneously attend to multiple stimuli. Thus there has been an increased focus on the ability to move while performing more than one task simultaneously. Originally described as "stops walking while talking", there are now multiple studies that have reported reduced performance in a variety of walking and balance tasks while simultaneously performing a cognitive task [26, 27].

Subtle cognitive deficits in areas not related to memory and Alzheimer's disease have been found to be associated with increased risk of falls. The cognitive domains most associated with fall risk include psychomotor speed, divided attention, motor sequence planning and visual monitoring. Some fallers have been found to perform well under simple walking conditions, but present more abnormalities when attempting challenging tasks such as stepping over obstacles, walking while carrying objects or negotiating curved pathways [28, 29].

Subtle alterations in walking may be early risk factors for falls. Beyond usual characteristics such as step frequency, step length and double support time (time spent with both feet on the ground), novel indicators of subtle gait alteration include step-to-step variability in the spatial and temporal aspects of walking and alterations in the smoothness of movement [26, 30].

A picture is emerging of falling associated with abnormal movement planning and cognitive impairment in the domains of attention and psychomotor speed that may be related to subclinical brain disorders of aging that have previously been poorly characterized [31–34]. These abnormalities, found on magnetic resonance imaging of the brain, are characterized by increased volumes of periventricular "white matter disease" and decreased gray matter volumes in the frontal and parietal lobes.

17.5.2.2 Pain

The potential role of pain as a risk factor for falls has emerged only recently. It is possible that some of the risk attributed to the use of analgesics is an example of reverse causation, where use of analgesics is a marker for pain and the pain itself is itself contributing to falls. Both the severity of pain and the number of pain locations in the body appear to contribute to fall risk after adjusting for multiple potential confounders, including the use of analgesics [35].

17.5.2.3 Anemia

Anemia is a common condition in older adults. Previously, it was thought that unless anemia was severe, it had no important effects on current health and function. More recently, anemia has been found to be associated with falls and mobility disorders, even after adjusting for multiple potential confounders. Anemia might contribute to falls due to its effects on fatigability, strength and physical function [36].

17.5.2.4 Alcohol Abuse

Alcohol use is known to be associated with unintentional injuries and falls in young and midlife adults. Heavy alcohol use and abuse among older adults is more common than previously recognized and is often not explored as a possible risk factor for falls in older adults. More recent studies suggest that heavy alcohol use may be an independent contributor to falls. There is also speculation that the combination of alcohol and psychoactive medications might be an important but unrecognized risk factor [37].

17.5.2.5 Vitamin D Deficiency

The role of vitamin D in optimal neuromuscular function and balance has become one of the major novel avenues of inquiry in the field of falls prevention. Low levels of vitamin D are common in older adults, especially those who spend little time outdoors in the sun. While there are numerous ongoing areas of disagreement regarding how to define a normal vitamin D level, who to treat and how to treat, there is growing evidence that vitamin D may play an important role in falls prevention. Vitamin D has been found to be important not only for healthy bones, but also for healthy muscles and nerves. It has even been suggested that vitamin D receptors may play a critical role at the neuromuscular junction, which is the main way-station for neurological signals to reach muscles. Multiple observational studies have found a relationship between vitamin D and falls [38].

17.5.2.6 Sleep Disorders

Sleep disorders, whether of insufficient, excess or fragmented sleep, are increasingly recognized as common in older adults and as important potential contributors to many adverse health states. Common sleep problems of aging include insomnia, sleep-disordered breathing (of which one common form is sleep apnea) and daytime sleepiness. There is emerging evidence that, as with the relationship with pain and analgesics mentioned above, there may be a reverse causation element in the known association between sedatives and falls. Since many people take sedatives because they have insomnia, it is possible that the sleep deprivation is contributing to inattention and falls separately from the medications [39]. Observational studies have demonstrated associations of falling with insomnia, too much sleep, too little sleep, and indicators of sleep-disordered breathing [40].

17.5.2.7 Diabetes and Other Chronic Diseases

Fall risk is increased in the presence of conditions such as diabetes, stroke, Parkinson's disease and dementia [39, 41–44]. This risk is likely due to the

impact of the disease on the systems that contribute to balance, as described above. Thus, diabetes may contribute to falls via its effect on peripheral nerves, vision, and through diabetes-related circulatory damage to critical brain functions.

17.5.3 Risk Factors for Mobility Disorders

Since falls, balance disorders and mobility disorders overlap greatly, their risk factors overlap greatly as well. Problems with walking are associated with sensory, brain, joint and muscle problems, as well as with deconditioning and cardiopulmonary contributors to low fitness [22]. Some factors that are associated with a risk of mobility disability, but have a less clear relationship with falls, include obesity and sarcopenia. Obesity, especially with a body mass index over 35, has been associated cross-sectionally with mobility limitations by self-report and performance, and longitudinally with greater declines in mobility [45]. Sarcopenia, defined as reduced muscle mass and strength, is associated with poor mobility and mobility decline [46]. While muscle weakness has a clear association with both falls and mobility problems, the link between falls and low muscle mass has not yet been explicitly demonstrated. The combination of obesity with inadequate muscle mass and strength has been called sarcopenic obesity, and it is an especially important risk factor for mobility disability. Sarcopenia is associated with a range of potential causal factors, including deficiencies of testosterone, growth hormone and certain nutrients [46]. Recent studies of walking have more fully characterized subtle changes in walking that are associated with gait variability, cognitive impairment and subclinical brain disorders, as described above. Vitamin D deficiency appears to play a role in reduced mobility.

17.5.3.1 Acute vs. Gradual Onset of Mobility Disability

Mobility disability can have a gradual or acute onset. Risk factors for gradual onset include advanced age and multiple chronic conditions. Acute onset is associated with stroke, hip fracture and cancer, but not with heart attack. These medical conditions account for only about half of acute onset mobility disability cases [6].

17.5.3.2 Intermittent vs. Persistent Mobility Disability

Mobility disability is dynamic and can be intermittent, persistent or even resolve over time. Factors that are associated with an increased likelihood of persistence and reduced likelihood of recovery include female gender, older age and worse baseline walking speed [7].

17.6 Public Health Approach to Screening and Prevention

Public health approaches to the prevention of falls and mobility disability can be based on primary, secondary or tertiary targeting strategies (Fig. 17.2). For the purpose of defining the types of prevention strategies, we must define the adverse event to be prevented and the risk factors to be detected early. Within our thematic area, the serious adverse outcome events that require preventive action include recurrent falls, fall injuries and mobility disability. The underlying pathological processes that might be detected early are gait and balance impairments. In this framework, the goal of primary prevention is to prevent or delay the onset of gait and balance disorders, with the ultimate goal of delaying, reducing and/or preventing falls, fall injuries and mobility disability. The goal of secondary prevention would be to identify individuals who have an increased risk of falls and mobility disability due to abnormalities of gait and balance, or perhaps a history of non-injurious falls. Tertiary prevention would involve efforts to restore gait and balance, and prevent future serious adverse outcome events among individuals who have already had multiple falls, fall injuries or who have mobility disability.

As is true elsewhere in public health, it is important to design interventions that are efficient.

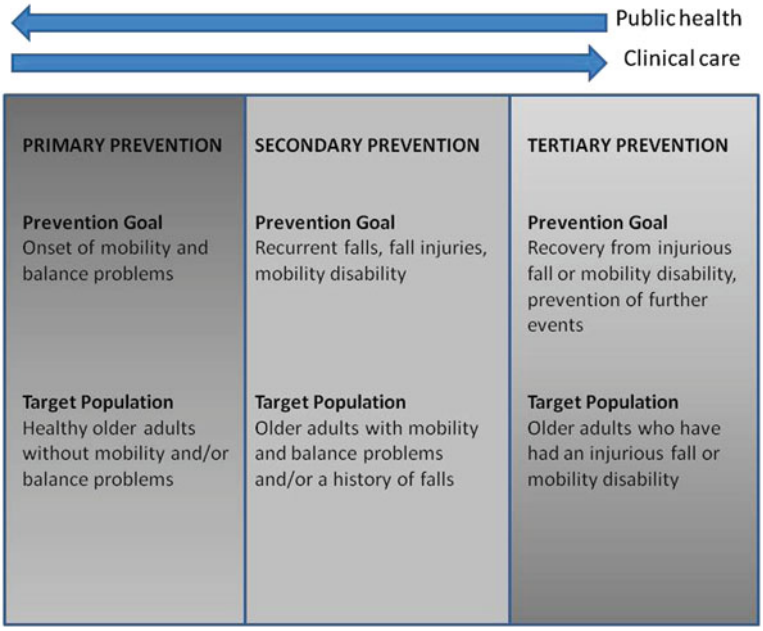

Fig. 17.2 Primary, secondary and tertiary prevention of falls and mobility disability

Efficient primary preventive interventions that involve large portions of the population should be inexpensive, safe and very convenient. Increased demands for resources and time should be linked to an increased targeting of those at risk and those with potential for benefit. In addition, as the underlying pathological processes become more advanced and complex with secondary and tertiary prevention, there is an increased need for input from clinical healthcare systems and health professionals regarding highly individualized evaluation and treatment. With these concepts in mind, we will now look at evidence regarding the effectiveness of interventions to prevent falls and mobility disability.

17.6.1 Screening and Prevention for Falls

Since older populations are exceptionally heterogeneous, it is especially important for the goals of preventive interventions to be linked to the needs of the target population. For fall prevention, needs vary based on setting and are related to the goals of primary, secondary or tertiary prevention. Community-based interventions can have any of the three sets of preventive goals, depending on whether the population to be addressed has gait and balance problems and/or a history of falls. Healthcare settings are more likely to have higher proportions of individuals with risk factors and a history of falls or fall injuries, and also much higher probabilities that risk factors such as gait and balance may change rapidly. Long-term care settings probably have the lowest probability of serving individuals who do not have gait and balance problems, but have a much higher likelihood of needing tertiary preventive services.

17.6.1.1 Primary Prevention of Falls

Primary prevention would largely target community-dwelling older adults who have not fallen and who have normal gait and balance, and would aim to prevent or delay declines in balance and reduce the incidence of falls. Many clinical trials of exercise, including elements of aerobic, resistance and balance, as well as combined programs, have demonstrated short-term gains in gait and

balance, but few have had sufficient follow-up to determine whether the intervention delays declines or prevents falls [47, 48]. Integrated forms of exercise, such as music and dance, have also demonstrated gains [48, 49]. Tai Chi has been shown to prevent falls, but not to consistently improve balance in healthy older adults [47, 48]. In most cases, home safety education has not been shown to reduce falls in healthy older adults. These types of interventions can be efficient in that they can be provided to groups rather than to individuals, they depend on community leaders with a range of expertise, and they are often implemented using tools of health education and self-monitoring.

17.6.1.2 Secondary Prevention of Falls

Most of the research on fall prevention has targeted high-risk populations based on some combination of risk factors. Since a history of falls is one of the most commonly identified risk factors, the preventive goal is to reduce the incidence of further falls and fall injuries. Risk can also be based on the identification of individuals who have impaired gait and balance. There are a number of available tools for screening for fall history and poor gait and balance, based on such simple performance tests as the Get Up and Go test, the SPPB or even just gait speed. The Physiologic Profile Assessment or QuickScreen of Lord et al. can be used for screening, but it is also useful for identifying contributing physiological abnormalities that might be used to individualize interventions (Tables 17.2 and 17.3).

Exercise to prevent falls in community-dwelling older adults who have gait and balance impairments can include strengthening, balance practice, functional activities, Tai Chi and/or dance [48–51]. Since the characteristics and causes of the gait and balance impairments vary in this very heterogeneous population, there is often a greater need for skilled professionals to define, implement and supervise the exercise program [47, 52]. There is also a greater need for individualization, which necessitates smaller groups and one-on-one attention. Many of these programs have demonstrated short-term improvements in gait and balance, and many also demonstrate a reduction in the incidence of falls. Again, most have not been of sufficient duration to determine whether decline is delayed over time or whether the intervention has a longer-term benefit regarding falls reduction. Many authorities believe that exercise interventions should combine multiple elements of strength, endurance and balance, and that practice should include integrated functional activities.

Vitamin D supplementation is emerging as a potentially useful intervention for falls prevention [19]. While some meta-analyses of completed clinical trials suggest an overall benefit for falls reduction, others do not. There are also recent concerns regarding the appropriate dosage.

Secondary prevention can also include other aspects such as medication review, home safety evaluation by a professional, evaluation and management of footwear, vision aids and assistive devices [52]. Some of these strategies have been tested as isolated interventions (e.g., vision correction [53], medication review [23] and podiatry services [54]), but many are implemented as part of a combined package. These multifactorial interventions often begin with a screen for risk factors, followed by an individually-tailored set of interventions [47]. Meta analyses by reputable groups have confirmed that multifactorial fall prevention interventions are effective [47]. Some authorities—but not all—believe that for high-risk individuals, combined interventions are more effective than exercise alone.

Secondary prevention is also implemented in care settings such as hospitals, nursing homes and home health agencies [55–59]. These interventions almost always combine multifactorial strategies with individual tailoring of the care plan. In addition to the elements described for community-dwelling older adults, interventions in care settings include actions by care staff such as supervised toileting, the use of technology such as bed alarms, and environmental design of flooring and doorways.

Secondary preventive strategies are obviously more resource intensive and thus depend on both effective targeting and intervention efficacy to justify their cost.

17.6.1.3 Tertiary Prevention of Falls

Tertiary prevention should be targeted at older adults who have already had multiple falls and/or fall injuries. Appropriate populations often have serious underlying impairments to gait, balance and sometimes cognition; common examples include older adults who have had hip fracture [60], a diagnosis of Parkinson's disease [41] or stroke [42]. Interventions are often delivered as a component of rehabilitation or post-acute care. These interventions are increasingly complex and require collaborations among medical, rehabilitative, psychosocial and community professionals to implement highly individualized plans of care. For example, in the case of hip fracture, plans of care to prevent further injuries must include elements that target not only bone health, but balance and gait as well. Many such interventions, whether for hip fracture, stroke or Parkinson's disease, require specific and skilled planning of therapeutic medications, exercise, assistive devices, caregiver training, home safety and management of other contributing risk factors. In such cases, interventions that do not include a comprehensive approach may actually increase falls and fall injuries. For example, Parkinson's medications can increase confusion and orthostasis, and thus increase falls. Increased activity as a result of rehabilitation for stroke can also increase falls.

17.6.2 Novel Preventive Interventions for Falls

17.6.2.1 Cognitive Interventions

Some non-memory cognitive deficits that might contribute to fall risk may be modifiable. For example, it may be possible to improve psychomotor speed, visual monitoring or attention levels during dual tasks. Emerging evidence indicates that dual task practice might improve performance of dual tasks, computer-based cognitive practice might affect gait speed and some measures of balance, and medications that enhance cognitive function might improve walking, balance and reduce fall rates [61]. There is not yet any strong clinical trial evidence that such interventions can prevent falls or fall injuries on their own.

17.6.2.2 Motor Control Exercise

Since balance is essentially the ability to remain upright while moving, a key element is motor control, or the ability to plan and sequence motions. This integrative brain activity involves highly over-learned motor skills which are then incorporated unconsciously into everyday movement planning. These motor control skills can be lost with aging and disease, and may be trainable with specific types of exercise that challenge movement timing and sequencing. Such forms of exercise can improve aspects of gait and balance, but have not yet been formally tested for effects on fall reduction [62]. Similarly, there is an emerging interest in the role of music and dance to not only enhance adherence but also to further integrate motor control and planning into exercise programs [50].

17.6.2.3 Technology and Equipment

Technology and equipment have the potential to help prevent falls and injuries in ways that are complementary to improving the health and function of the individual. Modern electronic technology is producing multiple novel devices for the noninvasive monitoring for fall risk and falls. Thus, there are a whole family of "smart homes" and wearable systems that can detect alterations in balance and falls. These systems detect motion and falls, but do not directly prevent falls. Several forms of harnesses have been developed to prevent rapid descent and injury, but they are largely too inconvenient for use in most settings. While in the past, restraining systems such as bed rails and physical body restraints were widely used in hospitals and nursing homes to prevent falls, it has been found that they failed to prevent many falls and their use has been associated with other adverse consequences. Currently, restraining systems are considered to be inappropriate elements of fall prevention in most settings.

Protective clothing may help prevent injuries from falls. Hip pads have become widely used in nursing homes and other settings that care for highly vulnerable populations [63]. Controversy remains regarding the efficacy of these devices, with some meta-analyses suggesting a detectable benefit in terms of reduced rates of fractures.

However, a recent large multisite trial with an elegant design based on the use of a hip pad on one but not the other hip showed no overall reduction in the rate of fracture of the padded compared to the unpadded hip.

17.6.2.4 Broad Community Initiatives

A key next step in prevention is to broadly implement programs in the community [8, 64, 65]. Such programs, representing partnerships between community service agencies, public health departments and sometimes healthcare providers, can offer widespread screenings, group education and exercise programs, and referrals for health care services. Programs are being implemented and evaluated across the globe. Other partnerships are being built between emergency departments, first responders, community agencies and home health agencies. To date, initial findings regarding effectiveness are mixed, with a continued need to refine program elements to improve targeting, adherence to recommendations and the knowledge and skills of the health professionals who receive referrals.

17.6.3 Screening and Prevention for Mobility Disorders

Since falls and mobility disability share many risk factors, they also share many preventive intervention approaches. Thus, interventions for the prevention of mobility disability tend to focus on exercise in primary and secondary strategies, while tertiary strategies form the basis for rehabilitation. Other target risk factors could include obesity, pain management and the use of assistive devices.

17.6.3.1 Primary Prevention of Mobility Disability

An extensive literature demonstrates the broad benefits that older adults can gain from physical activity such as aerobic and strengthening exercise [66, 67]. In the short term, there are gains in strength, fitness, walking distance and walking speed, as well as a range of physiological benefits to risk factors for heart disease, diabetes and other chronic conditions. While some long-term follow-up of exercisers and non-exercisers suggests that physical activity prevents mobility disability, most formal clinical trials have not been able to maintain randomization for long enough to confirm that it is the exercise itself rather than the overall health of the individual that caused the benefit.

17.6.3.2 Secondary Prevention of Mobility Disability

Fitness and strength training can improve mobility performance and perceived mobility in individuals who have an increased risk of mobility disability, including those who have poor mobility performance and those whose mobility limitations are due to conditions such as arthritis, heart failure, peripheral vascular disease or emphysema. There have not yet been clinical trials of sufficient duration or size to demonstrate that exercise can reduce the incidence of the main adverse outcome of mobility disability. The ongoing large multisite Lifestyle Interventions and Independence for Elders – Main (LIFE-M) trial is designed to answer this question. It builds on the evidence for feasibility and short-term benefits from the pilot (LIFE-P) trial [68].

17.6.3.3 Tertiary Prevention of Mobility Disability

One main focus of rehabilitation services is the restoration of mobility in individuals who have mobility disability. Thus, there are extensive clinical services and evidence bases for the efficacy of rehabilitation exercise and comprehensive rehabilitation services to restore mobility after a disabling event or condition such as a hip fracture, stroke or Parkinson's disease [41, 42, 60]. In general, the types, intensities, timing and duration of exercise interventions are quite heterogeneous, and the effects on mobility disability are modest and only assessed over time frames of months. These interventions tend to focus on acute-onset mobility disability. There is not yet an evidence base for the efficacy of interventions to recover from more gradual-onset mobility disability.

17.6.4 Novel Prevention Interventions for Mobility Disorders

17.6.4.1 Prehabilitation

Individuals who have mobility disability are known to be at an increased risk for further functional decline. These individuals might be targeted for anticipatory rehabilitation, which is sometimes called "prehabilitation". A clinical trial has suggested that a program of in-home exercise can, at minimum, stabilize overall disability and prevent worsening over a period of 1 year [51].

17.6.4.2 Obesity

Since obesity is a unique risk factor for mobility disability, interventions that combine exercise with weight loss for obese older adults can lead to better mobility performance. Resistance exercise may be especially important to prevent the loss of muscle mass that is otherwise induced by caloric restriction. There is not yet data on whether these interventions can ultimately delay the onset of mobility disability.

17.6.4.3 Sarcopenia

A number of endocrinologic and nutritional deficiencies are associated with low muscle mass and strength in older adults. Clinical trials are beginning to assess the effects of replacement and supplementation on muscle mass, strength and mobility. Novel agents that are in development are attempting to mimic the beneficial effects of hormones without the adverse effects. To date, there is no definitive evidence for beneficial effects on mobility performance or the prevention of mobility disability [46].

17.7 Research: Methodological Issues, Gaps in Knowledge and Future Research Needs

17.7.1 Methodological Challenges of Research in Falls and Mobility

The evidence regarding risk factors and interventions to prevent falls and mobility disability is hard to interpret because there are many methodological challenges. Methodological aspects, including (1) design and conceptual framework, (2) sampling and follow up, (3) measurement, and (4) analysis have a strong influence over research findings. Variability in these methodological issues helps to explain the variability in research findings. As we further refine research methods, we can improve the validity and interpretability of future research. This section will provide an overview of methodological challenges and opportunities, and their effect on research regarding falls and mobility.

17.7.1.1 Conceptual Framework and Design

All research is built either overtly or implicitly on a conceptual framework that defines what we think is happening. It drives who we study, what we measure and how we test effects. There are multiple unintended consequences of pursuing research without an explicit framework. A conceptual framework is especially needed for work in the field of falls and mobility disorders because causal factors are highly interrelated. When attempting to simultaneously evaluate multiple risk factors, these inter-relations conflict with each other in predictive models, a problem called multicollinearity, which produces confusing and sometimes counter-intuitive results. The solution to this problem is to start with a set of organized concepts about systems or processes that can cause falls, and to build the models from distinct domains [20] (see example in Fig. 17.1). As presented in the above section on risk factors, some authorities suggest that poor mobility and balance are the *sine qua non* of age-related falling and that health factors are domains that contribute to poor mobility and balance. The conceptual framework might also help define when two factors interact to cause an outcome like a fall. For example, environmental hazards might be especially important in individuals who have trouble monitoring the environment due to low vision or other problems. Thus, it is possible that environmental hazards would not emerge as independent risk factors for falls but would be clear-cut effect modifiers in combination with low vision. If effect modification is suspected,

then specific analytic techniques that involve interaction terms are required.

Study design decisions also affect how we interpret studies of falls and mobility. Longitudinal monitoring in observational studies must capture not only baseline status and outcomes but also changes over time in potential risk factors. Thus, many studies of falls and mobility capture important baseline predisposing factors, but rarely capture transient or intermittent intervening precipitating events. Regularly scheduled follow-ups can help to detect change, but they notoriously face missing data biases because older adults who have become sick or disabled are less likely to continue to participate. One solution to tracking potential intervening events and changes is called triggered sampling, where certain marker events—like a fall—trigger an additional evaluation.

The standard randomized controlled clinical trial design, where a single intervention such as a medication is compared to a placebo, is a poor fit for public health interventions for falls and mobility disability. Multifactorial, individually-tailored interventions make sense for the study of prevention of falls and mobility disability in complex heterogeneous older adult populations. The challenge of multifactorial interventions is that it is not possible to tell what components of the intervention "worked". One element of a solution is to operationalize and make reproducible all aspects of the intervention, including the frequency and intensity of treatments or exercises. This process is linked to structured guidelines for individualizing who should receive various components of the intervention. In the case of falls, only individuals who screen positive for low vision get referred for vision care. Some interventions might be targeted at a special subgroup that has a unique set of risk factors. Thus, some fall prevention interventions might focus only on individuals who have peripheral neuropathy or Parkinson's disease, and some interventions for mobility disability might focus on individuals who have arthritis pain or weakness and sarcopenia.

Intervention development design is highly influenced by the conceptual framework for drug development, which is guided by the US Food and Drug Administration (FDA). In the drug development process, treatment is based on an indication, which is usually a disease. It is not yet clear how to define balance and mobility problems as indications in the FDA sense. Yet it is quite critical that we do so since there are multiple potential agents that might work alone or in combination with multifactorial approaches to improve balance or mobility. If a condition is multifactorial and has multiple underlying pathophysiological and behavioral contributors, how should the condition be defined as an indication, and how should treatments be developed and tested? One pathway for the development of treatments for mobility and balance disorders might be based on precedents from other multifactorial conditions such as hypertension or obesity. In those cases, there are multiple contributors, and treatments are multifactorial with pharmacological and nonpharmacological elements.

17.7.1.2 Samples and Drop Outs

The population that participates in a study has overt as well as subtle effects on the findings. Risk ratios are heavily influenced by the prevalence of risk factors in the population under study. For example, many early studies of fall risk failed to identify cognitive impairment as a risk factor for falls because individuals with cognitive impairment were either intentionally excluded from the study, or were not recruited due to practical barriers to enrollment. Since risk factors are influenced by the range of the participants' health and function, they consequently vary greatly between settings. Thus, risk factors for falls in the community and in nursing homes may differ. Similarly, risk factors for falls may vary between individuals who cannot walk, those who walk poorly and those who are capable of undertaking challenging mobility tasks. For example, fall risk factors for an individual who depends on a wheelchair for mobility might be very different from those for a highly mobile person who trips over a crack in the sidewalk.

Drop outs and losses to follow-up affect the interpretation of findings in both observational studies and clinical trials. Older adults who have risk factors for falls and mobility disability are

also likely to have difficulty remaining in a research study because they have trouble traveling to a research site, get tired during research procedures or because they have episodes of serious illness. In almost all studies of falls and mobility, the dropouts have worse baseline status on measures of mobility and balance. Solutions include making specific plans to adjust study activities to accommodate to the needs of an increasingly fragile study population. One approach is to include home visits and phone calls to replace research site visits. Another is to always assess the differences in baselines characteristics between those who stay in the study and those who drop out, and to consider the influence of these dropouts on study results.

17.7.1.3 Measures

To interpret research in the area of falls, balance and mobility, it is essential to have well-characterized, widely-shared measures. Progress has been made with regard to the reporting of fall events. There are several well-characterized measures of mobility, including walking speed, 6-min walk, 400-m walk and the SPPB [3]. Mobility capacity is considered to be highly hierarchical in that individuals who can do difficult mobility tasks are highly likely to be able to do simple tasks, and individuals who cannot do simple tasks are highly unlikely to do more difficult tasks. Thus many mobility assessments, whether self-report or performance, take advantage of this hierarchy. For example, screening can begin with an assessment of simple walking. If the individual has difficulty or cannot walk, then the screen proceeds to lower-level tasks such as transfers and use of assistive devices. If usual walking is normal, then the screen can proceed to more challenging tasks such as tandem walking or stair climbing.

Many measures exist within the field of balance, but they are probably the least consistent between studies and the least well-developed. Part of the problem is that there is no agreement within the field regarding what we mean by balance itself. One common definition of balance is "the ability to remain upright in motion". To remain upright in motion, it is essential to keep the body above the moving feet or other body supports. Many current measures of balance, such as timed one-foot or tandem stands, or measures of sway, do not include movement of the feet and would be considered only "static" measures of balance. Others that require the displacement and recovery of a moving base of support over a moving body would be considered "dynamic" measures of balance. Examples include walking under usual conditions or under challenging conditions such as in a narrow path [28, 29]. The Get up and Go test, which includes walking, turning, rising and sitting back down, incorporates several dynamic balance tasks. As in the case of mobility measures, balance measures are hierarchical, so screening can begin at some middle level and adjust to easier or more difficult tasks depending on the individual.

A key next step in the field is to formally assess the relationships among static and dynamic measures of balance, and to attempt to recommend some for standard use. For both mobility and balance measures, it is also critical to align the measures with the capacities of the target population to minimize floor and ceiling effects. Thus, studies in healthier populations must use measures with higher levels of difficulty and studies in very frail populations should perform assessments that discriminate among several lower levels of mobility and balance function. It is also critical to account for "informative censoring", which is when data is missing due to some factor that affects the outcome. In this case, the key is to code why data is missing. For many balance and mobility tasks, such as tandem walking, data is missing because the individual cannot do the task or it would be dangerous for them to do it. "Can't do" is itself highly predictive of worse outcomes.

17.7.1.4 Analytic Strategies

In the field of falls and mobility, analytic strategies have powerful effects on the interpretation of data. In the case of falls, the analytic strategy is not determined only by the form of the outcome (e.g., ever having a fall or recurrent fall, time to

first fall, frequency/number of falls). Other factors that influence the analytic strategy include variable follow-up time, non-independence of recurrent falls and timing among recurrent falls. There are pros and cons of all analytic approaches. Since all commonly-used methods provide various forms of estimates for relative risk or hazard reduction, they reflect relative benefits to the population but not absolute risk to the individual. For example, in a trial to prevent participants from becoming a faller, a logistic regression analysis might yield a relative risk of 0.7. This result implies that the risk of becoming a faller is 30% lower in the intervention compare to the control group, but it does not speak to the effect on the absolute rate of becoming a faller. If there were 100 participants in each of the two study arms, the relative risk could be 0.7 if the rates were ten fallers in the control group and seven in the treatment group, or if there were 50 fallers in the control group and 35 in the treatment group. In the former case, the absolute risk is reduced by 3% and in the latter it is reduced by 15%. For this reason, it is always useful to provide descriptive statistics by treatment arm regarding the number and distribution of fall events over time, and the number and proportion of single and recurrent fallers.

Analyses that account for recurrent events can yield estimates about the reduction in fall frequency, but they can be hard to interpret at the individual level [69]. The result might be presented as an incidence rate ratio which suggests that there are 30% fewer falls with the treatment, but we cannot tell how much of this effect is due to many fewer falls among frequent fallers and how much is due to individuals who never had a single fall. If the analysis accounts for time-to-first-fall, as in survival analyses, then early falls might have to be excluded since they might have occurred before the intervention had a chance to work. Thus, in addition to sophisticated statistical techniques, it is again helpful to use simple descriptive presentations and graphics to help interpret the findings.

As discussed above, when there is high collinearity among factors, statistical approaches such as stepwise regression can have highly confounded results. Conceptual models with domain indicators can help to minimize this problem. Also, there are times when one factor is only influential in the presence of another, and statistical approaches must include interaction terms to assess them [20].

17.7.2 Gaps and Research Opportunities

17.7.2.1 Risk Factors

Several novel topics are emerging at the cutting edge of research on falls and mobility. One topic that continues to present great gaps in knowledge and offers unique potential for intervention is the role of aging and disease on the neural control of balance and mobility. While several common neurological conditions, such as stroke and Parkinson's disease, are known to have major effects on mobility and balance, recent evidence suggests that there are age- and disease-related changes in the brain that have a major impact on gait and balance. The most well-known of these brain effects is altered gait and balance related to increased white matter signals on magnetic resonance imaging, altered non-memory cognitive function and impaired ability to perform dual tasks. Other potential brain processes involve regional gray matter atrophy and age-related alterations in neurotransmitters and receptors. Many of these pathological processes have their effects on gait and balance through their impact on motor planning, as well as on the development, maintenance and recovery of specific motor skills. Further research is needed to characterize and classify the roles of the normal and aging brain in motor planning and skill in gait and balance.

Moving the body takes work and energy. There is a growing awareness that aging may affect biological energy efficiency in many ways. Gait and balance in older adults may be energy-inefficient due to alterations in the biomechanics and physiology of movement with aging. These energy inefficiencies may contribute to early

fatigue during mobility and could lead to falls. A new direction for research on risk factors and interventions is to focus on a better understanding of the role of energy cost and efficiency in movement and balance in older adults [70].

Low muscle strength is a known risk factor for problems with mobility and balance. However there are several more novel aspects of muscle strength that are emerging as critical to movement. In addition to the well-known role of muscle for force production, newer thinking suggests that muscle power (the combined effect of the magnitude of force production with the rate of force production) might be highly influential for mobility and balance. Another potentially important aspect of muscle function is the capacity to sustain muscle contractions and force over time. The loss of this capacity, called muscle fatigue, is a potentially important contributor to mobility and balance problems [71].

17.7.2.2 Outcomes

Perhaps the most critical factor to further work in this area is the need to increase societal awareness and acceptance of the major impact of falls and mobility on the health and quality of life of older adults. There is increasing attention being given to mobility status within the field of aging and public health but mobility status receives much less attention in the fields of healthcare and health policy. Within most healthcare information systems, including Medicare, there is absolutely no data on mobility and very little on falls. Even many epidemiological studies and clinical trials that involve older adults (e.g., those for dementia or diabetes) do not regularly assess mobility and balance. In the field of epidemiology, one action with the greatest potential impact would be to incorporate measures of mobility and balance into all cohort and clinical trials that involve midlife adults and/or older adults.

17.7.2.3 Interventions for the Individual

Presently, there are a number of exercise interventions for mobility, but interventions for balance are not nearly so well standardized or developed [57]. In order to be assessed for benefit, these interventions should be reproducible in terms of content, frequency, intensity and progression. While considerable advances have been made in operationalizing exercise for aerobic and resistance training, this is far less true regarding exercise for balance. Balance exercise trials have had very little consistency with regard to protocols. Balance exercises can be static and/or dynamic, can progress at varying rates and can be variably integrated into functional activities. Each of these factors can have a major influence over the impact of exercises. Major new efforts are needed to classify the varying parameters of balance exercise so that interventions can be characterized. It is possible that future trials should compare types of balance exercise.

A major direction of research in falls and mobility is to better incorporate the role of cognition, attention and the capacity to perform several tasks while moving. The next major opportunities in this field are to develop a series of intervention trials that focus on cognition and dual task training. Preliminary work in this area is already underway [61].

While there is strong evidence that exercise is a valuable and effective intervention for balance and mobility problems, there has been little effort to test potentially effective pharmacologic agents in the context of their additional benefit after exercise. Most trials of medications for balance and mobility problems, whether for conditions like Parkinson's disease or for more general conditions like weakness and low muscle mass, have been limited to comparisons of medications to placebo. It might be useful to compare exercise to exercise plus medication, to determine whether the medication provides important additional benefits or aids the effect of exercise on outcome. The potential pharmacologic agents could target a range of factors that affect mobility, balance and falls, including sensory, brain and/or effector factors. Some studies are beginning to consider the role of cognitive enhancers in fall prevention. Study designers should consider designs in which the pharmacological agent is added to standard care, including exercise.

Several emerging risk factor areas, such as sleep disorders and anemia, are potentially modifiable. Novel interventions on targeted

subgroups with these problems could be assessed in clinical trials.

One of the greatest barriers to achieving the benefits of exercise for promoting balance and mobility is the disappointingly low levels of participant adherence to exercise over the longer term. For most exercise studies, adherence drops off precipitously after the support from the trial is withdrawn. Strategies to promote longer-term adherence are desperately needed. One potential strategy is to increase the recreational "fun" aspects of exercise. Some aspects of recreation that can be incorporated include group socialization, music, dance and games. There is a major global initiative entitled, "Games for Health" that is exploring the exciting potential of this concept [72].

As computers become ubiquitous and are applied to treatment and recreation, there are numerous new avenues for interventions for balance and mobility. These opportunities include video games and virtual-reality environments. Games and systems that are currently available will need to be adapted to make them appropriate, safe and feasible for older adults. These games and systems have the potential to address several barriers to benefit, including the ability to individualize exercise, strategies to incorporate challenges to attention and dual tasking, and adding "fun" to exercise.

Assistive devices for mobility and balance, such as canes and walkers, are widely recommended for older adults who have difficulties moving, but there are major challenges to their use. One major barrier is the social stigma associated with their use. Individuals may object that they are embarrassed to be seen using such devices in public because they "make me look old". There are also practical problems with their use that are associated with physical barriers within homes and communities. There is great opportunity to develop new generations of devices that are more aesthetic and socially acceptable, as well as more adapted for use in various environments.

17.7.2.4 System Interventions

From a public health perspective, a major challenge to progress is the fragmented nature of current interventions. This fragmentation has two major components, one related to program goals and the other to program organization. First, it is striking that most public health efforts that target fall prevention have not overtly incorporated goals to prevent mobility disability. Since screening programs to detect fall risk often evaluate mobility, they could simultaneously and efficiently identify and manage prevention of mobility disability. At the same time, programs often tend to focus on one level of prevention, usually secondary prevention for individuals who have risk factors for falling. From a population perspective, it seems possible and useful to develop programs that have branched decision trees based on whether the goals are primary, secondary or tertiary prevention (Fig. 17.2). Such programs could begin with a screen to stratify individuals as (1) demonstrates excellent mobility and balance, (2) has limited mobility and balance and/or a fall history, or (3) is mobility disabled or has sustained a fall injury. This population screening could lead to a range of interventions of varying intensity, individualization and resource demand.

Integrating program goals would also require improvements in the integration of public health and clinical healthcare services. In general, as risk and complexity increase from primary to tertiary prevention, the relative roles of public health and clinical healthcare reverse (Fig. 17.2). Public health bears most of the responsibility for primary prevention and clinical healthcare bears most of the responsibility for tertiary prevention, while both share responsibility for secondary prevention. Even though responsibility and leadership may reside more with one system than the other, both are needed at all three levels. Monitoring for change in individuals who were initially targeted for primary prevention may require the input and involvement of healthcare professionals. Similarly, tertiary services are almost always time-limited and should become partnered with community-based maintenance and monitoring systems. In addition, providers in both public health and clinical healthcare require further education and training to enable them to deliver integrated and coordinated services.

17.8 Summary

Preventing fall injuries and maintaining good mobility are core issues for successful aging, and are critical areas of focus for public health and epidemiology. We have learned a great deal about risk factors and preventive strategies over the last three decades, and have achieved real gains in terms of benefits to older adults, communities and society. Public health professionals and epidemiologists can continue to make substantial contributions as they pursue research into causes and management, and explore novel ways to implement programs in the community.

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Medication Use in Older Adults

18

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Abstract

Knowledge about the safety and efficacy of individual medications in older adults (i.e., those ≥65 years of age) is often limited due to the frequent exclusion of this population from premarketing clinical trials of new medications. Regardless, multiple medications are commonly prescribed for community-dwelling older adults who may also choose to use over-the-counter medications and dietary supplements. Medications are prescribed at even higher rates in institutional settings, and the types of medications prescribed differ across care settings as well. The use of multiple medications can result in under-, over- or inappropriate prescribing and patient medication nonadherence, which can lead to a decline in patient functional status and an increase in use of health services. Understanding medication use and its effects in older adults who live in different care settings is likely to aid in designing future interventions for the improvement of health care for this population.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Medication use • Polypharmacy • Drug-drug interactions • Inappropriate prescribing • Side effects • Toxicity • Geriatric syndromes • Prevention • Risk factors

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18.1 Introduction

Medications are the most frequently used form of therapy for the medical problems of the aged. Unfortunately, the frequent exclusion of this age group from premarketing clinical trials of new medications has limited our knowledge regarding the safety and efficacy of individual medications in this population. Further, older patients often have various chronic conditions that may require

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multiple long-term medications. Of potential concern is that multiple medication use (polypharmacy) can lead to problems in the medication use process and related health outcomes.

This chapter will examine medication use in older adults with a focus on the prevalence of polypharmacy and its effect on aspects of the medication use process and on patient outcomes. We will begin by reviewing the various sources of medication use data in older adults and data coding systems for medications. Next, since medication use in older adults has been found to differ by care setting, we will separately review medication use in older adults who live in the community, who have been admitted to a hospital, and who live in a nursing home. After establishing the prevalence of multiple medication use in older adults in these three settings, we will review the impact of multiple medication use on two aspects of the medication use process (i.e., prescribing and medication adherence) and on adverse outcomes (e.g., functional status decline, adverse drug reactions [ADRs]) among older adults.

18.2 Medication Use Data

Medication use data is available from a number of government and research sources, and is gathered using a variety of methods. Below we describe a number of sources and data collection methods. We also review a number of medical data coding systems which are useful for identifying individual medication ingredients and therapeutic class level.

18.2.1 Sources of Medication Use Data

Information about medication use in older adults can be drawn from a variety of sources. Table 18.1 lists some of the medication use data sources that are available internationally (see http://riskfactor.cancer.gov/tools/pharmaco/epi/ for further details). One source of data, often considered to be the gold standard, is administrative/pharmacy dispensing/claims records [1]. Examples of this type of medication data source include state Blue Cross/Blue Shield plans, employer-provided retirement plans, closed-panel health maintenance organizations (e.g., HMO Research Network), health systems with integrated electronic health records (e.g., Veterans Health Administration), and government-funded programs (e.g., Medicaid, Pharmaceutical Assistance Contract for the Elderly [PACE]). A robust new source of data is medication information from Medicare Part D [2]. Unfortunately, there are limitations to using administrative/pharmacy dispensing/claims data for research purposes. It can be difficult to obtain permission to use this data. Also, these data only identify prescription medications dispensed; no information is provided regarding over-the-counter medications or dietary supplements and actual medication use by patients cannot be accurately captured.

Table 18.1 Examples of international sources of information on medication use in the elderly

Nation	Information source
Canada	British Columbia Linked Health Database (BCLHD)
	Manitoba Health Research Database
	Population Health Research Unit
	Québec Universal Medical Insurance Register
	Saskatchewan Health Services Databases
Scandinavia	Integrated Primary Care Information (IPCI)
	Odense University Pharmacoepidemiological Database (OPED)
	The PHARMO Institute
	Swedish Center for Epidemiology
United Kingdom	General Practice Research Database (GPRD)
	Medicines Monitoring Unit (MEMO), University of Dundee
	Primary Care Clinical Informatics Unit-Research (PCCIU-R)

Another source of information on medication use in older adults is data from epidemiology studies that gather self-reported data about medication use [3, 4]. This type of data can capture actual medication use that, in addition to

prescription medications, may include both over-the-counter medications and dietary supplements. Examples of such data sources include:

- Cardiovascular Health Study (CHS)
- Established Populations for Epidemiological Studies of the Elderly (EPESE)
- Health, Aging and Body Composition Study (Health ABC)
- Medicare Current Beneficiary Survey (MCBS)
- National Social Life, Health and Aging Project (NSHAP)
- Osteoporotic Fractures in Men (MrOS)
- Slone Survey
- Study of Osteoporotic Fractures (SOF)
- Women's Health and Aging Study (WHAS)
- Women's Health Initiative (WHI)

To gather this data, most studies use the in-home interview, also called a "brown bag" medication inventory, with the goal of capturing actual use of medications [5, 6]. They may also use phone surveys, during which participants are asked to gather all of their current medications and review them over the phone.

Whether the method of data collection is in-home or over-the-phone, typically participants are queried about the use of three types of medications (prescription, over-the-counter, and dietary supplements), are given examples of each and are asked to report their recent use. For prescription drugs, an interviewer will either read or ask the participant to read the name and strength of the medication and the directions for use. The interviewer will also document whether the label was seen by the interviewer or the participant was reading from the original prescription bottles. Typically, participants are asked to report whether the medication use is regularly scheduled or taken only as needed. Asking participants how many units of tablets/capsules they have taken over the previous day, week or month is also helpful, especially for assessing consistency with the directions. Asking the participant what the medication is intended to treat can also be helpful since studies have shown that patients can accurately report this to the organ system level (e.g., atenolol for the heart) [7]. This technique is repeated for over-the-counter drugs and dietary supplements, except that strength and directions for use are not queried since many of these drugs are taken as needed and have multiple ingredients. The correct coding and identification of dietary supplements can be difficult since many pharmacotherapy sources do not have complete information regarding these agents. A common approach is for interviewers to ask the participant to identify the supplement's manufacturer so a Web search may be conducted.

The validity of self-reported medication use by older adults is a potential concern. However, a study by Smith et al. [8] showed that "brown bag medication inventory methods," in which the older participant shows the actual medication containers with labeling to the interviewer, are reliable when compared to serum levels of cardiovascular drugs in the elderly. Another study showed that for prescription drugs, this in-home approach is highly concordant with pharmacy data [9]. Moreover, a study by Pit et al. [10] showed that self-reported use of medicines by patients interviewed over the telephone had high agreement and accuracy when compared to pharmaceutical claims data. Regardless of method, concerns regarding recall accuracy for past medication use leads most surveys of older adults to limit the recall period to the recent past (e.g., 1–4 weeks).

For all of the sources of medication use data, it is essential that one be able to aggregate and disaggregate the data to the individual ingredient and therapeutic class level. A useful tool for this purpose is data coding systems for medications.

18.2.2 Data Coding Systems for Medications

Data coding systems enable the precise identification of a medication and provide individual ingredient and therapeutic class level information. Pharmacy dispensing/claims data for United States (US) medications use National Drug Codes (NDC) in which each prescription or insulin product has an assigned 10-digit, 3-segment number. This listing is kept current by the Food and Drug Administration and is available free of

charge from their Web site or RxNorm, which is maintained by the National Library of Medicine. RxNav is a Web-based interface for RxNorm and provides a standardization and integration of NDCs with codes from other sources, including the Veterans Health Administration, Multum, First DataBank, Medi-Span and others. This latter coding system was purchased by the Cardiovascular Health Study, which utilized it in the development of a computer program for conducting data coding and entry [6]. A number of projects funded by the National Institute on Aging (e.g., Established Populations for Epidemiologic Studies of the Elderly; Women's Health and Aging Study; Health, Aging and Body Composition Study) use the commercially-available Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus for coding medications [11]. The advantage of this system over the NDC and other coding systems is that it provides codes for over-the-counter medications and dietary supplements. In Europe, many studies utilize Anatomical Therapeutic Chemical medication codes that can be purchased from the World Health Organization.

18.3 Medication Use in Older Adults by Care Setting

The use of medications by older adults differs by the setting in which care is delivered. Moreover, medication use can change dramatically as older adults transition from one care setting to another. Below, we describe the rates and types of medications used in ambulatory/community, hospital and nursing home settings.

18.3.1 Ambulatory/Community Setting

A group of investigators from Boston University published the most recent national Slone Survey in 2006, which consisted of interviews about medical history and medication use in 2,529 community-dwelling adults of whom 31.5% were ≥65 years of age [3]. Notably, this survey reported that medication use (i.e., prescription medications, over-the-counter medications and dietary supplements) increased steadily with age. It was found that 57% of community-dwelling women ≥65 years of age used ≥5 medications on a weekly basis, and 19% used ≥10 medications. Similarly, 59% of men ≥65 years of age reported using ≥5 medications every week while 17% reported using ≥10 medications. By comparison, only 8% of men <45 years of age reported regularly using ≥5 medications. This survey's results regarding the most commonly-used prescriptions and over-the-counter agents, and the most commonly-used dietary supplements, among older adults (by gender) are listed in Tables 18.2 and 18.3, respectively [3]. The longitudinal Slone

Table 18.2 The ten most common prescription and over-the-counter medications used by community-dwelling elders in the US [3]

Men	Women
Aspirin	Aspirin
Atorvastatin	Acetaminophen
Lisinopril	Hydrochlorothiazide
Metoprolol	Levothyroxine
Simvastatin	Atorvastatin
Acetaminophen	Metoprolol
Furosemide	Ibuprofen
Hydrochlorothiazide	Lisinopril
Warfarin	Amlodipine
Atenolol	Simvastatin

Table 18.3 The ten most common dietary supplements used by community-dwelling elders in the US [3]

Men	Women
Multivitamin	Multivitamin
Lycopene	Lutein
Lutein	Lycopene
Glucosamine	Glucosamine
Fish oil	Fish oil
Chondroitin	Chondroitin
Garlic	Garlic
Flaxseed oil	Co-enzyme Q
Ginseng	Flaxseed oil
Co-enzyme Q	Ginkgo biloba

Survey highlights the fact that the prevalence of medication use has not changed over time, but the prevalence of polypharmacy has increased in recent years.

Another national study conducted by Qato et al. [4] between June 2005 and March 2006 surveyed 3,005 community-dwelling adults in their homes, of whom 58.5% were ≥65 years of age. In the oldest age group (75–85 years of age), 36% of women and 37% of men reported using ≥5 prescription medications. Nonprescription medication (e.g., aspirin) use was found to be relatively common as well. Specifically, 55.4% of older female survey respondents (≥65 years of age) reported taking a dietary supplement, as did 43.1% of men. Similarly, the prevalence of over-the-counter medication use among older women and men was 41.9 and 42.6%, respectively. Of note, cardiovascular agents were the most common medications reported among all prescription and nonprescription medications.

Finally, the Centers for Disease Control and Prevention's National Center for Health Statistics recently released data on prescription medication use in the US and reported that among adults ≥60 years of age, more than 76% used ≥2 prescription medications and 37% used ≥5 [12]. The most common classes of medications used in these older Americans were cholesterol-lowering drugs (45%), beta-blockers (26%) and diuretics (20%) [12]. Overall, the medication use patterns reported by these sources of data are consistent with each other and bring to light the high prevalence of polypharmacy among ambulatory/community-dwelling older Americans.

18.3.2 Hospital Setting

Because there is no national data source in the US, there are limited data regarding medication use in older adults who are hospitalized. One study of 834 older frail inpatients (44% of whom were >75 years of age) from 11 Veterans Affairs (VA) hospitals found that the average number of prescription drugs on admission was 7.6 and the average number of nonprescription drugs used was 2.6 [13]. In contrast, a study from Ireland found that the average number of medications was 5 per older patient (average age 77) at the time of acute hospital admission [14]. Furthermore, a study in 2006 by Page and Ruscin [15] of older adults (18% of whom were in the oldest age group of ≥85 years of age) in a single hospital in Colorado found the average number of medications to be nearly 4 per patient. Finally, a study using data from the electronic health records used at the University of Pittsburgh Medical Center, a tertiary academic medical center in southwestern Pennsylvania, summarized the top 50 drugs taken by older (≥65 years of age) hospitalized patients [16] (Table 18.4). As might be expected, the use of opioid analgesics and anti-infectives are more prevalent in hospitalized elders compared to community-dwelling elders.

18.3.3 Nursing Home Setting

The 1996 Medical Expenditure Panel Survey – Nursing Home Component surveyed 5,899 nursing home residents (38% in the oldest age group of ≥85 years of age) and found that 32.4% were taking ≥9 medications [17]. The most common individual agents reported in this survey are shown in Table 18.5. More recently, the 2004 National Nursing Home Survey (NNHS) reported that approximately 40% of more than 13,000 nursing home residents (45% in the oldest age group of ≥85 years of age) were receiving polypharmacy, which was defined in this study as use of ≥9 medications [18]. Gastrointestinal agents (e.g., laxatives), central nervous system agents (especially psychotropics) and pain relievers were the most common agents among patients receiving polypharmacy. Laxatives were the most frequently used agents, with 47.5% of patients who were receiving polypharmacy taking at least one laxative [18]. In another study using data from the NNHS, researchers found that more than 1 in 10 nursing home residents were receiving

Table 18.4 The most common medications used by hospitalized elders at the University of Pittsburgh Medical Center [16]

#	Medication	#	Medication
1.	Warfarin	26.	Nitroglycerin
2.	Potassium	27.	Alprazolam
3.	Pantoprazole	28.	Gabapentin
4.	Metoprolol	29.	Zolpidem
5.	Furosemide	30.	Hydrochlorothiazide
6.	Digoxin	31.	Losartan
7.	Acetaminophen/oxycodone	32.	Citalopram
8.	Levothyroxine	33.	Amiodarone
9.	Nizatidine	34.	Enalapril
10.	Lisinopril	35.	Metronidazole
11.	Clopidogrel	36.	Allopurinol
12.	Amlodipine	37.	Captopril
13.	Prednisone	38.	Donepezil
14.	Simvastatin	39.	Temazepam
15.	Atorvastatin	40.	Rofecoxib
16.	Isosorbide	41.	Trimethoprim/sulfamethoxazole
17.	Diltiazem	42.	Paroxetine
18.	Atenolol	43.	Azithromycin
19.	Levofloxacin	44.	Carvedilol
20.	Oxycodone	45.	Glyburide
21.	Acetaminophen/hydrocodone	46.	Phenytoin
22.	Acetaminophen/propoxyphene	47.	Spironolactone
23.	Lorazepam	48.	Metformin
24.	Tamsulosin	49.	Mirtazapine
25.	Quinapril	50.	Sertraline

Table 18.5 Top medication classes used in nursing homes by older adults in the US [17]

Medication class	%
Analgesics/antipyretics	81.5
Gastrointestinal agents	76.4
Electrolyte, caloric and water balance agents	68.9
Anti-infective agents	67.9
Central nervous system agents	65.1
Cardiovascular agents	59.4
Topical or other	49.4
Kidney/urinary tract agents	45.1
Hormones/synthetic substitutes	39.3
Respiratory agents	31.4
Anti-allergy agents	20.8
Blood formation/coagulation agents	19.1

antimicrobial therapy at any given time. The most frequent subclasses of antibiotics prescribed were quinolones, urinary tract antiseptics, and sulfonamides and trimethoprim. Together, these three classes made up over 50% of the total antibiotics used [19].

18.4 Effect of Multiple Medication Use in Older Adults

The information in the previous section demonstrates that while multiple medication use among older adults differs in the various care settings, it is prevalent in all three. It is therefore important

to be aware of how multiple medication use affects key medication use process components and patient outcomes in older adults.

18.4.1 Effect of Multiple Medication Use on Key Medication Use Process Components

The medication use process involves four distinct steps: prescribing, order communication, dispensing, and monitoring/adherence [20]. The successful execution of each step involves sufficient clinical knowledge, effective communication and a safe healthcare system. Among these steps, the large majority of research has been conducted on the prescribing stage, including research on the overuse, underuse and inappropriate use of medications. Research on medication adherence among older adults is growing and highlights the complexity of medication-taking behavior among patients with multiple morbidities who are taking multiple medications. Below, we review the known impacts of multiple medication use on prescribing and medication adherence in older adults.

18.4.1.1 Impact of Multiple Medication Use on Prescribing

The complexity of multiple medication use can lead to suboptimal prescribing (i.e., under-, over- and inappropriate prescribing) [21]. For example, one US study that used a standardized implicit measure to assess underuse at hospital discharge among frail elderly veteran patients found a large amount of underprescribing for indicated medications [22]. Specifically, 62% of 384 older patients (47% of whom were ≥75 years of age) had underuse at discharge due to underprescribing, and the most common medication classes omitted were cardiovascular (e.g., antianginal), blood modifiers (e.g., anti-platelet), vitamins (e.g., multivitamin) and central nervous system agents (e.g., antidepressant). The same source provided data on unnecessary drug use (i.e., a drug that lacks an indication, effectiveness, or is a therapeutic duplication) and found that 44% of veterans had at least one unnecessary medication at hospital discharge. The most common problems were a lack of indication (33%), lack of efficacy (19%) and therapeutic duplication (8%). The most common unnecessary medications included gastrointestinal agents, central nervous system agents, and nutrients and minerals [23]. Furthermore, in one study of 597 hospitalized patients who were ≥65 years of age, 32% of patients were taking at least one inappropriate medication on admission according to the Beers' Criteria [15]. Notably, more than half of the inappropriate prescriptions were for psychotropic medications. In a survey of community-dwelling elders, Qato et al. [4] found that one form of inappropriate prescribing (i.e., major drug-drug interactions, defined as those that may be life-threatening or require medical attention) was present in 4% of patients surveyed.

18.4.1.2 Impact of Multiple Medication Use on Adherence

Medication adherence can be defined in several ways, but a common definition is "the extent to which patients take medications as prescribed by their health care provider" [24]. One study of older community-dwelling elders who were taking an average of nine medications found that the prevalence of overall medication nonadherence was 49.3% [25]. It is important to note that high-risk nonadherence was seen in only 6.1% of participants and that the most common type of nonadherence was underuse [25]. A study using Medicare Current Beneficiary Survey (MCBS) data (in which 10% of the participants were ≥85 years of age) before and after the implementation of Medicare Part D found that cost-related medication nonadherence (i.e., skipping or reducing doses due to cost) was reduced from 15.2 to 11.5% with the implementation of Part D [26].

18.4.2 Adverse Outcomes Associated with Multiple Medication Use

As reviewed above, multiple medication use is associated with suboptimal prescribing and medication nonadherence. These "quality of care"

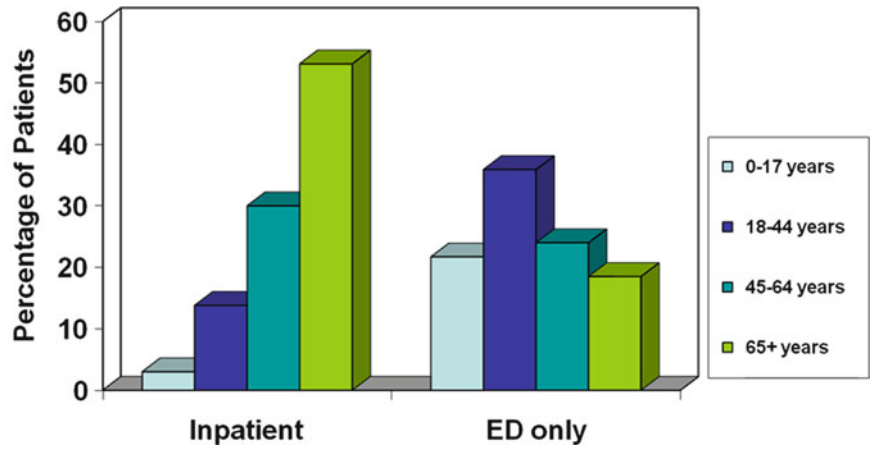

Fig. 18.1 Drug-related adverse outcomes, by setting and age [28]

problems are associated with an increased risk of a decline in functional status and increased use of health services [21, 27]. For example, data from the Agency for Healthcare Research and Quality (AHRQ)-sponsored Healthcare Cost and Utilization Project shows that older Americans (≥65 years of age) make up the majority of inpatient drug-related adverse outcomes, as well as a substantial proportion of treat-and-release emergency department visits due to drug-related adverse outcomes (Fig. 18.1) [28]. Furthermore, it has been estimated that for every dollar spent purchasing medications, approximately $1.75 is spent treating drug-related problems [29, 30]. This results in billions of dollars of unnecessary and preventable health care costs and increased mortality. This may be manifested by the high occurrence of therapeutic failures (TFs) and ADRs in older adults [31].

18.4.2.1 Therapeutic Failures (TF)

A TF can be defined as "a failure to accomplish the goals of treatment resulting from inadequate drug therapy and not related to the natural progression of disease" (e.g., omission of necessary medication therapy, inadequate medication dose or duration, and medication non-adherence) [32]. Few studies have assessed this phenomenon in older adults. One study of TF-related hospitalizations in 106 frail older adults who were admitted to 11 VA hospitals assessed these events using the reliable Therapeutic Failure Questionnaire [33]. Overall, 11% of the individuals studied experienced a probable TF leading to hospitalization. Heart failure and chronic obstructive lung disease were the most common conditions associated with TF. Italian investigators assessed TFs in the emergency department and found that 6.8% of patients had a TF, two-thirds of which occurred in patients ≥65 years of age [34]. Furthermore, a study of US older adults found TF to be implicated as the cause of emergency department admission in 28% of drug-related visits [35].

18.4.2.2 Adverse Drug Reactions (ADR)

An ADR is defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiologic function" [31]. ADRs occur in 5–35% of community-dwelling older adults [31]. A meta-analysis conducted in 2002 by Beijer and de Blaey [36] showed that up to 17% of hospitalizations in older adults are due to ADRs. In Europe, the rate of ADRs in older hospitalized patients ranges from 6.5 to 11.5% [37]. Furthermore, in 2006 Handler et al. [20] summarized the nursing home literature and reported that between 1.2 and 7.3 ADRs occur per 100 patient months.

18.4.2.3 Prevention Interventions for Therapeutic Failures and Adverse Drug Reactions

Clearly, TFs and ADRs are common in older adults and their prevention would be of great benefit in improving the health of older adults and reducing overall healthcare costs. How, then, can TFs and ADRs be prevented? Unfortunately, the answer to this question is unknown at this time. Very little research has focused on this area of study. Only three randomized controlled trials have targeted the prevention/reduction of ADRs and none have targeted TFs. Still, epidemiologists, health policy makers and health professionals must empirically consider implementing safer health system designs (e.g., providing computerized decision support at the time of prescribing), improved health services (e.g., greater use of clinical pharmacy services) and better patient/caregiver education and communication.

18.5 Conclusion

Multiple medication use is common among older adults, with different rates and types of medication use seen in different care settings. Multiple medication use can result in an increase in prescribing problems, suboptimal medication adherence and adverse health outcomes including TFs and ADRs. Understanding medication use and its subsequent effects in different health care settings should be helpful for designing future interventions to improve the quality of care for older adults.

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Visual Impairment

19

Barbara E.K. Klein and Ronald Klein

Abstract

Visual impairment accompanies a wide range of ocular and systemic diseases and is a common cause of disability in the United States (US). It has been estimated that about 10 million people in the US are visually impaired. The World Health Organization (WHO) estimates that 314 million people worldwide are visually impaired and that 45 million of them are blind. These estimates are based for the most part on high contrast acuity. Common factors associated with visual impairment, some predisposing to impairment, other than the result of impairment, are age, potential to contribute to the work force, their quality of life, depression, and the possible effect of poor vision on independence and cognition.

The economic burden of major adult visual disorder in the US was estimated to be 35.4 billion dollars annually, including 16.2 billion dollars in medical costs, 11.1 billion dollars in other direct costs, and 8 billion dollars in productivity losses. This is a transnational problem. For example, the economic cost of visual impairment in Japan was estimated to be 72.8 billion dollars in 2007. While assistive equipment exists to compensate for some of the disabilities, they do not restore vision and costs may be more than individuals and health care systems can afford. Thus, visual impairment is common and is a costly burden for individuals and for health care systems.

Visual impairment associated with aging accompanies a wide range of ocular and systemic diseases including age related cataracts, age related macular degeneration diabetic retinopathy, retinal vein occlusions and refractive error. Therefore, information is given specific to these entities.

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Age-related macular degeneration • Cataract • Diabetic retinopathy • Glaucoma • Presbyopia • Retinal vein occlusions • Refractive errors • Visual impairment • Aging • Epidemiology • Geriatrics • Older adults • Longevity • Prevention • Risk factors

Abbreviations

AMD	Age-related macular degeneration
AREDS	Age-Related Eye Diseases Study
CI	Confidence interval
C/D	Cup disk
GA	Geographic atrophy
ME	Macular edema
NA	Not applicable
NV	Neovascular
IOP	Intraocular pressure
RR	Risk ratio
US	United States
WHO	World Health Organization

19.1 Introduction

Visual impairment is one of the most prevalent causes of disability in the United States (US) and worldwide, with a high cost in terms of economic burden for affected individuals and for health-care systems. Visual impairment encompasses a broad range of deficiencies in a wide variety of visual functions, but the term is most commonly applied to a decrease in high contrast (black on white) visual acuity. The severity of visual impairment is related to several different diseases. In this chapter, we review some existing definitions of visual impairment and the public health significance of this disability. We then describe visual impairment with regard to specific disease categories, as well as the risk factors and preventative therapies (if any) for each category. Because this volume is concerned with the health issues of older adults, we limit our description/discussion to vision impairment issues related to aging and do not attempt to cover such problems in children.

19.2 Definition of Visual Impairment

There is some variation in the definitions of visual impairment and blindness. The World Health Organization (WHO) definition of visual impairment is based on the best corrected vision in the better eye, where best corrected implies the testing of vision with optimal refractive correction in place and usually with the eyes tested separately. The WHO defines low vision as a visual acuity of poorer than 20/60 (6/18 in the metric system) or a visual field (peripheral vision) of less than 10° from fixation. The WHO definition of blindness is a visual acuity poorer than 20/400 (3/60 in the metric system) in the better eye. In the US, impaired vision is usually considered to be a visual acuity of poorer than 20/40, and legal blindness is considered to be a visual acuity of poorer than 20/200, which differ only slightly from the WHO definitions.

These definitions have been used for assigning blindness benefits and are a crude guide for the visual function needed for specific tasks or for the criteria that must be met for driving licensure. The classifications are based on visual acuity, that is, high contrast acuity. They are not informative regarding color vision, contrast sensitivity and near vision, though in most individuals these abilities are correlated with high contrast acuity. Visual field criteria for blindness benefits are used only when there is an extreme loss of visual field. Depending upon the needs of the individual, the loss of a more modest amount of visual field can impair driving ability, the ability to perform athletics and the ability to perform some work tasks, such as when objects are present in the periphery

which can cause harm if not perceived when necessary. Stereoscopic vision (depth perception) is often ignored despite the fact that its absence, especially soon after the loss or severe compromise of vision in one eye, can leave an individual unable to quickly discern curbs, steps or the rim of a cup, the latter being important when pouring hot fluid. Thus, for optimal understanding of visual disabilities and the needs that accompany them, the definition of visual impairment should be situation-dependent.

19.3 Public Health Significance

Visual impairment is one of the ten most common causes of disability in the US [1], with about ten million people in the US being visually impaired. The WHO estimates that 314 million people worldwide are visually impaired and that 45 million of them are blind [2]. In 2004, the economic burden of major adult visual disorder in the US was 35.4 billion dollars, including 16.2 billion dollars in medical costs, 11.1 billion dollars in other direct costs and 8 billion dollars in productivity losses [3]. Visual impairment and its costs are a transnational issue. For example, in 2007 the economic cost of visual impairment in Japan was estimated to be 72.8 billion dollars [4]. While assistive equipment exists to compensate for some visual impairments, such equipment does not restore vision and costs may be more than individuals and health care systems can afford [5]. Thus, visual impairment is common and is a costly burden for individuals and for health care systems.

The public health significance of visual impairment is directly related to the personal characteristics of the individuals affected, including the age of the individuals with impairment, their age-dependent potential to contribute to the work force, their quality of life, the presence and severity of depression, the possible effect of poor vision on independence and cognition, and the availability of rehabilitation or therapeutic services.

19.4 Common Diseases Associated with Age-Related Visual Impairment: Description and Epidemiology

19.4.1 Age-Related Cataracts

The function of the eye's lens for vision is that it permits light and images to be transmitted to the retina. It also plays a role in focusing an object of regard on the retina. When the lens is not clear, the intensity and wave length (color) of objects are diminished or distorted while passing through the lens, which results in impaired imaging on the retina. A cataract is an opacity of the eye's natural lens. There are three common types of age-related cataract: nuclear, cortical, and posterior subcapsular. Each of these refers to the location of the opacity within the lens. All three types increase in prevalence and severity with increasing age, but they differ in frequency of occurrence, the relative importance of their other risk factors, and the severity of the visual impairment that they cause.

If there is no intervention in the form of cataract surgery, cataracts may progress to a 'mature' cataract, at which point the lens is opaque and the contribution of each of the aforementioned lesions cannot be determined. Considering them as single lesions, nuclear and cortical cataracts are the most common and similar in frequency (prevalence of about 16% in those 40–86 years of age [6]), while posterior subcapsular cataracts are far less common (about one third as common as the other two). Visual impairment via cataract is most commonly caused by nuclear cataract, though posterior subcapsular cataracts—the least common type—are nearly as common a predecessor of cataract-related decreases in vision and of cataract surgery.

Cataracts are the most common cause of visual impairment, both worldwide [7] and in the US [8] (Fig. 19.1). See Table 19.1 for prevalence rates in the US for cataracts by age, gender, and race/ethnicity. Cataracts are less commonly a cause for legal blindness in the US [8] (Fig. 19.2). It is to be noted that most publications do not categorize cataracts by subtype.

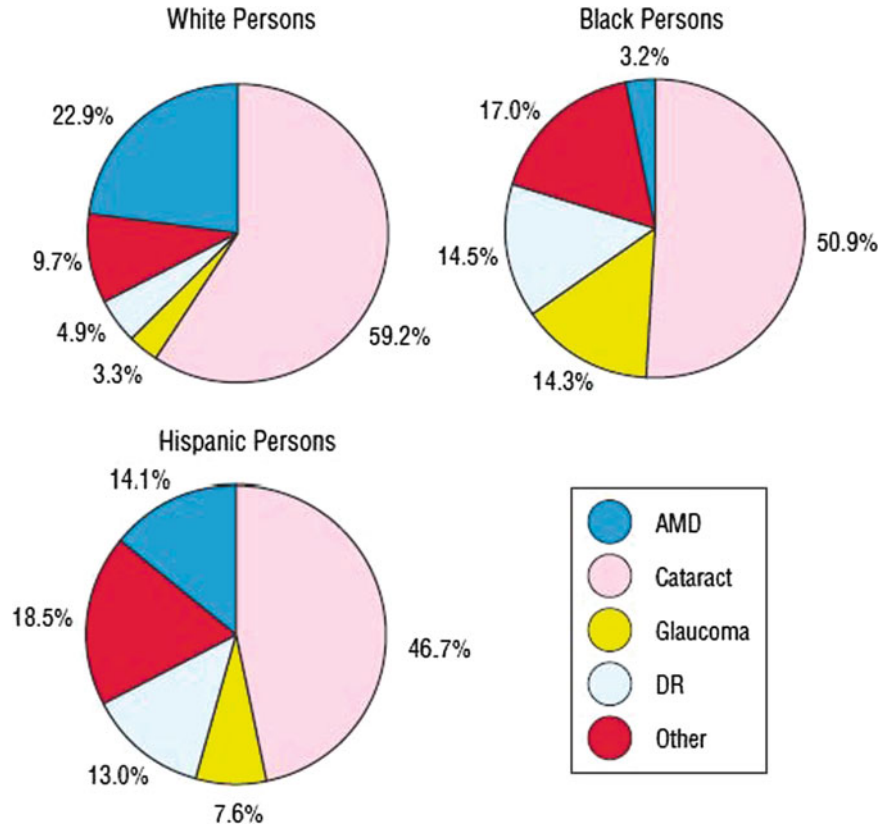

Fig. 19.1 Causes of low vision (best corrected visual acuity <6/12 [<20/40] in the better seeing eye, excluding those who were categorized as being blind by the US definition) by race/ethnicity. *AMD* indicates age-related macular degeneration; *DR* diabetic retinopathy (Permission granted by Archives of Ophthalmology to reuse Figure 3 from p. 481 of [8])

19.4.2 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) affects the central part of the retina and the macula, the region responsible for fine vision. The presence of this condition can be seen with an ophthalmoscope and can be imaged using film or digital imaging techniques. It is manifest in its early stages by discrete yellow areas that are related to the accumulation of lipid-containing deposits (called drusen) under the retina. Drusen range in size and shape from very small (<63 μ) well-defined lesions to large (>250 μ) amorphous lesions. They may be accompanied by areas of hypo- or hyperpigmentation. Late in the disease process, the drusen may disappear or become less apparent, but areas of atrophy of the retina and/or bleeding under the retina (neovascular [NV] AMD) may be seen. The atrophy and bleeding are often accompanied by decreased visual function, which may be profound. Grading schemes are used to describe the lesion characteristics, which are ordered in a severity scale that are useful when describing the progression of the disease when advising patients. The schemes are useful to facilitate epidemiologic studies and clinical trials.

AMD is a less common cause of decreased visual acuity than cataracts in virtually all populations studied [7] (Fig. 19.1). However, in the US and in other European-derived populations, it is not the most common cause of vision poorer than 20/200. AMD is also a relatively important cause of poor vision in Hispanics (Fig. 19.1) AMD is

Table 19.1 Prevalence of cataract by age, gender, and race/ethnicity[a]

	Prevalence per 100 individuals (95% CI)	
Age (years)	White persons	Black persons
Females		
40–49	1.9 (1.2–2.8)	2.2 (1.4–3.5)
50–54	5.0 (4.0–6.2)	7.3 (5.7–9.3)
55–59	9.4 (7.7–11.5)	12.8 (10.2–16.0)
60–64	16.9 (14.1–20.0)	20.1 (16.4–24.2)
65–69	27.7 (24.1–31.6)	28.5 (24.3–33.1)
70–74	41.0 (36.9–45.1)	37.4 (32.6–42.5)
75–79	54.7 (50.2–59.1)	46.1 (40.1–52.2)
≥80	76.6 (71.2–81.2)	60.9 (51.0–69.9)
Males		
40–49	2.8 (2.1–3.7)	1.7 (1.1–2.5)
50–54	4.9 (4.2–5.7)	4.5 (3.6–5.6)
55–59	8.2 (7.0–9.5)	7.6 (6.2–9.3)
60–64	13.8 (12.1–15.7)	11.9 (9.9–14.2)
65–69	22.4 (20.1–24.8)	17.5 (15.0–20.3)
70–74	33.9 (31.2–36.8)	24.1 (21.0–27.5)
75–79	47.2 (43.9–50.4)	31.3 (27.1–36.0)
≥80	71.3 (67.0–75.2)	46.2 (37.9–54.6)

Abbreviation: CI confidence interval

[a]Significant lens opacity was defined as the presence of 1 or more of the following in either eye: posterior subcapsular cataract of 1.0 mm or more, cortical cataract occupying 25% or more of the lens visible through a dilated pupil, or nuclear cataract greater than or equal to the penultimate grade in the system used (i.e., grade ≥3 in the Wilmer Cataract Grading System[100] and in the Lens Opacities Classification System II [101], and grade ≥4 in the Wisconsin Cataract Grading System [102]) (Permission granted by Archives of Ophthalmology to republish Table 2 from page 489 of [103])

relatively less common in blacks [9]. The importance of age is apparent in both men and women, and in whites and blacks (Table 19.2). AMD is more prevalent in women than in men, and more prevalent among whites than blacks. These general trends are apparent for any severity level of AMD [9]. See Table 19.2 for prevalence rates in the US for AMD and presence of drusen ≥125 μ by age, gender, and race/ethnicity.

19.4.3 Glaucoma

Glaucoma is a term applied to disease of the eye that is due to destruction of the nerve tissue of the retina, whether it involves ganglion cells or nerve fibers. Upon examination, this is manifest by enlargement of the optic cup, the depression in the center of the optic disc. This is referred to as an increased cup/disc (C/D) ratio. This may be accompanied by pallor of the disc, and may also be manifest as asymmetry of the cup with notching of the rim. The associated functional deficit is usually a characteristic pattern of diminished peripheral vision that can be detected by testing of the visual field. It is usually assumed to be due to intraocular pressure (IOP) that is 'too high' for that eye.

The specific level of IOP that is 'too high' varies from individual to individual, so an absolute value is not always a helpful criterion. In years past, an IOP that is 'too high' was taken to be an IOP greater than 21 mmHg. A specific episode of high pressure can be documented in some persons with glaucoma, especially those with acute angle-closure glaucoma associated with a specific morphology of the front part of the eye. However, in the US, angle closure is relatively uncommon. In groups in the US, it is more often the case that there is no obvious anatomic finding that is thought to predispose to glaucoma. Most cases are thus referred to as open-angle glaucoma. Its presence is defined using diagnostic criteria, but these criteria differ among studies and even among clinicians. Most studies include an increase in the C/D ratio, usually accompanied by an abnormal visual field that is characterized by constriction of the visual field. Some studies do not include IOP as a criterion, though most consider a high IOP to be a strong risk factor. Pooled epidemiologic data from several large studies has provided estimates of prevalence in the US. See Table 19.3 for prevalence of glaucoma in the US by age, gender, and race/ethnicity. It is assumed that pooling data from a large number of people with glaucoma overcomes some of the problems related to the heterogeneity of classification [10].

An age trend is apparent for whites, blacks, and Hispanic groups. Black persons have the highest prevalence in every age group (except for the very eldest group of women, whose numbers

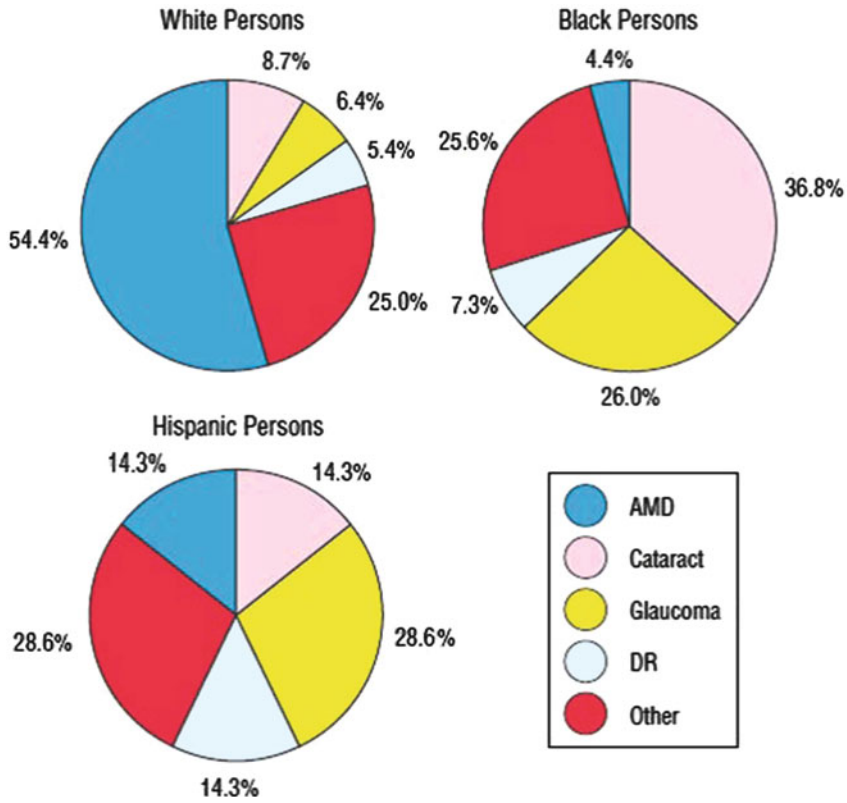

Fig. 19.2 Causes of blindness (best-corrected visual acuity <6/60 [<20/200] in the better-seeing eye) by race/ethnicity. *AMD* indicates age-related macular degeneration; *DR* diabetic retinopathy (Permission granted by Archives of Ophthalmology to reuse Figure 2 from p. 481 of [8])

are small), with prevalences in the black group nearly three times that in white individuals after age adjustment.

19.4.4 Diabetic Retinopathy

The lesions characteristic of diabetic retinopathy are microvascular. Microaneuryms are usually the first observable clinical lesions. These appear as red dots in the retina usually 15–60 μ in diameter and consist of cellular outpouchings of retinal capillaries. Other early microvascular lesions include retinal hemorrhages, 'cotton wool patches' or spots (retinal nerve fiber layer infarcts), other microvascular abnormalities, changes in the retinal veins (venous beading), growth of new retinal vessels, vitreous hemorrhage (secondary to bleeding from the new vessels), retinal detachment and phthisis bulbi (shrunken, scarred non-seeing eye). Some of these lesions can be seen in the presence of other conditions; however, the relentless progression of these lesions in those with diabetes is characteristic of this condition. While there are other ocular conditions that are more common in those with diabetes (e.g., earlier cataract formation and possibly increased risk of glaucoma), retinopathy is generally considered to be the most destructive to vision. It has been the most common cause of new cases of blindness in persons 20–74 years of age, though this may not be the case in the future due to more aggressive treatment of diabetes. For persons in the general population with diabetes (the majority of whom have type 2 diabetes), age and gender are not important factors with regard to prevalence. There does seem to be a modest effect of race/

Table 19.2 Prevalence rates for advanced age-related macular degeneration (AMD) and presence of drusen of 125 μm or larger in diameter by age, gender, and race/ethnicity

Gender and age, year	Prevalence per 100 individuals (95% CI)			
	Any AMD	Neovascular AMD	Geographic atrophy AMD	Drusen ≥125 μm[a]
White participants				
Females				
40–49	–	–	–	1.41 (1.24–1.60)
50–54	0.20 (0.17–0.24)	0.14 (0.10–0.19)	0.11 (0.09–0.13)	2.52 (2.29–2.78)
55–59	0.22 (0.20–0.24)	0.16 (0.14–0.19)	0.12 (0.11–0.13)	3.70 (3.41–4.00)
60–64	0.35 (0.33–0.39)	0.26 (0.20–0.30)	0.19 (0.17–0.21)	5.39 (5.03–5.78)
65–69	0.70 (0.64–0.76)	0.51 (0.45–0.59)	0.37 (0.34–0.40)	7.81 (7.30–8.34)
70–74	1.52 (1.41–1.64)	1.09 (0.96–1.24)	0.81 (0.74–0.88)	11.17 (10.39–12.00)
75–79	3.44 (3.22–3.69)	2.40 (2.14–2.70)	1.85 (1.72–1.99)	15.73 (14.48–17.06)
≥80	16.39 (14.97–17.91)	11.07 (9.46–12.91)	9.37 (8.53–10.29)	29.16 (26.34–32.15)
Males				
40–49	–	–	–	1.56 (1.27–1.90)
50–54	0.34 (0.23–0.50)	0.23 (0.16–0.33)	0.15 (0.11–0.21)	2.65 (2.28–3.08)
55–59	0.41 (0.34–0.50)	0.28 (0.23–0.34)	0.22 (0.19–0.26)	3.77 (3.33–4.26)
60–64	0.63 (0.53–0.75)	0.42 (0.36–0.50)	0.37 (0.32–0.43)	5.32 (4.79–5.92)
65–69	1.08 (0.91–1.29)	0.73 (0.61–0.87)	0.66 (0.56–0.76)	7.48 (6.74–8.28)
70–74	1.98 (1.69–2.32)	1.33 (1.14–1.56)	1.19 (1.04–1.37)	10.40 (9.29–11.63)
75–79	3.97 (3.18–4.24)	2.49 (2.15–2.88)	2.16 (1.91–2.46)	14.30 (12.55–16.25)
≥80	11.90 (9.78–14.41)	8.29 (6.76–10.12)	6.60 (5.52–7.89)	25.62 (21.69–29.98)
Black participants				
Females				
40–49	0.50 (0.40–0.63)	0.50 (0.40–0.63)	–	3.01 (2.41–3.76)
50–54	0.68 (0.57–0.80)	0.49 (0.41–0.59)	0.19 (0.15–0.22)	4.03 (3.41–4.75)
55–59	0.82 (0.71–0.96)	0.60 (0.52–0.70)	0.22 (0.19–0.26)	4.88 (4.26–5.59)
60–64	1.00 (0.86–1.15)	0.73 (0.63–0.84)	0.27 (0.23–0.31)	5.91 (5.25–6.63)
65–69	1.21 (1.04–1.42)	0.89 (0.76–1.03)	0.32 (0.28–0.38)	7.13 (6.35–7.99)
70–74	1.47 (1.23–1.76)	1.08 (0.90–1.28)	0.39 (0.33–0.48)	8.58 (7.53–9.75)
75–79	1.79 (1.45–2.21)	1.31 (1.06–1.61)	0.48 (0.39–0.60)	10.29 (8.81–11.98)
≥80	2.44 (1.85–3.20)	1.78 (1.35–2.33)	0.66 (0.50–0.86)	13.66 (11.14–16.64)
Males				
40–49	0.31 (0.16–0.60)	0.31 (0.16–0.60)	–	3.90 (2.79–5.43)
50–54	0.42 (0.25–0.70)	0.25 (0.15–0.41)	0.17 (0.10–0.29)	4.71 (3.67–6.03)
55–59	0.52 (0.33–0.80)	0.30 (0.20–0.47)	0.22 (0.14–0.33)	5.34 (4.35–6.53)
60–64	0.63 (0.42–0.95)	0.37 (0.25–0.56)	0.26 (0.17–0.39)	6.04 (5.06–7.19)
65–69	0.77 (0.50–1.18)	0.45 (0.29–0.70)	0.32 (0.20–0.48)	6.82 (5.73–8.11)
70–74	0.93 (0.57–1.53)	0.55 (0.33–0.91)	0.38 (0.23–0.63)	7.71 (6.32–9.37)
75–79	1.14 (0.63–2.05)	0.67 (0.37–1.21)	0.47 (0.26–0.84)	8.69 (6.84–10.97)
≥80	1.56 (0.72–3.35)	0.92 (0.42–1.98)	0.67 (0.29–1.38)	10.50 (7.63–14.29)

Data revised and is highlighted in yellow. Correction published: Error in Table and Text in: Prevalence of Open-Angle Glaucoma Among Adults in the United States Arch Ophthalmol 2011;129(9):1224 (Permission granted from Archives of Ophthalmology to reuse Table 2 from page 567 of [9])

Abbreviation: CI confidence interval

[a]At least 1 druse 125 μm or larger in diameter must be present in either or both eyes

Table 19.3 Prevalence of glaucoma by age, gender, and race[a]

	Prevalence/100 population (95% CI)		
Age, year	White subjects	Black subjects	Hispanic subjects
Women			
40–49	0.83 (0.65–1.06)	1.51 (0.94–2.41)	0.34 (0.15–0.72)
50–54	0.89 (0.78–1.02)	2.24 (1.59–3.14)	0.65 (0.37–1.15)
55–59	1.02 (0.89–1.16)	2.86 (2.16–3.78)	0.98 (0.61–1.58)
60–64	1.23 (1.07–1.41)	3.65 (2.83–4.69)	1.49 (0.97–2.28)
65–69	1.58 (1.37–1.82)	4.64 (3.54–6.05)	2.24 (1.43–3.49)
70–74	2.16 (1.87–2.49)	5.89 (4.28–8.05)	3.36 (2.00–5.60)
75–79	3.12 (2.68–3.63)	7.45 (5.06–10.84)	5.01 (2.68–9.15)
≥80	6.94 (5.40–8.88)	9.82 (6.08–15.48)	10.05 (4.35–21.52)
Men			
40–49	0.36 (0.27–0.47)	0.55 (0.31–0.95)	0.39 (0.18–0.85)
50–54	0.61 (0.50–0.74)	1.71 (1.25–2.32)	0.69 (0.39–1.25)
55–59	0.85 (0.72–1.00)	3.06 (2.30–4.04)	1.00 (0.61–1.64)
60–64	1.18 (1.02–1.37)	4.94 (3.69–6.59)	1.44 (0.92–2.24)
65–69	1.64 (1.40–1.91)	7.24 (5.40–9.63)	2.07 (1.32–3.23)
70–74	2.27 (1.90–2.72)	9.62 (7.29–12.59)	2.97 (1.79–4.89)
75–79	3.14 (2.53–3.90)	11.65 (8.81–15.25)	4.23 (2.32–7.60)
≥80	5.58 (4.15–7.47)	13.21 (7.85–21.38)	7.91 (3.53–16.77)

Highlighted cell revised. Correction published; Error in Table and Text in: Prevalence of Open-Angle Glaucoma Among Adults in the United States. Arch Ophthalmol. 2011;129(9):1224 (Permission granted by Archives of Ophthalmology to reuse Table 3 from page 535 of [10])

Abbreviation: CI confidence interval

[a]Glaucoma indicates primary open-angle glaucoma

ethnicity, with higher prevalence in persons of African and Hispanic background compared to those of European background [11].

Diabetic retinopathy is a significant source of visual impairment in all three of the aforementioned racial/ethnic groups, though it is notably lower in those of European background compared to those of African or Hispanic background (Fig. 19.1) [8]. In the past, those with type 1 diabetes were more likely to have more severe diabetic retinopathy than those with type 2 diabetes, and had poorer vision to accompany this [12, 13]. However, there are indications that better glycemic control may result in decreased levels of visual impairment in both groups [14].

Diabetic macular edema (ME) is another retinal lesion associated with diabetes and it, too, is associated with visual impairment. It is due to increased vascular permeability and hypoxia secondary to ischemia, and it results in swelling in the macular area of the retina. Diabetic ME occurs in individuals with type 1 and type 2 diabetes. However, when present, it is more often a cause of severe visual impairment in individuals with type 2 diabetes than in those with type 1 [15].

The public health importance of diabetic retinopathy is dependent upon the prevalence of diabetes itself. See Table 19.4 for estimated prevalence of diabetes mellitus in the US by age, gender, and race/ethnicity. Thus, diabetic retinopathy remains an important cause of eye disease in middle and older age adults.

19.4.5 Retinal Vein Occlusions

Vein occlusions can occur in the retina, just as they can in other parts in the body. When the central retinal vein is involved, retinal hemorrhage may occur and may involve all four quadrants of the retina that surround the optic nerve, often

Table 19.4 Estimated prevalence of diabetes mellitus in the United States by age, gender, and race/ethnicity[a]

Gender and age group, year	Prevalence per 100 persons (95% CI)		
	White persons	Black persons	Hispanic persons
Women			
40–49	3.1 (2.3–4.0)	7.2 (4.6–9.7)	6.3 (3.7–8.9)
50–64	7.1 (6.0–8.2)	21.3 (16.6–25.9)	24.1 (17.9–30.3)
65–74	10.6 (9.0–12.2)	23.3 (17.4–29.2)	16.3 (10.3–22.3)
≥75	10.5 (8.7–12.2)	22.4 (14.2–30.7)	18.4 (9.3–27.5)
Subtotal	7.0 (6.4–7.7)	16.1 (13.8–18.4)	14.8 (12.1–17.5)
Men			
40–49	2.5 (1.8–3.2)	5.5 (2.8–8.2)	6.2 (3.2–9.3)
50–64	9.0 (7.6–10.4)	12.4 (8.4–16.3)	15.4 (10.6–20.2)
65–74	15.3 (12.7–17.8)	21.4 (14.6–28.3)	16.5 (9.0–24.1)
≥75	11.6 (9.2–13.9)	22.1 (12.0–32.2)	27.1 (16.3–37.8)
Subtotal	8.0 (7.2–8.7)	11.3 (9.1–13.4)	11.7 (9.3–14.2)
Total	7.5 (7.0–8.0)	14.0 (12.4–15.6)	13.3 (11.5–15.2)

Abbreviation: CI confidence interval

[a]Estimates for the number of persons with diabetes mellitus are based on an adaption from the 1999 National Health Interview Survey Public Use Data Release [104] and 2000 US Census Population Estimates [105] (Permission granted by Archives of Ophthalmology to reuse Table 4 from page 558 of [106])

accompanied by dilation and tortuosity of the veins. Bleeding can break through the posterior hyaloids membrane into the vitreous cavity. Swelling of the optic nerve and of the macula may occur as well new vessel formation. Occlusion of only a branch of the central retinal vein (branch vein occlusion) may be accompanied by little in the way of symptoms or findings upon physical examination, though dilated veins may be seen in the distribution of the more peripheral venules that drain to the affected vein. Branch vein occlusion may be accompanied by swelling, small hemorrhages in the retina, and even new vessel formation if the occlusion has occurred some time before the diagnosing examination. Individuals with diabetes are more likely to experience branch retinal vein occlusions than those without diabetes (OR 2.43, 1.04–5.70) [16].

19.4.6 Refractive Errors, Presbyopia

The eye refracts light to focus an image on the retina, similar to the way a camera focuses an image on film. In the emmetropic (normal vision) state, this is done by the optical system of the eye unaided by external focusing lenses and is measured at a distance of 20 ft (6 m). The state in which external lenses are required for best focus at that distance is ametropia. This can manifest itself as myopia (nearsightedness) or hyperopia (farsightedness). While these two conditions may seem trivial compared to eye conditions for which lenses cannot improve visual acuity sufficiently (or at all), it has been estimated that visual impairment due to uncorrected refractive error affects about 83.3% of the US population [17]. It is estimated that 70% of individuals with severe impairment could achieve good vision with refractive correction [17]. Countries similar to the US in demographic and socioeconomic profiles also report high proportions of individuals whose visual impairment is related to uncorrected or undercorrected refractive error [18–20]. It is reasonable to assume that the proportions are greater in emerging countries. In the US, the impact of uncorrected refractive error is higher amongst ethnic minorities [17]. While the prevalence of myopia decreases with increasing age [21, 22], hyperopia correspondingly increases, an observation that has been confirmed using incidence data [23]. As one ages, the accommodation

power of the eye may diminish (presbyopia). The specific epidemiology of this condition is not well described.

19.5 Risk Factors

19.5.1 Age-Related Cataracts

Risk factors for cataracts vary by the specific type of cataract, but age is the most important risk factor for each. The mathematical relationship of incidence of cataracts to age for any of the cataract types is difficult to model with any accuracy. This is due to the availability and high rates of cataract surgery, which may be done at various stages in cataract development. This is further complicated because the costs associated with cataract surgery may influence when the surgery is performed relative to the course of development or progression of the cataract. However, the relationship of cataracts with age is likely to be monotonic after the age of 43 [24].

Environmental and personal factors other than age have been found to be associated with cataracts. One study found heavy drinking to be associated with all three types [25]. Smoking and being female sex have been associated with nuclear cataracts [26]; being female, having diabetes and exposure to ultraviolet (UV-B) light have been associated with cortical cataracts [27, 28]; and having diabetes and using steroids have been associated with posterior subcapsular cataracts [29–31]. In addition, gamma radiation exposure has been documented as a risk factor in atomic blast survivors and in those who work in environments where they are exposed to gamma radiation [32]. Generally, most of these studies have found differences in cataract prevalence, by education, or income status. Dehydration and/or diarrhea have been implicated as risk factors [33–36] in countries with greater socio-economic stress. There are many other factors that have been examined with respect to each type of cataract, but the contributions of each of these additional risk factors tend to be small. On a positive note, one population-based study in the US found that the incidence of cataracts is apparently declining in more recent birth cohorts [24].

Recently, studies have examined genetic factors that may be associated with cataracts. Data have indicated genetic contributions to syndromic cataracts or to cataracts that occur in conjunction with other systemic congenital conditions such as Down syndrome, progyria [37] and Lowe's syndrome, and congenital cataracts that occur without other obvious systemic conditions, such as crystal cataract [38, 39]. Recently, a specific gene has been found to be associated with typical age-related cortical cataracts [40]. However, the importance of these genes in explaining common age-related cataracts in the general population is not known. Since much of the variance in the distribution of age-related cataracts is explained by age and other personal and environmental factors, it is likely that further studies of genetic factors and both gene/environment and gene/gene interactions will reveal associations of smaller effects.

19.5.2 Age-Related Macular Degeneration

As with cataracts, many factors have been investigated as risk factors for AMD. Age is by far the most important risk factor. Cigarette smoking has been found to be related to the prevalence and incidence of late AMD [41–43].

Some studies have found hypertension to be associated with increased AMD [44, 45], though cross-sectional data do not consistently find a relationship [45]. The latter may be related to selective survival as well as the possible effects of successful anti-hypertensive treatment. Findings regarding the relation of systemic inflammatory disease and markers of inflammation with AMD have also been inconsistent. In the Beaver Dam Eye Study, a higher white blood cell count at baseline, independent of smoking, was associated with a greater 10-year incidence of drusen larger than 125 μ in diameter (Risk Ratio [RR] per k/μl 1.10, 95% Confidence Interval [CI] 1.03, 1.17), greater retinal pigment epithelial depigmentation (RR 2.08, 95% CI 1.01, 1.16) and increased progression of AMD (RR 1.09, 95% CI 1.03, 1.15). This association with higher white blood cell

count was also found in the Blue Mountains Eye Study [46] but was not found in the Cardiovascular Health Study [47]. As with cataracts, there appears to be a cohort effect such that more recent birth cohorts appear to be relatively protected [48].

In view of the strong heritability of AMD, genetic factors have been sought as suspected causes of this condition [49]. The finding of a strong association of a polymorphism in the complement factor H Y402H gene on Chromosome 1 [50–52] with AMD supports the hypotheses that the inflammatory process may have a role in the pathogenesis of AMD. The association of ARMS2/HTRA1 SNPs on Chromosome 10 with AMD has also been found in most racial/ethnic groups studied. The functional effect that this gene has on the retina that results in AMD is not known. The search for other genes associated with this disease in the general population continues, with several candidate genes having been found on genome-wide association studies in several large populations. To date, none have been found to have as strong an association as the complement factor H or ARMS2 genes.

19.5.3 Glaucoma

As noted above, the strongest risk factor for open-angle glaucoma is having African-American ancestry. There is some data to suggest that persons of Hispanic background may also be at greater risk than those of European descent [10].

Within ethnicity, high intraocular pressure is the strongest risk factor for open-angle glaucoma and its progression [53]. Diabetes has been associated with an increased risk of open-angle glaucoma [54]. Ocular perfusion pressure [55, 56] is also a risk factor for glaucoma. Having a relatively thin central cornea has been found to be a risk factor for glaucoma, but this characteristic may only influence the measurement of intraocular pressure and not by itself represent a true risk factor. There have been several genes that have been implicated in the development of open-angle glaucoma in adults, but most of these are associated with ocular or systemic syndromes. Evidence is slowly emerging of genetic factors that likely influence the development of open-angle glaucoma, but the effects are small. This area is currently being investigated.

19.5.4 Diabetic Retinopathy

Duration of diabetes has historically been the most important risk factor for diabetic retinopathy [57–59]. This characteristic is still very important, but its importance has been relatively reduced due to the now well-appreciated importance of glycemic control. It is likely that duration of diabetes incorporates the influence of hyperglycemia over time. Even now, when levels of glycemia are better controlled than they were before the results of the Diabetes Control and Complications Trial [60] and the United Kingdom Prospective Diabetes Study [61] were incorporated into clinical practice, the importance of other risk factors is dwarfed by that of diabetes and hypoglycemia. In some studies with long-term follow up, hypertension or relatively higher systemic blood pressure has also been associated with severity of diabetic retinopathy. In some studies, elevated triglycerides are significant correlates of the severity of diabetic retinopathy. This relationship was supported by the finding in the randomized controlled Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study (see Sect. 19.6.4) that individuals with type 2 diabetes who were randomized to fenofibrate had a lower risk of progression of diabetic retinopathy than those in the control group [62]. There is some evidence that pregnancy may exacerbate the development or progression of diabetic retinopathy [63], but retinopathy is likely to regress to pre-pregnancy levels of severity after parturition [64]. The most important risk factors for ME are higher glycemia levels, greater duration of diabetes and higher blood pressure [65].

19.5.5 Retinal Vein Occlusions

Risk factors for retinal vein occlusions include age, systemic hypertension, diabetes mellitus, ocular perfusion pressure, smoking, and renal

dysfunction [16, 66]. Limited data suggests that obstructive sleep apnea is associated with increased risk of retinal vein occlusion [67].

19.5.6 Refractive Errors, Presbyopia

The risk factors for refractive error in adults include having a family member with a specific refractive error [68] and associations with specific gene sites [69]. It is likely that shared environmental factors and perhaps more than one gene (polygenic influences) influence refraction [70]. In addition, there are important environmental/personal correlates of refractive error, including age and years of education [22]. Changes in refractive error in adulthood are commonly a shift in refraction toward hyperopia [71, 72], unless nuclear cataract develops or progresses which causes a myopic shift [71]. Perhaps the most important change for many adults over 40 years of age is the development of presbyopia that results from the decreasing accommodative ability of the eye with age. In most individuals, this causes diminished near acuity without the help of plus lenses such as reading glasses or bifocals. It has little effect on distance acuity for persons who are not hyperopic (farsighted). While age is the most important risk factor, it has been shown that in individuals with type 1 diabetes, the onset of presbyopia occurs earlier than in those without this condition. The age of onset of presbyopia in individuals with type 1 diabetes is affected in a predictable way by the duration of diabetes such that each year of duration is nearly commensurate with adding a year of age in its effect on accommodation [73].

19.6 Prevention, Clinical Trials

19.6.1 Age-Related Cataracts

There are no proven therapies to prevent or decrease the progression of age-related cataracts. In the Age-Related Eye Diseases Study (AREDS), a randomized trial to test the use of zinc and antioxidant supplements to prevent or delay the development of AMD, the investigators also evaluated whether these supplements provided protective effects for the lens. They reported no effect of vitamin C, vitamin E, beta carotene or zinc on the 7-year risk of development or progression of age-related cataracts [74]. A randomized trial in which vitamin E and vitamin C supplements were given for protection from cardiovascular disease found no effect on the self-reported history of cataract development [75]. In the Beaver Dam Eye Study, the use of statin drugs was associated with a protective effect for nuclear cataract [76], but this finding has not been tested in a clinical trial. Perhaps the most important evidence with regard to the potential prevention of cataracts has been the findings of epidemiologic studies that examined the avoidance of risk factors (e.g., smoking for nuclear cataracts and UV-B exposure for cortical cataracts).

19.6.2 Age-Related Macular Degeneration

The AREDS showed that the supplements tested were associated with a moderate benefit only in individuals at high risk of late AMD. The supplements were not effective in those at low risk of the severe endpoint at the time they were enrolled [77]. Other studies of diet and/or nutritional supplements for AMD have not demonstrated convincing evidence of benefit. Use of statins to prevent or retard progression of AMD lesions has also not shown evidence of benefit [78]. Some believe that protection from blue light decreases the incidence or progression of AMD, but no clinical trial has yet tested this belief.

Data from epidemiologic studies and clinical trials indicate that smoking is the most important personal/environmental exposure associated with neovascular age-related macular degeneration [41, 79, 80]. Perhaps avoiding this exposure will result in a lower likelihood of the development or progression of early lesions of this condition. Clinical trials for intravitreal anti-vascular endothelial growth factor or steroid treatment of AMD will not be discussed here.

19.6.3 Glaucoma

Prevention of primary open-angle glaucoma is, at this time, virtually impossible because there are no reliable methods to discover risk status for this disease. When intra-ocular pressure is found to be elevated in the absence of other characteristics of open angle glaucoma the chance of developing overt open angle glaucoma may be decreased by use of a variety of pharmacologic agents usually administered as drops. This was shown in the Ocular Hypertension Treatment Study and other studies [81, 82]. There have been many clinical trials of medical and surgical procedures to retard the progression of open-angle glaucoma. They will not be reviewed here except to note that surgical procedures often have limited success when the glaucoma is advanced.

19.6.4 Diabetic Retinopathy

The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study showed that control of glycemia decreased the development and progression of diabetic retinopathy in individuals with type 1 and type 2 diabetes, respectively [60, 61]. The findings reinforce similar conclusions from observational epidemiologic studies in individuals with type 1 and type 2 diabetes [83, 84]. Recently, the ACCORD Eye Study found a beneficial effect on retinopathy of using fenofibrate, a medication that is given to decrease triglyceride levels [62]. This study found that controlling higher blood pressure had no significant effect on diabetic retinopathy, although an association has been hypothesized [85] and reported in some cross-sectional studies [57, 58, 86].

19.6.5 Retinal Vein Occlusion

There are no known specific preventive treatments for retinal vein occlusions. Laser photocoagulation may improve vision for patients who have sustained retinal branch vein occlusion [87]. One study showed that treatment with intravitreal corticosteroids had a minimal beneficial effect and complications were common [88]. The intravitreal injection of anti-vascular endothelial growth factors appears to improve the visual outcome [89, 90] although which specific agent and long term risks associated with this class of medications require further study.

For central retinal vein occlusion, laser treatment does little to improve vision but decreases the risk of neovascular glaucoma, a dreaded complication of central retinal vein occlusion that occurs when iris neovascularization follows the vein occlusion [90]. Intravitreal steroids seem to offer some benefit, but increased intraocular pressure is a significant complication [91]. The injection of anti-vascular endothelial growth agents offers some improvement in vision [89].

19.6.6 Refractive Errors, Presbyopia

It has been suggested that education has a causal relationship to myopic refractive error. However, there is no clinical trial data to suggest that less education would temper the development of myopia, and such a trial would be questionable in terms of ethics. However, some studies have suggested that greater outdoor activity may reduce the effect of education. Once a refractive error has developed, there is no way to reverse this except through refractive surgery or, in some cases, lens surgery. The latter is rarely performed solely to correct a refractive problem. Refractive surgery, on the other hand, is now commonplace and decreases the amount of error, but many people who undergo this procedure still require corrective lenses for best vision. Refractive error may change progressively after the surgery, although most people have a long-term decrease in the amount of refractive error. Complications from these procedures include infection, overcorrection or undercorrection, unanticipated scarring, glare and—in rare cases—significant permanent decreased vision. Refractive surgery is uncommonly performed in older persons as some refractive error can be diminished by surgery would be done for age-related cataract.

19.7 Falls and Fractures as Related to Impaired Vision

Falls and fractures are important causes of morbidity and mortality in older persons. Falls are an important health problem for older adults with about 30% of persons 65 years of age or older sustaining at least one fall each year [92]. Falls result in significant morbidity [93–95] and mortality [96]. Costs for falls in the elderly in the United States are estimated at over $19 billion annually [97]. It has been found that three different measures of poor or impaired visual function are associated with risk of two or more falls [98]. Hip fractures after the age of 40 were significantly related to best corrected visual acuity, current binocular acuity, near acuity, contrast sensitivity, and visual threshold to light [99]. These data are consistent with the interpretation that visual function is consistently associated with falls and fractures. While these data cannot be interpreted as causal it is reasonable to assume that visual function contributes as a cause of falls and fractures. This gives further credence to importance of maximizing visual function throughout years of later life.

19.8 Conclusion

Visual impairment is a complex condition which can develop and progress as a result of a variety of diseases. The age at which visual impairment develops, the rate at which it progresses and the severity of its effect vary depending upon the disease with which it is associated. Cataracts are the most common cause of visual impairment in both in the US and worldwide. In the US, cataracts are the most common cause of blindness followed closely by open angle glaucoma in black populations, while AMD is the most common cause of blindness in whites. The data that are referred to in this chapter suggest that glaucoma is the most common cause of blindness in Hispanic populations. However, the estimates are based on few persons; more data is needed in this under-studied group of Americans. Diabetic retinopathy is generally considered to be the most destructive ocular condition in individuals with diabetes. It has been the number one cause of new blindness in individuals 20–74 years of age, but this may not be true in the future due to more aggressive treatment of diabetes. It should be remembered that cataract may be the earliest cause of decreased vision in individuals with diabetes.

The greatest risk factor for any type of cataract is age with additional but different risk factors for each of the three types. Age is also the greatest risk factor for AMD, with further risk factors including cigarette smoking and certain genetic factors. Both cataracts and AMD appear to be declining in more recent birth cohorts. The greatest risk factor for open-angle glaucoma is African ancestry, with high intraocular pressure also an important risk factor. Diabetes and hyperglycemia are the greatest risk factors for diabetic retinopathy. Risk factors for retinal vein occlusions include age and systemic vascular risk factors although the effect size of these factors renders them not helpful for prediction. For refractive errors, risk factors include having a family member with specific refractive error, associations with specific gene sites, and age.

Effective therapies for the prevention of cataracts and AMD do not exist at this time beyond avoidance of the risk factors, though surgery is common for treatment of decreased vision due to cataracts. There is no effective prevention for the development of primary open-angle glaucoma, but the chances of developing it may be reduced if high intraocular pressure is detected and treated early. Glycemic control decreases the development and progression of diabetic retinopathy, and fenofibrate may also have a beneficial effect. There is no preventive treatment for retinal vein occlusions, but the injection of anti-vascular endothelial growth agents may improve the vision of those affected and laser photocoagulation may improve vision for those with retinal branch vein occlusion. Visual impairment due to refractive errors are treated by corrective lenses.

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Age-Related Hearing Loss

20

Elizabeth Purchase Helzner

Abstract

Age-related hearing loss (ARHL) is an extremely common and disabling condition among older adults. Its detrimental effects on communication can be felt in the emotional, cognitive and functional domains. Epidemiologic studies of age-related hearing loss provide us with knowledge about the prevalence and incidence of hearing loss in older adults, as well as intrinsic and extrinsic factors that may serve as risk factors for the development and/or progression of hearing loss. Overall, the prevalence of hearing loss (including high-frequency hearing loss) increases with age, and ARHL is more prevalent in men than in women and more common among White and Mexican-American individuals than among Black individuals. Risk factors for hearing loss include lower socioeconomic status, the presence of diabetes mellitus or cardiovascular disease, cigarette smoking, exposure to toxic levels of noise, medication ototoxicity, lead exposure and genetic factors. Prevention methods primarily include limiting one's exposure to risk factors. While much hearing loss is not curable, there are strategies (e.g., conversation techniques, assistive devices) to aid individuals who have ARHL.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Hearing loss • Presbycusis • Hearing aid • Audiometry • Risk factors • Prevention • Tympanography • Prevention • Risk factors

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Abbreviations

APOE-ε4	Apolipoprotein ε4
ARHL	Age-Related Hearing Loss
CHS	Cardiovascular Health Study
CVD	Cardiovascular Disease
dB HL	Decibels Hearing Level
DM	Diabetes Mellitus
DSI	Dual Sensory Impairment
EHLS	Epidemiology of Hearing Loss Study
GRHL-2	Grainyhead-like 2
GSTM1	Glutathione s-transferase mu-1
GSTT1	Glutathione s-transferase theta 1
Health ABC	Health Aging and Body Composition Study
HHIE-S	Hearing Handicap Inventory for the Elderly-Screening Version
Hz	Hertz
KCNQ4	Potassium channel voltage-gated, kqt-like subfamily, member 4
MtDNA	Mitochondrial DNA
NAT-2	N-actyltransferase-2
NHANES	National Health and Nutrition Examination Survey
OAE	Otoacoustic Emissions
PTA	Pure-Tone Average
US	United States

20.1 Introduction

Of the chronic health concerns that face older adults, hearing loss is one of the most common disabling conditions, second only to arthritis (CDC 2003). The decline of hearing sensitivity can compromise an individual's quality of life by interfering with verbal language processing (even mild hearing impairment can interfere with speech processing, especially in multi-speaker situations [1]) and causing social withdrawal. This, in turn, negatively influences emotional well-being, cognitive status and functional status [2, 3].

With worldwide increases in longevity, major public health efforts have been aimed at maximizing health and function among older adults. The ability to communicate is an integral part of a healthy and productive old age. Not only is hearing important for safety and the maintenance of independence, it also plays an important role in maintaining overall life engagement. Thus, the study of age-specific changes in hearing function has become an increasing research focus in the epidemiology of aging. The population-based study of hearing loss and its correlates is making important contributions toward tailoring prevention efforts, and it provides clues to the pathophysiology that underlies this extremely common age-related condition.

In this chapter, we address the public health significance of age-related hearing loss (ARHL), describe its pathophysiology, outline current knowledge regarding the epidemiology of hearing loss in older adults in the United States (US), and describe approaches for the prevention of hearing loss and for rehabilitation.

20.2 Functioning of Normal Hearing

Sound information reaches the brain in two steps: (1) it is first conducted through the external and middle portions of the ear (conductive hearing), then (2) it is transformed into electrical impulses in the inner ear which are transmitted via the acoustic nerve to the auditory cortex of the brain (sensorineural hearing). Most age-related hearing loss is associated with pathology in the sensorineural portion of the auditory system, and is tied to inner ear pathology and changes in central auditory processing.

In a normally functioning individual, acoustic information travels through the air to the external ear, which acts as a resonator. Sound waves vibrate the tympanic membrane at the termination of the external auditory canal, which is connected to the fluid-filled inner ear by way of a chain of tiny bones: the ossicles of the middle ear. The conductive portion of hearing amplifies the pressure of sound waves, strengthening the sound signal which is then transmitted to the inner ear and eventually transformed into neural impulses. The cochlea, housed within the inner ear, is a snail-like structure with three turns. It contains three fluid-filled ducts. The middle of the three

ducts, the scala media, contains the organ of Corti, in which reside tiny hair cells: the sensory stereocilia. The displacement of fluid in the inner ear that results from stimulation of the outer portions of the ear stimulates the stereocilia, which in turn transduce sound information to the auditory nerve. Age-related decreases in the sensitivity of the stereocilia have been documented [4].

20.3 Pathophysiology of Hearing Loss

The inner ear is made up of several functional components, all of which can be affected by aging. Pathologic changes in the sensory, neural, vascular, supporting and mechanical components of the inner ear can all manifest in hearing loss. The most common cause of hearing loss in older adults is presbycusis, an age-associated, progressive, bilateral loss in hearing sensitivity. Presbycusis is caused in part by inherent age-related degenerative changes in the central and peripheral auditory systems; however, its incidence and progression is also influenced by a mixture of extra-auditory factors. The progression of hearing loss in older adults is influenced by the cumulative effects of chronic noise exposure, acoustic trauma, systemic and otological disease, and medication-related ototoxicity [5].

Distinct types of presbycusis have been proposed, based on specific pathologic changes that have been visualized in histopathologic studies of the temporal bones of humans who had age-related hearing loss. The most commonly identified presbycusis types include sensory, neural, strial, mixed and intermediate presbycusis. Sensory presbycusis is characterized by hearing loss that is more pronounced in the higher frequencies, with generally preserved speech recognition. Sensory presbycusis is most consistent with noise-induced hearing damage, and is not believed to be associated with aging itself [5]. Neural presbycusis is associated with degeneration in all three turns of the cochlea, with more marked hearing diminishment in the higher frequencies but with poorer-than-expected word recognition. The variant of presbycusis that is most strongly associated with age-related changes is strial presbycusis, which results from the atrophy of the stria vascularis, a bed of capillaries that nourishes the stereocilia. Strial atrophy may be an inherent part of the aging process, or it may be the result of systemic processes that inhibit vascular flow to the inner ear (e.g., cardiovascular disease, cerebrovascular disease, diabetes) [6, 7]. Strial atrophy and its associated cumulative damage to stereocilia result in a loss in hearing sensitivity that is more pronounced in the higher frequencies [5]. Intermediate presbycusis is characterized by submicroscopic cochlear changes, and typically results in a flat or subtly descending audiogram, while mixed presbycusis involves two or more of the other presbycusis types [8] .

Oxidative stress may play a role in cochlear degeneration. Recent studies suggest that in the aging cochlea, antioxidant defense systems in the inner ear are reduced while oxidative stress is increased [9]. In addition to inner ear degeneration, there are age-associated changes to the middle ear such as collapse of the cartilaginous auditory canal and stiffening of the tympanic membrane, both of which can result in age-related conductive hearing loss. However, this does not appear to contribute significantly to presbycusis [10].

In addition to age-related changes in the ear itself, age can bring changes in the brain's ability to perceive and process speech signals. Gates et al. [11] demonstrated a decline in performance on central auditory tests with increasing age, especially among adults >70 years of age. With increasing age, there is a diminished ability to understand rapid speech, and to understand speech in the presence of competing noise. The perception of rapid speech requires sustained attention and the ability to simultaneously attend to the incoming message while integrating previous segments of the message. It also requires the ability to quickly recall and recognize words. Thus, age-related deficits in memory and attention can influence speech recognition. Diminished central auditory processing might explain why the use of hearing aids, which simply amplify external sounds, often

does not completely correct hearing disability [12]. Thus, presbycusis reflects a combination of the loss of hearing sensitivity due to the degeneration of inner ear structures, and slowed central auditory processing in the context of age-related declines in memory and attention.

20.4 Measurement of ARHL in Epidemiologic Studies

The gold standard for hearing assessment in epidemiologic research is pure-tone audiometry performed under soundproofed conditions. Pure tone audiometry is used to determine the volume threshold (in decibels hearing level [dB HL]) at which an individual is able to perceive tones presented at various frequency (pitch) levels (in Hertz [Hz] [cycles per second]). Pure tone audiometry is a behavioral measure of hearing, as it requires the participant to indicate whether sound stimuli have been heard. Otoacoustic emissions testing (OAE), which measures sounds in the external auditory canal that are produced by cochlear activity and does not require a voluntary response from the participant, has been gaining popularity in population-based hearing research. The lack of the need for participant response makes OAE an especially valuable tool for measuring cochlear function in individuals who demonstrate inconsistent test responses to traditional audiometry, such as cognitively-impaired older adults [13].

Middle ear function is sometimes measured in studies of presbycusis to rule out conductive hearing loss conditions. It is typically tested in two ways. First, it can be assessed using bone conduction pure-tone audiometry, in which pure tones are presented directly to the temporal bone using a resonator. Hearing sensitivity is then compared to the results of air-conduction pure-tone audiometry. Better hearing via the bone conduction route is an indication of outer or middle ear interference in sound transmission. Middle ear function may also be assessed using tympanometry, which measures the mobility of the ear drum and middle ear ossicles. Tympanometry is less commonly used in large population-based studies. The measurement of central auditory function is accomplished mainly through tests of speech perception under various noise conditions.

Regardless of presbycusis type, hearing loss with age is generally first seen in the high frequencies, where its effects on the understanding of speech in noise are first noticed. Once hearing loss progresses to the range of 2,000–4,000 Hz, the perception of voiceless consonants in English (t, p, k, f, s and ch) is effected, which significantly diminishes the understanding of speech. As the loss progresses to the lower frequencies, the ability to detect speech becomes impaired [5].

In many population-based studies of hearing in older adults, impaired hearing is defined as decreased sensitivity to sound frequencies that are important for the comprehension of speech sounds: 500–4,000 Hz. Hearing impairment is commonly defined using a cut point of a hearing level >25 dB HL for the mean hearing thresholds at 500, 1,000 and 2,000 Hz or 500, 1,000, 2,000 and 4,000 Hz [14–17].

In large studies of aging that are not specifically designed to study hearing sensitivity, and in which the cost of pure-tone hearing assessment may be prohibitive, a gross estimate of hearing disability can be assessed via survey methods. The Hearing Handicap Inventory for the Elderly-Screening Version (HHIE-S) is a ten-question scale that is easily and quickly administered. It has shown sensitivities that range from 53 to 72% and specificities that range from 70 to 84% compared to various definitions of hearing impairment that are based on pure-tone audiometry [18].

20.5 Prevalence and Incidence

Several large studies on the epidemiology of age-related hearing loss have been conducted in the US. For each, we will present the characteristics of the study sample; the methodology, including measurement and definitions of hearing loss; and the primary prevalence and/or incidence findings. For a summary of ARHL prevalence estimates, refer to Table 20.1.

Table 20.1 Prevalence estimates of age-related hearing loss (*ARHL*) from selected epidemiologic studies

First author (year)	Sample characteristics	Definition of ARHL	Prevalence of ARHL
Agrawal (2008) [15]	NHANES sample; white, black and Mexican-American sample	$PTA_{0.5, 1, 2, 4\ KHz} \geq 25$ dB (speech frequency average) $PTA_{3, 4, 6\ KHz} \geq 25$ dB HL (high frequency average) in worse ear	Among 60–69 year olds, Speech frequency hearing impairment: 49%; High frequency hearing loss: 77%
Gates (1990) [19]	Framingham Heart Study; age range	$PTA_{0.5, 1, 2\ KHz} \geq 26$ dB	Men: 32.5% Women: 26.7%
Cruickshanks (1998) [14]	Epidemiology of Hearing Loss Study; age range 48–92 years	$PTA_{0.5, 1, 2, 4KHz} \geq 25$ dB, in one or both ears	Overall: 45.9%; 60–69 year olds: 42.8%, 70–79 year olds: 66%, 80–92 year olds: 90%
Helzner (2005) [16]	Health, Aging and Body Composition Study; White and black sample; age range 73–84 years	$PTA_{0.5, 1, 2\ KHz} \geq 25$ dB (hearing loss) $PTA_{2, 4, 8\ KHz} \geq 40$ dB (high-frequency hearing loss) in one or both ears	Hearing loss: 59.9%; High frequency hearing loss: 76.9%
Pratt (2009) [17]	Cardiovascular Health Study; white and black sample; age range 72–96 years	$PTA_{0.5, 1, 2, 4\ KHz} \geq 25$ dB	Younger than 80 years: 64%; 80 years and older: 84%
Gopinath (2009) [20]	Blue Mountain Hearing Study; age range 55–99 years	$PTA_{0.5, 1, 2, 4KHz} \geq 25$ dB HL in the better ear	Overall prevalence: 33% 60–69 year olds: 22% 70–79 year olds: 49.6% 80–99 year olds: 78.3%

Abbreviations: dB Decibels, *HL* Hearing level, *NHANES* National Health and Nutrition Examination Survey, *PTA* Pure-tone average

20.5.1 The National Health and Nutrition Examination Survey (NHANES)

A recent study by Agrawal et al. [15] examined the prevalence of hearing loss using 1999–2004 data from the NHANES sample. NHANES is a national cross-sectional survey of non-institutionalized civilian adults who were randomly selected based upon demographic criteria to reflect US demographic distributions. During three survey cycles (1999–2000, 2001–2002, 2003–2004), NHANES collected audiometric data on half of the study participants who were 20–69 years of age. The analysis sample was comprised of 5,742 adults, 3,064 of whom were 40–69 years of age. The sample included White, Black and Mexican-American participants. Hearing was measured using pure-tone audiometry under soundproofed conditions. Two hearing loss variables were analyzed. Speech frequency hearing loss was defined as a pure-tone average (PTA) hearing level ≥25 dB HL at 500, 1,000, 2,000 and 4,000 Hz in either ear. High-frequency hearing loss was defined as a PTA of 3,000, 4,000 and 6,000 Hz ≥25 dB HL in one or both ears.

The prevalence of speech-frequency hearing loss was 15% for those 40–49 years of age, 29% for those 50–59 years of age, and 49% for those 60–69 years of age. The prevalence of high-frequency hearing loss was 34% for those 40–49 years of age, 53% for those 50–59 years of age, and 77% for those 60–69 years of age. The prevalence of both speech-frequency and high-frequency hearing loss were highest among Whites, followed by Mexican-Americans and Blacks. Both types of hearing loss were more prevalent among men and less-educated participants [15].

20.5.2 The Framingham Heart Study

The Framingham Heart Study is a population-based study that began in 1948. The initial sample

was a stratified sample of all citizens of Framingham, MA, comprising 5,209 White men and women 30–62 years of age. Hearing assessment of 1,662 of the surviving 2,717 cohort members was carried out in 1977–1979. The participants ranged from 60 to >95 years of age. Hearing sensitivity was measured using pure-tone audiometry. Hearing loss was defined based on a PTA of 500, 1,000 and 2,000 Hz >26 dB HL. Based on these criteria, the prevalence of hearing loss was 32.5% among men and 26.7% among women [19].

20.5.3 The Epidemiology of Hearing Loss Study (EHLS)

The EHLS is a population-based study in Beaver Dam, WI that has been underway for more than 15 years. It is a substudy of the Beaver Dam Eye Study. The initial sample for the EHLS was comprised of 3,556 White men and women who ranged from 48 to 92 years of age. Hearing sensitivity was measured using pure-tone audiometry, and hearing loss was defined as a PTA of 500, 1,000, 2,000 and 4,000 Hz >25 dB HL in the worse-hearing ear. The overall prevalence of hearing loss was 45.9%, and it increased with age. Prevalence was 43.8% among those 60–69 years of age, 66.0% among those 70–79 years of age, and 90.0% among those 80–92 years of age [14].

The EHLS is the only US population-based study of hearing in older adults to measure the incidence of new hearing impairment in members of the initial cohort, which was followed from 1993–1995 to 2003–2005. The study included only those participants who had normal hearing at the baseline visit. The 10-year cumulative incidence of hearing impairment was based on a PTA of 500, 1,000, 2,000 and 4,000 Hz >25 dB HL. Of the 1,925 participants, the incidence was 45.5% for those 60–69 years of age at baseline, and 73.7% for those 70–79 years of age at baseline. The incidence was higher among men than among women; women developed hearing impairment approximately 6 years later than men (mean age at onset was 74 years of age for women vs. 68 years of age for men) [21].

20.5.4 The Health, Aging and Body Composition (Health ABC) Study

The Health ABC study is a community-based study of older adults in the areas surrounding Pittsburgh, PA and Memphis, TN. The initial cohort was recruited from a random sample of Black and White Medicare beneficiaries who were 70–79 years of age during the recruitment period (1997–1998). All participants were well-functioning at baseline. Hearing was assessed in the fifth-year clinical follow-up visit (2001/2002). Air-conduction pure-tone hearing assessment was administered to 2,208 of the surviving participants. At the time of the hearing assessment, participants ranged from 73 to 84 years of age. Hearing loss was defined as a PTA of 500, 1,000 and 2,000 Hz >25 dB HL. High frequency hearing loss was defined as a PTA of 2,000, 4,000 and 8,000 Hz >40 dB HL. The prevalence of hearing loss was 59.9%, and the prevalence of high frequency hearing loss was 76.9%. Hearing loss was more common among men than among women, and more common among Whites than among Blacks [16].

20.5.5 The Cardiovascular Health Study (CHS)

The CHS was a population-based prospective study of White and Black participants who were recruited from Medicare enrollment lists, and were randomized and stratified by age group. Participants were drawn from study sites in Sacramento County, CA; Washington County, MD; Forsyth County, NC and the greater Pittsburgh, PA metropolitan area. During the eleventh year of the study, a hearing assessment was carried out in 548 of the participants from the Pittsburgh site. The sample was comprised of White (77.7%) and Black (22.3%) adults who ranged from 72 to 96 years of age at the time of the hearing study. Mid-frequency hearing loss was assessed using two PTAs: PTA (500, 1,000 and 2,000 Hz ≥25 dB HL) and PTA-4 (500, 1,000, 2,000 and 4,000 Hz ≥25 dB HL). Hearing loss prevalence based on the first PTA was 42% in

participants <80 years of age, and 71% for those ≥80 years of age. Hearing loss prevalence based on PTA-4 was 64 and 84% for the two age groups, respectively. Similar to the findings from Health ABC, prevalence was higher among White participants and among men [17].

20.5.6 Prevalence Estimates from International Studies

Relatively little is known about the global prevalence of presbycusis. For example, most published reports of hearing impairment in developing countries provide statistics for all age-groups combined, or are limited to data from school-aged children [22]. A few large-scale epidemiologic studies of hearing sensitivity in older adults have been undertaken outside of the US. The Australian Blue Mountains Hearing Study, a study of 2,956 adults (mean age 68.4 years at baseline), found a 33% prevalence of hearing loss based on a PTA of 500, 1,000, 2,000 and 4,000 Hz >25 dB HL. The prevalence of hearing loss doubled for each 10-year increase in age. A 5-year follow-up study demonstrated that among the 870 participants who did not have hearing loss at baseline, the incidence of new hearing loss was 17.9%. [23].

A study of 1,221 older Taiwanese adults (>65 years of age) found that the mean better-ear PTA (500, 1,000 and 2,000 Hz), stratified by 5-year age groups, ranged from 34.9 to 46.4 dB HL. The prevalence of presbycusis (PTA of 0.5, 1 and 2 KHz ≥55 dB HL) ranged from 1.5% (65–69 years of age) to 14.9% (≥80 years of age) [24].

20.6 Correlates and Potential Risk Factors for Presbycusis

There are a number of correlates and potential risk factors for ARHL, which we will review in more detail in the following subsections. These include:

- Male gender
- Low socioeconomic status
- Diabetes
- Occupational noise exposure
- Oxidative cell damage
- Cardiovascular disease
- Cumulative lead exposure
- High systolic blood pressure
- Cigarette smoking
- Medication ototoxicity
- Genetic factors.

20.6.1 Demographic Factors

As seen in the data presented above, there are marked increases in hearing impairment with advancing age. Other demographic factors are also related to hearing impairment. Men are more likely than women to have poorer hearing sensitivity. The excess hearing loss in men compared to women is due, at least in part, to lifetime differences in vocational and recreational noise exposure. There is also evidence that hormonal factors may play an otoprotective role in women [17].

Age-related hearing impairment is more common among Whites and Hispanics than it is among African-Americans [16, 17]. It is not completely clear why hearing sensitivity in older age is better among African-American adults. This hearing advantage persists despite the fact that African-Americans are, on average, more burdened than are Whites by disease factors that may influence hearing (higher rates of vascular disease and diabetes mellitus chief among them). Melanin, concentrations of which are higher in individuals who have dark skin and eyes, has been suggested as a protective factor, though research findings have been inconclusive and controversial. Cochlear melanin may be protective against noise exposure as it enhances cochlear antioxidant activity [17].

20.6.2 Socioeconomic Factors

In cross-sectional studies, indicators of lower socioeconomic status, including lower levels of education and lower household income, have consistently been associated with poorer hearing sensitivity among older adults [16], and more recently have been associated with the 10-year

cumulative incidence of hearing impairment [21]. Lower socioeconomic status is associated with many correlates of hearing loss, including an increased likelihood of excessive occupational noise exposure, a higher likelihood of cigarette smoking, and a higher prevalence of obesity. These factors can contribute to metabolic disorders and/or cardiovascular disease, both of which may play a role in age-related hearing loss.

20.6.3 Diabetes

It is widely accepted that there is a relationship between adult-onset hearing loss and adult-onset diabetes mellitus (DM) [7, 16, 25–27]. DM has been associated with poor hearing sensitivity in the lower frequencies among both younger and older adults. Younger adult diabetics (≤60 years of age) are more likely than younger adult non-diabetics to demonstrate an early-onset hearing impairment in the high frequencies that is similar to presbycusis. The influence of DM on high-frequency hearing appears to be masked in older age, when the cumulative effects of other hearing loss risk factors (e.g., age-related cochlear degeneration, noise exposure) can surpass the detrimental effect of DM-associated oto-pathology [26, 27]. It is not completely clear what pathophysiologic mechanism underlies the diabetes/hearing connection, but several factors likely play a role. Diabetes may affect the inner ear from a vascular standpoint by promoting systemic atherosclerosis or atrophy within the stria vascularis, affecting the microvascular supply to the cochlea [7, 25, 28–31]. In addition, the cochlea may be a target organ for damage caused by hyperglycemia. Hyperglycemia initiates a metabolic cascade which results in oxidative stress, hypoxia, increased levels of advanced glycation end products, and neuropathy [32].

20.6.4 Cardiovascular Disease

Cardiovascular disease (CVD) appears to influence the pathophysiology of presbycusis, but epidemiologic studies of CVD and hearing have yielded inconsistent findings. Some studies found that older adults with CVD events and/or CVD risk factors were more likely to have elevated hearing thresholds [6, 13, 33, 34], while others did not [17, 35, 36]. Further, no consistent pattern of hearing-associated CVD risk factors has emerged across studies [6, 13, 16].

Studies of CVD biomarkers (e.g., lipids, glucose, clotting factors) have revealed few associations with hearing sensitivity [37, 38]. High systolic blood pressure [6, 16], high glucose, and low high-density lipoprotein cholesterol [6] have been associated with hearing loss in some studies. A large, multinational European study recently identified higher body mass index as a risk factor for poorer hearing sensitivity [34].

It has been suggested that, like diabetes, CVD may result in hearing loss by causing reduced vascular supply to the cochlea [6]. Atherosclerosis has been hypothesized to cause reduced blood flow to the cochlea via stiffening or constriction of the internal auditory artery. Insufficient nutrient supply due to microvascular damage or capillary constriction within the stria vascularis can lead to the death of stereocilia and result in a reduced hearing sensitivity, particularly in the lower frequencies [6, 39]. Regardless of whether it is caused by micro- or macro-vascular pathology, an insufficient cochlear blood supply can disrupt the chemical balance of the inner ear fluid, endolymph. This, in turn, affects the electrical activity of the hair cells and subsequently the activation of the auditory nerve.

20.6.5 Cigarette Smoking

Cigarette smoking has been associated with hearing loss in multiple studies [40–42], though not in all [6]. Hearing loss appears to occur earlier in life among smokers, and smoking appears to be particularly associated with high-frequency hearing impairment [15]. Additionally, there appears to be a synergistic effect between noise exposure and cigarette smoking wherein smokers who are exposed to occupational noise experience a greater diminishment in hearing sensitivity than do exposed non-smokers [43]. Cigarette smoking

may affect the vasculature of the inner ear through a cardiovascular disease pathway, or it may interfere with protective antioxidative mechanisms in the auditory system [40].

20.6.6 Noise Exposure

Noise exposure is a known risk factor for hearing loss among working-age adults. It results in a permanent worsening of hearing that is most marked in the frequencies from 2,000 to 6,000 Hz. Exposure to toxic levels of noise can occur in the work setting, through exposure to gunfire, or through leisure activities that involve the use of noisy equipment. One recent widespread exposure to toxic noise levels is the inappropriate use of small electronics that are equipped with earbuds/earphones (e.g., MP3 players). In the coming years, the widespread use of these devices may result in an increase in hearing impairment prevalence and in hearing impairment at younger ages.

There is some controversy regarding whether noise-induced hearing loss in earlier adulthood is a risk factor for more rapid decline in hearing sensitivity with age. Since noise exposure and aging both result in the loss of hearing sensitivity in the higher frequencies, it is difficult to study interactions between aging-induced and noise-induced hearing loss [5]. For example, it is unclear whether age- and disease-related damage to the inner ear makes older adults more susceptible to the effects of toxic noise exposure. However, in animal studies (mostly in mice), old and young animals demonstrate similar levels of hearing impairment after exposure to moderate-level noise, while older animals demonstrate a greater pronounced hearing loss after exposure to high-intensity noise than do younger animals. This research suggests that older adult humans may also be more susceptible to excess noise than are young adult humans [10].

Studies on the influence of noise exposure over the lifespan on the incidence and progression of presbycusis have yielded inconsistent findings. In one study, an accelerated decline in hearing was observed among noise-exposed older adults [44], but a more recent study of older adults that included serial measures of hearing sensitivity found that noise exposure was not associated with either the incidence of presbycusis or a more accelerated decline in hearing sensitivity [45]. Future research will be needed to unravel the relative contributions of aging and noise exposure on hearing loss, and to examine the possible synergistic effects of noise exposure and other exposures (e.g., cigarette smoking) on hearing loss.

20.6.7 Medication Ototoxicity

Certain medications are cochleartoxic and result in decreased hearing sensitivity, especially in the high frequencies. Permanent high-frequency hearing loss can be caused by aminoglycoside antibiotics and by certain chemotherapy agents (notably cisplatin). Quinine derivatives, loop diuretics (notably furosemide), statin drugs and salicylate analgesics can result in hearing loss which is usually reversible. The simultaneous administration of loop diuretics and aminoglycoside antibiotics (as well as some non-aminoglycoside antibiotics) results in synergistic cochleotoxic effects. Similar potentiation of cochletoxicity is seen with the co-administration of loop diuretics with cisplatin. Noise exposure can also amplify the effects of medication-related cochleotoxicity [46].

20.6.8 Environmental Exposures

Cumulative lead exposure, as measured by x-ray fluoroscopy at the patella and after controlling for occupational noise exposure, has been associated with significantly higher hearing thresholds across frequencies [47].

20.6.9 Genetic Susceptibility to Age-Related Hearing Loss

Genetic factors appear to play a role in the susceptibility to presbycusis. Familial aggregation of presbycusis has been documented, and it is more pronounced among women than among

men. It has been estimated that 35–55% of the variance of sensory presbycusis can be attributed to genetic influences, and genetic effects appear to play an even greater role in strial presbycusis [48].

While much is known about genetic influences in congenital hearing loss, the study of the genetics of presbycusis is relatively new. Association studies have identified several genes associated with age-related hearing loss. Genes associated with presbycusis include N-actyltransferase-2 (NAT-2), glutathione s-transferase mu-1 (GSTM1) and theta 1 (GSTT1), KCNQ4 (potassium channel, voltage-gated, kqt-like subfamily, member 4), and the grainyhead-like 2 (GRHL-2). The apolipoprotein $\varepsilon 4$ (APOE-$\varepsilon 4$) allele appears to play a protective role [49].

Mitochondrial DNA (mtDNA) mutations may also influence presbycusis. Mitochondrial mutations, which have been found in the temporal bones of patients who have hearing loss, cause hearing loss that mimics presbycusis: the hearing thresholds are first compromised in higher frequencies, with the loss in sensitivity eventually progressing to affect all frequencies. A possible pathophysiologic mechanism is diminished protection against oxidative damage within the ear, as mtDNA mutations result in decreased oxidative phosphorylation activity [50].

Future research is necessary to explore the possibility of gene-environment interactions in the development of presbycusis. For example, individuals who carry high-risk genes for age-related hearing loss may be at a higher risk for noise-induced damage, or may be more vulnerable to the effects of CVD. If this is the case, it will eventually be possible to tailor prevention efforts to high-risk individuals.

20.7 Prevention

At present, the best known methods for preventing age-related hearing loss are to limit one's lifetime exposure to toxic noise levels, avoid exposure to ototoxic medications, and adhere to healthy eating and lifestyle habits so as to avoid the development of vascular and metabolic diseases that may worsen age-related changes to the cochlea. Alcohol consumption in moderation may lend some protection against high-frequency hearing loss, most likely due to the cardioprotective benefits it affords [16, 34].

New approaches to hearing maintenance are being explored in animal models of age-related hearing loss, typically in mice, rats and gerbils. Promising developments from animal research suggest that antioxidant enhancement, electrical stimulation to restore the endocochlear potential, and salicylate therapy may all be hearing-protective [51]. Future research in human participants will be necessary to confirm these exciting possibilities.

20.8 Rehabilitation

Because presbycusis is associated with the permanent loss of the neurosensory cells that are necessary for sound transmission, it is not curable *per se*. Nonetheless, older adults who have hearing loss can be helped through the use of several strategies. Assisted listening devices can be of help, including telephone amplifiers; infrared systems; the captioning of television and live events; and the use of flashing visual signals for doorbells, telephones and household alarms. The conversation partners of individuals who have presbycusis can improve the individual's speech comprehension through the implementation of several communication techniques. Competing noise may interfere with speech processing in the central auditory system. Therefore, when speaking to a hearing-impaired individual, it is important to reduce or eliminate competing sound sources such as television and radio, and to generally hold conversations in quiet environments that are relatively free of background noise. It is also imperative to ensure that the hearing-impaired individual can see the face of the speaker so as to fully take advantage of visual cues such as facial expressions and the shape of the lips during speaking.

For older adults who have moderate or severe hearing loss, amplification with personal hearing aids can be helpful. Although they do not restore

normal hearing and are very expensive, hearing aids (particularly newer models that use digital technology) can result in clear functional gains, especially when used in combination with the aural rehabilitation techniques described above. Cochlear implants are also being increasingly used in older adults who have severe bilateral hearing loss. They are generally well-tolerated and, in most cases, successfully improve speech comprehension at least to some degree [5].

20.9 Dual Sensory Impairment

Hearing impairment with concurrent visual impairment has been termed Dual Sensory Impairment (DSI). The two most common causes of age-related vision impairment are cataracts and age-related macular degeneration, and both of these conditions have been associated with hearing loss [52]. In population-based studies of older adults that employed instrumental measures of sensory function, the prevalence of DSI ranges from 4.6 to 9.7%. DSI can cause a significant compromise in an affected individual's ability to communicate, and therefore can lead to functional disability, social isolation and decreased emotional well-being [53].

20.10 Summary

Age-related hearing loss is an extremely common, chronic and disabling condition among older adults. With the aging of the US population, age-related hearing loss is destined to become an even greater public health concern. For generations following the baby boom, the incidence of hearing impairment will likely increase and will likely occur at younger ages due to widespread exposure to excessive noise levels caused by the inappropriate use of small electronic devices that have earbuds/earphones, such as MP3 players. Further population-based research in adult-onset hearing loss is necessary to verify existing studies' findings of potentially modifiable risk factors, and to elucidate genetic influences and potential gene-environment interactions. Epidemiologic research into age-related hearing loss has great potential to eventually manifest in meaningful gains for our aging population regarding their functioning and quality of life.

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Oral Health and the Epidemiology of Oral Disease in Older Adults

21

Robert J. Weyant

Abstract

The most common oral diseases in older adults (≥60 years of age) are dental caries, chronic periodontal disease and tooth loss, with oral cancer also important. Dental caries are caused by metabolic changes in a biofilm. Dry mouth is an important risk factor. Preventions include fluorides, toothbrushing and flossing. Periodontal disease (i.e., gingivitis, periodontitis) is associated with pathological changes in oral biofilm microbial ecology, supragingival biofilm in gingivitis and subgingival in periodontitis. Both cause localized gingival tissue inflammation, but periodontitis can result in destruction of tooth-supporting bone and gingival tissue, leading to tooth loss. Risk factors include genetic and other immune-response-altering factors. Preventions include daily personal oral hygiene for gingivitis, professional dental hygiene for periodontitis and smoking cessation for both. Tooth loss was once expected with aging, but now more tooth-retaining approaches to oral disease management are used. Lower income and less educated individuals have fewer retained teeth and higher rates of complete loss of teeth. Oral cancer is most common in older adults, with tobacco use being the most important risk factor. Overall, oral disease can detrimentally affect social functioning and quality of life.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Oral Health • Gum Disease • Oral Disease • Caries • Periodontal disease • Malocclusion • Oral cancer • Screening • Prevention • Risk factors • Edentulism

Abbreviations

CAL	Clinical Attachment Loss
CDC	Centers for Disease Control and Prevention
CRI	Root Caries Index

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CRP	C-reactive protein
DMF	Decayed, Missing and Filled index
DMFT	Decayed, Missing and Filled Teeth
GOHAI	Geriatric Oral Health Assessment Index
HPV	Human Papillomavirus
HT	Hormone Therapy
NHANES	National Health and Nutrition Examination Surveys
OHIP	Oral Health Impact Profile
PPD	Periodontal Probing Depth
RR	Relative Risk
SE	Standard Error
US	United States
WHO	World Health Organization

21.1 Introduction

"The mouth is the gateway to the body, performing dozens of functions that place high demands on its unique hard and soft tissues." (Dr. David Satcher, Surgeon General of the United States [1]).

The main oral functions include chewing, swallowing, speech, communication, digestion and immune function. In addition, the oropharyngeal structures control access to the respiratory and digestive systems. The mouth and craniofacial complex also play important roles with regard to social functioning and self image, and they have a profound effect on the overall quality of life [1].

There are dozens of oral diseases and conditions that can occur throughout the lifecourse. These include developmental disorders, injuries, chronic and disabling acquired conditions, infections and neoplasms. Many have serious consequences that can affect longevity and quality of life. There are over 120 specific diseases that have oral manifestations [2].

The most prevalent oral disease among older adults is dental caries (tooth decay), followed by chronic adult periodontal (gum) disease. Both of these are oral-biofilm-mediated chronic infections that, once established, are rarely self-limiting. Furthermore, when longstanding and left untreated, both caries and periodontal disease lead to tooth loss and associated oral disability. Oropharyngeal squamous cell carcinoma is by far the most concerning oral condition found in older adults, with a case fatality rate that has remained at nearly 50% for many decades.

Due to space limitations, this chapter will focus on only the most common oral conditions, defined as those conditions that have a large social impact among older adult populations due to their high prevalence (in this chapter older adults are defined as individuals ≥60 years of age unless otherwise specified). Specifically, after a brief review of oral disease prevalence and oral health in older adults and the limitations on oral disease epidemiology research in this population, this chapter will be limited to a discussion of dental caries, chronic adult periodontal disease and tooth loss, with some mention of oral cancer. In addition, we will briefly review the relationship between oral and systemic conditions and the impact of oral conditions on quality of life.

21.2 Oral Disease Prevalence, Oral Health and Research Limitations in Older Adults

21.2.1 Aging and Disease Prevalence

Oral diseases are generally more common among older adults than among younger adults. They contribute to an excess morbidity and mortality, and compromise quality of life. Several factors contribute to the high prevalence of oral diseases in older adults. First, the tissue damage caused by common oral diseases is often irreversible and it therefore accrues over the lifecourse, leaving older adults carrying a higher burden of many oral conditions than any other age-defined group. For example, the carious destruction of teeth, once past a certain point, is irreversible. At best, a person so affected is left with a restoration (filling) or denture. In another example, periodontal disease damages both hard (alveolar bone) and soft (gingival) tissue, and it requires extensive therapy to arrest. Even after treatment, the gingival tissue rarely returns to its full coverage or provides the full tooth support that it did prior to disease onset.

Second, the functional and cognitive impairments that are more common among older adults can contribute to a reduced capacity to engage in oral self care (e.g., tooth brushing, flossing). This contributes to ongoing disease development. Third, access to preventative and restorative dental care is substantially reduced among many older adults, particularly in the United States (US). Over 90% of dental care in the US is paid out of pocket or through employment-based dental insurance [3]. Both of these payment methods tend to decrease among older adults after retirement. The lack of public funding for dental care further reduces access. There are no provisions for dental care within Medicare, and only about 6% of all dental care in the US is paid for by public funds [3]. In addition to the financing problems encountered by older adults, functional limitations that result in decreased mobility make accessing care difficult in many dental offices. Moreover, when an individual becomes institutionalized, the ability to access dental care decreases further, with many institutionalized older adults never seeing a dental professional during their entire institutionalized lifetime.

As a result of these factors, oral disease—particularly caries, periodontal diseases and tooth loss (edentulism)—can be considered epidemic among older adults. Tooth loss is decreasing among all age groups, though this has increased the number of older adults who have caries and periodontal disease. Moreover, some chronic oral conditions can have an impact on overall health by exacerbating other medical conditions and negatively influencing diet, quality of life, and social functioning. As the number of older adults increases, the demand for dental services will also increase. So, too, will the public health importance of ensuring access to oral health care and maintaining overall oral health for older adults.

21.2.2 Normative Aging and Oral Health

Like the rest of the body, the tissues and structures of the mouth undergo normative aging. As is true of the skin, the oral mucosa thins and becomes less hydrated. The jaws are affected by both local and systemic changes. Tooth loss results in atrophy of the alveolar bone, and generalized osteopenia will also manifest in decreased jawbone density. In general, there is little loss of sensory function with age, with the exception of olfaction. However, this age-related decrease in smell can result in dissatisfaction with food taste and can lead to changes in diet and the increased need for the seasoning of food. Overall oral muscle tone may decrease with age and can result in some difficulty with speech and swallowing. The salivary glands, which play a central role in maintaining oral health, have a substantial reserve capacity and consequently show little age-related decrement in salivary flow. However, there can be some change in salivary chemistry that may diminish the saliva's lubricating ability [1].

Fortunately, biomedical science has now shown conclusively that tooth loss is not an inevitable consequence of aging, but rather the result of disease or injury [1], and many of these diseases can be effectively prevented. This understanding is now becoming the common wisdom, and with it a slow but steady improvement in many dimensions of oral health is occurring across the lifespan.

21.2.3 Limitations on Research

Research on the epidemiology of oral disease in older adult populations is very limited. Most studies examine non-representative convenience samples of small regions or of clinic populations. Representative samples, such as those found in the National Health and Nutrition Examination Surveys (NHANES) are limited to the non-institutionalized population. Thus caution must be exercised when trying to make valid estimates of oral disease prevalence and incidence that apply across large segments of the older adult population. For example, there are undoubtedly substantial differences in disease levels between institutionalized and non-institutionalized populations of older adults.

It is also important to realize that approaches to prevention and treatment have changed in

remarkable ways over the last 80 years. With the introduction of effective local anesthesia, antibiotics, high-speed handpieces and the expansion of the science base that underlies dental treatment, care is now delivered in much more effective ways, with an emphasis on retention of the dentition throughout a person's entire lifetime. This was not always so. Dentistry was once characterized by long painful appointments, ineffective prevention interventions and a nearly universal prevalence of decay. Due to this, many young people viewed teeth as a liability and opted for early removal. Thankfully, this thinking has changed, albeit slowly. However, the result of this earlier thinking is a substantial cohort effect with regard to edentulism and the value of an intact dentition that will persist for many years. The cohorts that opted for early clearance of all teeth and those that have continuing and well-founded memories of fear-inducing dental treatment will be around for several more generations.

21.3 Dental Caries

21.3.1 Definition and Pathophysiology

The most prevalent oral disease at all ages is dental caries (decay). In the US, over 90% of adults have some history of current or past dental caries [4]. Dental caries is a localized chemical dissolution of a tooth surface that results from metabolic events taking place in a biofilm (also known as dental plaque) that is covering the affected tooth area [5]. In health, the biofilm associated with the tooth is in a dynamic equilibrium with regard to the tooth's mineral composition and no net loss of mineral content or tooth structure occurs. The tooth surface undergoes loss of mineral content and remineralization innumerable times each day, but remains in equilibrium. This equilibrium is influenced by the pH at the tooth surface and the degree of saturation of minerals in the fluid phase that is in contact with the tooth surface. The minerals are derived from both saliva and, when present, from fluoride (e.g., fluoridated water or toothpaste). Any long-term change in the pH or in the degree of mineral saturation can, over time, lead to a net loss of mineral content from the tooth. This loss is known as the caries lesion [5].

Factors that can create cariogenic changes in the equilibrium of the biofilm and tooth interface include changes in diet, which can alter microbial metabolism in the biofilm, and changes in the mineral saturation that affect the rate of tooth remineralization. Factors that can reduce mineral saturation include medications that reduce salivary flow and changes in exposure to fluoride (e.g., toothpaste).

Exposure to dietary sources of fermentable carbohydrates, primarily sucrose, is considered a necessary but not sufficient cause for caries to occur. The dietary carbohydrates are readily metabolized by certain bacterial species, which leads to acid production and a lowering of the pH of the biofilm. These acids act directly on the tooth surface, dissolving mineral content, which creates the caries lesion. In addition, the pH change in the biofilm alters the ecology of the microbial community that lives within the biofilm. Over 700 species of microbes have been identified in the oral biofilm [6]. As the pH is lowered from exposure to dietary sugar, aciduric species are favored and begin to increase in relative numbers within the microbial community. Streptococcus mutans appears to be the most important species with regard to the cariogenic changes that occur in biofilms, due to its acidogenic and aciduric nature. This process creates a feedback loop that favors the overgrowth of S. mutans within the biofilm.

21.3.2 Measuring Dental Caries

Dental caries are measured in different ways depending on the purpose of the measurement. Clinical assessments are used to guide patient-based treatment and prognosis estimates. Clinicians identify caries using visual and tactile (manual probe) inspection of the teeth, often supplemented by radiographs and other technology-based techniques (e.g. lasers). The diagnostic threshold is quite variable and can be influenced by personal

experience, educational background and culture [3]. Once identified, the caries lesion is classified by location on the tooth (coronal or root), location of tooth surfaces affected, depth of lesion into the tooth and whether the lesion is currently active or inactive (arrested). The latter requires no treatment, but often remains as a visible "scar" on the tooth. Treatment decisions follow from this classification in broadly predictable ways.

For epidemiological studies, the need is often for a measurement that can be done rapidly in a non-clinical (e.g., field) setting, with high intra- and inter-examiner reliability. This is often accomplished with just a visual exam, sometimes augmented with a probe and some form of artificial lighting (e.g., a headlamp). Radiographs are rarely used in epidemiological caries studies. Well-designed caries studies are characterized by extensive examiner training and calibration for reliable and valid caries detection.

Population-based caries studies usually include estimates of both caries prevalence and severity of disease within the population. As is generally the case, prevalence estimates are expressed as the percentage of the population with either current disease or a history of the disease (caries experience). Prevalence measures are dependent on the case definition, and with caries there are many definitions that can be applied. For example, by including "early" pre-cavitated lesions—also known as white spot lesions—in the count along with the more advanced cavitated lesions, there is often more than a 100% increase in the number of teeth classified as carious [5].

Measuring disease severity for epidemiological purposes is most commonly done through use of the Decayed, Missing and Filled Index (DMF) [7]. To apply this index, the examiner evaluates each tooth to determine if it is decayed (D), missing (due to decay) (M), or has a filling (due to decay) (F). All teeth so classified are then summed (D + M + F = DMF) to create a total count of teeth affected by caries. This count is referred to as the DMFT (the T stands for "teeth") score or index for that individual. The DMF index applies only to the permanent dentition and thus can range from 0 to 32 in whole numbers. It is also possible to calculate the DMF score for each individual tooth surface. This is then referred to as the DMFS and it ranges from 0 to 168.

It is important to note several features of the DMF index. First, it is a count rather than a proportion, as it does not consider the number of teeth present in the mouth. Thus in older adults, where teeth can often be lost for a variety of non-caries-related reasons (e.g., periodontal disease, trauma), it can be difficult to make comparisons among individuals or groups with regard to their caries experience due to possibly large differences in the number of teeth present and hence "at risk" for caries. Second, depending on the diagnostic threshold being used, the DMF index can be considered irreversible. That is the case when a caries is considered to be present only when tooth cavitation (loss of tooth surface integrity) has occurred. Thus one's DMF score can remain constant over time or increase, but never decrease, because cavitated surface cannot be biologically repaired but rather will remain as a "cavity" or a "filling". Increases in the DMF score over time, referred to as the caries increment, are often used as an outcome measure when evaluating prevention interventions. Third, the DMF index is used exclusively to measure caries on the crowns of permanent teeth. Lower case letters (df) are used to indicate caries in the primary dentition. Additionally, missing teeth are excluded from caries scores in the primary dentition due to natural exfoliation being common in the primary dentition. Thus dft (teeth) and dfs (surfaces) are the typical scores reported for caries in primary teeth.

Root surfaces of teeth can also become carious. Root caries are measured using a different index, the Root Caries Index (RCI), which—as with the DMF index—measures decayed and filled root surfaces but does not consider missing teeth. However, root caries can only exist when the tooth root surface has undergone gingival recession, exposing the root surface to the oral environment. Thus the RCI considers only teeth with gingival recession, and it is expressed as a proportion (D + F root surfaces/total root surfaces with gingival recession).

21.3.3 Prevalence, Incidence and Risk Factors

21.3.3.1 Coronal Caries

Epidemiologic studies of caries in older adults were rare until the 1970s, with most research consisting of regional or small area studies of non-representative populations. This was due in large part in the difficulty in accessing large representative segments of the older adult population. Consequently, there remains a poor understanding of the prevalence and natural history of caries in older adults, especially with regard to secular trends in oral disease.

The World Health Organization (WHO) makes an effort to track oral health indicators globally; however, few studies are available regarding caries in older adults. The WHO reports that in developed nations, the range of decayed and filled coronal tooth surfaces lies between 22 and 35, and the mean number of decayed and filled root surfaces lies between 2.2 and 5.3. Data from developing nations is less common and difficult to generalize given the variability in risk factors across nations. The WHO identified patterns associated with caries across nations that indicate that the population-based indicators of income, personal oral hygiene behaviors, diet, smoking and access to dental care all contribute to the overall caries rate within a nation [8].

The most recent US data available from NHANES show that caries experience is extremely prevalent at all ages, ranging from 86.6% in adults 20–39 years of age to 93.1% in adults ≥60 years of age. Across the entire adult population ≥20 years of age, whites had higher caries rates (93.3%) than did African-Americans (84.6%) or Mexican-Americans (83.5%). The DMFT of dentate adults ≥60 years of age was 17.46 (Standard Error [SE] 0.30). The prevalence of untreated coronal tooth decay was 18.57% (SE, 1.02). Increased prevalence of untreated decay was strongly associated with non-white race, poverty, having less than a high school education, and current smoking [4].

Data on caries incidence in older adults is very rare. Thomson [9] reviewed four recent cohort studies of caries in older adults (age 50+) in the US. These studies confirmed that older adults remain caries active and the incidence of new lesions is at least as great as the rate found among adolescents. Caries increment (increase in DMFS) ranged between 0.8 and 1.2 new carious surfaces per year. The only consistent risk factor for new caries lesions was the presence of partial dentures.

21.3.3.2 Root Caries

As with coronal caries, studies of root caries among older adults are rare. The most recent national data show that root caries is strongly age dependent, increasing from 9.4% among adults 20–39 years of age to 31.6% among those ≥60 years of age [4]. By age 75, roughly 50% of older adults have experienced root decay and a majority of these lesions remain untreated. As with coronal caries, the highest rates of untreated root caries are associated with non-white race, poverty, less than a high school education, and current smoking [1].

A recent systematic review of adults ≥45 years of age summarized root caries incidence results from five studies [10] and found root caries increments of 0.47 tooth surfaces per year. Predictors of root caries increment include prior root caries, high plaque levels and number of teeth present [11].

21.3.4 Prevention, Clinical Trials

Prevention of caries in older adults is similar to caries prevention at any age. Fluorides are effective in preventing both coronal and root caries, and they should be considered as the first intervention for caries-active adults. A topical fluoride delivered in frequent (daily) low dosages (e.g., toothpaste) is the most effective and sustainable intervention for the control of caries at all ages. Water fluoridation adds additional protective benefits [10].

Removal of dental plaque through personal oral hygiene practices (e.g., toothbrushing and flossing) are intuitively attractive approaches for the prevention of both caries and periodontal

disease. However, the successful elimination of plaque to a level sufficient to prevent caries and periodontal disease is rarely achievable. Studies consistently show a poor correlation between oral hygiene interventions and the reduction of caries and periodontal disease. Therefore, the use of topical fluorides in conjunction with toothbrushing is essential for caries control. Additional approaches are used in cases of severe disease, including prescription-strength fluorides and topical antimicrobial therapy with chlorhexidine.

Among older adults, a particularly important risk factor for caries—particularly root caries—is decreased salivary flow (xerostomia or dry mouth). Decreased salivary flow is a common side effect of many medications used by older adults and can occur in association with systemic diseases [12]. For individuals with low saliva flow rates, commercial saliva substitutes are prescribed. These products can improve overall quality of life as well as reduce the risk of caries.

21.4 Periodontal Disease

21.4.1 Definition and Pathophysiology (Clinical Measurements)

The predominant periodontal diseases found in older adults are gingivitis and chronic adult periodontitis. Gingivitis is a mild condition limited to localized inflammation of the gingival tissue, without loss of the periodontal tissue attachment to the tooth. This condition results from poor oral hygiene (e.g., poor disruption or removal of the biofilm). When left undisturbed, the biofilm transitions within days from one composed of primarily aerobic streptococci to one of anaerobic rods and spirochetes. The tissue response to this change in the microbial ecology is inflammation, characterized by gingival tissue that is clinically red, swollen and bleeds easily. Improved personal oral hygiene or a professional dental cleaning is often all that is needed to resolve this condition. However, in older adults with compromised mobility and dexterity, lack of personal oral hygiene care may pose a significant and ongoing risk factor.

Periodontitis is a general term for a group of related conditions that, like caries, are associated with pathological changes in the microbial ecology of the oral biofilm. In periodontitis, the pathogenic biofilm is subgingival and results as an extension of the supragingival biofilm that is associated with gingivitis. A migration of the biofilm into the subgingival space occurs in conjunction with pathological changes in the microbial community. The details of the pathological microbial changes in the biofilm are beyond the scope of this text, but they can be broadly characterized by a transition from gram-positive cocci to obligate anaerobes [13].

The periodontal diseases share a common clinical manifestation: gingival inflammation. But unlike gingivitis, periodontitis results in destruction of the tooth-supporting alveolar bone and gingival tissue, leading ultimately to tooth loss. The tissues' inflammatory response to the microbial challenge results in a pathological detachment of collagen fibers from the cementum (root surface) of the tooth, which is known as clinical attachment loss (CAL). When longstanding, this inflammatory response leads to further tissue destruction, including loss of the tooth-supporting alveolar bone. Over time, this ongoing loss of attached gingival tissue and supporting bone results in increasing tooth mobility and eventually tooth loss [14].

The pathological changes that lead to periodontitis are an extension of the changes that begin as gingivitis [15]. For many years, it was believed that if gingivitis was left untreated, it would inevitably transition to periodontitis in essentially all individuals. It is now evident from epidemiological studies that this transition occurs only in a subset of susceptible individuals. In fact, the most severe, dentition-threatening types of periodontitis occur in only about 15% of the general population. The factors that govern susceptibility are not well characterized, but likely include genetic and possibly other factors that modulate the immune response.

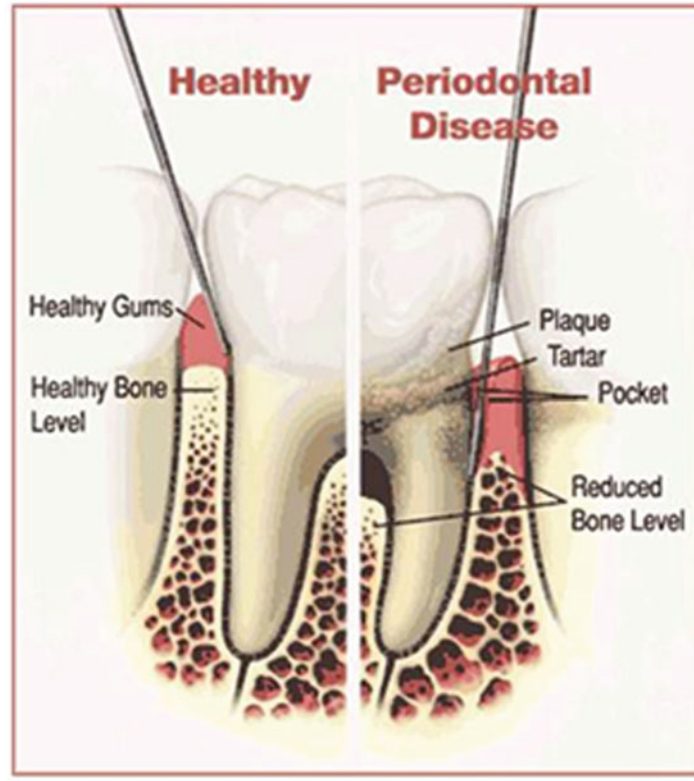

Fig. 21.1 Schematic of periodontal disease diagnosis

21.4.2 Periodontal Disease Measurement and Classification

The measuring and classifying of periodontal diseases are two distinct steps. Gingivitis is measured clinically by assessing the degree of gingival inflammation. This can be done visually, but that is an admittedly subjective process. Alternatively, the tissue can be gently probed to detect bleeding. However, probing pressure is itself difficult to standardize. Probing of the gingiva to induce bleeding also adds an additional concern of infection control in field studies. The classification of gingivitis is done using one of several measures to stage the disease on a categorical scale. The most commonly used non-probing index is probably the Gingival Index [16], which uses a four-point categorical scale based on a visual assessment and ranges from a score of 0 (no inflammation) to 3 (severe inflammation).

Measuring periodontal tissue changes to detect periodontitis is usually done with a periodontal probe marked in millimeter increments. The probe is inserted into the gingival sulcus around the neck of the tooth, and the point at which the tissue attachment is detected by resistance to further insertion (the so called periodontal pocket) is measured (Fig. 21.1). Two measurements are typically made, the depth of the periodontal pocket, called periodontal probing depth (PPD), and the amount of loss of tissue attachment along the root of the tooth, called CAL. These measures are expressed in millimeters at each probing site. Generally, up to six sites around each tooth are probed, resulting in a large number of clinical measures for a given individual. When PPD exceeds 3 mm, it is considered as indicative of pathology. Radiographs are used to further assess the destruction of the underlying alveolar bone as an aid in clinical evaluations and treatment planning. But radiographs are rarely used in epidemiology field studies.

The classification of periodontal disease into broad types is done based on clinical characteristics of the disease. These characteristics include age of onset (juvenile vs. adult), rate of disease progression (chronic vs. aggressive) and the number of affected tooth sites (generalized vs. localized). Generalized chronic adult periodontitis is the disease most commonly found in older adults. It is a matter for concern because it can threaten the overall dentition and it is associated with chronic localized and systemic inflammation. However, there are no generally-accepted definitions of either moderate or severe periodontal disease [3].

Variations in case definitions for periodontal disease and methodological inconsistencies are the norm across studies of periodontal disease prevalence [17]. Most case definitions are based on the number of periodontal probing sites (either PPD or CAL) that exceed some criterion. Definitions for classifying an individual as a case range from the presence of only one tooth-site demonstrating CAL >2 mm to the need for a generalized destruction of periodontal tissue across many teeth [18]. This lack of an agreed-upon case definition has led to great difficulty in comparing prevalence estimates across various studies. The consequence of various case definitions was documented in a study that found prevalence estimates to vary by a factor of 10 based on changes in case definitions [19]. Adding to the effect of changing case definitions is the fact that the actual measurement process is quite technique-sensitive, requiring the examiner to apply a consistent pressure to a manual probe across numerous tooth sites. This can result in a lack of consistency of measurement both within and across patients, as well as a high degree of inter-examiner variation.

21.4.3 Prevalence, Incidence and Risk Factors

Demmer and Papapanou [19] summarized prevalence for periodontal disease estimates across a number of populations using various case definitions. They concluded that meaningful estimates of periodontal disease prevalence are at best problematic. However, a summary of findings from their review does provide some broad sense of periodontal disease prevalence. Roughly 50–70% of adult populations have some inflammatory gingival condition, either gingivitis or periodontitis, though the majority of these individuals have very mild to moderate disease levels. The most severe levels of periodontal disease (i.e., disease that is widespread across most teeth, is actively progressing and, if untreated, would likely threaten the entire dentition) was much less common. The US Centers for Disease Control and Prevention (CDC) report that only 5–15% of most US populations suffer from this severe form of generalized periodontitis [20].

It is also clear from numerous studies that the prevalence of severe periodontal disease increases with age (Fig. 21.2). Representative data for the entire US from NHANES results showed the prevalence for moderate to severe periodontal disease to be 11% among adults 50–64 years of age, 14% among adults 65–74 years of age, and 20% among adults ≥75 years of age [21]. Though the prevalence of periodontal disease increases with age, this is likely due to the accumulation of periodontal tissue damage and the longstanding exposure to pathogenic biofilms. There does not seem to be an age-related increase in susceptibility to the disease [22].

Globally, the WHO reports that the prevalence for significant levels of periodontal disease range from 5 to 70% among older adults across a wide number of nations [24]. This wide range in prevalence is likely attributable to variations in population-level risk factors (e.g., smoking, oral hygiene, access to care) among nations, as well as to variations in the measurement methods used in various studies.

Hampered by changing definitions of the disease, Page and Eke [25] concluded that data on secular trends of periodontal disease are too unreliable to allow for meaningful summaries. However, based on NHANES data, they concluded that there has been a decrease in the prevalence and severity of periodontitis over the last 50–60 years. These decreasing trends in

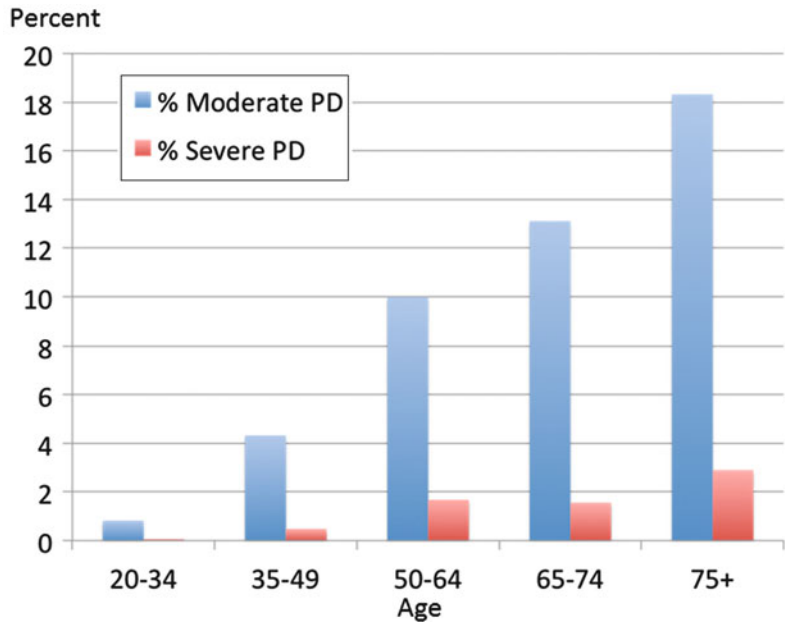

Fig. 21.2 Prevalence of periodontal disease [23]

periodontal disease prevalence seem to be occurring more among the mild to moderate disease levels, with the prevalence of severe periodontal disease remaining more stable [26].

21.4.3.1 Risk Factors

Periodontal disease is episodic, whereby the disease cycles through periods of exacerbation and then remission on a site-specific level. The current model of periodontal disease progression is known as the burst theory. This theory posits that in susceptible individuals, each tooth site periodically undergoes a burst of disease activity that results in loss of soft tissue attachment to the tooth. Disease progression then stops and often the site can undergo repair and long periods of remission with no further tissue destruction [3].

Individual susceptibility is multifactorial and is likely based somewhat on genetic factors and other factors that alter host immune response. Demographic factors associated with increased periodontal disease include male gender, ethnicity and lower socioeconomic status [3]. Borrell et al. [17] reported that among older US adults, African-Americans and Mexican-Americans have nearly twice the prevalence of periodontitis than do whites. Among other risk factors, smoking is probably the most important. When compared to non-smokers, smokers have from a 2.5 to 6.0 times greater risk for developing CAL. Psychological stress, diabetes and HIV infection are also associated with greater CAL [20]. Surprisingly, plaque levels correlate poorly with periodontal disease risk [3].

21.4.4 Periodontal Disease Complications

Periodontal disease is associated with numerous systemic conditions. Aspiration pneumonia is a common condition in older institutionalized adults and periodontal disease appears causally related. Active periodontal disease, as well as untreated dental caries and generally poor oral hygiene, pose an increased risk for aspiration pneumonia [27]. The presence of periodontal pathogens in the saliva increases the odds of developing aspiration pneumonia by more than 4-fold [27]. Given the high morbidity and mortality associated with pneumonia in older adults, particularly those in institutions,

the role of periodontal disease and poor oral health as a cause of premature death should not be minimized.

Numerous small cross-sectional and case–control studies have suggested—but not yet established—a causal link between periodontal disease and several other important systemic conditions. These conditions include myocardial infarction; stroke; type 2 diabetes; osteoporosis and rheumatoid arthritis, all of which share a common altered inflammatory etiology.

An association between periodontal disease and cardiovascular disease has been evident for more than 20 years [28]. However, firmly establishing a causal link between periodontitis and cardiovascular disease remains elusive. The current literature is filled with studies that show significant correlations, with relative risks that range from 1.2 to 4.0 [29]. However, these studies have been criticized for methodological failings that establish a temporal relationship between cause (periodontal disease) and effect (cardiovascular disease). In addition, many of these studies are limited by small sample sizes, poor disease characterizations, and residual confounding (e.g., smoking), making a causal conclusion difficult. One recent meta-analysis reported a weak association between periodontal disease and coronary heart disease across five prospective studies (Relative Risk [RR] 1.14; 95% CI: 1.074–1.213) [30].

There are two hypothesized mechanisms that attempt to explain the increased risk of coronary heart disease in periodontal disease patients. One hypothesized mechanism involves periodontal-disease-induced increases in levels of systemic inflammation [31]. A review of intervention trials for periodontal disease demonstrated that periodontitis contributes to the overall systemic inflammatory burden, and patients who are treated for periodontal disease show improvement in systemic markers of inflammation (e.g., C-reactive protein [CRP]) [32]. Tonetti [29] concluded that the current evidence suggests that periodontal therapy can reduce systemic inflammation, and periodontitis—if left untreated—may contribute to the systemic inflammatory burden and lead to an increased risk of atherosclerosis in otherwise healthy individuals.

A second hypothesized mechanism involves the induction of bacteremia whereby oral bacteria enter the systemic circulation and infect remote areas of the body. This is supported by the presence of oral (gram negative) bacteria frequently being found in atheroma. It is hypothesized that the bacteria themselves provide the initial stimulus for atheroma formation [33].

Periodontitis has been called the sixth complication of diabetes [34]. The risk for developing periodontal disease among individuals with diabetes is clear [35]. There is also evidence that periodontitis exacerbates diabetes and results in poorer glycemic control. A meta-analysis by Darr et al. [36] showed evidence that periodontal therapy can improve glycemic control.

In a review of the literature that has related periodontal disease to rheumatoid arthritis, Bartold et al. [37] concluded that there was a strong association between rheumatoid arthritis and periodontal disease, but the link was likely not causal. They concluded that the two conditions share a common etiologic pathway.

Given the crucial support function of the bones of the jaw for maintaining the teeth, it seems reasonable that diseases that affect bone quality, such as osteoporosis, would have a relationship to periodontal disease and edentulism. However, the evidence of a link between osteoporosis and periodontal disease remains conflicted. Evidence from cross-sectional studies has demonstrated a link between osteopenia and both CAL and tooth loss [38, 39]. Another study provided indirect evidence of an association with a finding that estrogen replacement therapy, when used to treat systemic osteoporosis, also resulted in decreasing the risk of periodontal disease and tooth loss [40]. Other research, however, has failed to find an association between markers of periodontal disease and systemic measures of bone mineral density in either older women [41, 42] or men [43].

Hormone therapy (HT), as used frequently with postmenopausal women, has been shown to have a possible role in improving the oral health of postmenopausal women. Postmenopausal women who received HT had improved periodontal

status compared to postmenopausal women who did not receive HT, with improved periodontal status defined as less dental pain, less tooth mobility and less periodontal probing depth [44, 45]. It is becoming evident that HT is generally protective against periodontal disease and tooth loss [46].

Finally, five different longitudinal studies [47] found periodontal disease to be a marker for increased risk of all-cause mortality, with risk levels for death in a range similar to that caused by smoking (RR 1.5–2.2).

Regardless of the exact nature of the link between periodontal disease and inflammatory-associated systemic disease, the presence of periodontal disease should be viewed as a potential marker of risk for numerous serious conditions. The careful clinician will use this information when risk-assessing a patient and decide for which diseases the patient needs to be screened.

21.4.5 Prevention of Periodontal Disease

Gingivitis responds well to personal oral hygiene interventions such as toothbrushing and flossing. The biofilm that causes gingivitis is supragingival and is therefore relatively easy to remove mechanically. Thus, daily effective personal oral hygiene is the most effective means of preventing gingivitis.

Periodontitis is much more difficult to prevent. The pathogenic biofilm is subgingival and difficult to remove mechanically. Prevention is generally managed through therapy delivered by dental professionals (e.g., dental hygiene for prevention) where mechanical control of subgingival plaque can be achieved. Smoking cessation is the most effective personal behavior change that individuals can engage in to prevent periodontal disease.

21.5 Tooth Loss

Edentulism is the complete loss of all teeth. However, people are also referred to as being partially edentulous, meaning that they have lost some but not all of their teeth. Since tooth loss is an irreversible condition, the number of retained teeth is strongly age-related. The process leading to tooth loss is a complex interplay of biological, personal and cultural factors. Among older adults, partial and complete edentulism remains a significant problem. The good news is that in most developed nations the prevalence of both partial and complete tooth loss shows an ongoing secular trend toward greater tooth retention across all ages. The reduction of partial and complete edentulism in developing nations is more difficult to generalize, but there clearly does seem to be some improvement in tooth retention among the more economically-advantaged groups within most nations [48]. As teeth are retained throughout life, however, caries and periodontal disease will become lifelong concerns and the demand for dental services will increase.

The most recent NHANES survey data (1999–2002) show that US adults ≥20 years of age had on average retained approximately 24 permanent teeth (a full dentition is considered to be 28 teeth, with third molars excluded). However, adults ≥60 years of age had on average only 19.4 retained teeth. The prevalence of complete edentulism was only 1% of 20–39 year olds, but rose to nearly 25% among adults ≥60 years of age. In comparison, the previous NHANES data (1988–1994) reported that complete edentulism in adults ≥60 years of age was 31%. This represents a nearly 20% reduction in the prevalence of edentulism among older adults in a span of about 10 years [49].

The major reported cause of tooth loss across all ages is caries, with periodontal disease being a significant factor in adults after age 35 [3]. However, it is important to note that tooth loss is strongly influenced by culture, access to dental care, and the general standards of care within a region or nation. Within the US, there is great variation in edentulism between states. Among adults ≥65 years of age, Hawaii reported the lowest rate of edentulism (15.9%) and Kentucky the highest (44.3%). This tremendous cross-national variation is more reflective of patient and dentist attitudes toward edentulism that it is of underlying

Table 21.1 Prevalence of edentulous in the elderly for selected countries [49]

WHO region/ country	Percentage edentulous	Age group (years)
African		
Madagascar	25	65–74
The Americas		
Canada	58	65+
USA	26	65–69
Eastern Mediterranean		
Egypt	7	65+
Lebanon	35	65–75
Saudi Arabia	31–46	65+
European		
Albania	69	65+
Austria	15	65–74
Bosnia and Herzegovina	78	65+
Bulgaria	53	65+
Denmark	27	65–74
Finland	41	65+
Hungary	27	65–74
Iceland	72	65+
Italy	13	65–74
Lithuania	14	65–74
Poland	25	65–74
Romania	26	65–74
Slovakia	44	65–74
Slovenia	16	65+
United Kingdom	46	65+
South-East Asia		
India	19	65–74
Indonesia	24	65+
Sri Lanka	37	65–74
Thailand	16	65+
Western Pacific		
Cambodia	13	65–74
China	11	65–74
Malaysia	57	65+
Singapore	21	65+

Adapted from: Petersen [49]

caries or periodontal disease rates [3]. For many generations, edentulism was considered an inevitable result of aging by both patients and dentists. Consequently, they mutually agreed that full clearance was an appropriate way to manage ongoing caries and periodontal disease. Fortunately, this attitude is now mostly gone from dental practice, and both patients and dentists insist on a more conservative, tooth-retaining approach to disease management.

In addition to age, demographic factors associated with tooth loss include gender, race and socioeconomic status. In the US, women tend to become edentulous at higher rates and younger ages than do men. Edentulism rates are higher among African Americans than among whites. Among individuals ≥20 years of age who have teeth, African-Americans have on average two less teeth than do whites. Predictably, there is a strong gradient in tooth loss and the prevalence of complete edentulism across both economic and educational levels, with lower income and less educated individuals having the least number of retained teeth and the highest rates of complete edentulism [21].

The WHO provides data on edentulism among adults ≥65 years of age in selected countries. Table 21.1 shows more than a 10-fold difference in the prevalence of complete edentulism, ranging from 7% in Egypt to 78% in Bosnia and Herzegovina [49]. Variations are attributable to economic factors, tobacco use and cultural attitudes toward the inevitability of tooth loss. Fortunately, there is a general trend in many nations for a temporal decrease in edentulism in recent years [8].

21.6 Oral Cancer

More than 35,000 Americans were diagnosed with oral cancer in 2009 and over 7,600 died [50]. Approximately 90% of oral cancers are squamous cell carcinomas. Recurrence is a common feature, with the development of a second primary tumor occurring at a rate of approximately 4% annually [51]. Most victims of oral cancer are older adults, with prevalence rates strongly dependent on age and race. The median age at diagnosis is 64. Five-year survival for whites is 54% and for African-Americans is 35%. Compared with whites, African-Americans are more than twice as likely to be diagnosed with oral cancer and at the time of diagnosis, to have more advanced disease with greater likelihood of distant metastases [50]. Stage at diagnosis is

important for survival. The 5-year survival rate for individuals with localized disease is 81%, but only 17% for those with distant metastases [52].

Across all races, men are more than twice as likely as women to be diagnosed with and die from oral cancer. This difference is primarily based on a differential in lifetime smoking exposure. Women with similar smoking histories are as likely as men to develop oral cancer [50].

Tobacco is the most important risk factor for oral cancer. Of individuals >50 years of age who have been diagnosed with an oral cancer, more than 75% are current smokers. In combination with alcohol, the risk for oral cancer development is 15 times greater than that among non-smokers and non-drinkers. Recent evidence suggests that oral infection with human papillomavirus (HPV) is an independent risk factor as well [53]. On a global basis, oral cancer is much more common in developing countries than in developed countries, and it is linked with socioeconomic conditions, diet, and tobacco and alcohol consumption [24, 54]. Figure 21.3 shows the global variation of oral cancer among men and women.

A comprehensive set of oral cancer prevention recommendations were created in 1996 by the Oral Cancer Work Group. The work group was a consortium of stakeholders from the federal government (CDC, National Institute for Dental and Craniofacial Research) and organized dentistry (American Dental Association). This work group developed over 50 recommendations in 5 categories related to oral cancer prevention and control. The categories were: (1) advocacy, collaboration and coalition building; (2) public health policy; (3) public education; (4) professional education and practice and (5) data collection, evaluation and research. Details can be found in the August 28, 1998 issue of the CDC Morbidity and Mortality Weekly Report [55]. The CDC also undertook a systematic review of current science to determine whether sufficient evidence exists to recommend population-based interventions for the early detection of oral cancer. They concluded that there was insufficient evidence to determine the effectiveness of such interventions [55]. Consequently, population-based screening programs are not supported by current science.

21.7 Consequences of Oral Diseases on Oral and Social Functioning, and Quality of Life

In the earliest stages, which often last for years, caries and periodontal disease are usually asymptomatic. It is not until substantial tissue damage has occurred that patients become aware of many oral problems. These problems manifest as abscesses, tooth mobility, tooth loss, malocclusions, esthetic concerns, oral malodor, and chronic or acute pain. It is at this time that oral diseases lead to substantial oral functional limitations, as well as social and esthetic concerns, that begin to have an impact on the overall quality of life.

The consequences of tooth loss can be substantial. Tooth loss and subsequent denture wearing can result in a nutritional disadvantage among older adults by altering food choices [56]. There is evidence that when chewing ability is compromised through tooth loss and poorly fitting dentures, food choices tend toward a diet lower in fruits and vegetables and a reduction in micronutrients [57–59]. This suggests an increased risk to overall health status mediated by changes in dietary choices.

Oral conditions such as tooth loss and pain have a substantial impact on quality of life and social functioning. Foerster et al. [60] reported that 23% of older adults had difficulty in chewing and 10% had difficulty in speaking. In a cohort study of adults in Florida, Gilbert et al. [61] found that during a 6-month period, 25% of participants reported some oral health concern or impairment. In a British study of adults ≥65 years of age, Sheiham et al. [62] found a high prevalence of impacts on daily living from oral problems. Among older adults, 17% reported that their mouth affected their pattern of daily living, with the impact most commonly affecting eating or speaking. Among those with an impact, 42% had some impact on a near daily basis. In a United Kingdom study, Smith and Sheiham [63] reported that tooth loss and associated dental conditions among older adults created embarrassment and resulted in decreased social contact. In another United Kingdom study, Fiske et al. [64] found

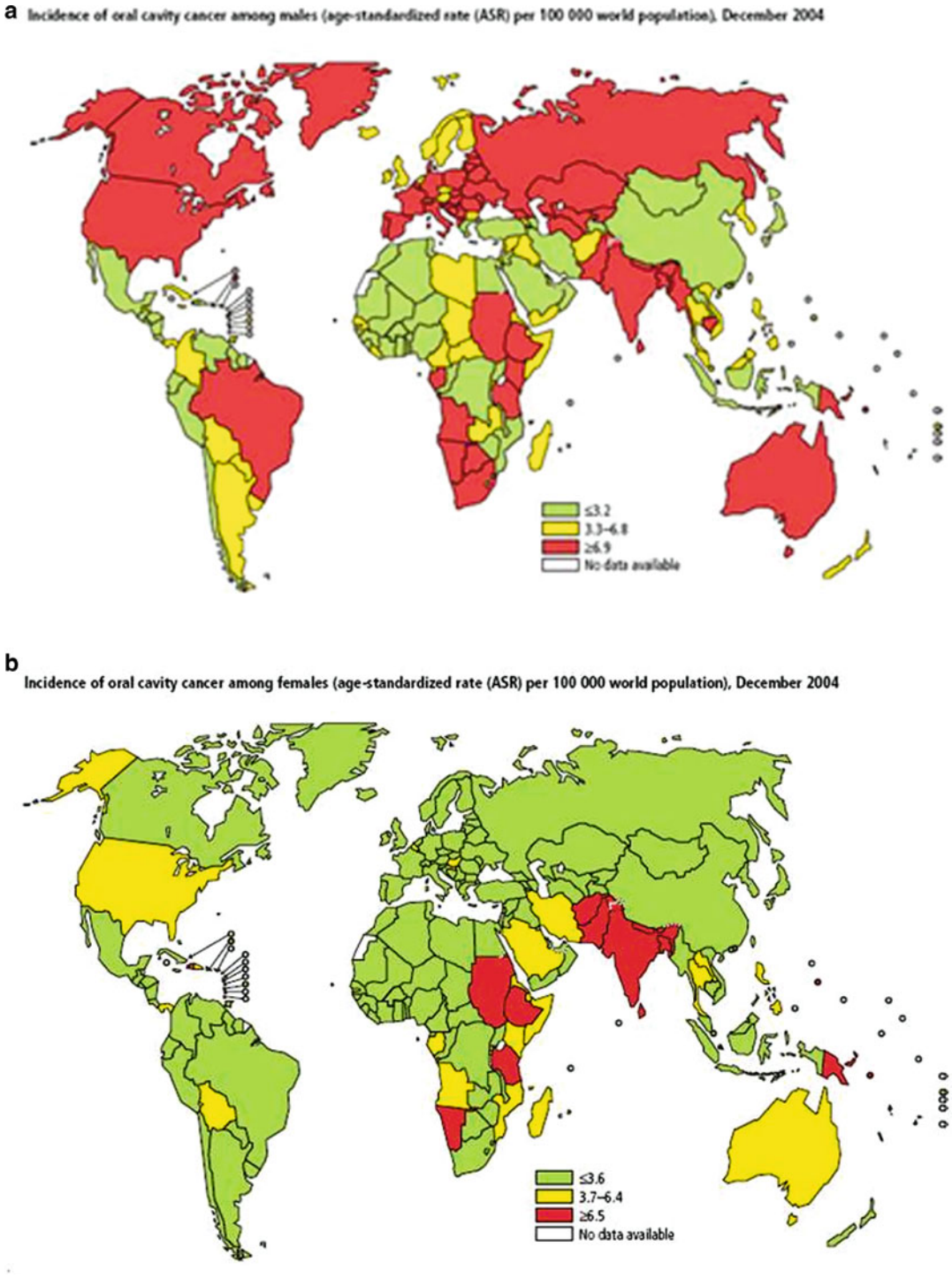

Fig. 21.3 Incidence of oral cavity cancer (age-standardized rate per 1,000) 2004 [24], (**a**) Among males, (**b**) Among females

that older adults altered their social behaviors based on lowered self-confidence and an altered self-image. They concluded that tooth loss was a disabling condition with profound impact on the lives of some older adults who had difficulty in coping well with edentulism and denture wearing.

Although there is no significant decline in salivary output with age, numerous medical conditions, medication usage and salivary disorders that are common among older adults often result in reduced salivary flow and the discomforting sensation of dry mouth (xerostomia) [65]. Medication usage is the most common cause of dry mouth, with over 400 medications reporting dry mouth as a side effect. Additionally, several medical conditions that are common in older adults, such as diabetes and Alzheimer's disease, can contribute to dry mouth, as can head and neck radiation therapy. The role of saliva in oropharyngeal health includes protection from caries and as an aid to swallowing, oral cleansing, speech, digestion and taste. The lack of saliva can lead to increases in caries, and in denture-related sores and poor denture retention. Additionally, low saliva flow is associated with oral bacterial infections and oral candidiasis [66].

Recently, more emphasis is being placed on assessing patient-based outcomes and personal perceptions of oral conditions. The concept of oral-health-related quality of life has been advanced as an important dimension of overall quality of life. The measurement of oral-health-related quality of life is itself a multidimensional concept, and measurements of it should attempt to capture factors that are important to people in their everyday life. These typically include functional, social and psychological factors [67]. Instruments such as the Geriatric Oral Health Assessment Index (GOHAI) [68] and the Oral Health Impact Profile (OHIP) [69] have been developed to assess patient concerns regarding oral status, and are now being used more frequently as part of population-based research to provide a patient-based assessment of the impact of oral diseases. As a result, research that focuses on patient-centered outcomes is now more common and is leading to new approaches to prevention and treatment interventions that are aimed at improving quality of life, particularly among older adults.

21.8 Conclusions

The common oral diseases of caries, periodontal disease, tooth loss and oral cancer continue to affect older adults in important ways. These effects include increased morbidity, mortality and decreased quality of life. The cumulative nature of oral conditions means that older adults tend to carry a greater burden of oral disease compared to younger cohorts. In addition, among older adults, functional and economic constraints often make it difficult to access professional dental services, so much of the oral disease that is present in older adults is untreated and long-standing in nature. Among institutionalized older adults, oral health status and access to dental care have become degraded even further. The once-common belief in the inevitability of oral disease and tooth loss as one ages has historically led to a social acceptance of oral disease in old age. It is now clear that this is not the case and that society in general needs to change its view of oral health in aging, as well as how it provides for access to care for economically disadvantaged and physically dependent older adults.

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Epidemiology of Cancer and Aging

22

Kerri M. Clough-Gorr and Rebecca A. Silliman

Abstract

Aging is related to changes (mostly negative) in multiple domains (physical, cognitive, emotional, social and economic) that influence the status and wellbeing of older adults. Age is the major risk factor for many cancers and older adults make up the largest segment of the cancer population. The increase in risk of cancer with age, projected growth in older populations and increasing cancer survivorship lead to the expectation that the number of older cancer survivors will increase in the years ahead. The diagnosis and treatment of cancer in older adults is complicated by the heterogeneity of the older populations (chronological age does not correlate well with physiological age in the later years), the pathophysiologic differences in older cancer patients compared to younger ones, and the lack of randomized controlled trial data on older adults. In addition, cancer in older populations results in long-term and late physical and psychosocial effects that differ from those found in younger populations. The continued epidemiologic study of cancer, aging and their interaction in older adults must take these issues into account if it is to contribute significantly to our understanding of the consequences of increased cancer incidence with longer life spans in aging populations worldwide.

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Aging • Epidemiology • Geriatrics • Older adults • Longevity • Cancer • Breast cancer • Colon cancer • Lung cancer • Prostate cancer • Cancer treatment • Cancer surveillance • Cancer screening • Survival • Cancer recurrence • Chemotherapy • Radiation therapy • Prevention

22.1 Introduction

Aging is related to changes in multiple domains (physical, cognitive, emotional, social and economic) that influence the status and wellbeing of older adults. Increasing age is primarily associated with negative changes in these domains (e.g., increased chronic comorbid health conditions, decreased physical function, limited social support). The changes that come with aging are ongoing throughout the human life span. For the purposes of this chapter, the term 'aging' will refer only to those changes which are concentrated in the last decades of life.

One of the most common and dreaded late-life experiences is a diagnosis of cancer. Increasing age is the major risk factor for many cancers. In fact, older adults make up the largest segment of the cancer population. An important yet problematic issue is that chronological age does not correlate perfectly—or even necessarily well—with physiological age in the later years. For example, two older adults of the same chronological age may differ considerably in mental and physical capacities. Furthermore, the gap between chronological and physiological age broadens over the life course, so increased longevity brings increased heterogeneity. It is essential that the study of the epidemiology of cancer in older adults take this understanding of heterogeneity into account.

Cancer screening is more complex in older adults. Treatment is more complex as well, often encompassing the treatment of other age-related illnesses in addition to the cancer and most often requiring that multidimensional factors be addressed. With improvements in screening and treatments, larger numbers of older cancer patients are experiencing longer-term survival and thus must contend with corresponding late physical and psychosocial effects.

Understanding the epidemiologic patterns of both cancer and aging will be essential if we are to cope with the changes that a larger proportion (in developed countries) and greater number (in developing countries) of older adults will bring to bear. Likewise, understanding the implications of these changes will provide a framework for addressing age-related disparities in the treatment of and research in this growing population of older adults living longer with cancer.

This chapter provides an overview of important topics that pertain to the epidemiology of cancer and aging. We first examine cancer burden (incidence and prevalence) and risk factors, and describe the unique characteristics (pathophysiological differences) of cancer in older adults. We then consider cancer screening in older adults and conclude with the cancer survivorship experience (long-term and late physical and psychosocial effects).

22.2 Incidence and Prevalence

In the United States (US), cancer is the fourth most common chronic disease and second leading cause of death in older adults (Fig. 22.1). Cancer is an age-specific disease, with incidence and mortality trends demonstrating a consistently greater and growing burden in older adults compared to younger populations (Fig. 22.2) [1]. Data from the National Institute of Aging (NIA)/National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program showed that from 2000 to 2003, 55.9% of all cancer tumors occurred in individuals ≥65 years of age (Fig. 22.3) [4]. The American Cancer

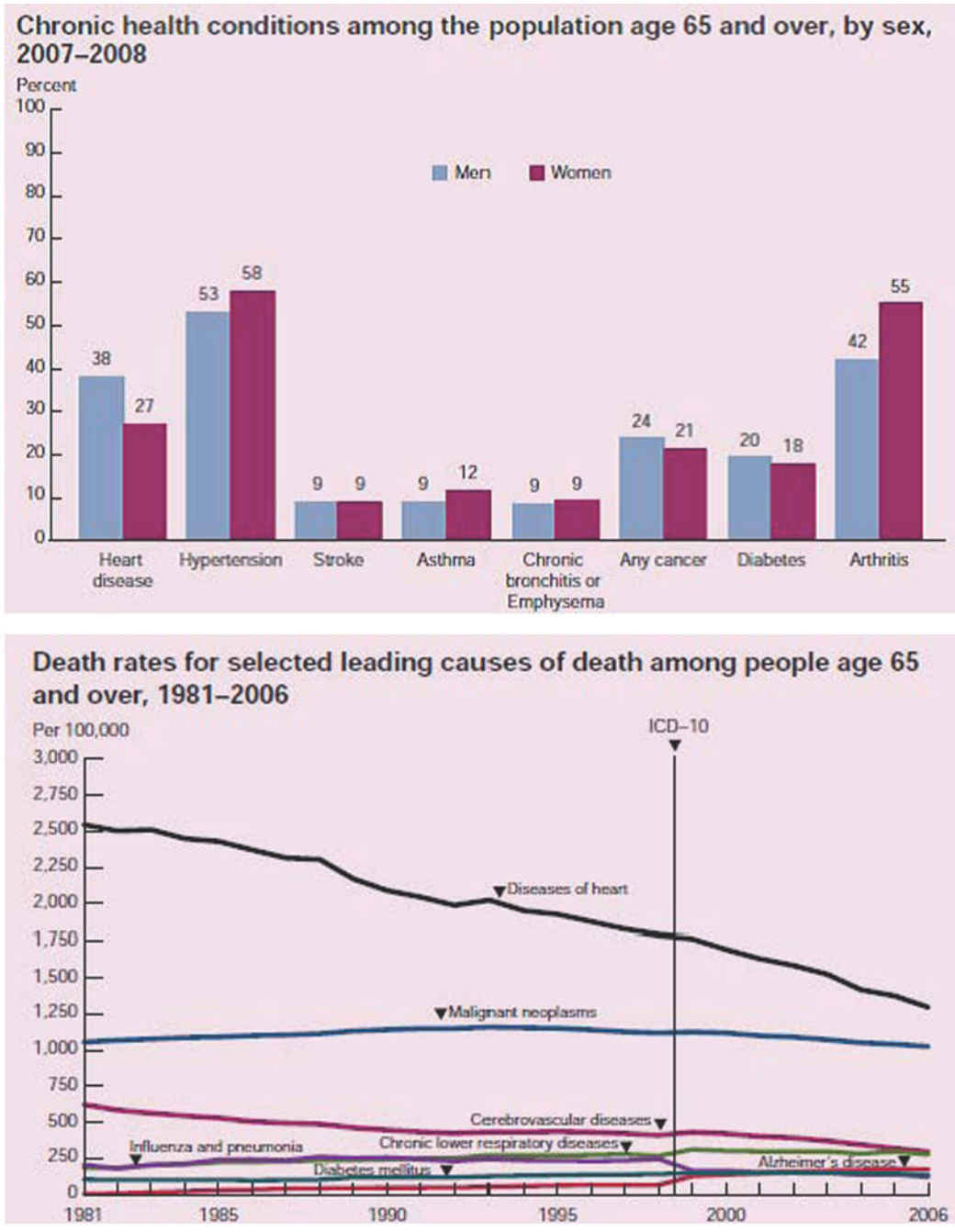


Fig. 22.1 Proportion of chronic diseases and mortality rates of chronic conditions in the population ≥65 years of age in the United States [1, 2]. (**a**) Proportion of chronic diseases, (**b**) Mortality rates of chronic conditions (Source: Adapted from Older Americans 2010: key indicators of well-being)

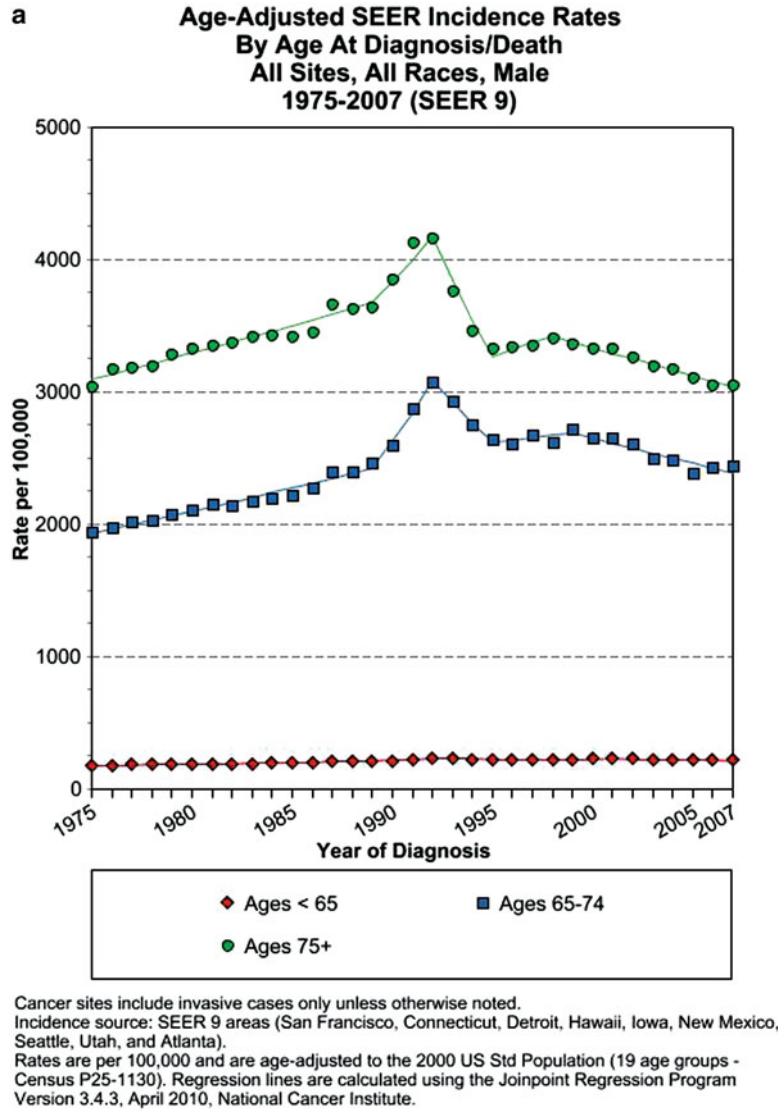
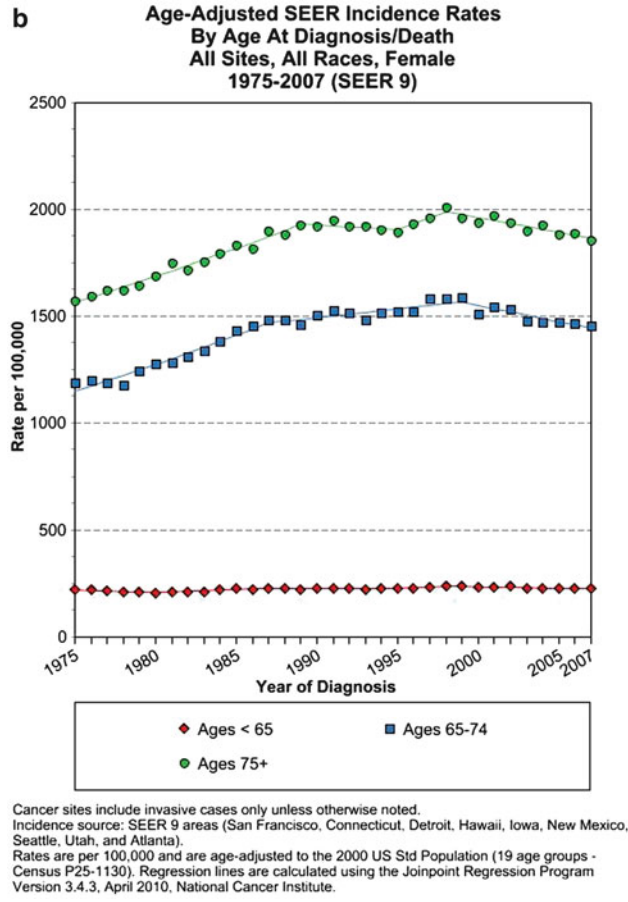


Fig. 22.2 Trends of age-adjusted all-cause cancer incidence rates for the United States population, by age group, 1975–2007 [1, 3]. (**a**) Male, (**b**) Female (Source: Adapted from National Cancer Institute SEER Fast Stats)

Society has estimated that 60% of all cancer survivors are ≥65 years of age [3]. The overall burden of cancer in older Americans ranges from 7.48 to 21.04% (the proportion of people in the US ≥60 of age who were alive on January 1st, 2007 and had a cancer diagnosis in the previous 17 years), as measured by the estimated percentage of cancer at all sites. Many cancers occur commonly in older adults, the most common being bladder, colorectal, pancreas, lung and stomach. Prevalence is higher in men than in women, and this disparity increases with advancing age (Table 22.1) [1]. The most common sex-specific cancers are breast cancer in women and prostate cancer in men.

22.2.1 Reasons for Greater Prevalence in Older Adults

The increased risk of cancer in older adults is thought to be related to several age-linked



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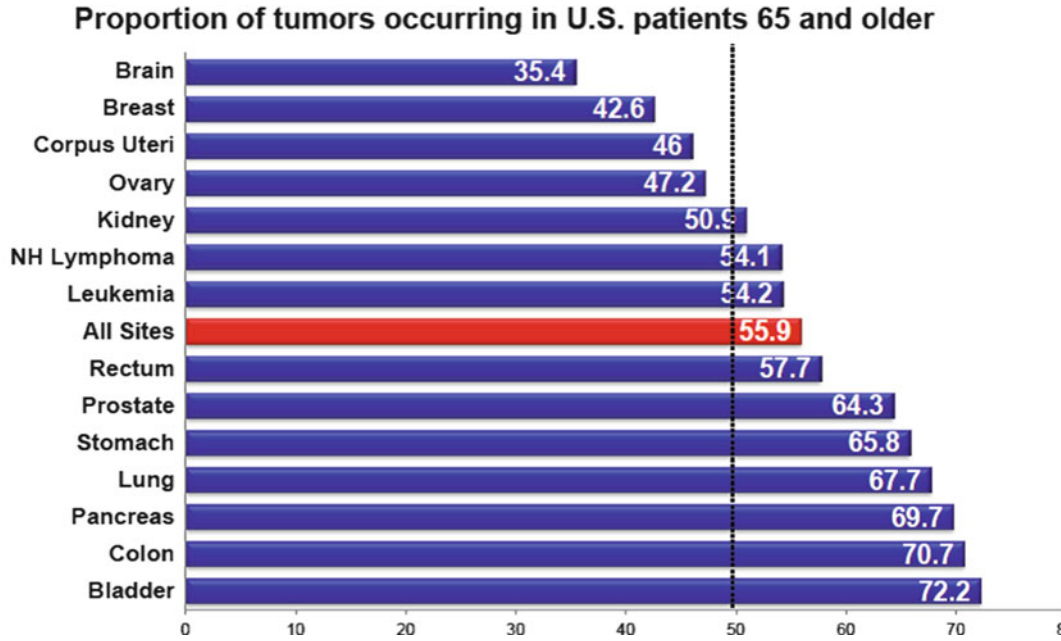


Fig. 22.3 Proportion of tumors occurring in the United States population ≥65 years of age by primary site, 2000–2003 [4] (Source: Yancik IOM 2007 SEER data 2000–2003)

Table 22.1 Estimated all cancer sites age-specific[a] prevalence percent[b] on January 1st, 2007 of the U.S. SEER 11 population age 60 and older (all races) diagnosed in the previous 17 years

Sex	60–69 years old (%)	70–79 years old (%)	80+ years old (%)
Both Sexes	8.21	13.63	14.38
Females	7.48	10.00	10.67
Males	9.01	18.29	21.04

[a] Age at prevalence
[b] U.S. 2007 cancer prevalence counts are based on 2007 cancer prevalence proportions from the SEER 11 registries. U.S. population estimates based on the average of 2006 and 2007 population estimates from the U.S. Bureau of the Census for SEER 11 areas. Prevalence was calculated using only the first malignant primary for persons (Source: Adapted from National Cancer Institute SEER Fast State [3])

processes [5, 6]. Cancer is a multi-step process, and over a longer life there is both an increased opportunity for DNA damage and longer exposures to potential carcinogens. Thus, older adults have a greater potential for accrued molecular damage. Cancer also has a very long incubation period (i.e., most cancers by their innate biology take years to become detectably large), so with greater age there comes an increased potential for the immune system to fail in removing cancer. In addition, older adults have an age-related decrease in cellular repair activity that ultimately allow for the development of malignancies.

22.2.2 Differential Rates of Diagnosis in Age Groups ≥65 Years of Age

As stated above, the median age at diagnosis for cancers at all sites in 2003–2007 was about 66 years [3]. However, in the same period approximately 24.7% of all cancers were diagnosed in persons 65–74 years of age, 21.8% in those 75–84 years of age, and 7.7% in those ≥85 years of age. This pattern of fewer cancer diagnoses in the oldest age group holds across most cancer types. There is controversy as to whether there is an actual drop of cancer incidence in the oldest age group or whether this is an artifact of small numbers and decreased screening and diagnostics (Fig. 22.4). If the effect is real, putative reasons include selective survival (including genetic factors), an interaction with late life biology, or both.

22.2.3 Incidence, Prevalence and Mortality by Cancer Site, Sex and Age

Figure 22.5 shows changes in trends of age-adjusted cancer mortality and incidence rates by primary cancer site from 1998 to 2007 for the US population ≥65 years of age. From 2000 to 2007, cancer trends in older Americans show overall decreases in age-adjusted cancer incidence and mortality (−1.0 and −1.4 annual percent change [APC], respectively) [1]. However, these trends vary considerably by cancer site, sex and age. For example, incident lung cancer decreased slightly for women 65–74 years of age (−0.3 APC), increased for women ≥75 years of age (2.8 APC) and decreased for men across all age groups (65–74 years of age: −4.0 APC, ≥75 years of age: −0.5 APC) [1]. Nonetheless, the lung was the second leading cancer site and lung cancer the most fatal cancer for both men and women (approximately 30% of all cancer deaths). The second- and third-ranked most fatal cancers were breast and colorectal cancer in women, and colorectal and prostate cancer in men. All of these types showed varied but decreased mortality and incidence over time [1, 4]. Nearly half of all cancer survivors are survivors of breast (22%), prostate (19%) or colorectal (9%) cancers [7].

Differences in incidence, prevalence and mortality over time may be attributed to both improvements in early detection and improvements in treatment. Unfortunately, the effects of these

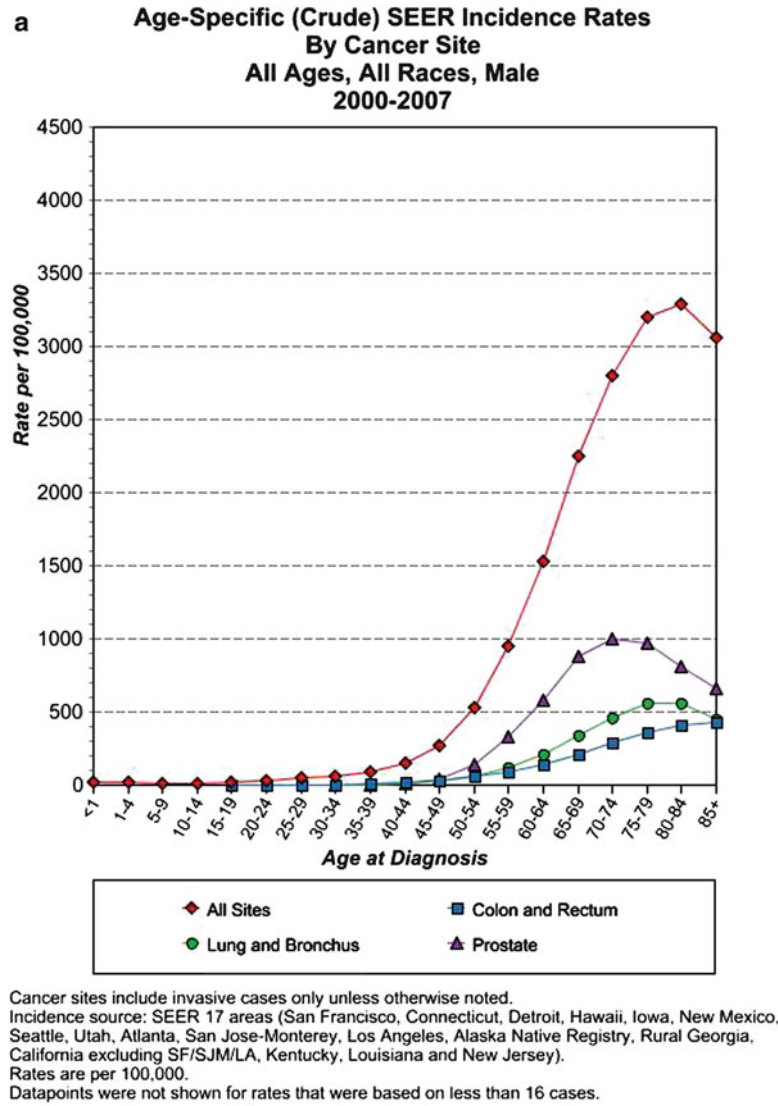
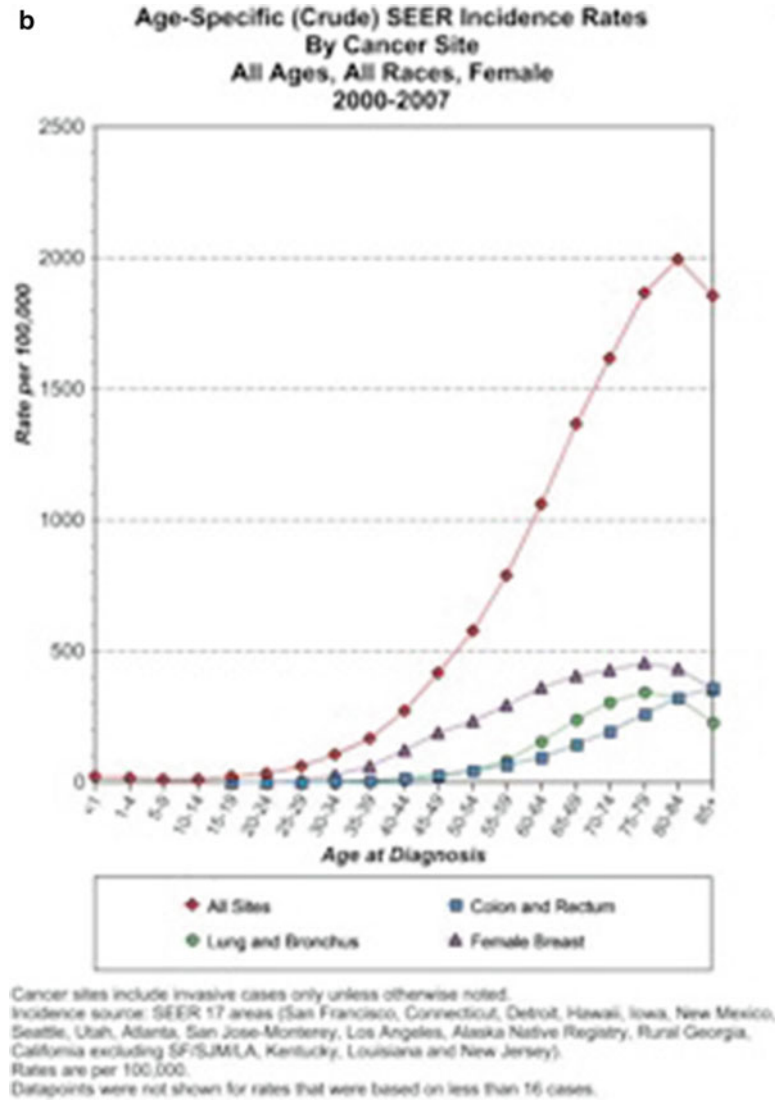


Fig. 22.4 Age-specific all-cause and cancer-specific incidence rates in males and females in the United States, 2000–2007 [3, 4]. (**a**) Males, (**b**) Females (Source: Adapted from National Cancer Institute SEER Fast Stats)

factors cannot be separately interpreted in time-trend analyses of incidence, prevalence and/or mortality.

22.2.4 Variations in Cancer Burden by Race/Ethnicity

Given the projected growth and aging of minority populations, it is important to consider variations in cancer burden across race and ethnicity [8]. Considerable differences exist in cancer burden and survival across racial and ethnic populations [3]. Overall, cancer incidence and mortality rates are higher and relative survival rates are lower for African-Americans compared to whites. Yet Hispanic, Asian/Pacific Islander, American Indian and Alaska Native populations generally have lower incidence rates compared whites, except for specific cancers (e.g., stomach, liver, cervix, kidney, gallbladder). Age-adjusted 2007 SEER all-site cancer incidence



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rates per 100,000 individuals were as follows: Whites, 2,101.43; African-Americans, 2,073.71; Asian/Pacific Islanders, 1,444.92; American Indian/Alaskan Natives, 1,452.87; and Hispanics, 1,510.53. This general pattern of lower incidence has been attributed to the younger age structures of these populations.

Cancer disparities in incidence, mortality and late-stage presentation exist in these racial/ethnic groups regardless of geography, national origin, economic status or other factors. By 2050, racial and ethnic populations will transition into older age groups. Demographic changes (i.e., rapid growth in older and minority populations) will intersect to increase cancer incidence. From 2010 to 2030, as the older population expands, the percentage of cancers diagnosed in older adults is estimated to increase from approximately 60 to 70% or more, while the estimated percentage of minorities diagnosed with a cancer will simultaneously increase from 21 to 28% [2]. For minorities in the US, the increase in cancer incidence

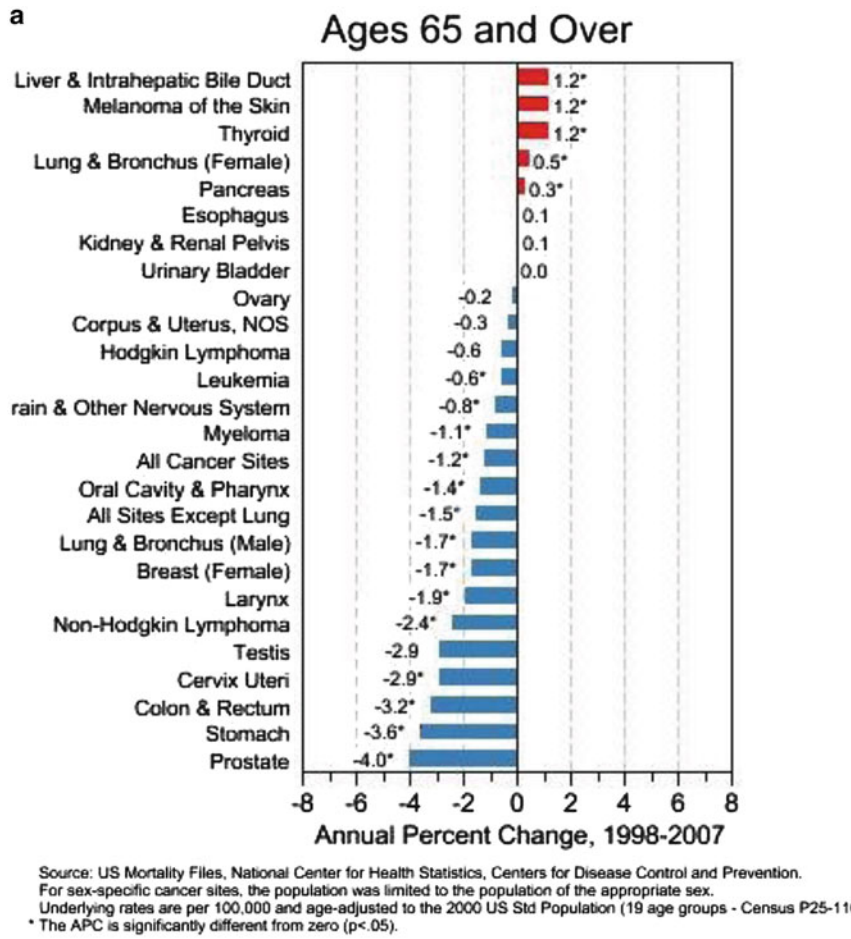

Fig. 22.5 Change in trends of age-adjusted cancer mortality and incidence rates for the population ≥65 of age in the United States, by primary cancer site, 1998–2007 [3]. (**a**) Cancer mortality, (**b**) Cancer incidence (Source: Adapted from National Cancer Institute SEER Fast Stats)

over the next four decades is projected (primarily due to aging) to be nearly three times higher than that for whites (99 versus 31%, respectively) [2]. The increase and simultaneous aging of US minority populations in the coming years will result in considerable demographic changes marked by an increase in the number of cancer diagnoses in minorities and older adults.

The cancer statistics reported for some minority groups (e.g., Hispanics, Asians) may mask wide variations in the true cancer burden for individual populations based on country of origin. Many of the factors that influence the incidence and prevalence of cancer may vary considerably by country of origin, not just by race and/or ethnicity. There are also other important potential sources of variability across minority groups that may be related to cultural and individual health behaviors, health literacy, linguistic fluency, poverty and access to health care. Further, cancer rates may be affected by acculturation (adaptation of immigrants to an adopted culture). This is reflected in rates of risk factors (e.g., smoking, obesity) and diseases of second (and beyond) generations of immigrants being more similar to levels of their adopted country rather than their country of origin. For example, a 2008 study showed total cancer incidence rates

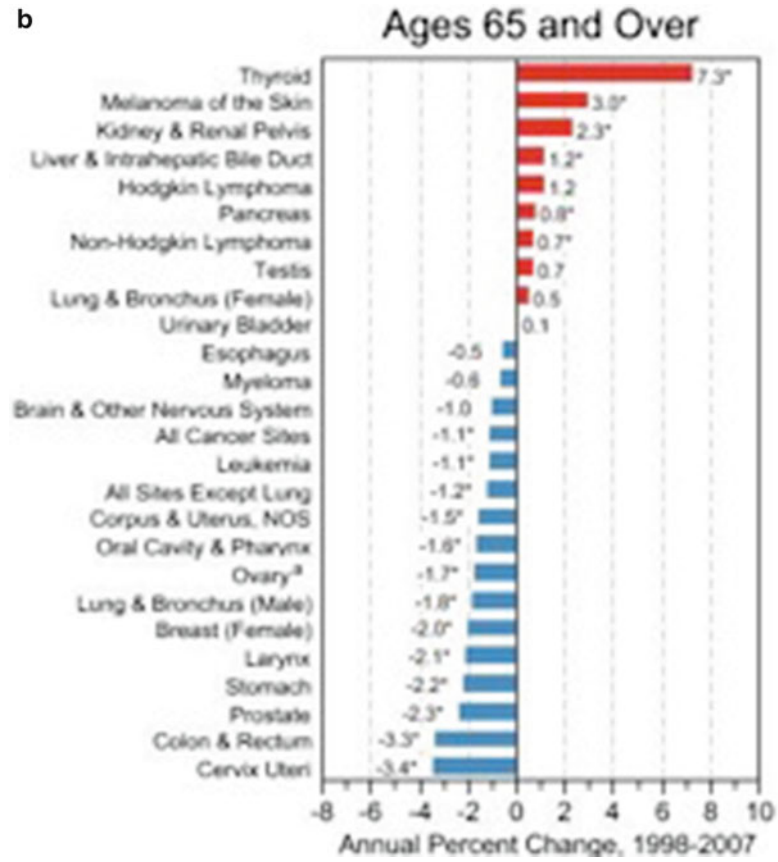

Fig. 22.5 (continued)

were lower in India than among Indians in Singapore, England and the US, which suggests the role of environmental and lifestyle factors, as well as possible diagnostic and screening practices, of the adopted country [9]. To fully understand these roles, it will be necessary to conduct additional epidemiologic explorations of these factors, their associations with cancer burden and their influence on growing aging minority populations in developed countries.

22.3 Risk Factors for Cancer in Older Adults

Cancer epidemiology suggests that age is the single most important risk factor for developing cancer. However, many of the risk factors that affect the general population (e.g., family history, race, smoking, obesity, diet, physical activity) also contribute to cancer risk in older adults. These general population risk factors are often not only associated with cancer, but also with the common diseases and disabilities of aging (e.g., chronic comorbid health conditions such as heart disease or hypertension, limitations in physical function). In turn, these risk factors and associated conditions can greatly impact treatment decision-making, responses to treatment, and outcomes. Some risk factors such as smoking, diet and physical exercise are modifiable, while others such as family history and race are not (e.g., family history is estimated to account for up to 10% of prostate, breast and colorectal cancers [10–12]). This is particularly important for the developing world, where increases in smok-

ing and obesity in the face of increasing life expectancy will accelerate the burden of cancer.

The World Health Organization estimates that more than 30% of cancer deaths in the general population can be prevented by modifying risk factors [13]. The effect of these factors may be magnified in older adults due to their association not just with cancer, but with other common causes of morbidity and death as well.

22.4 Unique Pathophysiologic Differences in Older Cancer Patients and Their Impact on Treatment

The experience of older adults with cancer differs from that of younger adults. Many of the differences can be attributed to the unique pathophysiologic characteristics of older cancer patients. We review these characteristics below.

22.4.1 Chronic Comorbid Health Conditions and Functional Decline

As noted in the preceding sections, cancer is largely a disease of older adults and the incidence of most cancers increase with age. The incidence and prevalence of chronic comorbid health conditions also increase with age, a fact which emphasizes the differences between younger and older cancer patients. Older adults are affected by most chronic diseases more than are younger persons. These diseases, especially when co-existing, have a significant impact on the lives of older adults, their support networks, and the healthcare systems that provide their care. For example, late-life functioning can be disrupted by chronic diseases that limit physical and/or mental abilities and increase the need for supportive care.

Cancer patients who are ≥70 years of age have an average of three chronic comorbid health conditions [14]. The impact of chronic comorbid health conditions increases with age, and in the setting of a cancer diagnosis this impact can greatly affect outcomes. A study of colon cancer patients (mean age 66.9 years) that used three different comorbidity indices showed consistently that severe chronic comorbid health conditions were associated with decreased survival after surgery [15].

The consequences of chronic comorbid health conditions are related to their pathophysiology, prognosis and treatment, and have broad implications in the lives of older adults, especially in those with cancer [16]. The most systematic data that describes chronic comorbid health conditions in newly-diagnosed older cancer patients derive from the SEER study of over 7,600 older persons with cancer, which gathered data on 24 chronic comorbid health conditions abstracted from hospital medical records. Targeted chronic comorbid health conditions were found to be common, and were determined to be present on the basis of having a history of disease or as a current management problem (within 4 months before the diagnosis of cancer) [17]. As expected, the number of chronic comorbid health conditions increased with age, with the mean number of conditions increasing from 2.9 in those 55–64 years of age to 3.6 in those 65–74 years of age and 4.2 among those ≥75 years of age [18]. Further, compared to individuals without cancer, those with cancer were more likely to have chronic comorbid health conditions such as arthritis, diabetes and hypertension.

Dementia is a chronic comorbid health condition that could possibly impact older cancer patients. However, while case reports have been published on this subject, no systematic study to date has examined cancer care in the context of dementia. Potential reasons for this include (1) individuals with dementia, especially those with advanced dementia, may not be diagnosed or treated for cancer, and (2) epidemiologic studies have observed that Alzheimer's Disease is less common in individuals with cancer.

Functional decline is also prevalent in older populations and can pose unique difficulties for an older person's ability to do normal daily activities. In 2007, over 40% of people ≥65 years of age in the US reported at least one functional limitation [19]. As with chronic comorbid health conditions, the impact of functional decline increases with age, and in the setting of a cancer diagnosis it can greatly impact outcomes.

Goodwin et al. [20] studied nearly 800 newly-diagnosed cancer patients in New Mexico and found that assistance with activities of daily living and the instrumental activities of daily living increased with age. One-third were dependent on others for transportation and only about one-quarter lived alone.

So we can see that unlike in younger patients, the major determinants of cancer outcomes in older cancer patients are not restricted to age and tumor characteristics, but also include chronic comorbid health conditions and functional decline. Many studies have examined the effects of age, chronic comorbid health conditions and functional status and found that all have independent effects on treatment for breast cancer [21]. A recent study of patients who were eligible for lung resection to treat early-stage lung cancer found that doctor-patient communication, older age, multiple chronic comorbid health conditions and African-American race were independently associated with the decision not to undergo surgery [22].

There are several reasons why chronic comorbid health conditions and functional impairments are particularly relevant to the older cancer patient. First, they may decrease a patient's ability to tolerate cancer therapies [23]. Recent studies indicate that chronic comorbid health conditions in older adults are associated with a greater risk of adverse effects from chemotherapy [24, 25]. Similarly, a study that related chronic comorbid health conditions to adverse outcomes from radical cystectomy for bladder cancer found increasing chronic comorbid health conditions to be associated with 90-day mortality and early postoperative complications (both major and minor) [26]. Second, chronic comorbid health conditions and functional impairments may limit adherence to treatment if, for example, transportation to and from daily radiation treatments is not available. Third, treatment side effects may interact with existing impairments to cause additional problems. For example, a deconditioned patient who receives chemotherapy that causes a peripheral neuropathy will be at increased risk of falls and fractures. Fourth, increased chronic comorbid health conditions and functional impairment are associated with lower life expectancy. Thus the treatment of a cancer may not prolong life or maintain quality of life due to other life-limiting conditions, making the treatment of questionable value.

All of the above emphasize that health issues related to cancer and its treatment in older adults should not be considered in isolation, but rather with consideration of the relationship of each issue with other prevalent diseases and aging-related issues (e.g., adequate transportation, social support). This is supported by evidence that suggests that a primary cancer diagnosis interacts with chronic comorbid health conditions, that survival is inversely related to the number of chronic comorbid health conditions, and that death more commonly results from chronic comorbid health conditions—rather than from cancer—with advancing age [27–30]. However, cause of death varies according to the aggressiveness of the cancer (i.e., cancer-specific for aggressive cancers and chronic comorbid health conditions for less aggressive cancers). Unfortunately, it is difficult to fully isolate the individual contributions of chronic comorbid health conditions, functional status and/or treatment modification to prognosis [14, 27, 30].

22.4.2 Tumor Characteristics

Another important consideration in older adults is the extent to which tumor characteristics vary as a function of age. Determining this can be a challenge due to the greater likelihood of missing data with age. Analysis of SEER data for prostate cancer diagnoses from 2000 to 2007 illustrate that a larger proportion of older adults (≥65 years of age) have an undetermined histological tumor grade and unknown tumor size and node status (See Table 22.2 for summary of SEER data) [1]. This is not consistently the case for other common cancers in older adults (breast and colorectal), where diagnoses within the same time frame generally show that only the oldest age group (diagnosis at ≥85 years of age) has a larger proportion of unknown staging information. Thus, one should be cautious when interpreting tumor

Table 22.2 Comparison of proportions of older adults (≥65 years) with small tumor size, unknown tumor characteristics, and no node examination to younger adults (<65 years) by cancer site, SEER cancer diagnoses 2000–2007

Cancer type and age	Tumor size <1 cm	Unknown tumor size	Unknown histological grade	No node examination
Breast Cancer				
65–74 years	≈	≈	≈	↑
75–84 years	≈	≈	≈	↑
85+ years	↓	↑	↑	↑
Colorectal Cancer				
65–74 years	↓	≈	≈	≈
75–84 years	↓	≈	≈	≈
85+ years	↓	↑	↑	↑
Prostate Cancer				
65–74 years	↓	↑	↑	↑
75–84 years	↓	↑	↑	↑
85+ years	↓	↑	↑	↑

"↓"Proportion less than <65 years population
"≈" Proportion similar to <65 years population
"↑" Proportion greater than <65 years population

characteristics by age and acknowledge that the varying greater likelihood of missing data with age is an inestimable potential source of bias (i.e., could attenuate, amplify or have no effect).

Nonetheless, of those with SEER-reported tumor size for all three cancer sites (prostate, breast, colorectal), the oldest older adults have the lowest proportion with smaller tumor size (<1 cm) in every year, indicating a later diagnosis [1]. The oldest older adults are consistently less likely to have their lymph nodes evaluated, while the proportions of older adults with prostate or colorectal cancers who have a tumor size <1 cm decreases with age and the proportion of those with no node examination increases with age for prostate and breast cancer. These SEER data indicate that there is variation by age, not just in the availability of tumor characteristics but also in the characteristics themselves.

Published studies which are analogous to the SEER data described above have also shown differences related to age and tumor characteristics. A recent study using SEER data from 1992 to 2003 (restricted to women ≥67 years of age with stage I and II breast cancer) found similar tumor characteristics (grade and hormone receptor status) in the restricted older age and lower stage range. However, the proportion with estrogen-receptor-positive tumors increased with age among those with known status (82% in 67–69 years of age versus 85% in ≥90 years of age), and the proportion with unknown status increased from 18 to 28% in these same age groups, respectively. The examination of lymph nodes decreased dramatically by age, but among those who did have their lymph nodes evaluated, a greater proportion of the very oldest (≥90 years of age) had positive lymph nodes [31]. Wildiers et al. [32] found that, in addition to older women (≥70 years of age) being more likely to have positive nodes, there was an interaction between age and tumor size such that among these older women the increase in node positivity was found primarily in relation to small tumors. The increase in positive nodes in those with smaller tumors suggests that small breast cancers behave differently in older cancer patients. This raises the question as to whether age-related decreased immune defenses might be an explanation.

22.4.3 Genetic Factors

The role of genetic factors in the etiology of cancer is a burgeoning area of investigation, although there is a substantial emphasis on early-onset

cancers rather than on those that occur in late life. Genetic factors may be the sole etiology of late-life cancers, or they may interact with environmental factors to produce such cancers. The tumor suppressor genes *BRCA1* and *BRCA2* are examples of genes that confer a very high risk of breast cancer. The cumulative risk of breast cancer in carriers increases with age, reaching 60–80% by 70–80 years of age and being greater depending on the number of affected first- and second-degree relatives [33, 34]. In addition, *BRCA2* appears to confer risk for other cancers in older age, specifically buccal, pharynx and prostate cancer [35].

There are likely to be many genetic mutations that increase the risk of cancer in older age. One of the most intriguing derives from the epidemiologic observation that cancer is less common among persons with neurodegenerative diseases such as Parkinson's and Alzheimer's Disease [36, 37]. Pin1, an enzyme that influences protein folding as well as cell cycle control, may explain this association [37]. The overexpression of Pin1 promotes oncogenesis and it is overexpressed in many cancers. Conversely, it is down-regulated in the brains of patients with Alzheimer's Disease. A functional variant of the Pin1 promoter that results in decreased Pin1 activity has been associated with both a decreased risk of head and neck cancer and an increased risk of Alzheimer's Disease. Such insights increase our understanding of the basic mechanisms of disease development in old age, and may also prove fruitful in terms of therapeutic targets [36].

22.4.4 Biology of Aging and Its Interactions with Cancer

Among the pathological difference in older cancer patients that must be considered are the biology of aging and its interactions with cancer. Unfortunately, our understanding of these interactions is incomplete and is complicated by their heterogeneity across cancer types. There is evidence indicating that cancers may behave differently depending on the age of the patient [5, 38, 39]. It is hypothesized that two types of mechanisms are involved: (1) changes in the intrinsic biology of the tumor cells, and (2) changes in the ability of an older host to sustain and stimulate tumor growth. In the case of breast cancer, early-onset breast cancers are thought to be primarily due to inherited or early-life cellular damage of immature breast tissue, whereas late-onset breast cancers are considered to be due to extended exposures and age-related cellular damage. Clinical observations and biomarker studies indicate that late-onset breast cancers grow more slowly and are biologically less aggressive than early-onset breast cancers, even when the studies are controlled for hormone and growth factor receptor expression [5, 21]. Regarding other cancers, some have worse prognoses in older adults compared to younger adults (e.g., non-Hodgkin's lymphoma) while others have improved prognoses (e.g., breast, lung).

Age-related physiologic changes due to both genetic (e.g., organ and systems functional reserve) and environmental influences (e.g., disease, physical and emotional stresses, life-style, carcinogenic exposures) involve a progressive loss of stress-coping ability [40, 41]. They may be particularly relevant to cancer biology and treatment in that they may affect the growth rate of the tumor, the pharmacokinetics of drugs and the risk of drug-related toxicity [41].

There is little doubt that the mechanisms and pathways of cancer and aging are interrelated. To illustrate this point, we present some examples of their interplay. The age at which certain malignancies peak maybe related to the biology of both cancer and aging. For example, in the US, melanoma incidence peaks earlier in the life course (in men at approximately 60 years of age) than does prostate cancer (which peaks at approximately ≥80 years of age) [3]. These types of differences are thought to be related to the complexity of and/or number of steps in the carcinogenic pathway [5]. When a specific cancer biology involves a greater number of intermediate stages (e.g., prostate cancer), its incidence tends to steadily increase over the life course in a setting where the cells and tissues of older adults may also have molecular changes that favor carcinogenesis.

It has been suggested that mechanisms of age-related immune function decline may also contradictorily affect cancer incidence. Some immunological changes may create an environment that favors less aggressive tumors and a leveling off of cancer incidences in the oldest older adults [5], while others (e.g. increases in interleukin 6 levels) are implicated in the pathogenesis of highly immunogenic tumors such as lymphoma and multiple myeloma [5].

In another example, chronic inflammation may present a pathway for environmental exposures that can potentially injure the functional reserve of multiple organ systems and simultaneously predisposes to carcinogenic pathogenesis [41]. Similarly, frailty (a syndrome in older adults that is described as a critical depletion of physiological reserve) may uniquely, or in combination with other mechanisms of aging, result in an environment where otherwise minor stresses may cause severe and lasting functional compromise. Such compromises may themselves increase susceptibility to carcinogenesis pathways. These examples demonstrate that the biology of aging is dynamic, evolving, and includes effects to multiple different but potentially synergistic influences that are also related to the biologic mechanisms of cancer.

Evidence suggests that interaction between the biology of cancer and aging can also impact cancer risk, tumor activity and the responses of older patients to treatment [41–43]. However, the evidence should be interpreted with caution since the effects of underlying aging biology may be disguised by differences in study populations compared to general cancer populations [21]. In addition, our understanding of the biology of aging and its interactions with cancer is complicated by the fact that older adults tend to be diagnosed at more advanced stages than young individuals, limiting treatment choices and prognosis. [44]. Therefore, extrapolating evidence may be particularly problematic for older cancer patients for whom treatment complications can have serious health effects. In particular, it is likely that there is selection bias in pursuing cancer diagnosis and staging in older adults with competing problems.

22.5 Cancer Screening

The primary purpose of screening for cancer is early detection before symptoms become apparent. From a clinical perspective, early detection implies earlier-stage cancers that are easier to treat and/or cure. This, in turn, translates into better outcomes. From an epidemiological perspective, age is one of the most important risk factors for developing many cancers. As a result, cancer screening tests are recommended for individuals who are ≥50 years of age. Unfortunately, commonly-proffered screening tests, such as mammography, colonoscopy and the prostate-specific antigen (PSA) test, may not extend life and may have associated risks.

The decision of whether or not to screen an older adult for cancer must take several factors into account. Older adults are more likely than younger adults to have comorbid conditions that could cause complications with the screening test. Screening in the presence of such comorbid conditions also brings with it the possibility of competing risks. In addition, the heterogeneity of older populations makes the decision of whether or not to screen an older adult challenging from the perspectives of both clinical guidelines and the individual patient. The central question to be considered when deciding whether or not to screen an older adult for cancer is: "Will finding the cancer improve the older person's health or help him or her live longer with a satisfactory quality of life?"

22.5.1 Potential Benefits of Screening

It is estimated that 3–35% of premature cancer deaths could be avoided by cancer screening [3]. These estimates are not age-specific, so the effect of screening on cancer mortality in older populations compared to younger ones remains unclear. Another important limitation of these estimates is that they assume that the cause of death can be accurately determined, and that screening and subsequent treatments have negligible effects on other causes of death. Age may significantly influence the accuracy of these assumptions.

In addition to potentially high, albeit imperfect, estimates of reduced cancer mortality, there are other potential benefits of detecting earlier-stage cancers. Treatments for early-stage cancers may be better tolerated than those for more advanced-stage cancers. However, diagnosing a cancer early may only identify a cancer that will not impact an older person's quality of life or life expectancy, and thus create unnecessary anxiety, treatment burden and limitations on interpretation benefits. The limitation of lead time bias (i.e., an apparent lengthening of survival due to earlier diagnosis without any actual prolongation of life) should always be carefully considered when interpreting the benefits of cancer screening, especially in older adults.

22.5.2 Screening Efficacy

There are varying levels of evidence to determine the efficacy of treatments and screening, with randomized controlled trials providing the strongest. The levels used for evidenced-based medicine decision-making are categorized as: level I, evidence obtained from at least one properly-designed randomized controlled trial; level II, evidence obtained from well-designed controlled trials without randomization, well-designed cohort or case–control studies (preferably multiple sources), or multiple time series with or without the intervention; and level III, opinions of respected authorities based on clinical experience, descriptive studies or the reports of expert committees. Unfortunately older adults remain an understudied population. Evidence-based clinical recommendations for older adults, especially with regard to cancer screening, are usually based on level II or III evidence.

There are several reasons for this discrepancy. First, older adults have historically been excluded from trials in an attempt to reduce the heterogeneity of the study populations and/or reduce concerns regarding equipoise (balance between potential harm and benefit). Second, exclusion criteria (e.g., age, chronic comorbid health conditions, study site restrictions) and other barriers (e.g., medical literacy, transportation) result in older adults being less likely to participate in clinical trials. Furthermore, study design (e.g., long follow-up); physician, patient and logistic issues (e.g., physicians recommendation of older patients, availability of caregivers, travel constraints); and/or financial costs are factors that influence not only study participation but also retention [45]. These factors result in the availability of only limited evidence and/or lower-level evidence for older adults (e.g., case–control studies of older adults require no participant enrollment or complications of intervention and/or follow-up). The under-representation of older adults in cancer screening studies represents a challenge for evidenced-based decision-making in geriatric care.

22.5.3 Challenges and Inconsistencies in Common Cancer Screening Recommendations

The only trial evidence with regard to determining the benefits and harms of screening mammography in women ≥75 years of age comes from two screening trials in Sweden. The results, restricted to women 65–74 years of age and based on small numbers, were mixed (one trial showing benefit, one trial showing none) [46]. The overall paucity of clinical trials data for older adults emphasizes the important role that lower levels of evidence, such as observational and case–control data, play in the screening of older populations. Unfortunately, the lower level of screening evidence—often with mixed results available in older adults—can lead to inconsistency and/or lack of screening recommendations. For example, lower-level evidence suggests that breast cancer screening should be stopped at about 75–80 years of age [46, 47]. Yet the US Preventive Services Task Force makes no recommendations for women ≥75 years of age while the American Geriatric Society guidelines recommend that screening be stopped at more advanced ages [47]. Many—though not all—of these level II studies included mixed-age populations and/or used age-truncated populations (i.e., up to a maximum of 75 years of age) [47].

The interpretation of observational breast cancer screening evidence with regard to the benefit of mammography in older women (this applies to screening in general as well) may be affected by issues of lead time, length biases and selection factors [48], issues that are important for patient and physician alike.

For colorectal cancer, the US Preventive Services Task Force recommends against routine screening at 76–85 years of age. It does acknowledge, however, that there may be situations in which screening might be reasonable, such as a healthy 78-year-old who has never been screened [49]. Again, these recommendations were not made based on level I data in older populations. Despite an increasing incidence of colorectal cancer with age, there is little evidence in older adults that indicates any gain in life-years associated with extending screening beyond 75–85 years of age (compared to risks), or that competing risks outweigh any screening mortality benefit for persons ≥85 years of age. The caveats to these colorectal screening guidelines for older adults underscore the need for accurate physiological age and life-expectancy estimations for decision-making in screening.

With regard to PSA testing, there is an ongoing debate as to whether prostate cancer screening increases or decreases morbidity and mortality. The US Preventive Services Task Force recommends against screening men ≥75 years of age [47]. Two facts underlie this recommendation. First, most men who are screened repeatedly will be found to have an elevated PSA. Second, older men typically die with—and not from—prostate cancer. This recommendation is based primarily on observational evidence. The long-term adverse effects of false-positive PSA screening test results are unknown.

Given the issues described above, the decision of when to stop screening in older adults is a challenge. There is ample non-trial evidence that older adults are both over-screened and under-screened [50–52]. Further, though physicians do take the increased risks that come with chronic comorbid health conditions and disability into account [53], persons with limited life expectancy continue to be screened.

22.5.4 Costs of Screening Inaccuracies

Screening tests can have false-negative and false-positive results, which may result in under- or over-treatment. The accuracy of screening tests not only impacts patients but also the overall cost-effectiveness of screening. False positives are followed by additional testing which is both costly and psychologically traumatic. False negatives delay diagnosis and the provision of effective early and better-tolerated treatment.

22.5.5 Need for Improved Cancer Screening Guidelines

Clearly, there is a need for improved guidelines with regard to cancer screening in older adults. In their seminal article, Walter and Covinsky provide a framework for cancer screening decision-making that considers the risk of dying, benefits and harms of screening, as well as patients' values and preferences [54]. They note that since chronic comorbid health conditions and functional impairments are strong predictors of life expectancy, the assessment of these factors should inform screening decisions, particularly since the benefit of screening is usually not seen until 5 years after screening. The potential risk that comes with each screening test should also be taken into account. Finally, the likelihood as to whether or not the treatment of an early cancer in an older adult will impact quality of life or life expectancy should be measured against the possibility of complications such as the worsening of comorbid conditions and the subsequent loss of function and independence.

22.6 Survivorship, Long-Term and Late Physical and Psychosocial Effects

Progress toward more effective cancer screening and treatments has steadily reduced the risk of cancer mortality following diagnosis for most cancers. This has resulted in a growing

number of cancer survivors who are living longer. It also means that since the majority of cancers are diagnosed in older adults, the majority of cancer survivors are also older. This majority is likely to increase since, despite advances in screening and treatment, the overall burden of cancer in older adults is projected to increase over time. Indeed, the number of older cancer survivors is expected to double over the next two decades [55].

For older survivors as compared to younger ones, the functional consequences of cancer and its treatment have a greater impact due to the interaction of these functional consequences with cancer treatment effects, co-existing diseases and age-related disabilities. This is particularly important since both chronic comorbid health conditions and functional impairments increase with age; appear to be more prevalent in older cancer survivors; and influence morbidity, mortality and quality of life [56]. For older patients, survivorship beyond the shorter-term cancer recovery phase means living with the potential of longer-term complications from cancer surgery, chemotherapy, and radiation and hormonal therapy in conjunction with the common diseases and disabilities of aging. Of greater concern for older cancer survivors, as well as for their caregivers, are the residual effects of cancer treatments combined with the effects of pre-existing or newly-developing chronic comorbid health conditions and/or functional impairments. Yet similar to younger patients, older cancer patients also have primary worries about the potential recurrence of their cancer and/or the occurrence of new cancers.

When the decision to undergo cancer treatment is made, the benefits to an older patient are considered to outweigh the side effects, the risks of developing a subsequent cancer, and any potential negative effects on their other comorbid conditions and quality of life. Although this considered calculation may be accurate, it does not mean that the effects of cancer treatment are non-existent or even minimal. In fact, there are many known physical and psychosocial effects of cancer treatment. These effects may result from any of the main types of cancer treatment (surgery, radiation therapy, chemotherapy and hormone therapy). They also may differ by age, type of cancer, type and intensity of treatment and the underlying heterogeneity and clinical complexity of older cancer patients.

Primary cancer treatments can result in a wide range of physical and psychological long-term and late effects. Long-term effects are those that begin during treatment and persist for up to 5 years afterward. Some examples of long-term effects include neuropathies (with related weakness, numbness or pain), fatigue, cognitive difficulties and elevated anxiety or depression [57]. In contrast, late effects are defined as problems not present or identified during or after treatment, but which develop later as a consequence of treatment. Examples of these late effects include musculoskeletal complications, osteoporosis or late-onset stamina deficits related to cardiovascular complications or hypothyroidism [57]. The list of cancer-related long-term and late effects is long and we will only address it in part. Table 22.3 provides an overview of the common long-term and late physical effects of cancer that are experienced in older cancer patients, organized by type of cancer treatment.

22.6.1 Cancer Recurrence or Occurrence of New Cancer

For cancer survivors of any age, one of the most serious events they can experience is the diagnosis of a recurrence of their cancer or of a new cancer. For cancer survivors, the risk of recurrence and of second primary malignancy depends on factors such as age, type and stage of primary cancer, type of cancer treatments, and time since primary cancer treatment. As with first primary cancers, the incidence of second (multiple) primary cancers increases with age. The risk of developing second or multiple cancers varies from 1 to 16% depending on the primary cancer site, and nearly 7% of older cancer survivors are affected [58, 59]. Thus, older cancer survivors are at greater risk for both recurrences (due to more frequent under-treatment) and for developing

Table 22.3 Common long-term and late physical effects[a] of cancer in older cancer patients by cancer treatment type

Treatment	Long-term side effects	Late side effects
Chemotherapy	Fatigue Neuropathy Cognitive problems Heart failure Kidney failure Liver problems	Cataracts Liver problems Lung disease Osteoporosis Reduced lung capacity Second primary cancers
Radiation therapy	Fatigue Skin sensitivity	Cataracts Cavities and tooth decay Heart problems Hypothyroidism Lung disease Intestinal problems Cognitive problems Second primary cancers
Surgery	Scars Chronic pain	Lymphedema

[a]Long-term effects are those that begin during treatment and persist up to 5 years afterwards. Late effects are defined as problems not present or identified during or after treatment but that develop later as a consequence of treatment

second primary malignancies (due to age). For instance, there is a subset of older women with aggressive breast cancer and for whom there is evidence that suggests they are at increased risk of adverse breast cancer outcomes such as recurrence and second primaries. Several large studies have documented that tumor characteristics and treatment intensity are major determinants of breast cancer recurrence and mortality [60, 61]. These findings suggest that subgroups of older women at high risk of distant relapse should receive more aggressive treatment [62].

22.6.2 Health and Functional Status

Studies using national probability surveys [56, 63] have compared the health and functional status of older cancer survivors to those of older persons with no cancer history. All document poorer health and functional status among older cancer survivors compared to persons without cancer. Although these studies used large representative samples, study limitations include reliance on the self-report of cancer, chronic comorbid health conditions, and functional status, as well as unknown or widely-varying lengths of survivorship. Furthermore, these studies included no detail regarding the burden of chronic comorbid health conditions before diagnosis, the stage at diagnosis or the treatments received.

More recent studies have overcome these shortcomings. Taking advantage of the Iowa Women's Health Study and linking it with the Iowa SEER registry, Sweeny et al. [64] compared older women cancer survivors with those who had not had cancer. Long-term (≥5 years) cancer survivors were more likely to report the inability to do heavy housework, walk a half mile, or walk up and down stairs. Examination by cancer type identified that breast cancer survivors reported an excess of functional limitations. Among these survivors, the report of their limitations was not associated with stage or treatment. In a more recent study that linked SEER with the Medicare Health Outcomes Survey, participants with cancer were propensity-matched to controls and data were collected using the 36-item Short Form Health Survey at a mean of 12.4 months after diagnosis. Participants with all cancer types reported decrements in physical health compared to controls. Participants with lung, colorectal and prostate cancer had declines in mental health [65].

22.6.3 Interactions with Common Aging Conditions

The long-term and late physical effects of cancer may interact with common conditions of aging. In a patient with gait instability due to painful hip osteoarthritis and macular degeneration, a peripheral neuropathy resulting from chemotherapy may precipitate falls and lead to fractures. Cancer-related fatigue, one of the most common physical late effects of cancer treatments, if left untreated can have a dramatic effect on the lives of older cancer survivors because it leads to reduced physical activity. Reduced physical activity can result in deconditioning and subsequent decreases in physical function. Osteoporosis is a common long-term effect of cancer therapies. Bone health and fracture prevention have also become important health issues among cancer survivors, particularly for older women with an elevated baseline risk who have received chemotherapy and/or aromatase inhibitors for breast cancer and men treated with hormone deprivation therapy for prostate cancer [66, 67].

22.6.4 Emotional Well-Being

Having cancer threatens not only patients' physical health but also their emotional well-being. It is common for persons diagnosed with cancer to develop anxiety and depression during the first years after diagnosis. Physical and psychological effects may persist much longer, affecting the overall quality of life [57]. Some studies suggest that cancer survivors have higher rates of depression and worse quality of life than those without cancer [68, 69]. However, there is inconsistency in the quality-of-life evidence for older survivors, which likely relates to differences in comparison groups (older versus younger, with or without cancer), types of measures used, timing of measurement (e.g., at diagnosis, 1–2 years or 5 years post-diagnosis), and variability and selectiveness of study populations (e.g., specific cancers, randomized control trial participants, no comparisons, small sample size).

Social support has been shown to provide many benefits associated with the overall health and well-being of older adults [70]. A social network provides a reservoir for social engagement and buffers the impact of major life events by providing emotional and instrumental social support in times of crisis. Social support from family, friends, partners, community and physicians is associated with a better sense of hope and better emotional health, especially among people with preexisting life stress such as cancer. A study of long-term older breast cancer survivors found that women with adequate social support and positive ratings with regard to the quality of medical interactions with their physicians were less likely to have poor emotional health 5 years after diagnosis [71]. Intervention studies have consistently demonstrated the beneficial effects of psychosocial support in the changing of attitudes from pessimism to optimism [72, 73]. In general, the greater the resources available to an older survivor, the better are his/her chances of managing negative long-term effects.

22.7 Conclusion

The long-term and late effects of cancer in older survivors may reflect late sequelae of treatment as well as the effects of aging, lifestyle factors, environmental exposures, host factors, and combinations of influences. Given the combined increased risk of cancer with age, projected growth in older populations and lengthening of survivorship, the number of older cancer survivors is expected to increase.

In this chapter, we have explored the epidemiology of cancer and aging by addressing the following key areas: incidence and prevalence, unique pathophysiologic differences, screening, survivorship, and long-term and late physical and psychosocial effects. The consequences of cancer and its treatment can have a greater impact on older patients than on younger ones, particularly due to the interaction of cancer treatment effects, chronic comorbid health conditions and age-related disabilities. This impact extends into the survivorship experience of older adults. Chronic

comorbid health conditions are of special concern in older cancer patients due to their high prevalence and because they may be directly and significantly affected by cancer and, in turn, similarly affect cancer and its treatment. Aging and cancer share pathways and interact to form complex challenges from both an epidemiological and clinical perspective, including assessing cancer burden, identifying risk and devising optimal care for older cancer patients.

As older adults live longer than ever before, the inevitable shift in the population age structure foreshadows many challenges, especially with regard to cancer, aging and their intersection. Whether or not years added in later life are healthy, enjoyable and productive depends in great part upon the prevention and control of potentially debilitating and sometimes fatal chronic diseases such as cancer. As such, it is inevitable that the interaction between common diseases and conditions of aging in individuals with cancer, and their interconnected impact on society, will be of growing epidemiologic concern in the future.

The majority of individuals who develop and survive cancer are older adults. Although primary prevention through lifestyle changes is promoted as the primary means to reduce cancer burden regardless of age, some of these changes cannot be practically achieved in older adults. A greater understanding of cancer and aging will provide valuable opportunities to devise treatment strategies that maximize survival, minimize morbidity and maintain quality of life, specifically in older cancer patients. The development and appropriate use of cancer treatments in the complex setting of the older cancer patient requires an understanding of the epidemiology of cancer and aging. Furthermore, older adults remain an understudied population, especially with regard to the survivorship experience of older adults with cancer. Despite considerable ongoing lengthening of survival, we still have little evidence regarding the impact of long-term and late effects of cancer in the growing population of older cancer patients who live a decade or two post-diagnosis. Recovering from the physical and psychosocial trauma of cancer may take longer than recuperating from the treatment itself, and this can commonly be amplified in older survivors due to interactions with aging. The continued epidemiologic study of aging, cancer and their interaction in older adults will contribute significantly to our understanding of the consequences of increased cancer incidence with longer life spans in aging populations.

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The Epidemiology of Coronary Artery Disease in Older Adults

23

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Abstract

Cardiovascular disease is the primary cause of death in older adults. It has pervasive effects on the quality as well as the quantity of years in late life. Atherosclerotic disease is the most common type of cardiovascular disease in older adults, with the coronary arteries being the most commonly involved arterial bed and myocardial infarction the most common clinical manifestation. Coronary artery disease (CAD) has well-known dietary and behavioral contributors, yet age remains a very strong risk factor across the life span and well into old age. The incidence of acute myocardial infarction increases dramatically with age, though rates have been declining at every age. CAD can cause substantial disability due to reduced exercise tolerance or chest pain with exertion. CAD is also associated with systemic atherosclerosis, which incurs substantial disability. Methods for the prevention of CAD are well established and include smoking cessation, lipid lowering and blood pressure control. These have been shown to be beneficial in older adults, yet they remain underutilized. There is great potential that the declining rates of CAD will translate to a compression of morbidity in older adults.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Coronary artery disease • Coronary artery calcium • Myocardial infarction • Angina • Coronary artery bypass • Angioplasty • Prevention • Risk factors • Hypertension • Smoking

Abbreviations

AAI	Ankle-Arm Index
ABI	Ankle-Brachial Index
ACE	Angiotensin-Converting-Enzyme Inhibitor
ApoB	Apolipoprotein B

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ASPREE	Aspirin to Reduce Events in the Elderly
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CHS	Cardiovascular Health Study
CI	Confidence Interval
CPK-MB	Creatine Kinase-MB
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardiovascular Disease
DHA	Docosahexanoic Acid
EBCT	Electron-Beam Computed Tomography
Echo EF	Ejection fraction by electrocardiography
ECG	Electrocardiogram
EPA	Eicosopentanoic Acid
HDL	High-Density Lipoprotein
Health ABC	Health Aging and Body Composition
HYVET	Hypertension in the Very Elderly Trail
IC-IMT	Intima-to-media wall thickness of the internal carotid artery
Il-6	Interleukin-6
LDL	Low-Density Lipoprotein
Look AHEAD	Action for Health in Diabetes
MDCT	Multi-Detector Computed Tomography
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAI-1	Plasminogen Activation Inhibitor-1
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
RR	Relative Risk
SHEP	Systolic Hypertension in the Elderly Program
SD	Standard Deviation
US	United States
VLDL	Very Low-Density Lipoprotein

23.1 Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in older adults and is a major contributor to disability. Atherosclerotic disease is the most common type of cardiovascular disease in older adults, with the coronary arteries of the heart being the most commonly involved arterial bed and myocardial infarction (MI) the most common clinical manifestation. In 2005, coronary artery disease (CAD) was the primary cause of 445,687 deaths in the United States (US), of which 80% were in individuals ≥65 years of age [1]. The incidence of CAD increases with age such that by age 70, the lifetime risk of a first CAD event is 35% in men and 24% in women [1]. Rates of MI have been declining in all age groups, yet it remains the most common cause of death and the major contributor to medical expenses in the US [2].

The most serious and life threatening manifestation of CAD is acute MI. CAD can also present as angina pain due to myocardial ischemia, or as sudden cardiac death when acute ischemia results in a fatal arrhythmia. Congestive heart failure, which causes poor exercise tolerance and shortness of breath, is most commonly due to myocardial damage from CAD, though other factors can cause or contribute to it. CAD is a manifestation of systemic atherosclerosis, which involves the aorta, peripheral arteries and arteries to the brain. In this chapter, we will focus on the unique aspects of CAD epidemiology in older adults, including prevalence, incidence, risk factors and prevention. We will also review the relationship of peripheral atherosclerosis to CAD and the functional consequences of atherosclerosis in old age.

23.2 Clinical Coronary Artery Disease

23.2.1 Clinical Manifestations

The major clinical manifestation of CAD is MI. Patients with MI classically present with a sudden onset of severe chest pain or pressure,

sometimes with diaphoresis or shortness of breath. MI is a syndrome of acute damage to the myocardial muscle wall due to occlusion of a coronary artery that supplies blood flow to the corresponding region of the heart. Occlusion is usually due to the rupture of an atherosclerotic plaque followed by acute thrombosis or clotting of the coronary artery [3]. Necrosis of the myocardium is resolved through a process of repair with fibrosis and scarring.

In older adults, the symptoms of MI can be atypical in location and severity. A diagnosis of MI is made when such symptoms are accompanied by a loss of voltage amplitude on an electrocardiogram (ECG) in a pattern that indicates the location of the involved artery. Additionally, a diagnosis of MI requires evidence of myocardial damage from blood markers. Levels of creatine kinase-MB (CPK-MB) fraction or troponin will rise and fall subsequent to an acute infarction, rising to levels of at least twice the norm and often much higher. More subendocardial infarctions have been identified using more sensitive markers of myocardial damage, such as troponin-I [4]. These do not result in the classic ECG pattern of voltage loss that accompanies transmural MI [5].

Arrhythmias are a very serious consequence of MI, with ventricular tachycardia and fibrillation potentially resulting in sudden death. MI can also cause acute congestive heart failure or valve dysfunction. Myocardial wall rupture can occur and cause acute cardiac tamponade. More chronically, MI can eventually lead to weakening and scarring of the myocardial wall with reduced contractility and a more gradual onset of symptoms of heart failure.

Not all MIs are acutely symptomatic. Many times, there are signs of a prior infarction but no history of classic symptoms. These unrecognized infarctions can be detected by ECG and other imaging tests. In older adults >65 years of age, the Cardiovascular Health Study (CHS) found a >5% prevalence of voltage changes in the Q/QS wave on ECG consistent with MI, and prevalence increased with age [6]. Changes on the ECG consistent with a prior transmural infarction have been reported to account for 20–30% of incident MIs in the Framingham [7] and Honolulu Heart Studies [8]. Sensitive imaging tests with echocardiography, thallium and magnetic resonance have revealed that many older adults have had prior episodes of significant myocardial ischemia with scarring and fibrosis that would not have otherwise been clinically detected. Coronary artery calcium (CAC) scanning has also been used to detect subclinical CAD [9], though it does not detect myocardial damage *per se*. Together, these imaging techniques show that older adults who have no or minimal CAD are the exception.

CAD can also cause a syndrome intermittent chest pain called angina, which is due to insufficient coronary artery blood flow to the myocardium. It can occur with exertion, but when coronary disease is advanced, it can also occur at rest. Stressors other than exercise, such as severe anemia, hypoxemia, hypotension and tachyarrhythmias (rapid heart rate) can also precipitate acute chest pain. Other symptoms, such as shortness of breath, can sometimes be considered as "anginal equivalents".

Large infarctions or multiple smaller ones can compromise cardiac function and cardiac output, leading to congestive heart failure. Though there can be many causes, chronic CAD is the most common cause of congestive heart failure. CAD is also associated with a higher risk of chronic atrial as well as ventricular arrhythmias. Chronic heart valve incompetency can also result from infarction, especially of the mitral valve. Together, these consequences of CAD can result in fatigue, chronic chest pain, shortness of breath and limitations in exercise tolerance, which result in substantial disability in old age.

23.2.2 Acute Management

Anticoagulation with aspirin and thrombolytics are used acutely to reverse occlusion and salvage myocardial viability [10]. Coronary angioplasty with or without stenting and coronary artery bypass surgery can also be used to

preserve myocardium in an acute situation [10]. Patients should be routinely discharged from the hospital on aspirin, a beta-blocker, angiotensin-converting-enzyme inhibitor (ACE) and lipid-lowering therapy [11]. Due to the risk of sudden death, primary prevention is of paramount importance at all ages, including in older adults. Secondary prevention clearly prevents recurrence [11].

23.2.3 Pathophysiology

There are two major types of vascular disease, arteriosclerosis and atherosclerosis. Arteriosclerosis is a disease of the medium- and small-sized arteries, and its prevalence increases with age. In arteriosclerosis, the increase in connective tissue and other changes in the medial layer of the artery result in increased arterial stiffness and elevated systolic blood pressure, and contribute to congestive heart failure. Major risk factors for arteriosclerotic disease are hypertension and diabetes mellitus.

Atherosclerosis is primarily a disease of elevated apolipoprotein B (ApoB) lipoproteins (i.e., low-density lipoprotein [LDL] cholesterol, LDL particles and very low-density lipoprotein [VLDL] triglycerides) that involves medium- and larger-sized arteries. There is a long incubation period for the development of atherosclerosis from fatty streaks to complex lesions. The development and progression of atherosclerosis is a function of the levels of ApoB lipoproteins, duration of exposure, genetic susceptibility and levels of other important risk factors such as cigarette smoking, high blood pressure and diabetes. Older individuals have a very high prevalence of atherosclerosis in major vascular beds due to long-term exposure to even moderately elevated ApoB lipoproteins over time.

CAD becomes increasingly common with increasing age, though it can remain silent throughout the lifespan. Autopsy studies show that coronary disease is almost uniformly found in 90-year-old individuals [2]. CAC scanning is well correlated with atherosclerotic disease of the coronary arteries [12], thus non-invasive testing for CAC gives an accurate assessment of subclinical disease prevalence. Based on CAC scanning, fewer than 10% of men and women in their 80s are free of CAD [13].

The pathophysiology of coronary atherosclerosis is no different in older vs. younger adults, except that disease in older adults is often diffuse and extensively calcified [14]. Atherosclerosis is a process of injury and repair, with initial injury due to endothelial damage to the vessel wall. This is followed by the invasion of inflammatory cells, including macrophages which accumulate lipid and form lipid-laden atherosclerotic plaques. Medial smooth muscle hyperplasia, fibrosis and calcification follow [15]. Lesions can impede blood flow and thus oxygen delivery to the heart as they encroach on the lumen, but compensatory dilation and collateral flow can mitigate this to a certain extent.

The precipitants or determinants that convert the chronic underlying atherosclerotic disease to clinical events (i.e., MI, sudden death) have a relatively short incubation period (i.e., they often occur within minutes). The pathophysiological changes can include rupture, erosion and hemorrhage within a plaque or possible changes in myocardial blood flow or myocardial metabolism. The distribution of heart attacks in older adults is not random. Heart attack risks are higher in colder temperatures and in the morning after getting up. There appears to be an increased risk of MI or sudden death following upper respiratory infections, including influenza and pneumonia. Also, the risk of MI and sudden death is elevated during and immediately after exercise, especially in individuals who are not very physically "fit" and possibly during greater exposure to air pollution, especially particulate air pollution.

Psychosocial stressors may also be important precipitants of MI and sudden coronary heart disease (CHD) deaths among older adults. Unfortunately there are no good methods to identify the specific short term precipitants of a heart attack among older adults. Changing symptomatology, such as increasing fatigue, tiredness, chest pain and shortness of breath, are generally the only markers of the incubation period to a heart attack or sudden death.

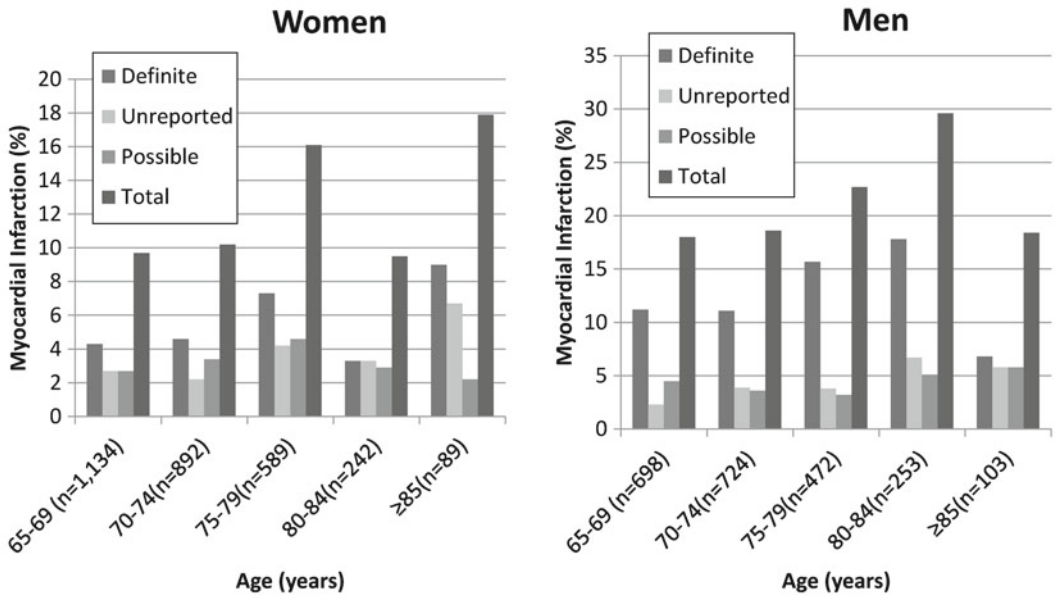

Fig. 23.1 Prevalence of *definite*, *unreported*, *possible* and total myocardial infarction in the Cardiovascular Health Study [17]

23.2.4 Prevalence and Incidence

In epidemiologic studies, the prevalence and incidence of CAD are defined according to rates of MI. Much of what we know about CAD epidemiology in older adults comes from several long-term observational studies. The CHS is a longitudinal cohort study of 5,888 community-dwelling older adults in four US communities that was started in 1988 specifically to assess the epidemiology of CVD in older adults. It has improved our understanding of the burden of both clinical and subclinical CVD in older adults [16]. Much of the review of the epidemiology of CAD and atherosclerosis presented here is derived from the CHS.

In the CHS cohort, the prevalence of MI was strongly associated with age. In men and women 65–69 years of age, the prevalence of MI was 11.2 and 4.3%, respectively [17] (Fig. 23.1). MI prevalence in women 80–84 years of age was twice that in women 65–69 years of age. Similarly, the prevalence of MI in men 80–84 years of age (17.8%) was higher than that in men 65–69 years of age. The prevalence of unreported MI, detected using ECG, was three times higher (6.7 vs. 2.3%) in the oldest (80–84 years of age) group compared to the youngest (65–69 years of age) group in the CHS, and overall it was about 5% [6]. These rates are similar to estimates from national reports [2].

The incidence of MI was also strongly associated with age in CHS adults ≥65 years of age (Fig. 23.2) [19, 20]. Though rates were about twice as high in men, an age-related increase was observed in both men and women. In both African-American and Caucasian women, the incidence of MI is nearly three times higher in women >85 years of age compared to those 65–69 years of age. In Caucasian women, the MI incidence rate of 21.4 per 1,000 person-years in those ≥85 years of age was about 3-fold higher than the 6.9 per 1,000 person-years in those 65–69 years of age. In African-American women, the MI incidence rate of 9.4 per 1,000 person-years in those ≥80 years of age was also nearly 3-fold higher than the 2.7 per 1,000 person-years in those 65–69 years of age. Similarly, the MI

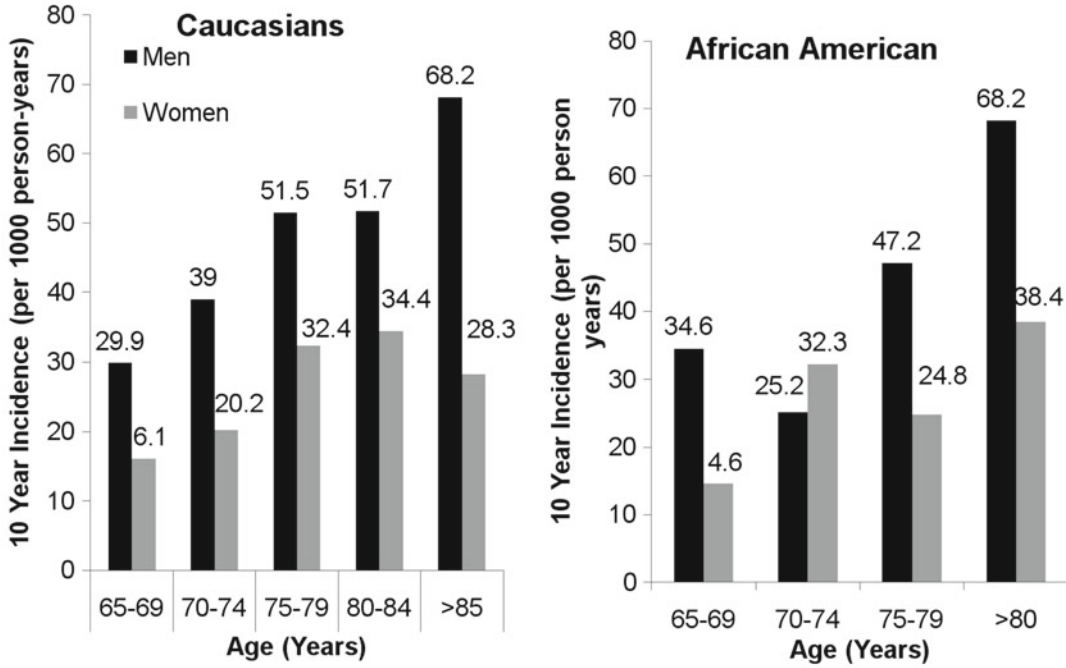

Fig. 23.2 Incidence of myocardial infarction in men and women and by Caucasian vs. African-American race in the Cardiovascular Health Study [18]

incidence rate in older men increased with age, though more dramatically in Caucasians. In older Caucasian men, the MI incidence rate of 28.4 per 1,000 person-years in those ≥85 years of age was 2-fold higher than the 14.8 per 1,000 person-years in those 65–69 years of age. In African-American men, the incidence rate of 26.5 per 1,000 person-years in those ≥85 years of age was less than twice the 15.3 per 1,000 person-years in those 65–69 years of age.

23.2.5 Risk Factors

Age is a major risk factor for CAD. By age 65, only a miniscule 3% of men and 2% of women are considered to have an optimal low risk of CHD, and two-thirds have at least one major risk factor elevated and are considered to be at high risk of MI. At age 75, even with a relatively short life expectancy, the risk for heart attack is still about 35% for men and 23% for women. Risk prediction scores, such as the Framingham risk score, are not very useful among older adults due to the high prevalence of atherosclerosis pathology in the coronary arteries. Treatment of elevated risk factors such as systolic blood pressure, ApoB lipoproteins and smoking cessation are still very effective, even in the older age groups.

Risk factors for CAD in older adults are similar to those in middle-aged adults, but the relative risks in old age are often of smaller magnitude. There are several reasons for this phenomenon. First, risk factors assessed in late life may have changed and do not reflect life-long exposures. There are many reasons for risk factors to change. After a diagnosis of CAD, older adults may change their behavior, such as quitting smoking or adopting physical activity. Older adults who are ill are more likely to take medications or lose weight, and these changes can lower lipid levels and blood pressure [21–23]. Second, substantial numbers of older adults develop CAD despite having few risk factors. In fact, age itself becomes the major risk factor for CAD in old age. Older adults without a history of prior CVD have a high

Table 23.1 Traditional risk factors for myocardial infarction in older adults

Risk factor	Comparison group	Prevalence/mean	Relative risk for myocardial infarction (95% CI)	Comment	Reference
Systolic blood pressure	21-mm increment	40% (for systolic blood pressure ≥140 mmHg)	1.24 (1.15–1.35)	Graded risk above 120 mm	[25]
High density lipoprotein cholesterol	Per mmol	56.5 mg/dL	0.89 (0.64–1.22)	Associated only in unadjusted models	[26, 27]
Low density lipoprotein cholesterol	Per mmol	131 mg/dL	Non-significant	Not associated in unadjusted models	[26, 27]
Diabetes	Fasting glucose <126 mg/dL (7.0 mmol/L)	13%	2.14	Higher risk mainly with subclinical disease	[26–28]
Smoking	Not currently smoking	12.3%	1.36 (0.96, 1.93)	Risk attenuated by subclinical CVD	[26]
Alcohol	Abstainers	17.3% (1–6 drinks per week)	0.84 (0.67, 1.07)	Lower risk for 7–14 and ≥14 drinks per week as well	[29]
Physical activity	Inactive (physical activity index)	33% active	0.43 (0.19, 0.99)	Age 64 and older	[30]

Abbreviations: CVD Cardiovascular disease

burden of subclinical disease [16], so there are very few truly healthy individuals with whom to compare. As the base rate rises with age, the relative rates increase less than in a younger population, for which the referent group has a much lower base risk. Age alone drives the risk score in many of the risk algorithms, such as in the Framingham risk index [24], so that older adults who have no risk factors can have a much higher absolute risk than do younger adults who have risk factors. In the CHS, the absolute risk of MI exceeded 20% over 10 years in men who were >65 years of age [18]. This level of risk is considered high-risk for CVD prevention.

23.2.6 Other Traditional Risk Factors

Epidemiologic studies have extensively examined cardiovascular risk factors in older adults, including lipid levels, cigarette smoking, blood pressure, diabetes, obesity and low physical activity. These risk factors and their associations with MI in the CHS and the Honolulu Heart Program are summarized in Table 23.1.

Systolic blood pressure, diabetes and smoking are very clearly associated with risk of MI. The association is continuous and graded throughout the range of blood pressure, with a 24% increase in risk for each 21 mmHg increment in blood pressure [25]. Risk is clearly mitigated by the treatment of hypertension, but it does not return to baseline [31]. Having diabetes, defined by self-report or fasting glucose ≥126 mg/dL, has been associated with over a 2-fold higher risk compared to not having diabetes. High-density lipoprotein (HDL) cholesterol is significantly protective for MI, while total and LDL-cholesterol were not associated with CAD in the CHS [32]. Equivocal or paradoxical associations between cholesterol and CAD, as well as total mortality, have been noted in other studies as well [33]. Current smoking was associated with a 36% higher risk of incident MI in the CHS [26]. This appeared to be mediated through a higher prevalence of subclinical atherosclerosis in the smokers as it did not remain statistically significant when the consequences of smoking, in terms of higher atherosclerotic burden, were included in the model.

There is strong and ample evidence that low physical activity is a risk factor for CAD in several populations, including in older adults [30, 34, 35]. In the Honolulu Asia Aging Study, the relationship of physical activity to the development of definite CHD was examined separately in middle-aged (45–64 years of age) and older adult men (65–69 years of age) who participated in the Honolulu Heart Program. Among those 45–64 years of age, the rate of definite CHD in men who led active lifestyles was 30% lower than the rate experienced by those who were less active (relative risk [RR], 0.69; 95% confidence interval [CI], 0.53–0.88). In those who were >64 years of age, the risk of definite CHD in active men was even stronger (RR, 0.43; 95% CI, 0.19–0.99).

Recent studies have found a relatively weak association between the extent of physical activity and measures of subclinical CAD, such as coronary calcium or carotid intema-media thickness IMT. There was also a relatively weak-to-nonexistent association between fitness based on maximal exercise testing and the amount of coronary calcium. These studies suggest that the beneficial effects of physical activity in older individuals are probably modulated by factors other than the association with atherosclerosis. They are more likely associated with collateral circulation in the heart or myocardial metabolism, or perhaps coronary plaque characteristics or prevention of thrombosis [36]. Physical activity has more recently been better quantified using accelerometers and the doubly-labeled water technique. In the Health, Aging and Body Composition (Health ABC) study, higher energy expenditure by direct measurement with doubly-labeled water was protective for mortality [37], but there were too few deaths to examine CAD death.

CHD mortality rates, even in the older age groups, vary by country. For example, Japan and France have relatively low death rates from CHD compared to the US. The Japanese consume a much higher amount of omega-3 fatty acids compared to Americans, 1,000 vs. 100 mg/day. Studies in Japan have suggested that the higher intake of omega-3 fatty acids accounts for the lower risk of CHD and MI in the Japanese population, possibly through affecting the development of atherosclerosis and thrombosis, and also possibly through having an anti-arrhythmic effect. In the CHS, combined levels of the omega-3 fatty acids eicosopentanoic acid (EPA) and docosahexanoic acid (DHA) (per standard deviation) were associated with a 70% lower risk of fatal CHD (odds ratio [OR], 0.30; 95% CI, 0.12–0.76) [38]. However, there was no association with non-fatal MI. These results are consistent with an anti-arrhythmic effect of n-3 fatty acids. However, several recent clinical trials have not found an association between the recent consumption of omega-3 fatty acids and the risk of MI or CHD.

In some studies, alcohol intake has been found to have a U-shaped association with CVD as well as other outcomes. In men in the Health Professionals follow-up study, compared with abstaining from any alcohol, the hazard ratios for MI were 0.98 (95% CI, 0.55–1.74) for an alcohol intake of 0.1–4.9 g/day, 0.59 (95% CI, 0.33–1.07) for an alcohol intake of 5.0–14.9 g/day, 0.38 (95% CI, 0.16–0.89) for an alcohol intake of 15.0–29.9 g/day, and 0.86 (95% CI, 0.36–2.05) for an alcohol intake of ≥30.0 g/day [39]. Similar results were found in the CHS.

23.3 Subclinical Coronary Artery Disease and Atherosclerosis

Atherosclerosis and arteriosclerosis are systemic diseases that affect multiple vascular beds. There is a very high correlation of disease in the different vascular beds. Older individuals who have disease in one vascular bed are therefore at a very high risk of having arterial disease in another vascular bed, which leads to a higher risk of clinical disease. For example, older adults who have had a stroke are at a very high risk of subsequent MI or lower extremity peripheral vascular disease. The measurement of vascular disease in one accessible site other than the coronary arteries can be used to identify the likelihood of atherosclerotic disease in the coronary arteries and the risk of MI. For example, ultrasound imaging of carotid IMT and plaque is a very strong predictor not only of the risk of stroke

but also of CHD. Similarly, the measurement of blood pressure in the ankles using a Doppler instrument compared to the measurement of blood pressure in the arm (i.e., the ankle-brachial index [ABI]) is a measure not only of lower extremity arterial disease—especially if the ratio is <0.9—but also of MI.

Studies using non-invasive testing for vascular disease in older adults have demonstrated a substantial burden of vascular disease in older adults. CAD with significant obstruction can be detected using exercise stress testing with electrocardiography or exercise stress testing with thallium imaging, but the exercise testing must be supervised by a physician in a medical setting, which prevents its use in field studies. Furthermore, these tests only detect obstructive coronary disease in which blood flow is limited during exercise. CAD can also be inferred from evidence of wall motion abnormalities on echocardiography or loss of voltage on ECG. Since CAD can result in lethal plaque rupture with infarction long before obstruction limits exercise tolerance, tests that do not rely on the detection of induced ischemia have been developed to detect CAD. With the development of the rapid acquisition of images that are synchronized with the cardiac cycle, "stop-motion" CAC scanning by computerized tomography (CT) and magnetic resonance imaging (MRI) can now provide more specific evidence of the high prevalence of undiagnosed CAD in older adults. Currently, CT scanning for CAC has been well validated in epidemiologic studies of older adults, with newer studies undertaking the evaluation of cardiac MRI [24, 40–42].

CAC scanning provides direct visualization of the coronary arteries and is useful in epidemiologic studies due to its rapid acquisition, precision and reasonable cost. Coronary arteries with plaque develop calcification as part of the pathophysiologic process and this correlates with pathologically-assessed atherosclerotic plaque burden [43, 44]. The amount of CAC can be quantified using electron-beam computed tomography (EBCT) and multi-detector computed tomography (MDCT), and it is commonly reported using the Agatston scoring method [45]. The extent of CAC is useful in CVD risk prediction and it adds to models that incorporate traditional CVD risk factors [46]. Therefore, some national guidelines have incorporated CAC into risk stratification models [47]. The prognostic utility of CAC has been demonstrated in various races [41]. There is a strong association between CAC and age, with a wide range of CAC scores in the oldest older adults (Fig. 23.3) [13]. Older adults with CAC are more likely to have prevalent subclinical and clinical CVD [9], though the correlation between measures of disease in various vascular beds with CAC is only 0.3 or less. Given its association with prevalent CVD, CAC remains discriminatory for future CAD in older adults [42].

Other tests that assess atherosclerosis in the periphery can be used to detect the risk of CAD. Because atherosclerosis is a systemic disease, evidence of atherosclerosis in the carotid arteries, in the aorta and in the lower extremities are associated with CAD and its risk factors [26]. Evidence of prior regional wall motion abnormalities in echocardiography and on ECG indicates prior MI and subclinical disease. Subclinical vascular disease is very common in older adults (Fig. 23.4). Using an index of these subclinical disease measures, Kuller at al. [16] reported that 49% of the women and 62% of the men in the CHS who had no clinical history of previous CVD were found to have substantial subclinical disease [16]. These peripheral measures have been shown to each independently predict MI in older adults [26] (Fig. 23.5).

23.3.1 Novel Risk Factors

There has been great interest in trying to identify markers in older individuals that correlate with the extent of atherosclerotic disease, the risk of thrombosis or evidence of subclinical myocardial damage and/or heart failure. There is substantial inflammation within atherosclerotic plaques. Interestingly, it has been very difficult to show an advantage to using these additional risk factors in explaining the risk of MI that is related to age itself [50].

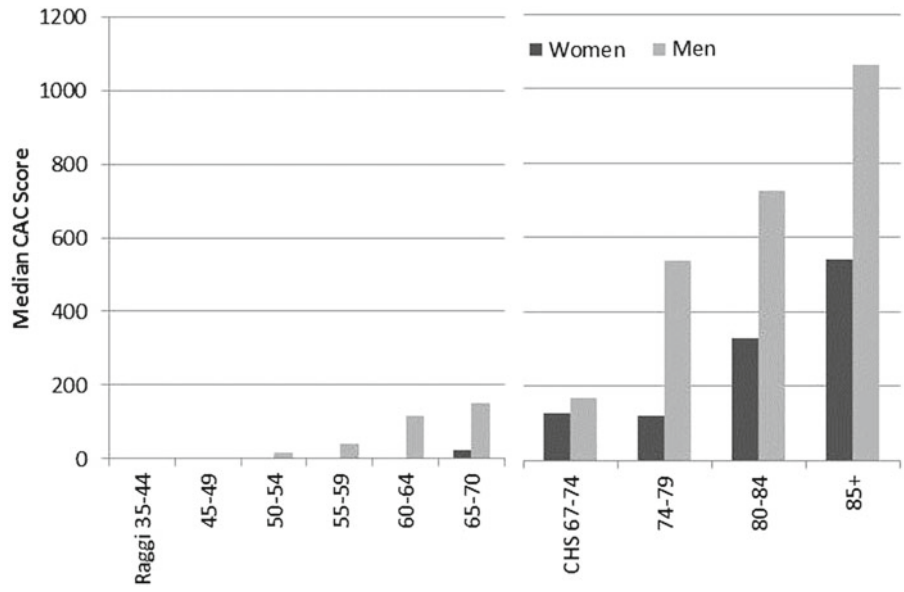

Fig. 23.3 Median coronary artery calcium scores across age groups from two populations [13, 48] (Abbreviations: *CAC* Coronary artery calcium, *CHS* Cardiovascular Health Study)

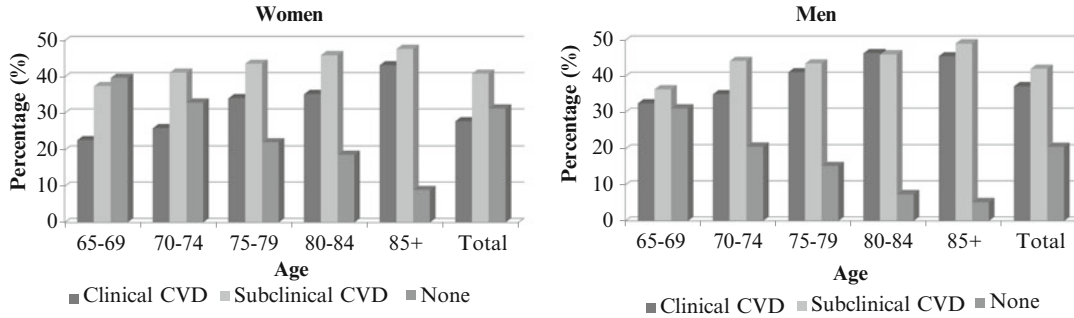

Fig. 23.4 Prevalence of clinical and subclinical CVD by age group and sex in the Cardiovascular Health Study [49] (Abbreviation: *CVD* Cardiovascular disease)

Inflammatory markers were among the first "novel" risk factors (Table 23.2) studied in older adults. In one of the first studies of novel inflammatory markers, C-Reactive Protein (CRP) levels >2.79 mg/L were found to confer a risk of RR, 4.5 (95%CI, 0.97–20.83) for incident MI in the CHS [53]. Subsequent studies have confirmed this and extended these findings to interleukin-6 (Il-6) [54], another marker of chronic inflammation. Inflammation may also play an important role in the activation of a procoagulant state and an increasing risk of thrombosis. Hemostatic markers that reflect a procoagulant state—including D-dimer, plasmin-anti-plasmin complex and plasminogen activation inhibitor-1 (PAI-1), fibrinogen and factor VIII coagulant activity—have each been tested and found to be significantly associated with MI in the CHS [29].

Elevated blood pressure is a major risk factor for congestive heart failure and MI. Elevated blood pressure and diabetes have a major impact

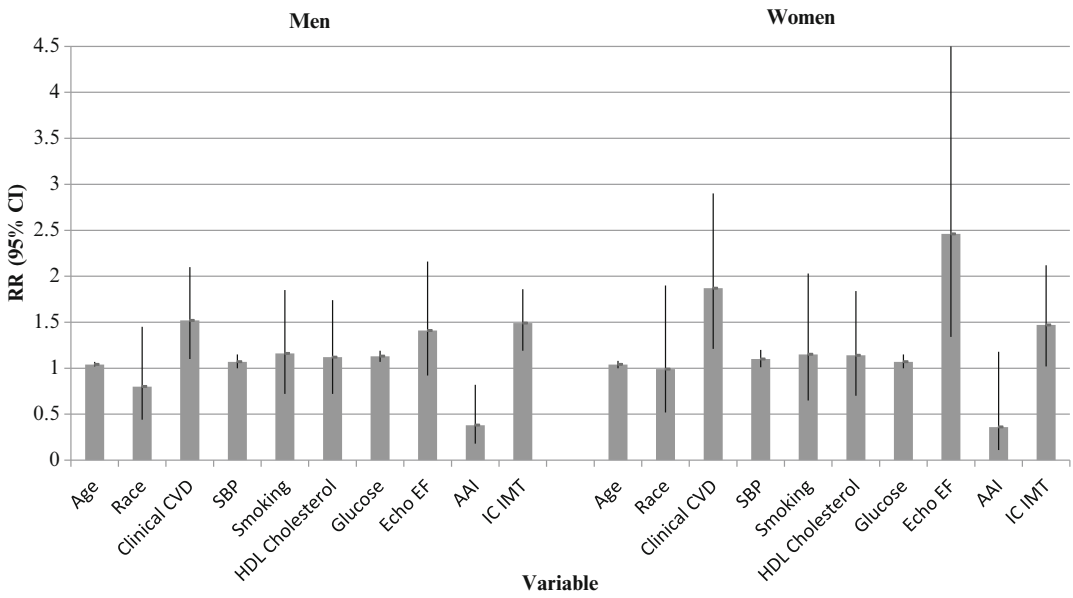

Fig. 23.5 Relative risks for myocardial infarction by individual risk factors in multivariate model in the Cardiovascular Health Study [26] (Abbreviations: *AAI* Ankle-arm index, *CI* Confidence interval, *CVD* Cardiovascular disease, *Echo EF* Ejection fraction by electrocardiography, *HDL* High-density lipoprotein, *IC-IMT* Intima-to-media wall thickness of the internal carotid artery, *MRI* Magnetic resonance imaging, *SBP* Systolic blood pressure, *RR* Relative risk)

on kidney function. Kidney disease markers, particularly cystatin-C levels and estimations of glomerular filtration rate, have emerged as important predictors of CVD. The reasons for this are not fully understood, but may include alterations in lipid metabolism, mineral metabolism and the clearance of inflammatory markers [55].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) has emerged as a useful marker of congestive heart failure, both acutely for diagnostic purposes and prospectively for risk prediction. It has also been found to be useful for the diagnosis of MI [60]. In experimental studies, NT-proBNP is released with acute ischemia prior to the onset of necrosis. It is also an indicator of wall stress and possibly fibrosis [61], and it has been shown to predict CVD death [57] and sudden death [62].

Troponin levels indicate myocardial cell death. A newer supersensitive assay that has been previously used to detect acute MI in the hospital setting has shown that troponin can be detected in asymptomatic older adults and that levels in a low normal range are predictive of future MI and congestive heart failure [56].

Genetic factors have been studied using candidate gene approaches, and more recently using genome-wide association studies, which have demonstrated numerous allelic associations with very small effects. The strongest and most consistent association for the risk of MI has been found for a variant on chromosome 9p21 in a non-coding region [58]. Few genes associated with MI appear to be associated through traditional risk factors. Most of these are common variants with frequencies >5% [63]. A full list of the discovered variants that are associated with CAD can be found at http://www.genome.gov/gwastudies/. Newer studies are identifying rarer variants within candidate genes or through whole exome or genome studies. To date, there does not appear to be age-related effect modification. Interactions with environmental factors might be expected due to cohort differences in environmental exposure over the years. Currently, genetic variants only explain a small proportion of risk, and the incor-

Table 23.2 Novel risk factors for myocardial infarction in older adults in the Cardiovascular Health Study

Risk factor	Comparison group	Prevalence or mean	Relative risk for myocardial infarction	Comment	Reference
Hemostatic					
D-Dimer	Extreme quartiles	124 μg/L (median)	4.1 (1.2–14.5)	RR for MI/coronary death	[51]
Plasmin-antiplasmin complex	Extreme quartiles	5.25 nmol/L (median)	3.6 (0.9–14.2)	RR for MI/coronary death	[51]
PAI-1 antigen	Extreme quartiles	38 μg/L (median)	0.4 (0.1–1.2)	RR for MI/coronary death	[51]
Factor VII coagulant activity	1-SD increment (36% for women, 29% for men)	135% for women, 114% for men	Non-significant	RR for angina amount men	[52]
Inflammatory					
C-Reactive Protein	<2.79 mg/L	1.58 mg/L (median)	2.67 (1.04–6.81) with subclinical disease	No association with angina	[53]
IL-6	Highest vs. lowest quartile	1.37 (SD 1.74) pg/mL in subclinical free controls	3.94 (2.31–6.73)	Comparing case to subclinical disease free controls	[54]
Fibrinogen	Highest vs. lowest quintiles	321 mg/dL	2.1 among men (94% C I not reported)	RR for mortality within 2.5 years; no associations in women	[52]
Factor VIII coagulant activity	1-SD increment (38% for women, 36% for men)	125% for women, 119% for men	1.13 (1.00–1.27) among men	RR for mortality; no associations for MI among women, stroke among men	[52]
Kidney function					
Cystatin C	Highest vs. lowest quintile	25% ≥1.29 mg/L	1.48 (1.08–2.02)	Stronger and more linear association than for creatinine	[44, 55]
Cardiac injury					
Troponin T	Highest vs. lowest quintile	8.17 pg/mL (median)	2.91 (2.37–3.58)	HR for CVD mortality	[56]
N-Terminal Pro-B-Type Natriuretic Peptide	Highest vs. lowest quintile	190 ng/mL (median)	3.02 (2.36–3.86)	HR for CVD mortality. Change also associated with higher risk of CVD death	[57]
Genetic					
variants on chromosome 9p21	Rs10757278 G vs. C	45%	1.28 (1.22–1.35)	Non-coding	[58]
Numerous other variants			Small effects		[59]

Abbreviations: *CVD* Cardiovascular disease, *HR* Hazard ratio, *Il-6* Interleukin-6, *MI* Myocardial infarction, *PAI-1* Plasminogen activation inhibitor-1, *RR* Relative risk, *SD* Standard deviation

poration of these variants into risk assessment has not proven to add to traditional risk factor assessment [64]. Older adults with extreme longevity are likely protected from CAD, and are thus of interest for the study of protective alleles.

23.4 Subclinical Atherosclerosis and Physical and Cognitive Function

Subclinical atherosclerosis is related to physical and cognitive function as well as frailty and successful aging in older adults. CAC in older adults has been associated with reduced physical function and cognitive function testing, more so in women than in men [65]. CAD can reduce exercise tolerance due to the limitations of exercise-induced angina or shortness of breath. In a study of treadmill testing in relationship to CAC, there was little relationship between CAC scores and walking ability. Rate-limiting angina on treadmill testing was rarely found in spite of high levels of CAC [66]. This suggests that the disabling effects of CAC may be more related to atherosclerosis in other vascular beds, which is more common in individuals who have CAD.

Atherosclerosis in the lower extremities or peripheral artery disease (PAD) is more clearly rate-limiting for exercise tolerance, including in older adults who have no previous diagnosis of PAD [67]. Long-distance walking was predicted by ABI in both the CHS and the Health ABC studies [68, 69]. PAD was also related to future disability in the CHS and this could only be partly explained by the onset of interim CAD events [70].

Frailty and successful aging have also been linked to subclinical vascular disease. In the CHS, all measures of subclinical vascular disease were correlated with frailty. For example, older adults ≥65 years of age with an ABI <0.8 had a 3.5-fold increased risk of frailty [71] compared to those with a normal ABI (i.e., ≥0.9) (Fig. 23.6). In a paper that analyzed the role of subclinical vascular disease with active life expectancy, the presence of subclinical CVD among participants in the CHS was associated with a loss of approximately 6.5 years of "successful" life (i.e., with good health and function) in women and 5.6 years in men (Fig. 23.7) [71, 72]. Frailty has also

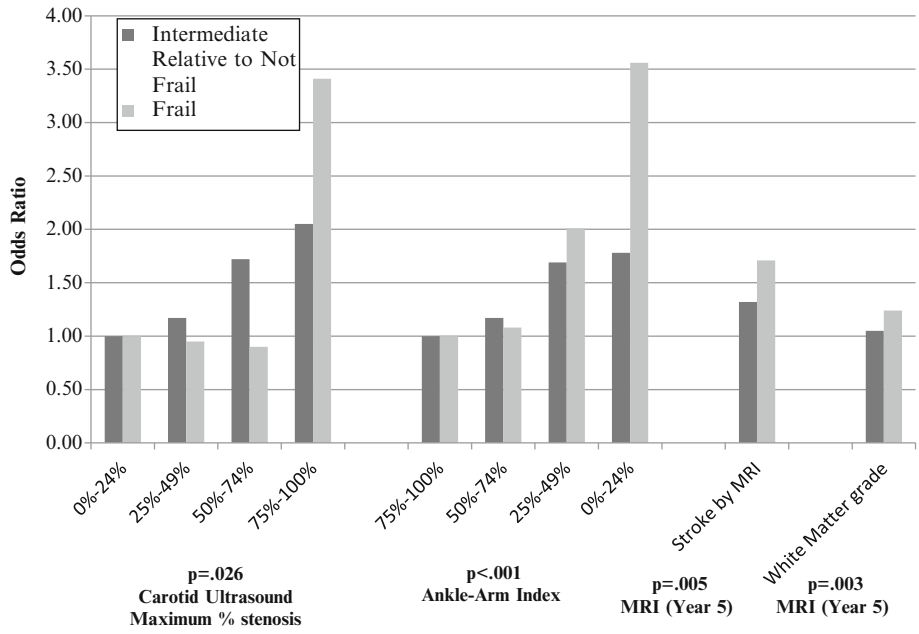

Fig. 23.6 Associations of subclinical cardiovascular disease markers with frailty in the Cardiovascular Health Study [71] (Abbreviations: *MRI* Magnetic resonance imaging)

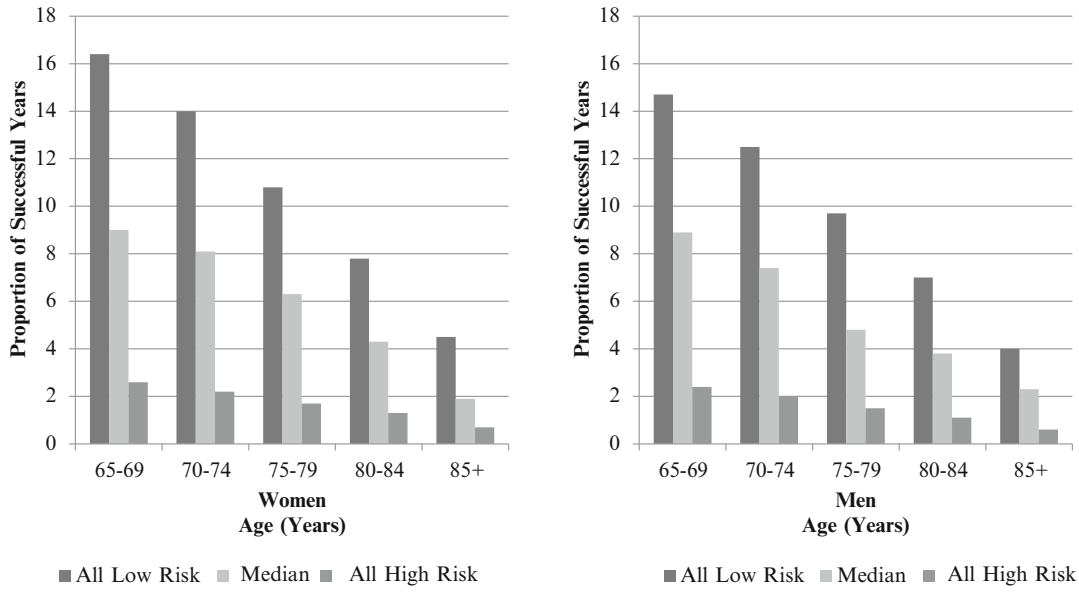

Fig. 23.7 Years of successful life by high, median and low CVD risk in women and men in the Cardiovascular Health Study [72] (Abbreviation: *CVD* Cardiovascular disease)

been shown to be an independent predictor of outcomes after MI, and it also predicts less aggressive care [73].

Atherosclerosis, including CAD, has also been shown to be associated with depression in older adults [74]. The idea that some depression is, in part, vascular is supported by an association between vascular disease and worsening depression. Depression can magnify existing disability and is, in itself, disabling. Though the cause and effect mechanisms are not clear, the treatment of depression in CAD patients, such as patients who have had recent bypass surgery, is an effective and important part of secondary prevention [75].

23.5 Prevention

Both primary and secondary prevention measures are effective in older adults [76]. Smoking cessation remains a mainstay of CVD prevention and is effective for improving health outcomes even in late life. Although CVD rates tend be low in surviving older adults, it is never too late to benefit from quitting smoking [77].

The cardiovascular benefits of treating hypertension in older adults were first demonstrated in the Systolic Hypertension in the Elderly Program (SHEP), in which 4,376 participants were randomized to stepped care based on chlorthalidone. Mean systolic blood pressure was 170 mmHg at baseline. After 4.5 years, there was a 36% reduction in stroke, a 27% reduction in CAD and a 55% reduction in congestive heart failure [78]. A 14-year follow-up analysis showed a 14% reduction in cardiovascular mortality in the chlorthalidone group, in spite of educational efforts to treat the control group after the study was unblinded. The Hypertension in the Very Elderly Trail (HYVET) [79] studied 3,845 participants >80 years of age who were treated with another thiazide, indapamide, as initial therapy and showed substantial reductions in stroke, mortality and heart failure. The study was stopped early and no significant reduction in MI was achieved. Other studies are attempting to further refine target blood pressure levels and refine drug choice. A meta-analysis of available studies supports the recommendation of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood

Pressure: the use of a low-dose thiazide diuretic as the first line of therapy in older adults [80].

Lipid lowering for both primary and secondary prevention has been shown to be effective in older adults. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial included 5,804 patients aged 70–82 years of age who had either prior CVD or CVD risk factors. It showed a risk reduction of 15% (RR, 0.85; 95% CI, 0.74–0.97) in the composite cardiovascular outcome of CVD death, MI or stroke. Current guidelines recommend treating older and younger adults similarly, lowering LDL cholesterol to <100 mg/dL in patients who have CAD or CAD risk equivalent regardless of age, and lowering LDL cholesterol to 70 mg/dL in patients who have established CAD [81]. It is important to remember that levels of ApoB or blood LDL cholesterol are very poor predictors of clinical CHD among older individuals due to the long incubation period to the development of atherosclerosis and the extensive amount of underlying disease in older populations. Therefore, decisions to lower LDL cholesterol with statin therapy in older individuals should not be based primarily on ApoB or blood LDL cholesterol, but rather on a combination of the other risk factors such as hypertension, cigarette smoking, diabetes, obesity, etc.; the extent of subclinical atherosclerosis and the quality of life and life expectancy of older individuals. Based on data from the CHS, most older men and women have extensive subclinical atherosclerosis as well as high coronary calcium scores even if their LDL levels are low (i.e., <130 mg/dL).

Aspirin has been demonstrated to be effective in the secondary prevention of CAD, but its use for primary prevention remains controversial, mainly due to the unclear bleeding risk and uncertain overall benefit [82]. A large international clinical trial, the Aspirin to Reduce Events in the Elderly (ASPREE) trial, is underway to address the question of whether aspirin can prolong a healthy life in older adults who are free of previous MI or stroke [83]. The benefit of aspirin for secondary prevention in older adults who have already had an MI is well established, with the benefits outweighing the risk of bleeding for most patients.

Dietary interventions, including omega-3 fatty acids, a high fiber diet and weight loss, have not been proven to reduce CAD in younger or older adults [84]. The Action for Health in Diabetes (Look AHEAD) clinical trial, a study of type 2 diabetic adults, will address the question of weight loss and physical activity for reducing CVD events, and it includes a substantial number of older adults. The use of folate and B12 to lower homocysteine, and antioxidants such as vitamins E and C, have not been found to prevent CAD [85, 86]. Control of blood sugar in older adults has not been shown to prevent CVD and may be harmful [87]. Older adults have a reduced caloric need, so dietary interventions that include weight loss can reduce critical nutrient intake and reduce muscle mass. Therefore, the effectiveness of such dietary interventions must be well documented before they can be recommended.

To date, no clinical trial has specifically tested physical activity for the prevention of CAD. While studies have well described the short-term physical and cognitive function benefits of physical activity in older adults, it is not known whether long-term activity in the context of a clinical trial would prevent incident CAD in older adults. However, cardiac rehabilitation is effective in reducing recurrent events, including in older adults [88, 89]. Due to the high prevalence of CAD among older adults, the careful evaluation of cardiovascular status—including measurements of subclinical disease—should be considered for older adults who are planning to undertake a new physical activity program. Exercise testing alone is probably not adequate to identify the individuals who may be at high risk due to extensive CAD.

23.6 Outstanding Issues

In developed countries, the rates of CVD and mortality from CAD have been in decline, and this decline includes in older adults [90]. This can be viewed as a major public health success. Recent efforts endorse primordial prevention by taking a life course approach to prevention and focusing on the prevention of the development

of risk factors in youth. A second issue is that prevention measures have not been uniformly applied in the US, so disparities continue to exist and need to be addressed [91]. A third issue is the impact of CVD on global health. Developing countries are facing new epidemics of CAD and atherosclerosis, which are likely to increase rates of disability in older adults in countries such as India and China [92, 93]. A fourth issue is the impact of CVD survival on longevity. With better prevention of primary CAD events and better long-term survival related to secondary prevention, new problems are emerging: greater numbers of older adults are surviving to face the competing risks of cancer and dementia. Nevertheless, reduced rates of CAD and atherosclerosis could improve rates of disability related to these conditions. We still do not know whether CVD prevention is translating into improved functional survival and a compression of morbidity in older adults.

23.7 Summary

CAD rates have declined in the US, yet it remains the number one cause of death in older adults and a significant cause of morbidity. Epidemiologic studies have identified numerous modifiable risk factors for CAD in older adults. Measures of subclinical atherosclerosis appear to summarize the impact of these risk factors over many years and have similar predictive values as do risk factor equations, which are strongly weighted by age. Clinical trials that include older adults demonstrate the benefits of primary and secondary preventive therapy. The lessons learned should be used to prevent the emerging epidemic of CAD in developing countries.

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Asthma and COPD

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are clinically important in older adults because like heart failure, they are common causes of chronic shortness of breath, which reduces the quality of life by limiting an individual's activity. In developed countries, about 4% of older adults have been diagnosed with asthma and another 4% have been diagnosed with COPD, but the prevalence is doubled for each of these chronic respiratory diseases when objective tests are performed. COPD has become the fourth leading cause of death in some developed countries. COPD onset occurs almost exclusively in older age due to the cumulative effects of cigarette smoking in genetically-susceptible individuals. An upper respiratory viral infection commonly leads to the initial diagnosis of asthma at any age. About half of older adults with asthma have allergic triggers, compared to about 90% of asthmatic children. Exacerbations with dyspnea, wheezing and cough are the major morbidity of asthma and COPD, which limits activity, reduces quality of life and increases health care utilization and costs. In older adults as in younger adults, the most effective prevention for both asthma and COPD is smoking cessation.

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Abbreviations

BHR	Bronchial Hyper-Responsiveness
BNP	B-type natriuretic peptide
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
DLCO	Carbon Monoxide Diffusing Capacity
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
hMPV	Human Metapneumovirus
IgE	Immunoglobulin E
LLN	Lower Limit of the Normal range
MIP	Maximal Inspiratory Pressure
NHANES	National Health and Nutrition Examination Survey
Pre-BD	Prior to inhalation of a Bronchodilator
Post-BD	After inhalation of a Bronchodilator
RSV	Respiratory Syncytial Virus
TENOR	The Epidemiology and Natural History of Asthma study
US	United States

24.1 Introduction

Asthma, chronic obstructive pulmonary disease (COPD) and chronic heart failure are clinically important in older adults because they are common causes of chronic shortness of breath (dyspnea), which reduces quality of life by limiting activity. An older adult with any of these diseases is more likely to experience morbidity (exacerbations and hospitalization) and mortality. Asthma and COPD both cause airway narrowing, which can be detected by spirometry testing. While asthma can start during any decade of life, COPD only develops after decades of cigarette smoking and so is very rare before 40 years of age. It is important to distinguish between asthma, COPD and heart failure because the interventions differ; treatment for asthma is more successful and the prognosis is much better. About 20% of older adults with any one of these causes of dyspnea will also have one of the others (co-morbid conditions).

24.2 Definitions

The definitions of asthma and COPD are based on symptoms, self-reported diagnosis, and/or the testing of pulmonary function using spirometry. Asthma is defined as episodic and reversible airways obstruction. COPD is defined as chronic and irreversible airways obstruction. Other chronic conditions can also cause dyspnea. We define two of these here to distinguish them from asthma and COPD. The definition of chronic bronchitis is based on a history of a chronic cough (productive of sputum or not) which has been present for at least 2 years. Epidemiologic studies use a standardized set of questions to define chronic bronchitis; no objective tests are needed. Emphysema is a term used to describe the irreversible destruction of lung tissue, which is detected using a breathing test called carbon monoxide diffusing capacity (DLCO) or by high-resolution CT scans of the lungs that show reduced lung density or holes in the lungs (blebs or bullae). Overlap amongst the above chronic lung disease phenotypes does occur since decades of cigarette smoking can cause any one or all of them (asthma, chronic airway obstruction, chronic bronchitis and emphysema).

24.3 Spirometry

Airway obstruction is reliably detected in older adults through the use of a spirometer [1]. The study participant is coached to take as deep a breath as possible and then blow into the

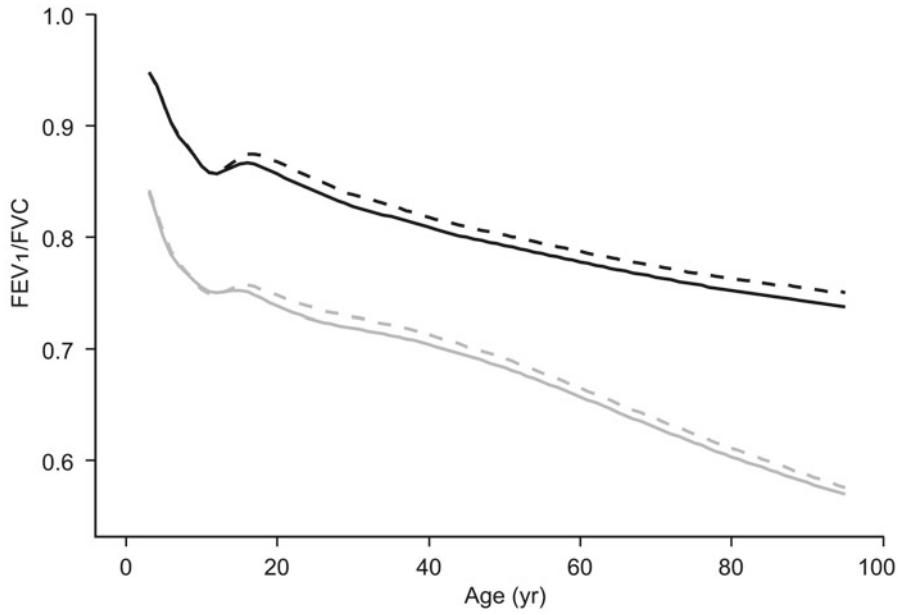

Fig. 24.1 The predicted (*black lines*) and the lower limit of the normal range (LLN, *grey lines*) for FEV1/FVC—which defines airway obstruction—decrease with age. The values for females (*dashed lines*) are slightly higher than for men (*solid lines*)

spirometer mouthpiece as quickly as possible for at least 6 s. The volume of air forcefully exhaled during the first second is called the forced expiratory volume (FEV1) and the total amount of air exhaled is called the forced vital capacity (FVC) (measured in liters). Healthy middle-aged adults can exhale about 75% of their air in the first second, so the ratio of their FEV1/FVC is about 0.75. Smokers who have developed COPD have a permanently reduced capacity to exhale rapidly, so their FEV1 and their FEV1/FVC fall below the lower limit of the normal range (LLN).

Almost all clinical and epidemiological definitions of COPD are based on a low FEV1/FVC in a patient with COPD risk factors. However, the LLN for this ratio has been controversial. The pulmonary function standards committee of the American Thoracic Society [2]—the largest and most influential pulmonary professional society—recommends using the fifth percentile LLNs from spirometry reference equations from the healthy, never-smoking subset of participants from the National Health and Nutrition Examination Survey (NHANES) III for use throughout North America [3]. The mean and LLN for the FEV1/FVC from this study (and from most studies of lung function in healthy population-based samples) decrease with aging. So the LLN for this ratio is about 0.75 for young adults and falls to about 0.60 for adults ≥85 years of age (Fig. 24.1). In the year 2000, an industry-sponsored, international group of key opinion leaders published and began extensive worldwide promotion of a COPD clinical practice guideline which defined COPD as a FEV1/FVC ratio <0.70 (a fixed threshold) after inhaling a fast-acting bronchodilator (post-BD). Many COPD guidelines developed for individual countries quickly adopted this definition. However, compared to the use of an age-adjusted LLN, the use of this fixed threshold to define COPD greatly increases the apparent prevalence of COPD in population-based samples of healthy older adults [4]. The vast majority of patients given a diagnosis of COPD in clinical settings present with symptoms; however, in population-based studies which included spirometry, half of adults with severe airway obstruction did not report respiratory symptoms. Therefore, epidemiologic studies with spirometry should base the COPD prevalence only on spirometry results.

Spirometers designed in the 1960s collected exhaled air in a container for measurement of the

Fig. 24.2 An older woman blowing forcefully into a spirometer for 6 s. Due to COPD, her FEV1 is only 0.35 l (very severe airway obstruction) and she has required continuous oxygen therapy (2 l per minute to maintain her oxygen saturation above 90%) during the past decade. Note the nasal prongs which deliver the supplemental oxygen. She kindly gave us written permission to publish this 2012 photo of her

vital capacity (Fig. 24.2). Since tall people can exhale up to two gallons of air, these devices were bulky and heavy. During the 1990s, flow-sensing spirometers, many of which are hand-held and battery-powered, replaced the older devices. The American Thoracic Society provides standards for the accuracy of spirometers and spirometry procedures [2].

24.4 Differentiating Asthma from COPD and Chronic Heart Failure (CHF)

One difference between asthma and COPD is that the airway obstruction of patients who have asthma is more likely to quickly respond to an inhaled bronchodilator medication (such as albuterol, also called salbutamol). Amongst individuals who have asthma, the majority of asthma is mild and intermittent. There is no airway obstruction between asthma exacerbations (which are usually triggered by an upper respiratory viral infection). Therefore, in epidemiological surveys, participants with mild asthma usually have normal spirometry tests (no airway obstruction). Those with moderate or poorly-controlled asthma have some degree of airway obstruction, but their lung function returns toward the normal range (due to increased FEV1) within 10 min post-BD (Fig. 24.3). For those who report asthma-like symptoms, if their spirometry results improve into the normal range post-BD, COPD is ruled out and the probability of asthma is greatly increased.

In spirometry testing, CHF causes a small decrease in the FVC, but there is no airway obstruction [5]. CHF causes an increase in blood levels of B-type natriuretic peptide (BNP), while BNP levels are normal in patients who have asthma or COPD. Echocardiography shows left heart failure in CHF and right heart failure (i.e., cor pulmonale) in very severe COPD, but electrocardiography is normal in asthma (Table 24.1).

The agency which funds the majority of pulmonary research in the United States (US), the Lung Division of the National Heart, Lung and Blood Institute, made asthma a high priority in the 1980s–1990s, so standardization of asthma definitions was advanced for both reporting purposes and clinical practice guidelines. However, the emphasis was on the control of asthma in children. Although the US Centers for Disease Control and Prevention reported that the majority of asthma deaths occurred in older adults [6], very little asthma research (observational or intervention) was done in this age group. Around the year 2000, the Lung Division shifted its major research funding and disease awareness programs to COPD, a disease almost exclusively of older adults. Still, controversy exists regarding the definitions of asthma and COPD in older adults.

24.4.1 Controversy in Defining Asthma and COPD

Older adults who have respiratory symptoms and airway obstruction that remains post-BD are

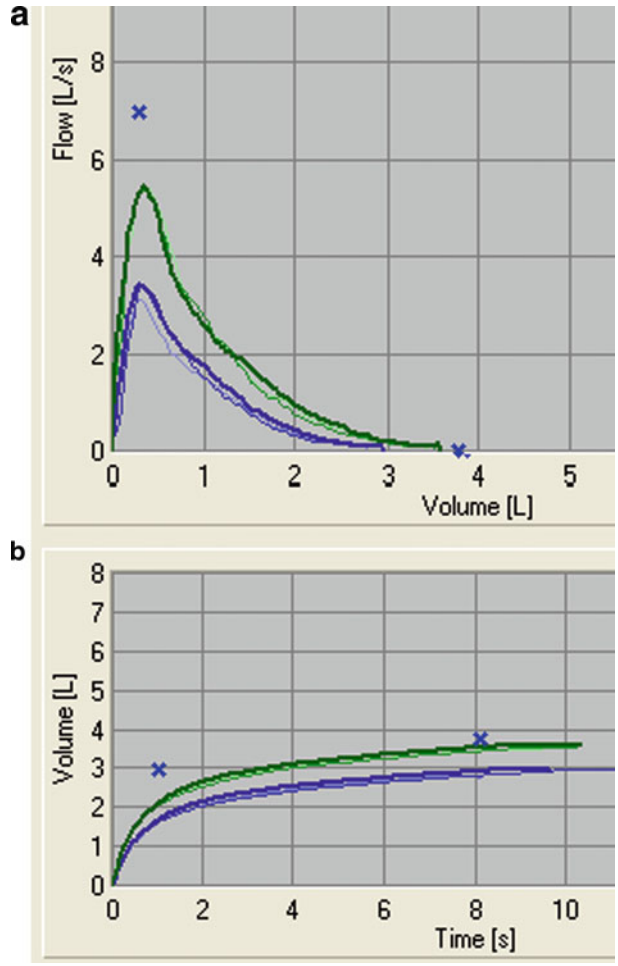

Fig. 24.3 Spirometry graphs from a 75-year-old man with asthma. The *top graph* (**a**) shows flow-volume curves with the characteristic bowl-shape of airway obstruction. The *bottom graph* (**b**) shows traditional volume-time curves, from which the FEV1 and FVC are measured. The man's FEV1 was 1.5 l (from the pre-bronchodilator smaller curve); his FVC was 3.0 l; and his FEV1/FVC was only 0.50, confirming airway obstruction. The small *x-marks* indicate the predicted normal values. Ten minutes after inhaling a bronchodilator (albuterol), his FEV1 increased to 2.0 l (about 33% larger) and his FVC increased to about 3.7 l. If he had been a smoker with COPD, his bronchodilator response would have been much smaller (usually less than 0.25 l)

classified by some studies as having asthma and by others as having COPD. Asthma has to be defined on the basis of a physician diagnosis, but in the future, there should be some consideration of a reversibility of chronic obstruction. Some investigators use smoking status to classify the respiratory disease of those with post-BD airway obstruction (never smokers as having asthma or ever smokers as having COPD). Large epidemiological surveys of adults have demonstrated that about one-third of participants who have mild airway obstruction before inhaling a fast-acting bronchodilator (pre-BD) do not have airway obstruction post-BD. However, the majority of studies of chronic lung disease in adults do not take the time to perform post-BD spirometry (since it takes 15–20 min).

A chronic cough is a very common feature in smokers who have developed COPD, so some studies wrongly include people with a chronic cough or chronic bronchitis under their definition of COPD. However, even in adult smokers, there

Table 24.1 Tests to differentiate asthma, chronic obstructive pulmonary disease, and chronic heart failure

Test	Asthma	Chronic obstructive pulmonary disease	Chronic heart failure
Spirometry	Reversible obstruction	Fixed obstruction	Low FVC (restriction)
Chest x-ray	Hyperinflation	Hyperinflation	Increased vascularity
BNP	Normal (<100)	Normal (<100)	High (>500)
Echocardiography	Normal	Normal	Low ejection fraction

Abbreviations: *BNP* B-type natriuretic peptide (pg/mL), *FVC* forced vital capacity

are many other causes for a chronic cough (e.g., rhinosinusitis, gastro-esophageal reflux and asthma), so large COPD misclassification rates result when an objective measurement of airway obstruction is not performed.

The definition of asthma for epidemiological surveys is less controversial than for COPD [7, 8]. For diagnosis of asthma, most studies of adults rely on participant recollection of a physician diagnosis of asthma, using a set of standardized questions. Study participants may also be asked to list their breathing medications or to bring them to a study visit. Objective measurements of the bronchial hyper-responsiveness (BHR) and eosinophilic airway inflammation of asthma are available [9], but they have not come into widespread use due to the time needed to perform the BHR measurement (45–60 min for a methacholine or mannitol inhalation challenge test) and the expense of exhaled nitric oxide analyzers. Also, as discussed above, a spirometry test only detects moderate or poorly-controlled asthma.

A physician diagnosis of asthma underestimates the true prevalence of asthma because many people do not seek medical attention for what they consider to merely be "a cold that goes to my chest" [10]. However, the morbidity that is experienced by older adults who have recurrent, intermittent episodes of wheezing with shortness of breath but no diagnosis of asthma is similar to those who have a diagnosis of asthma.

24.4.2 Implications of Disease Definitions

As with other common chronic diseases for which expensive drugs are available, the exact definition of the disease has large financial implications (for the payors and sometimes for the individual patients). The market for medications that control airway obstruction greatly expands when definitions for disease extend into the normal range and when clinical practice guidelines call for early detection and treatment of more mild disease. Currently, there is no evidence that early detection and treatment changes the natural history of COPD.

24.5 Prevalence and Incidence

Two large population-based studies of adults from many countries have provided good estimates of the prevalence of COPD based on post-BD spirometry measurements [11, 12] (Fig. 24.4). The prevalence of COPD in the moderate range (50–90% predicted FEV1) in men and women ≥60 years of age ranges from 3 to 6% (depending on the country). The prevalence of severe COPD (FEV1 below 50% predicted) is only about 1%. However, COPD is now the fourth leading cause of death in the US [13].

Population-based samples of older adults have provided estimates of the prevalence of asthma in adults ≥60 years of age [14, 15]. Using a large community-based cohort of individuals >65 years of age in the US, the CHS defined *definite* asthma as positive responses to the questions: "Has a physician ever told you that you have asthma?" and "Do you still have asthma?" *Probable* asthma was defined as a history of wheezing in the past year associated with chest tightness or breathlessness. Excluding smokers and those with a diagnosis of congestive heart failure, 4% of individuals had definite asthma and 4% had probable asthma [16]. Among current smokers, 11% had definite asthma and 14% had probable asthma. The age of asthma onset was spread approximately evenly among decades, with 25% reporting onset before age 20 and 27% after age 60.

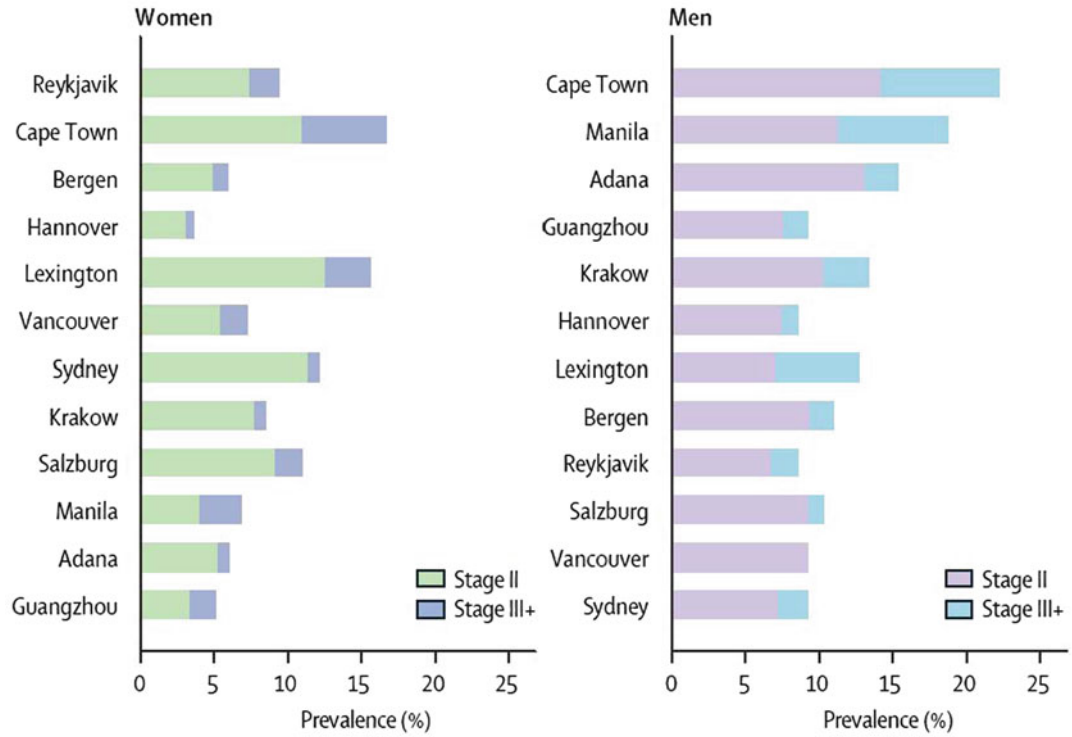

Fig. 24.4 Prevalence rates for mild-moderate COPD in women (**a**) and men (**b**) ages 40–90 from 12 different countries. Stage II is mild-moderate with post-bronchodilator FEV1 between 50 and 80% of predicted. Individuals with severe stage III+ COPD have an FEV1 below 50% of predicted. Predicted FEV1 values are based on height, age and gender (Results are from the BOLD study [11]). No adjustment was made for predicted FEV1 for African race in Cape Town, South Africa or Lexington, Kentucky

In the US, the National Health Interview Survey asks questions regarding lifetime history of asthma, current asthma prevalence, and asthma attacks in the last 12 months [17]. For all age groups, asthma prevalence has been steadily increasing since 1980. For example, the prevalence of current asthma in those aged 65 and above rose from 6.0% in 2001 to 7.0% in 2004. For those ≥65 years of age, asthma is consistently more prevalent in women than in men. In 2003, 3.3% of women over age 65 reported an asthma attack during the previous 12 months, compared to 1.7% of older men. The National Center for Health Statistics tracks data on physician encounters for asthma. Using this data, the National Ambulatory Care Survey reported that those ≥65 years of age have the second-highest rate of outpatient office visits for asthma after preschool children, but do not have significantly different rates for emergency room visits compared to other adult age groups [18]. The 65+ age group accounts for a greater proportion of hospitalizations (23%) than the size of its population (13%) would indicate, and has higher asthma mortality rates than do young adults [6].

24.6 Risk Factors

24.6.1 Age

Within the age range of 65–95, the risk of the clinical appearance of asthma or COPD does not increase appreciably with age. Allergic asthma commonly begins in childhood, but it can begin at any age. Older patients who have asthma often note the onset of asthma after age 60, usually associated with a serious cold or influenza [16].

In contrast, age is a risk factor for COPD since it develops very slowly, with the onset of dyspnea upon exertion prompting a diagnosis in the fifth or sixth decade of life. After age 85, the prevalence of COPD falls, probably due to mortality from other smoking-related diseases.

Aging is a cause of decreased lung function in older adults. Lung function grows with height in childhood and adolescence, reaches a peak in the 20s or early 30s then declines linearly throughout adulthood. FVC starts at 4–5 l in young adults (depending on height and gender) then declines by about one-third of a liter per decade. On average, the functional reserve of the lungs continues to slowly erode throughout older age, even in healthy individuals who have never smoked and had no measurable environmental exposures. The FEV1 declines at a somewhat faster rate than the FVC (largely due to a loss of lung tissue elasticity), so the FEV1/FVC also declines with aging. Age-related impairments in respiratory physiology become most problematic during maximal exercise or in an episode of acute lung injury (e.g., pneumonia), as well as in individuals who already have a reduced ventilatory reserve due to lung disease.

24.6.2 Gender

For a given exposure history (such as pack-years of smoking), women and men have a roughly equivalent risk of developing COPD [19–21]. Older women are more likely than older men to have asthma-like symptoms and to report dyspnea upon exertion (even after adjustment for other risk factors).

24.6.3 Genetic Risk

Studies have identified some racial differences in susceptibility to asthma and COPD. However, large projects have had only limited success in determining the exact set of genetic polymorphisms that are responsible for increased susceptibility for developing these chronic airway diseases [22]. African-Americans are more likely to have a genetic polymorphism that increases their risk of asthma (at all ages) and reduces the effectiveness of the long-acting bronchodilators which are commonly used to control asthma (inhaled beta-agonists). Amongst Hispanics, a greater percentage of African ancestry correlates with lower FVC and a greater risk of asthma and asthma severity [23]. On the other hand, African-American women are less susceptible to the risk that cigarette smoking will cause COPD [19].

24.6.4 Smoking

About one in five people who begin smoking before age 20 will slowly develop COPD. About 90% of clinically-important COPD is caused by smoking. The respiratory system has a very large functional reserve, so decades of slow loss in lung function usually occurs (as in COPD caused by cigarette smoking) before shortness of breath prompts the individual to seek medical attention [24]. Smoking also increases the risk of asthma (at all ages) and continued smoking makes asthma more difficult to control because smoking reduces the effectiveness of inhaled corticosteroid therapy.

24.6.5 Viruses

All of the common respiratory viruses have been associated with asthma and COPD exacerbations: respiratory syncytial virus (RSV), parainfluenza viruses, coronaviruses, human metapneumovirus (hMPV) and rhinoviruses. Wheezing is a common symptom in older adults who are infected with any respiratory virus, particularly with RSV and hMPV, and 7 percent of adults who are hospitalized with RSV pneumonia will have a discharge diagnosis of asthma [25].

24.6.6 Allergies

Many risk factors for asthma in young and middle-aged adults have been identified. Most remain as risk factors for asthma in older adults. In the CHS cohort, 58% of older-adult asthmatics

reported the most common trigger of an asthma exacerbation to be an upper respiratory viral infection (upper respiratory infection, common cold or influenza), while 30% reported that contact with animals caused their asthma to worsen. Two-thirds reported seasonal worsening.

About 50% of older adults with asthma have allergic triggers, compared to about 90% of asthmatic children. The Epidemiology and Natural History of Asthma (TENOR) study compared the natural history of asthma in younger and older patients [26]. The older patients had lower total immunoglobulin E (IgE) levels, fewer positive skin prick tests and less concomitant allergic rhinitis or atopic dermatitis. There is also evidence for an age-related decline in skin-prick test responses to allergens; however, older adults who have greater levels of IgE remain more likely to have allergic rhinitis and asthma [27].

24.6.7 Environmental Risk Factors

A few epidemiologic studies have suggested an association between short-term worsening of outdoor air pollution and emergency department or hospital admissions for asthma in older adults [28]. Decades of exposure to severe outdoor air pollution may increase the risk of at least mild COPD in older ages [29]. Like the skin, the lungs have a very large surface area which is directly exposed to the environment. Inflammatory responses to these exposures usually promote long-term health, but they can also cause long-term damage in a susceptible subset of individuals, damage which often accumulates decade-by-decade. Occupational exposures to inhaled dusts, fumes, smoke and chemicals increase the risk of chronic airway obstruction which persists into older age [30]. Decades of exposure to second-hand smoke, or to smoke from cooking with biomass fuels in developing countries, increases the risk of chronic bronchitis [31]. It remains unknown whether these environmental exposures also cause clinically-important COPD because almost all studies used pre-BD FEV1/FVC <0.70 to define COPD, which caused high false-positive rates for airway obstruction.

24.7 Dyspnea, the Primary Outcome of Asthma and COPD

Older adults with asthma or COPD frequently have respiratory symptoms such as chronic cough, phlegm and wheezing, all caused by their chronic airway inflammation [32]. Reduced lung function causes shortness of breath which limits their activity, reduces the quality of their lives and prompts them to utilize health care during exacerbations (visit emergency departments, sometimes leading to hospitalizations) [33]. This morbidity, along with the drugs prescribed for their dyspnea, is expensive [34–36].

Dyspnea is the most distressing feature of chronic lung disease and is a leading cause of disability and healthcare utilization [37]. In the CHS cohort, dyspnea upon exertion was 1.6-fold more likely to be present in patients diagnosed with asthma than in those without the diagnosis [16]. Asthma had a significant impact on quality of life, with 35% of older adults who have definite or probable asthma reporting a fair or poor health status compared to 17% of older adults who do not have asthma. Depression, restless sleep and daytime sleepiness were substantially more common in those with asthma.

Dyspnea may be considered an imbalance between ventilatory capacity and ventilatory demand. Increased ventilatory demand is commonly caused by comorbid conditions such as heart failure, anemia, obesity and peripheral vascular disease. The ability of the chest wall to expand easily is reduced by osteoporosis (vertebral compression, kyphosis and scoliosis) and osteoarthritis.

Very severe COPD and CHF (but not asthma) commonly cause skeletal muscle weakness (sarcopenia). Respiratory muscle weakness is a major factor that causes respiratory failure in COPD and pneumonia. The strength of the diaphragm, which is the primary breathing muscle, can be measured by a simple pressure meter. Maximal inspiratory pressure (MIP) ranges from 20 (very low) to 150 cm of water (normal), and is the best index of respiratory muscle strength [38]. MIP is an independent predictor of all-cause, cardiovascular and respiratory death in older adults [39].

24.8 Prevention

The most effective primary and secondary prevention for asthma and COPD after age 65 is the same as for middle age: smoking cessation. About half of older adults who have asthma and about one-third of those who have COPD are current smokers. Smoking cessation, both in middle age and older ages, is the only intervention that has been proven to slow the progression of COPD (thereby altering the natural history of the disease). Smoking cessation has been proven to make asthma respond better to inhaled corticosteroids, thus improving asthma control, and has been proven to prolong the life of those with COPD. The chronic cough and phlegm production of COPD will improve with successful smoking cessation, but the loss of lung function and emphysema are not reversible. The cough may get worse for a few weeks, but the degree of dyspnea on exertion tends to remain.

Influenza and pneumococcal vaccinations reduce asthma and COPD exacerbation rates [40]. It is likely that avoiding exposure to young children who have upper respiratory infections also reduces the risk of exacerbations, but no clinical trials have studied the benefit of avoiding exposure to these young children.

Another prevention method for asthma and COPD is avoiding the inhalation of respiratory irritants (e.g., smoke, fumes, dusts chemicals), which cause airway inflammation that persists for several hours after inhalation. This temporary inflammation increases coughing and phlegm from the lower airways. It also causes nasal congestion, leading to mouth breathing which bypasses the heating, humidification and dust removal of nasal passages which naturally protects the lower airways (in the lungs).

24.9 Summary

Asthma, COPD and heart failure are clinically important in older adults because they are common causes of dyspnea, which reduces the quality of life by limiting activity. In developed countries, about 4% of older adults have been diagnosed with asthma and another 4% with COPD. Epidemiologic studies use standardized questionnaires to determine the presence of asthma and post-BD spirometry to detect and verify COPD. An upper respiratory viral infection commonly leads to the initial diagnosis of asthma in older adults. About 90% of COPD is due to the cumulative effects of cigarette smoking in genetically-susceptible individuals. About half of older adults with asthma have allergic triggers. Periodic exacerbations with dyspnea, wheezing and cough are the major morbidity of asthma and COPD. Both conditions are associated with a higher risk of death. In older adults, the most effective prevention for both asthma and COPD is smoking cessation.

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The Pre-Diabetic, Insulin-Resistant State

25

Joshua Barzilay

Abstract

Adult-onset type 2 diabetes is a late outcome of metabolic and inflammatory processes that predate glucose level elevation by many years. The negative effects of these processes on the health of older adults are enhanced by the inter-relationship of these processes with those associated with "aging". Insulin resistance occurs prior to the elevated serum glucose levels that define diabetes. Obesity is the primary factor that leads to insulin resistance. The pre-diabetic insulin-resistant condition can have serious cardiovascular consequences, including subclinical or clinical cardiovascular disease and cardiovascular autonomic dysfunction. It can also have serious non-cardiovascular consequences, such as renal disease, cognitive decline, impaired mobility, frailty, interference with circadian rhythms, sleep apnea, bone disease and liver disease. Methods for attenuating the rise in glucose levels in those who have insulin resistance include pharmacological interventions and lifestyle change. Lifestyle changes include weight reduction and increased physical activity, which can be effective even in those with a genetic predisposition to diabetes and can ameliorate the decreased insulin sensitivity that is associated with aging.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Insulin resistance • Diabetes • Impaired fasting glucose • Risk factors • Outcomes • Prevention • Obesity

Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
AGE	Advanced Glycation Endproduct
ARB	Angiotensin Receptor Blockers
ARIC	Atherosclerosis Risk in Communities
ATPIII	Adult Treatment Panel III

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BP	Blood Pressure
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CHS	Cardiovascular Health Study
CI	Confidence Interval
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DPP	Diabetes Prevention Program
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
ECG	Electrocardiogram
FFA	Free Fatty Acid
GDM	Gestational Diabetes Mellitus
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard Ratio
HRV	Heart Rate Variation
ICAM	Intercellular Adhesion Molecule
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IL-6	Interleukin-6
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
MetS	Metabolic Syndrome
MMP	Matrix Metalloproteinases
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steato-Hepatitis
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
NEFA	Non-Esterified Fatty Acids
NHANES	National Health and Nutrition Examination Surveys
NNT	Number Needed to Treat
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
p38-MAPK	p38-Mitogen-Activated Protein Kinases
PAI-1	Plasminogen Activator Inhibitor type-1
RAS	Renin Angiotensin System
RR	Risk Ratio
TNFα	Tumor Necrosis Factor Alpha
TRANSCEND	Telmisartan Randomized Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease
US	United States
VCAM	Vascular Cell Adhesion Molecules
VEGF	Vascular Endothelial Growth Factor
VSMC	Vascular Smooth Muscle Cell

25.1 Introduction

An appreciation of the impact of adult-onset, type 2 diabetes on the health of older adults begins with an understanding of the factors that underlie its development. Such knowledge will lead one to appreciate that diabetes is a late outcome of a continuum of metabolic and inflammatory processes that predate glucose level elevation by many years. The inter-relationship of these factors with processes that are associated with "aging" enhances their negative effects on the health of older adults.

This chapter is divided into three parts. In the first part, we shall define insulin resistance and discuss its prevalence in population studies and how it relates to the metabolic syndrome (MetS) (a group of risk factors which occur together and increase the risk for diabetes, coronary artery disease and stroke). In the second part, we shall describe the cardiovascular and non-cardiovascular disorders that are associated with the insulin-resistant state. In the third part, we shall discuss pharmacological and lifestyle methods that prevent or attenuate the effects of the insulin-resistant state on health.

Much of the information cited here will be derived from the Cardiovascular Health Study (CHS), a prospective, observational study of risk factors for cardiovascular disease in older adults [1].

25.2 Insulin Resistance, Its Prevalence and How It Relates to the Metabolic Syndrome

25.2.1 Definition and Prevalence of Insulin Resistance

The pre-diabetic, insulin-resistant state is characterized by resistance to the effects of insulin in skeletal muscle and adipose tissue, low-grade increased levels of inflammation proteins, and the presence or development of hypertension. These factors are present prior to elevated serum glucose levels, which are the defining characteristic of diabetes.

Adiposity (obesity), with or without a genetic predisposition, is the primary factor that leads to insulin resistance. The majority of middle-aged adults in the United States (US) who have insulin resistance or diabetes are either overweight or obese (~70–80%). This is so for older adults as well. In an analysis of 4,193, participants from the CHS [2] who were ≥65 years of age at entry, the adjusted hazard ratio (HR) for diabetes (an outcome of insulin resistance) was 4.3 (95% confidence interval [CI], 2.9–6.5) and 4.2 (95% CI, 2.8–6.2) for the highest quintile of BMI and waist circumference, respectively, as compared to the lowest quintile. When stratified by age, participants who were ≥75 years of age had half the risk of diabetes of participants who were 65–74 years of age. When compared to participants who were weight-stable from 50 years of age, participants who gained the most weight (≥9 kg) until entry into the CHS cohort were 2.8 (95% CI, 1.9–4.3) times more likely to develop diabetes.

Not all individuals who have MetS are overweight. In a cross-sectional sample of 5,440 participants in the National Health and Nutrition Examination Survey (NHANES) 1999–2004 [3], 23.5% of normal-weight adults were metabolically abnormal, whereas 51.3% of overweight adults and 31.7% of obese adults were metabolically healthy. The independent correlates of clustering of cardiometabolic abnormalities among normal-weight individuals were older age, lower physical activity levels and larger waist circumference. In addition, genetic predisposition to insulin resistance (e.g., family history of diabetes) also plays a role.

There are multiple metabolic consequences from insulin resistance (Fig. 25.1) [4]:

1. Fat cells that are swollen secrete elevated levels of inflammation proteins, such as interleukin-6 (IL-6). These factors interfere with insulin signaling, making insulin-dependent tissue (like muscle) less responsive to insulin. At the same time, the fat cells produce lower-than-normal levels of insulin-sensitizing hormones (e.g., adiponectin), which exacerbates the insulin resistance.
2. Elevated levels of free fatty acids (FFAs) from the excess abdominal fat have direct access to the portal vein. Consequently, FFAs accumulate in the liver as triglycerides ("fatty liver"). This excess fat leads to the liver producing above-normal levels of inflammation proteins, such as tumor necrosis factor alpha (TNFα). This further impairs insulin signaling in muscle cells. To overcome this resistance, more insulin is produced (hyper-insulinemia).
3. Insulin normally prevents the release of FFA that is stored as triglycerides in adipocytes. This capacity is lost in the presence of insulin resistance. Consequently, high levels of FFAs are present in the blood. These FFAs enter muscle cells, further aggravating resistance to insulin's effects.
4. There is a loss of muscle mass with aging. Even if an individual maintains a constant weight, the percentage of body fat increases with age. Approximately 80% of insulin-sensitive tissue in the body is muscle. Loss of such tissue results in a diminished ability to utilize glucose. While this is not technically a form of insulin resistance, the loss of muscle mass leads to a reduced effectiveness of insulin to control blood sugar.
5. Visceral fat cells produce proteins that raise blood pressure, such as angiotensinogen. Hypertension is present in ~70% of individuals who have pre-diabetes.

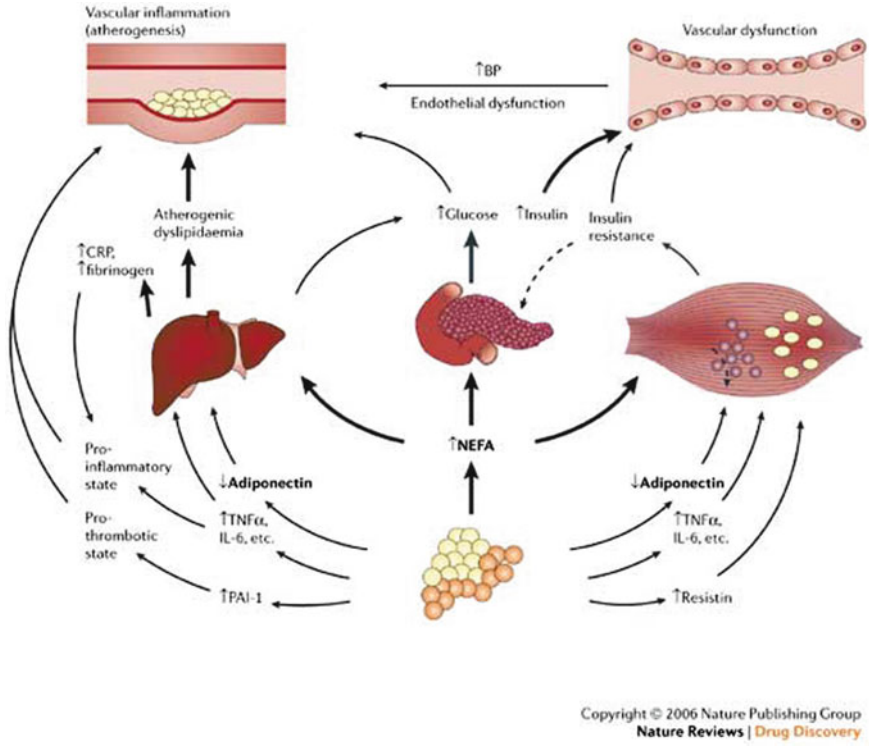

Fig. 25.1 The metabolic consequences from insulin resistance [5]. *Abbreviations: BP* Blood pressure, *CRP* C-reactive protein, *IL-6* Interleukin-6, *NEFA* Non-esterified fatty acids, *PAI-1* Plasminogen activator inhibitor type-1, *TNF [alpha]* Tumor necrosis factor alpha

6. Once insulin resistance has been established for many years, the insulin-producing cells in the pancreas are no longer able to produce the increased amounts of insulin that are necessary to compensate for the resistance to insulin so as to keep blood glucose levels normal. "Exhaustion" sets in, the consequence of which is rising blood glucose levels. The rise in glucose is gradual. Early on, the response to a mixed meal or to a glucose challenge is blunted, leading to raised postprandial glucose levels. If the glucose level 2 h after a 75 g glucose challenge is 140–199 mg/dl, it is called *impaired glucose tolerance*. Later, with the further progression of "exhaustion", the fasting glucose level rises. If the fasting glucose level is 100–125 mg/dl, it is called *impaired fasting glucose*. Normal fasting glucose is less than 100 mg/dl.

25.2.2 Metabolic Syndrome

MetS is a construct that has recently gained popularity and is often used interchangeably with insulin resistance. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]) [6] defines five criteria for the MetS. These include abdominal obesity, hyper-triglyceridemia, a low level of high-density lipoprotein cholesterol, hypertension and altered glucose metabolism. A diagnosis of MetS requires the presence of three or more of these criteria.

A multivariate correlation technique called factor analysis has been used to reduce these many interconnected metabolic and physiologic variables into a smaller number of unique, independent "factors" [7]. While results have varied depending

on the population studied, two factors have emerged as common to all studies. These are a *metabolic* factor, loading on insulin resistance, elevated glucose levels and obesity; and a *blood pressure* factor, loading on systolic and diastolic blood pressure. Other studies have extended these findings and have reported an *inflammation* factor, loading on elevated levels of inflammation and coagulation analytes [8, 9]. Insulin resistance, hypertension and elevated levels of inflammation factors are individually and collectively risk factors for cardiovascular disease. Consequently, most studies have considered cardiovascular disease to be the main consequence of the MetS [10, 11]. While this view is certainly correct, insulin resistance, inflammation and hypertension have other far-reaching and important effects on health which will be discussed below.

25.3 Consequences of the Pre-Diabetic Insulin-Resistant Condition

25.3.1 Cardiovascular Outcomes

25.3.1.1 Background

Beyond its metabolic role, insulin has hemodynamic effects [12]. The infusion of insulin into peripheral arteries leads to vasodilation and an increased blood flow. Insulin also opens precapillary sphincters, enabling more blood to be directed to the micro-circulation of insulin-sensitive tissue, such as skeletal muscle. By so doing, the metabolic effect of insulin is ensured. Insulin's hemodynamic effect acts through its ability to stimulate the enzyme nitric oxide synthetase in the endothelium, the one-cell-thick layer that lines the inner surface of arteries. This enzyme produces nitric oxide, a potent vasodilator. Insulin resistance impairs the ability of insulin to stimulate nitric oxide synthetase, which leads to impaired vasodilation (Fig. 25.2).

The effect that mild elevations in fasting and post-prandial glucose levels have on the blood vessel wall compounds the impaired vasodilation that is associated with insulin resistance. The mechanism for this effect is through redox imbalance [14, 15]. Endothelial cells are ill-equipped to handle the ingress of even minimally-elevated glucose levels into their interior. Such ingress affects the ability of the cell's antioxidant defense mechanisms to "quench" the production of oxygen radicals which occurs during the oxidation of glucose for energy production. Under conditions of hyperglycemia, the excess production of oxygen radicals cannot be sufficiently neutralized by the existing anti-oxidant defense systems. As a consequence, excess amounts of free radicals are formed. These molecules stimulate stress-related signaling mechanisms (e.g., p38-mitogen-activated protein kinases [p38-MAPK] and janus kinase-signal transducer and activator of transcription [JAK-STAT]), which results in vascular smooth-muscle migration and proliferation. In endothelial cells, free radicals mediate cell death and impaired production of nitric oxide. Last, redox imbalance stimulates nuclear factor kappa (NF-kB), the master gene of inflammation. Among the genes expressed by NF-kB stimulation are growth factors (e.g., vascular endothelial growth factor [VEGF]); inflammatory cytokines (e.g., TNFα), and adhesion molecules (e.g., vascular cell adhesion molecules [VCAM]) which initiate and propagate the atherosclerotic process.

25.3.1.2 Subclinical CVD

The development of noninvasive cardiovascular technology has led to the appreciation that individuals who do not have clinical cardiovascular disease (CVD) (e.g., heart attacks, stroke, claudication) often have significant underlying vascular disease. This is especially so for older adults who develop vascular illness due to the damaging effects of aging. We examined the prevalence of subclinical CVD in the absence of clinical CVD in CHS participants who did not have a glucose disorder and in those who had impaired fasting glucose levels (most of whom had insulin resistance) [16]. Those who had impaired fasting glucose status showed an incremental increase in the prevalence of major electrocardiogram (ECG)

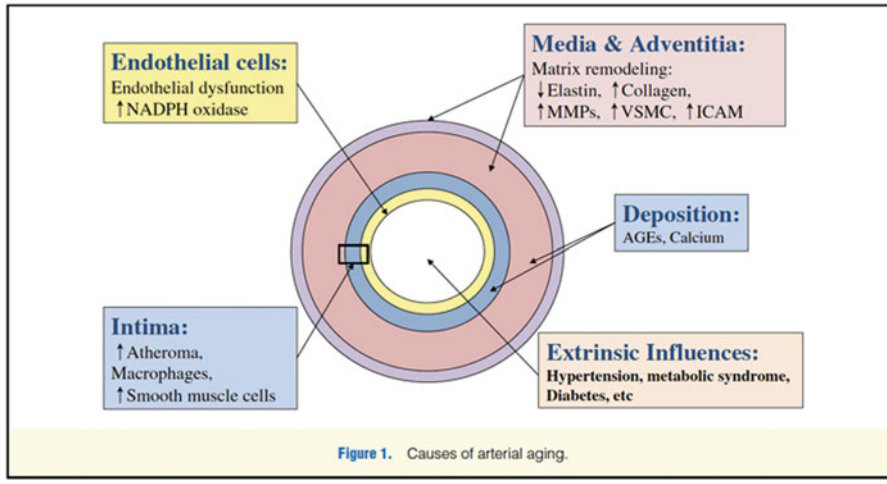

Fig. 25.2 Cross-sectional view of an artery showing where disease develops [13]. *Abbreviations: AGE* Advanced glycation endproduct, *ICAM* Intercellular adhesion molecule, *MMP* Matrix metalloproteinases, *NADPH* Nicotinamide adenine dinucleotide phosphate, *VSMC* Vascular smooth muscle cell

changes, abnormal ejection fraction, abnormal left ventricle wall motion, and intima media thickness of the internal and common carotid arteries (Table 25.1). These results suggest that subclinical disease develops prior to the onset of diabetes.

In the Atherosclerosis Risk in Communities (ARIC) Study [17], ultrasonography was used to noninvasively measure average intima-media carotid wall thickness (an indicator of atherosclerosis) in adults 45–64 years of age who were free of symptomatic CVD. For a 0.07-unit (one SD) larger waist-to-hip ratio (a measure of central obesity), mean wall thickness was greater by 0.02 mm in women and 0.03 mm in men. Adjusted mean wall thickness was thicker in participants who had hyperglycemia (fasting glucose 115–139 mg/dl) than in those who had a fasting glucose <115 mg/dl. Adjusted mean wall thickness was also increased with increased serum insulin levels. In sum, individual components of the MetS were associated with subclinical atherosclerosis.

In a 6.4 year follow-up analysis in the CHS [18], most traditional cardiovascular risk factors were not significant predictors of clinical CVD among individuals who had impaired glucose tolerance or diabetes once subclinical CVD was taken into account. Among participants who had glucose disorders (mean age 73 years), the presence of subclinical vascular disease was the strongest risk factor for total mortality, CVD mortality, incident myocardial infarction and incident coronary heart disease (Fig. 25.3). This suggests that the impact of elevated lipids, smoking and renal disease for clinical CVD was through their impact on subclinical CVD. It is noteworthy that having diabetes but no subclinical disease was not found to be at high risk.

25.3.1.3 Clinical CVD

We examined the CHS data set to determine the effects of pre-diabetic glucose levels on CVD [19]. Compared to participants who had normal fasting glucose (<100 mg/dl) and normal 2-h post-prandial (<140 mg/dl) glucose levels, those who had impaired fasting glucose (100–125 mg/dl) or impaired glucose tolerance (2-h glucose: 140–199 mg/dl) had a relative risk [RR] for coronary artery disease, stroke or cardiovascular death of 1.28 (95% CI, 1.02–1.61) and 1.22 (95% CI, 1.01–1.48), respectively. The risk for the participants who had impairments was approximately 50% that of individuals who had diabetes (>125 mg/dl fasting glucose and/or >199 mg/dl on 2-h post-prandial glucose level). From these findings, it may be concluded that mildly increased glucose levels have a negative effect on the vascular system.

Table 25.1 Prevalences and ORs of clinical and isolated subclinical CVD categorized by glucose status and sex in the CHS cohort [16]

	Prevalence				Odds ratio[a]				
Category	Normo-glycemia	Impaired fasting glucose	Newly diagnosed diabetes	Known diabetes	Normo-glycemia	Impaired fasting glucose	Newly diagnosed diabetes	Known diabetes	Test of trend
Men									
Clinical									
Cardiac	28.8	27.6	35.8	44.1	1.00	0.95	1.41[b]	2.08[b]	<0.001
Cerebrovascular disease	8.6	8.6	13.5	12.6	1.00	1.03	1.61[b]	1.52[b]	0.02
Peripheral artery disease	3.4	3.1	5.6	7.1	1.00	0.94	0.67	2.20[b]	0.002
Any clinical disease	34.5	34.0	44.7	51.3	1.00	1.00	1.56[b]	2.12[b]	<0.001
Subclinical									
Cardiac	23.7	29.5	34.5	29.3	1.00	1.42[b]	1.66[b]	1.35	0.14
Cerebrovascular disease	49.7	53.2	57.1	56.0	1.00	1.18	1.32	1.45	0.06
Peripheral artery disease	7.5	7.6	16.0	21.6	1.00	1.06	2.29[b]	3.63[b]	<0.0001
Any subclinical disease	61.8	66.2	76.5	73.3	1.00	1.27	1.97[b]	1.85[b]	0.002
Women									
Clinical									
Cardiac	19.2	24.6	25.1	42.4	1.00	1.39[b]	1.41[b]	3.01[b]	<0.0001
Cerebrovascular disease	5.2	4.3	7.0	12.7	1.00	0.82	1.32	2.22[b]	0.0001
Peripheral artery disease	2.2	2.4	3.5	6.5	1.00	1.10	1.60	3.00[b]	0.0004
Any clinical disease	23.6	27.5	30.4	49.8	1.00	1.25	1.40[b]	3.09[b]	<0.0001
Subclinical									
Cardiac	18.7	21.6	25.9	28.5	1.00	1.20	1.54[b]	1.43[b]	0.06
Cerebrovascular disease	45.1	44.5	51.3	65.0	1.00	1.03	1.30	2.53[b]	<0.0001
Peripheral artery disease	8.7	9.6	8.2	26.8	1.00	1.20	0.87	3.49[b]	<0.0001
Any subclinical disease	56.4	56.8	66.5	78.9	1.00	1.06	1.55[b]	2.83[b]	<0.0001

Note: Data are *n*

[a]Age- and race-adjusted

[b]Statistically significant ($p < 0.05$)

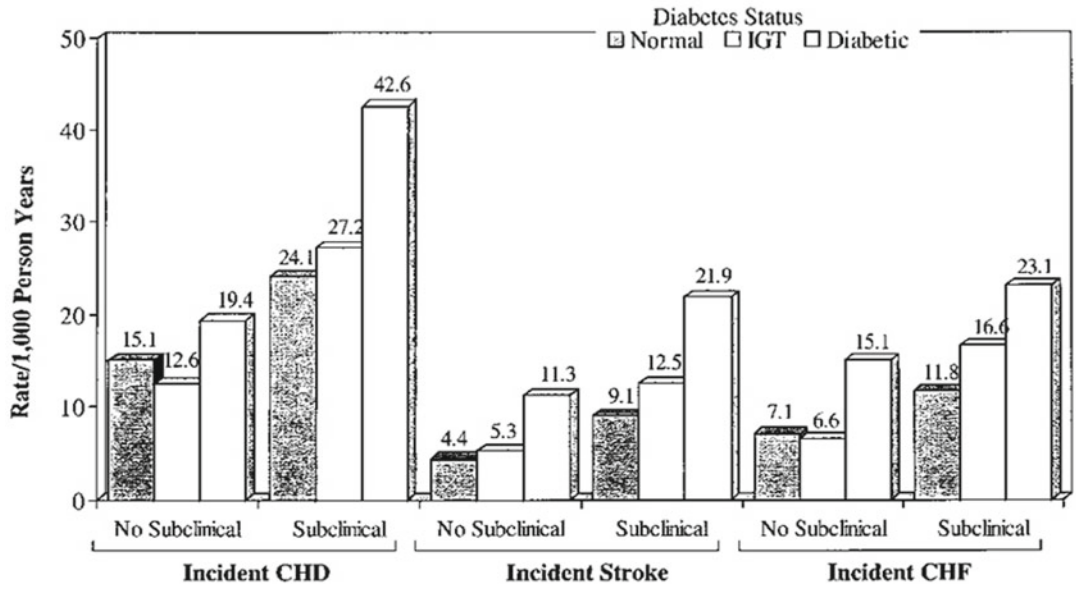

Fig. 25.3 Diabetes status and presence of subclinical/clinical CVD at baseline and incidence of specific events among men and women in the CHS [18]. *Abbreviations: CHD* Coronary heart disease, *CHF* Congestive heart failure, *IGT* Impaired glucose tolerance

We also examined CHS data to determine whether the insulin-resistant state (defined here as MetS)—without diabetes or prevalent CVD—was related to an increased risk of CVD in older adults [10]. We found that the MetS was moderately and significantly associated with coronary heart disease (women: HR, 1.30; 95% CI, 1.07–1.57) (men: HR, 1.35; 95% CI, 1.10–1.66), heart failure (women: HR, 1.40; 95% CI, 1.12–1.76) (men: HR, 1.47; 95% CI, 1.14–1.90) and stroke (women: HR, 0.94; 95% CI: 0.73–1.21) (men: HR, 1.51; 95% CI, 1.08–2.12). Using a composite endpoint that included the first incidence of these outcomes, women and men with MetS were 20–30% more likely to experience a CVD event than were those without MetS. The coronary heart finding was modified by age. For participants 65–74 years of age, the relative risk in association with MetS was 1.40; no association was observed in participants >75 years of age. This effect may be due to increased mortality among the 65–74 year old group. Those older than age 74 years may have had additional "protective" factors that protected them from the negative effects of the insulin resistant state.

25.3.1.4 Cardiovascular Autonomic Dysfunction

It is customary to ascribe the increased risk of CVD that is associated with the MetS to atherosclerosis. While this is so, another important risk factor for CVD in the context of MetS is impaired cardiovascular autonomic function. The autonomic nervous system controls the body's internal organs, including the rhythm of the heart. With the MetS, the variability of the heart rate (heart rate variation [HRV]) is reduced. Diminished HRV is an independent marker of risk for cardiovascular morbidity and mortality [20]. Decreased HRV has an estimated prevalence of 25–50% [21] in adults who are ≥65 years of age, which is similar to the prevalence of MetS in this age group [22].

We examined cardiovascular autonomic dysfunction in a subset of CHS participants who underwent 18–24 h of ECG (Holter) monitoring from which were derived markers of autonomic control of heart rhythm [23]. In our first study, we found that there were noticeable decreases in HRV when fasting glucose level was above 110 mg/dl. This suggests that impairment of cardiac autonomic

function precedes the development of diabetic glucose levels. In a follow-up study, we reasoned that the majority of individuals who had fasting glucose levels of ≥110 mg/dl had insulin resistance. We found that an increasing number of components of the MetS (but glucose levels that were not in the diabetic range) were associated with diminished HRV. Further study showed strong independent associations of increased levels of the inflammatory factors IL-6, C-reactive protein (CRP) and fibrinogen with diminished HRV, as well as a strong negative association with insulin resistance. It was our conclusion that both insulin resistance and inflammation were associated with impaired autonomic cardiovascular function.

25.3.2 Non-Cardiovascular Outcomes

25.3.2.1 Renal Disease

The excretion of excess albumin (or protein) in the urine—termed albuminuria—is a common finding in the general population as it ages. Up to ~15–32% of adults >60 years of age have albuminuria [24]. In an analysis of NHANES III, participants who had MetS were almost twice as likely as participants without MetS to have albuminuria [25]. Participants with 4 or 5 components of the MetS were 2.5 and 3.2 times more likely, respectively, to have albuminuria compared to those with no or one component. Thus, a large percentage of older adults with MetS have albuminuria.

This issue is of importance to older adults for two reasons. First, albuminuria is an independent risk factor for CVD morbidity and mortality. In a cross-sectional analysis, we evaluated 3,312 CHS participants who were tested for albuminuria [26]. Participants were divided into three groups: those without diabetes or hypertension (33%), those with hypertension only (52%), and those with diabetes, with or without hypertension (15%). In each of the three groups, the adjusted odds of prevalent clinical CVD in the presence of albuminuria were increased 1.70–1.80-fold, independent of other CVD risk factors. The prevalence of elevated urine albumin excretion was 14.3% in those 68–74 years of age, 17.1% in those 75–84 years of age and 26.9% in those 85–102 years of age. Over 5.4 years of follow-up [27], CVD incidence and all-cause mortality were doubled in those who had low levels of albuminuria (microalbuminuria) (7.2 and 8.1% per year, respectively) and tripled in those who had had levels of albuminuria (macroalbuminuria) (11.1 and 12.3% per year, respectively) compared to those with normal urine albumin excretion (3.3 and 3.8% per year, respectively). The increased CVD mortality risks were observed in all age groups after adjustment for conventional risk factors. For those who had elevated urine albumin excretion, the adjusted population-attributable risk percentages of CVD and all-cause mortality were 11 and 12%, respectively.

The second reason that albuminuria is important to older adults is because it is a risk factor for cognitive decline. Kidneys that excrete excessive amounts of albumin have many of the same microvascular features that are found in the brains of people who have cognitive impairment, namely capillary basement membrane thickening, luminal narrowing and leakiness [28, 29]. These observations suggested to us that both conditions may share a common pathogenesis, and may share similar natural histories. In our first study, based on the CHS [30], we found that the odds of dementia (as measured by standardized tests of cognition) were 33% higher in the presence of albuminuria compared to its absence (19.3 vs. 10.5%; odds ratio [OR], 1.33; 95% CI, 1.22–1.45) Adjustment for cardiovascular risk factors, lipid levels, CRP and apolipoprotein E-4 genotype attenuated this association, but it remained statistically significant (OR, 1.16; 95% CI, 1.02–1.32). There were no differences between those with and without albuminuria regarding the distribution of prior stroke, ankle-arm index or internal carotid artery intima media wall thickness. In a more recent analysis [31] that was based on the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease (TRANSCEND) studies (in which almost all participants had hypertension), we

demonstrated a prospective association between the presence of albuminuria and the development of cognitive decline. Participants who developed new albuminuria during follow-up had an increased risk of cognitive decline compared to those who remained normoalbuminuric (new microalbuminuria: OR, 1.30; 95% CI, 1.12–1.52) (new macroalbuminuria: OR, 1.77; 95% CI, 1.24–2.54). It is important to note that these associations were independent of clinical cardiovascular and renal disease, and cardiovascular risk factors.

25.3.2.2 Cognitive Decline

Cognitive impairment due to vascular disease can be from overt and covert causes. Overt disease refers to cognitive impairment that is associated with a stroke event. This can occur in approximately 65% of stroke patients. In about 30%, the cognitive impairment is severe enough to meet the criteria for dementia (compared to 3% in age-matched controls) [32]. Covert vascular disease occurs with small vessel disease. In individuals >65 years of age, MRI frequently shows small infarcts, generally 3 mm or more in diameter. In the CHS, 28% of older adults (average age 75 years) showed silent infarcts [33]. In the Framingham study (mean age 62 years), 12% of participants had silent infarcts [34]. Moreover, in the CHS, 18% of participants who did not have baseline silent strokes had new infarcts at the 5-year follow-up [35]. These lesions are not benign. In the Rotterdam study—a longitudinal study of ~1,000 healthy older adults 60–90 years of age who were followed for 4 years—participants with baseline silent infarcts had more rapid cognitive decline than did those without infarcts, and they had twice the risk of incident dementia [36].

Studies have demonstrated that cognitive impairment predates the appearance of diabetes [37], which is consistent with the notion that factors that are present prior to the onset of elevated glucose levels lead to cognitive impairment in individuals with diabetes. Chief among these factors are those related to the insulin-resistant state: inflammation, hypertension and insulin resistance.

With regard to inflammation, a study of middle-aged and older adults who were community–dwelling found that participants with MetS did worse on tasks that assess memory and executive function than did those without MetS [38]. Stratification by sex demonstrated that metabolic syndrome was related to cognitive dysfunction in men but not in women. Only in men was an increasing number of metabolic syndrome components associated with worse cognitive performance. Inflammation appeared to mediate this relationship in men, since men who had MetS and high levels of CRP had more severe cognitive dysfunction than did those who had MetS and low CRP levels. The interaction between CRP and MetS was significant with regard to executive functions, and it showed a non-significant trend for memory. The Longitudinal Aging Study Amsterdam reported similar results [39]. MetS was negatively associated with cognition in participants who had high inflammation levels, whereas the association was absent in participants who had low levels of inflammation. The Italian Longitudinal Study on Aging [40] found that participants with MetS had an increased risk of dementia due to vascular disease (HR, 3.71; 95% CI, 1.40–9.83) compared to those without MetS. When results were categorized by inflammation factors, those with MetS and high levels of inflammation had an almost 10-fold higher risk of vascular dementia (HR, 9.55; 95% CI, 1.17–78.17), whereas those with low inflammation did not have a significant risk of dementia.

Insulin resistance is a risk factor for cognitive decline in the context of MetS. In a study of older adults (mean age 73 years), insulin resistance was significantly associated with poor visual scanning and poor cognitive flexibility [41]. In the Nurses' Health Study [42], during >10 years of follow up, elevated levels of insulin (the marker of insulin resistance used in that study) were associated with faster cognitive decline compared to lower levels of insulin. In a study of women 50–65 years of age who had intact cognitive function, there was a significant negative association between insulin resistance and right and total hippocampal brain volume, overall cognitive performance and selective tests of verbal and

non-verbal memory [43]. It should be noted that not all studies have found an association between insulin resistance and cognitive impairment. A European study of middle-aged and older men found no such association [44].

Hypertension is associated with cognitive decline. Much of the association is owing to hypertension's strong association with vascular disease events such as strokes and lacunar infarcts. Beyond these associations, the evidence is inconclusive. Longitudinal epidemiological studies show that elevated blood pressure and hypertension in middle age are associated with mild cognitive impairment and dementia later in life [45, 46]. The association is strongest for vascular dementia and less so for Alzheimer's disease. In the CHS, individuals with mild cognitive impairment had a higher prevalence of hypertension [47]. In a study from New York City [48], hypertension was associated with an increased risk for the development of mild cognitive impairment in general (HR, 1.40; 95% CI, 1.06–1.77). Hypertension was associated with the rate of change in executive ability but not in memory or language, which suggests that most of its impact was in the areas of the frontal lobes.

25.3.2.3 Impaired Mobility and Frailty

Mobility is defined as the ability to walk, climb stairs, transfer body weight and generate walking speed. Limitation of mobility is common in older adults. It is strongly related to health outcomes, including mortality [49].

Using data from the CHS [50], we studied the relationship between body composition (fat mass and fat-free mass) and self-reported, mobility-related disability (difficulty walking or stair climbing) in 2,714 women and 2,095 men 65–100 years of age. In a cross-sectional analysis, disability was reported by 26.5% of the women and 16.9% of the men. A positive association was observed between fat mass and disability. Compared to participants in the lowest quintile of fat mass, the odds ratio for disability in the highest quintile was 3.04 (95% CI: 2.18, 4.25) for women and 2.77 (95% CI: 1.82, 4.23) for men. Low fat-free mass (i.e., muscle) was not associated with a higher prevalence of disability. In a longitudinal analysis among individuals who did not report disability at baseline, 20.3% of the women and 14.8% of the men reported disability 3 years later. Fat mass at baseline was predictive of disability. For those in the highest quintile of fat, the risk ratios for diabetes were 2.83 (95% CI: 1.80, 4.46) for women and 1.72 (95% CI: 1.03, 2.85) for men. The increased risk was not explained by age, physical activity, chronic disease, lean mass or other potential confounders. Low fat-free mass was not predictive of disability. The results showed that high body fat mass is an independent predictor of mobility-related disability in older men and women.

Another study examined data from 2,984 women and men 70–79 years of age who participated in the Health, Aging, and Body Composition Study and had no mobility limitation at baseline [51]. Obesity was defined as a body mass index ≥30 kg/m^2. Mobility limitation was defined as having any difficulty walking one-quarter mile or climbing 10 steps during two consecutive semi-annual assessments, with assessments continuing for more than 6.5 years. The incidence of mobility limitation was 55% in women and 44% in men. In women, the adjusted risk of developing mobility limitation (relative to non-obese participants without the MetS) was progressively greater in non-obese participants with the MetS (HR, 1.49; 95% CI, 1.24–1.80), obese participants without the MetS (HR, 1.95, 95% CI, 1.51–2.53) and obese participants with the MetS (HR, 2.16, 95% CI, 1.78–2.63). In men, the corresponding adjusted HRs (95% CI) were 1.07 (0.87–1.32), 1.64 (1.19–2.25) and 1.41 (1.12–1.78), respectively. Elevated inflammatory markers partly explained the association between obesity, the MetS and mobility limitation, particularly in non-obese and obese participants with the MetS.

An extreme example of mobility impairment is the geriatric syndrome of frailty which is characterized by a decreased reserve in multiple physiological systems [52]. It predicts adverse health outcomes independent of advancing age, chronic disease and functional limitations, thereby suggesting that it is a distinct condition [53]. Based on data derived from the CHS, frailty is phenotypically characterized by involuntary

weight loss, exhaustion, low physical activity, slowness and muscular weakness. Older adults who have three or more of these criteria are considered to be frail, whereas those who have one or two of the criteria are considered to be "pre-frail", an intermediate syndrome with increased risk for the development of frailty. The most common factors of frailty are weakness (diminished grip strength), diminished walking speed (time to walk 15 ft), exhaustion ("everything is an effort") and low activity levels (<383 kcal/week for men; <272 kcal/week women); weight loss is less common.

We examined the association of MetS and its components of insulin resistance and inflammation with frailty. In our first paper [54], based on a cross-sectional evaluation of the CHS, we found a significant elevation in fasting insulin levels (our measure of insulin resistance) to be associated with a decline in physiological function. We also found that the inflammation proteins CRP, fibrinogen, and factors VII and VIII, were elevated among participants who had declines in physical function. In a subsequent study, we re-examined these findings prospectively [55] and found that insulin resistance and increased levels of the inflammation protein CRP were associated with an increased risk for the development of frailty. A one-standard-deviation increase in each factor independently and significantly increased the risk of incident frailty by 15 and 16%, respectively.

25.3.2.4 Circadian Rhythms and Sleep Apnea

Clinical studies of healthy individuals show that artificially interfering with circadian rhythms has adverse effects on metabolism. Individuals whose "day" is artificially extended to 28 h [56]—under controlled conditions with dim light—develop hyperinsulinemia, fasting hyperglycemia and elevated post-prandial glucose levels, and their blood pressure rises. It is hypothesized that an altered duration of sleep and activity disrupt the synchrony of feeding, energy storage and periods of energy utilization. Up to 20% of genes are entrained to a 24-h rhythm pattern [57]. Some of these genes are found in tissues that are important to metabolic processes, such as fat, liver and skeletal muscle tissues. Asynchrony of gene activity expression with the availability of energy leads to altered metabolism [58]. It follows that a disruption to the function of metabolic genes that are sensitive to circadian rhythms may set the stage for the MetS. Altered circadian rhythms are common with aging [59] and shift work.

Obstructive sleep apnea (OSA) is a case in point. OSA is characterized by the cessation of air flow during sleep for a minimum of 10 s despite continuous respiratory effort, which causes intermittent hypoxemia, recurrent arousals and sleep fragmentation. Chronic sleep insufficiency or deprivation not only leads to frequent mental and physical distress, but also contributes to the risk for diabetes and obesity. The intermittent hypoxemia that is associated with sleep disturbances increases sympathetic activity, provokes the release of inflammation and oxidative stress molecules from hypoxic tissue, impairs vascular endothelial function, raises blood pressure and leads to altered circadian glucose hemostasis.

Glycemic status was examined in an analysis of community-dwelling participants (n = 2,656) in the Sleep Heart Health Study (1994–1999) [60], in which CHS participated. Compared to participants who had less than 5.0 hypopnea/apnea events per hour (the reference category), those who had 5.0–14.9 events per hour and ≥15 events per hour had adjusted odds ratios of 1.27 (95% CI, 0.98–1.64) and 1.46 (95% CI, 1.09–1.97), respectively, for fasting glucose intolerance (p [trend] < 0.01). In another analysis of the Sleep Heart Health Study [61], similar metabolic findings were found for obese and non-obese individuals with OSA.

25.3.2.5 Bone Disease

Factors that are associated with the development of osteoporosis and osteoporotic fractures include increasing age; loss of estrogen in women and men; hypogonadism in men; chronic medical conditions such as liver, lung and kidney disease; increased levels of inflammation factors; and metabolic disorders of vitamin D, calcium and elevated glucose levels. Some of these factors are present in the MetS. In some—but not all—studies, diabetes itself has been linked to hip fracture and peripheral fracture.

It is not certain whether the MetS is associated with osteoporosis and osteoporotic fractures. Population studies have reported conflicting results, with some demonstrating a protective effect on bone health, while others show a detrimental effect. This conundrum is most likely due to the competing effects of concomitant obesity, which increases mechanical loading on bone; and the pro-inflammatory effect of visceral adiposity, which decreases bone health.

In an analysis of the NHANES III data set, participants with the MetS had higher bone density in the femoral neck than did those without the MetS [62]. This association was believed to be due to increased abdominal obesity and indices of insulin resistance. In that study, higher numbers of MetS components were associated with greater levels of bone density in the femoral neck. In contrast, the Rancho Bernardo Study [63] (a study of predominantly white, middle class older adults) found decreased bone density in participants who had MetS when adjustment was done for body mass index. There were also more incident fractures in the MetS group. Statistically significant negative associations were found between the number of MetS components and hip and spine density. A third study, from the US Veterans Administration [64] found that non-diabetic men with the MetS had lower bone density than did non-diabetic men without the MetS. Other conflicting results have also been reported [65–67]. Thus, at this point, no firm conclusions can be reached regarding the association of MetS and bone health.

25.3.2.6 Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the Western world. Pathologically, it is characterized by excess triglycerides in the liver. A more advanced form of the disorder, when inflammation and liver injury set in, is called non-alcoholic steato-hepatitis (NASH). NASH has a prevalence of 2–3% in lean individuals, but it may reach a prevalence of 20% in the obese and 50% in the morbidly obese [68]. It is estimated that up to 10% of individuals with NAFLD develop NASH. Whereas NAFLD rarely leads to advanced liver disease, 5–8% of individuals who have NASH can develop cirrhosis within 5 years [69].

The prevalence of NAFLD in the general population is not known with certainty. Unexplained increases in liver enzyme blood tests are detected in ~5% of the population, most of which are likely due to liver disease from excess fat [70]. Ultrasound studies of the liver show a prevalence of fatty liver in 20–30% of Western populations [71]. Using MRI, it has been determined that one third of individuals have excess liver fat [72].

The pathogenesis of NAFLD is not certain, but insulin resistance, obesity and cytokine production are its most common correlates [73]. Longitudinal studies have confirmed a temporal relationship between the progression of clinical MetS and the occurrence of NAFLD. It is hypothesized that fatty acids travel from the adipose tissue to the liver through the portal vein. The inflow of fatty acids into the liver stimulates hepatic gluconeogenesis and the synthesis of triglycerides, thereby impairing the ability of insulin to suppress hepatic glucose output. There is also inappropriate *de novo* lipo-genesis and a reduction in the hepatic export of lipoproteins. With further progression of disease and the induction of inflammation, fibrogenesis sets in and chronic liver disease ensues. This issue will be discussed in the next chapter.

25.4 Prevention of Glucose Elevation

The above review makes it clear that the pre-diabetic state of insulin resistance has pervasive effects on health and well-being. A cost analysis study from CHS estimated that over a 10-year period of time, the total costs to Medicare were 20% higher among participants with MetS compared to those without it [74]. Therefore, efforts at preventing insulin resistance or ameliorating its impact are of interest.

This section will discuss two methods for attenuating the rise in glucose levels in individuals who have insulin resistance. The first is through pharmacological methods and the second is through lifestyle change. Treatments of hypertension, lipids and obesity as means of attenuating the effects of insulin resistance will not be discussed.

25.4.1 Pharmacological Interventions

25.4.1.1 Diabetes Medications

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study [75], a cohort of adults who had impaired fasting glucose or impaired glucose tolerance and no previous CVD was randomly assigned to receive the thiazolidinedione rosiglitazone (n = 2,365) or a placebo (n = 2,634). Rosiglitazone reduces insulin resistance and may preserve insulin secretion. After 3 years of follow-up, 1,330 (50.5%) participants in the rosiglitazone group and 798 (30.3%) in the placebo group became normoglycemic (HR, 1.71; 95% CI, 1.57–1.87; p < 0.0001) [76], which demonstrates a protective effect of this class of medications for individuals who are at risk of diabetes (Fig. 25.4). In a follow-up study 1.6 years after the end of the trial and 4.3 years after randomisation [77], rosiglitazone participants had 17% more regression to normoglycaemia (95% CI, 1.01–1.34; p = 0.034) than did those on placebo. It was concluded that a time-limited exposure to rosiglitazone reduces the longer-term incidence of diabetes by delaying, but not reversing, the underlying disease process. These encouraging results are tempered by recent developments that have severely restricted the use of rosiglitazone. Several other studies, using metformin or acarbose [78], have also shown promise in delaying the onset of diabetes in individuals who have impaired glucose tolerance.

25.4.1.2 Non-Diabetes Medications

It would be of benefit if the treatment of diabetes-related comorbidities or of diabetes risk factors would prevent the elevation of glucose. In this regard, medications that block the renin

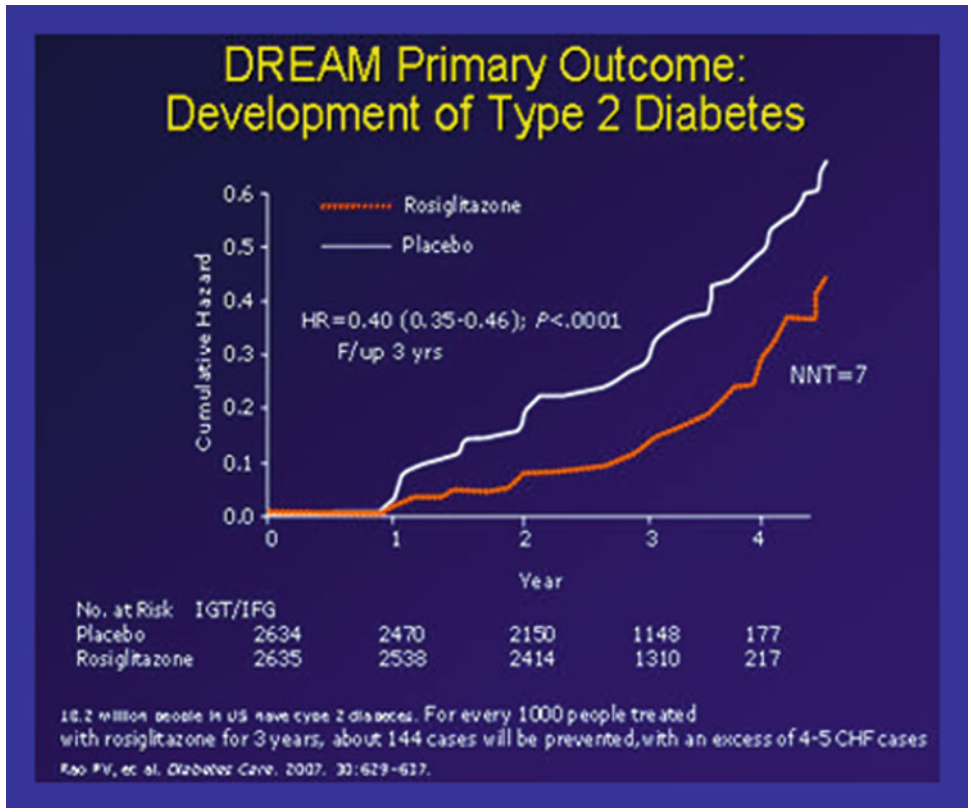

Fig. 25.4 DREAM primary outcome: development of type 2 diabetes [76]. *Abbreviations: HR* Hazard ratio, *IFG* Impaired fasting glucose, *IGT* Impaired glucose tolerance, *NNT* Number needed to treat

angiotensin system (RAS) have garnered attention. These medications include angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). Meta-analyses of hypertension studies show that RAS blockade by ACEi and ARB is more effective than other classes of blood-pressure-lowering medications for the prevention of incident diabetes mellitus [79]. It is less clear whether RAS blockade, as compared to placebo, reduces the risk of incident diabetes when added to usual care therapy in individuals at high risk for CVD. In the Heart Outcomes Prevention Evaluation (HOPE) trial [80], the ACEi ramipril decreased the risk of self-reported incident diabetes (3.6 vs. 5.4%; Relative Risk [RR], 0.66; 95% CI, 0.51–0.85; $p<0.001$). In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial [81], the ARB valsartan decreased the risk of new diabetes (33.1 vs. 36.8%; RR, 0.86; 95% CI, 0.80–0.92; $p<0.001$). In contrast, the DREAM study [75], which was designed to specifically study the effects of RAS blockade on diabetes prevention, found that RAS inhibition with ramipril did not reduce diabetes in participants who had impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (17.1 vs. 18.5%; RR, 0.91; 95% CI, 0.80–1.03; $p=0.15$). The TRANSCEND study [82] also found no effect of the ARB telmisartan on incident rates of diabetes compared to placebo. In summary, it is uncertain whether the use of RAS blocking agents is useful for the prevention of diabetes.

25.4.2 Lifestyle Modification

Skeletal muscle insulin resistance is the primary defect in the pathogenesis of diabetes. It precedes the onset of elevated glucose levels by several decades. In the Diabetes Prevention Program (DPP) [83], the study investigators reasoned that a program of physical activity that enhances muscle insulin sensitivity could prevent the progression to diabetes in individuals who are at high risk for diabetes. In the study, 3,234 non-diabetic participants who had elevated fasting and post-load plasma glucose levels were randomized to placebo, metformin, or a lifestyle-modification program that had the goals of at least a 7% weight loss and at least 150 min of physical activity per week. The mean age of the participants was 51 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 34.0. The average follow-up was 2.8 years. 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. Compared to placebo, the lifestyle intervention reduced the incidence of diabetes by 58% (95% CI, 48–66%) and metformin reduced it by 31% (95% CI, 17–43%). To prevent one case of diabetes during a period of 3 years, 6.9 individuals would have had to participate in the lifestyle-intervention program, and 13.9 would have had to receive metformin. The risk reduction that was associated with the lifestyle intervention was the same as that in studies conducted in Finland [84] (Fig. 25.5) and China [85].

In the DPP study, one finding of special interest was that lifestyle intervention was effective in overcoming genetic predisposition to diabetes [89]. Polymorphisms in the gene TCF7L2 are associated with an increased risk of diabetes. Participants in DPP who were randomized to placebo and had polymorphisms of this gene were more likely to develop incident diabetes than were participants on placebo who did not have these gene variants. On the other hand, among those randomized to lifestyle intervention, there was no difference in the risk of new diabetes between those with and without the gene variants (Fig. 25.6).

Further evaluation of the DPP [90] showed that diabetes incidence rates did not differ by age in the placebo group, but the intensive lifestyle intervention was more effective in preventing incident diabetes with increasing age (6.3, 4.9, and 3.3 cases per 100 person-years in the 25–44, 45–59 and 60–85 year age groups, respectively; p (trend) = .007). Participants 60–85 years of age had the most weight loss and physical activity. The metformin group showed a trend toward higher diabetes incidence among

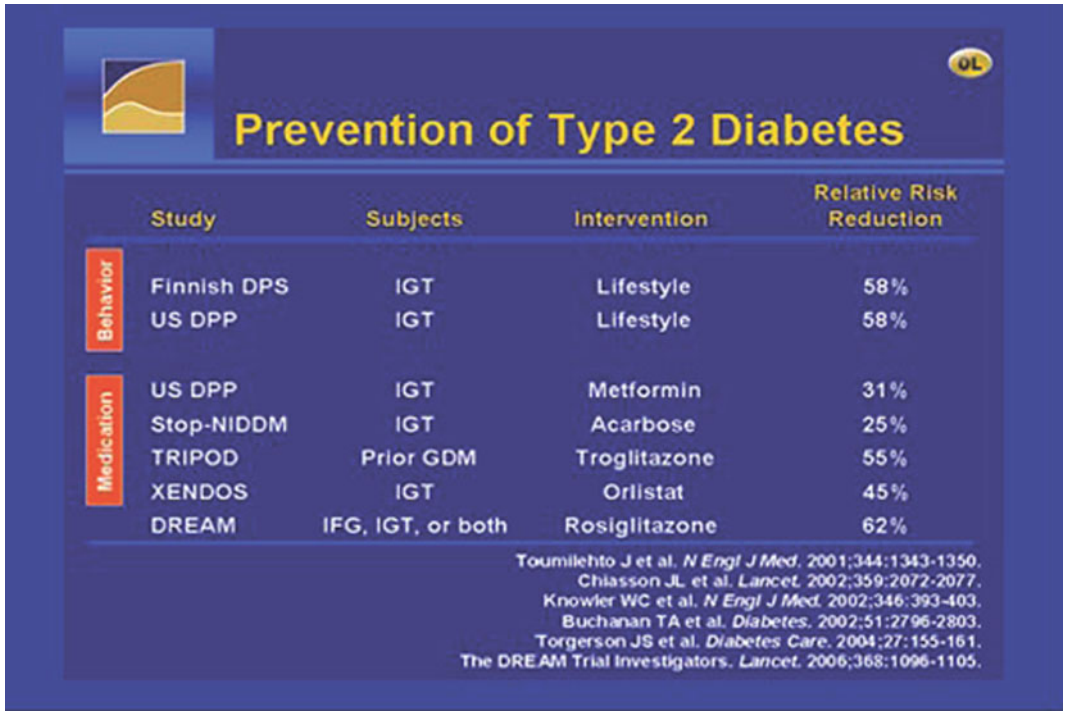

Fig. 25.5 Prevention of type 2 diabetes [76, 83, 84, 86–88]. *Abbreviations: GDM* Gestational diabetes mellitus, *IFG* Impaired fasting glucose, *IGT* Impaired glucose tolerance

older participants (6.7, 7.7 and 9.3 cases per 100 person-years in the 25–44, 45–59 and 60–85 year age groups, respectively; p (trend) = .07); and diabetes risk increased with age (HR [age 60–85 vs. 25–44] 1.63; p = .02) after adjusting for the greater weight loss in the 60–85 year age group. The authors of the study concluded that lifestyle modification was exceptionally effective in preventing diabetes in older adults. This was largely explained by greater weight loss and physical activity.

During follow-up of participants who completed the study (median: 5.7 years) [91], diabetes incidence rates were similar between treatment groups: 5.9 per 100 person-years (5.1–6.8) for lifestyle, 4.9 (4.2–5.7) for metformin and 5.6 (4.8–6.5) for placebo. Thus, from a cumulative point of view, diabetes incidence over a total follow-up of 10 years was reduced by 34% (24–42%) in the lifestyle group and 18% (7–28%) in the metformin group compared to placebo.

In another study of older adults, the question was asked whether decreased insulin sensitivity in older age was due to aging *per se* or whether it was a consequence of decreased activity and adiposity [92]. The authors found that age-related declines in oxidative capacity were largely ameliorated by regular endurance exercise, which highlights the fact that physical inactivity plays an important role in age-related oxidative dysfunction. However, certain mitochondrial markers—specifically mitochondrial DNA, transcription factors and mitochondrial-encoded proteins—remained depressed with increased age despite endurance exercise. Neither hepatic nor peripheral insulin sensitivity was impaired with age in healthy, relatively lean individuals who exercised, which was in keeping with the notion that adiposity is a primary determinant of age-related reductions in insulin sensitivity. In sum, endurance-trained older adults exhibited elevated insulin sensitivity in a manner independent of age.

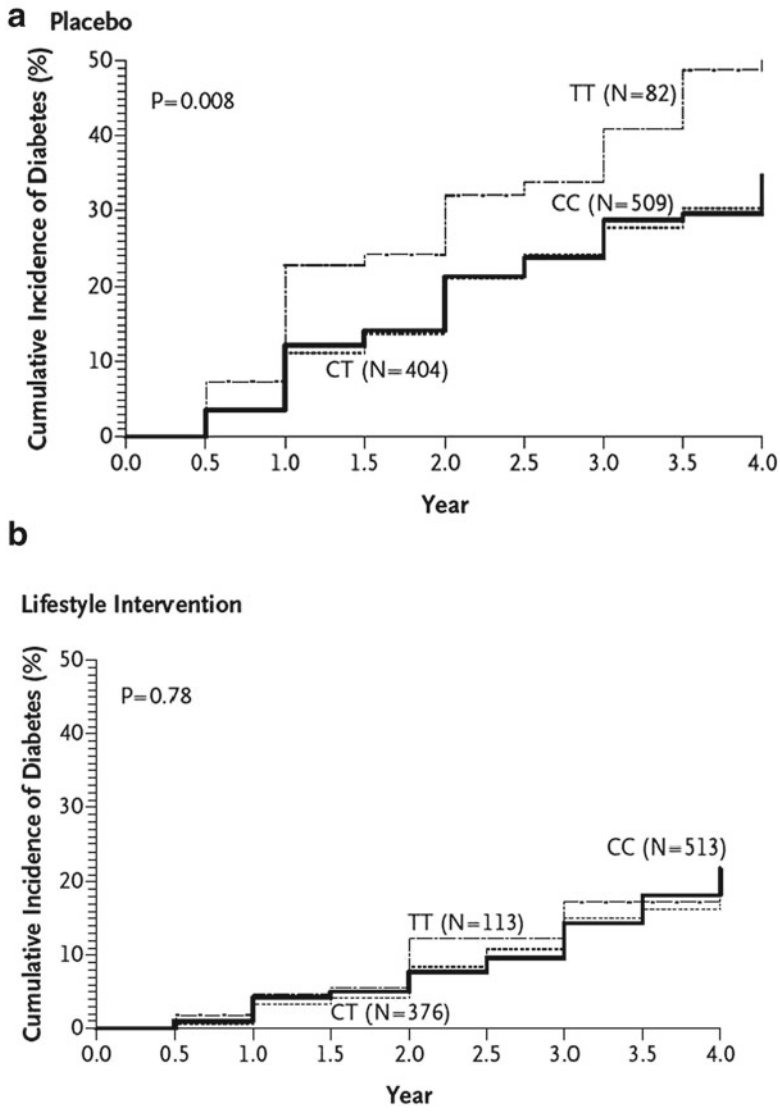

Fig. 25.6 Incidence of diabetes according to treatment group and genotype at variant rs7903146: (**a**) placebo, (**b**) lifestyle intervention [89]. *Note:* All *p*-values were determined using the log-rank text

25.5 Summary

Insulin resistance occurs years before the development of adult-onset type 2 diabetes and its negative effects on the health of older adults are enhanced by the processes associated with aging. The primary factor that leads to insulin resistance is obesity. Insulin resistance can have serious cardiovascular consequences, and can have serious non-cardiovascular consequences such as interference with circadian rhythms, sleep apnea, impaired mobility, frailty, cognitive decline and renal, bone or liver disease. In those who have insulin resistance, pharmacological interventions and lifestyle changes can be effective for controlling the rise of glucose. The lifestyle changes of weight reduction and increased physical activity can be effective even in those who are genetically predisposed to diabetes, and they appear to be especially effective in older adults.

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The Impact of Diabetes in Older Adults

26

Joshua Barzilay

Abstract

Nearly 8% of the United States population has diabetes mellitus, and nearly 25% of those who have diabetes are undiagnosed. Older adults have the highest prevalence and incidence of diabetes and diabetes among this group presents a large medical and economic challenge to society. Diabetes greatly impacts the health of older adults with regard to both cardiovascular and non-cardiovascular complications. Cardiovascular diseases impacted by diabetes include coronary artery disease, stroke, congestive heart failure, autonomic dysfunction, atrial fibrillation, peripheral artery disease and hypertension. Non-cardiovascular diseases include cognitive decline; liver, bone, kidney and eye disease; disability, mobility decline; and cancer. With the increasing incidence and prevalence of diabetes, the prevention of these conditions is becoming increasingly urgent.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Diabetes • Risk factors • Prevention • Fasting glucose • Post-prandial glucose • Criteria • Outcomes • Impaired fasting glucose • Obesity • Complications

Abbreviations

4S	Scandinavian Simvastatin Survival Study
ABI	Ankle-Brachial Index
ACE	Angiotensin-Converting Enzyme
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORD-MIND	Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes
ADA	American Diabetes Association
AGE	Advanced Glycation End product
ALLHAT	Antihypertensive Lipid Lowering Heart Attack Prevention Trial

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ATLAS	Assessment Trial of Lisinopril and Survival
Bpm	Beats Per Minute
CAN	Cardiovascular Autonomic Neuropathy
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CHS	Cardiovascular Health Study
CI	Confidence Interval
CVD	Cardiovascular Disease
eGFR	estimated Glomerular Filtration Rate
HbA1c	Hemoglobin A1c
HMO	Health Maintenance Organization
HR	Hazard Ratio
HRV	Heart Rate Variation
LEAD	Lower Extremity Arterial Disease
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutrition Examination Survey
NRMI2	National Registry of Myocardial Infarction 2
ONTARGET/ TRANSCEND	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial and Telmisartan Randomized Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease
OR	Odds Ratio
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
RR	Relative Risk
SMO	Standardized Mortality Ratio
SOLVD	Studies of Left Ventricular Dysfunction
TICS	Telephone Interview for Cognitive Status
US	United States
V-HeFT II	Vasodilator-Heart Failure Trial II

26.1 Introduction

Diabetes affects a significant and growing proportion of the United States (US) population. A significant percentage of those with diabetes have not been diagnosed. The highest prevalence and incidence are among older adults, and the largest increases in diabetes incidence have been among middle-aged and older adults. Diabetes can have a profound effect on the overall health of older adults, impacting cardiovascular disease; non-cardiovascular systems such as the liver, bones, kidneys and eyes; cognitive decline; functional and mobility disorders; and cancer. In this chapter, we will define diabetes and review diabetes prevalence and the impact it has on older adults. We will then review the impact that diabetes has on cardiovascular disease and non-cardiovascular outcomes.

26.2 Definition

The defining characteristic of diabetes mellitus is an elevated blood glucose level. Several criteria are used by the American Diabetes Association (ADA) [1] to diagnose diabetes:

1. A fasting glucose level ≥126 mg/dL (7.0 mmol/L) is diagnostic. Fasting is considered as no caloric intake for at least 8 h. This value should be repeated since fasting glucose levels can vary.
2. A glucose value ≥200 mg/dL (11.1 mmol/L) 2 h after a challenge with 75 g of anhydrous glucose dissolved in water.
3. A Hemoglobin A1c (HbA1c) test ≥6.5% done in a certified laboratory standardized to Diabetes Control and Complications trial assay.
4. An individual with classic symptoms of hyperglycemia (excess thirst and urination), a random glucose ≥200 mg/dL (11.1 mmol/L).

This gluco-centric definition of diabetes was chosen because diabetic retinal disease begins to appear at a fasting glucose level of ≥126 mg/dL [2]. Unlike atherosclerotic vascular disease or kidney disease (which can be present in the

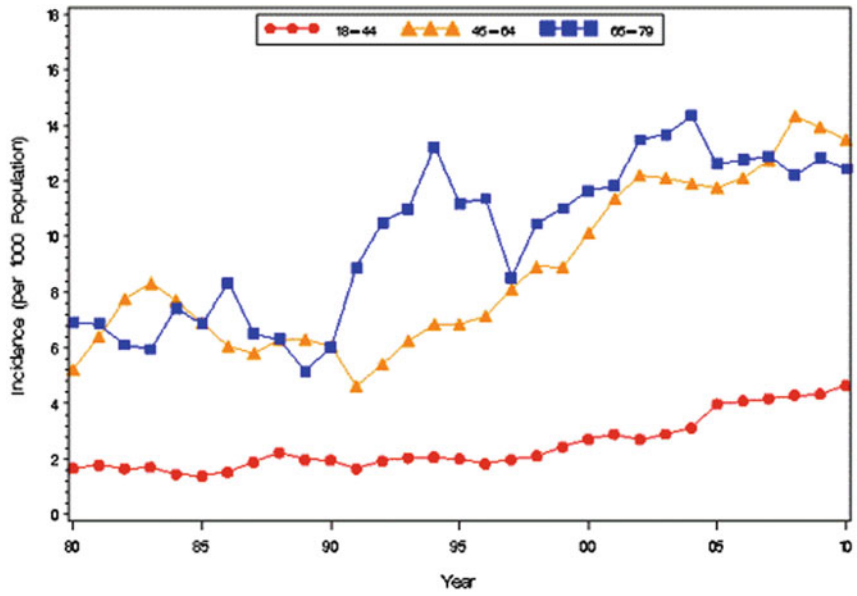

Fig. 26.1 Incidence of diagnosed diabetes per 1,000 individuals (18–79 years of age), by age, United States, 1980–2009 [4]

absence of diabetes), diabetic retinal disease is unique to the diabetic state.

26.3 Overview of the Incidence and Impact of Diabetes Among Older Adults

According to data collected in 2010 by the US Centers for Disease Control and Prevention (CDC) [3], 23.6 million individuals in the US (7.8% of the total population) have diabetes mellitus. Of these, 5.7 million (24.2%) have undiagnosed diabetes. The number of new cases of diabetes has more than tripled in the past 30 years (Fig. 26.1). Most of the increase has been in those 45–64 years of age and those ≥65 years of age [4]. In 2007, about 1.6 million new cases of diabetes were diagnosed in individuals who were ≥20 years of age. If current trends continue, one in three Americans will develop diabetes at some point in their lifetime, and those with diabetes will lose, on average, 10–15 years of life. Up to 95% of those with diabetes have the adult-onset form of the disease, called type 2 diabetes. Almost all older adults with diabetes have this form of the disease.

According to the most recent estimates from the CDC [5] in 2008, age-standardized incidence of medically-diagnosed diabetes was greater for nonwhite groups than for whites. These included older adults who were ≥65 years of age. Higher incidence was statistically significant ($p<0.05$) for blacks, both overall and for either sex. The age-standardized prevalence of diagnosed diabetes was greater for those of lower socioeconomic status. Statistically significant absolute differences of greater prevalence were found in those who had the lowest level of education, those living below the federal poverty level and those with disability. Black women tended to have the highest age-specific prevalence of diabetes.

With regard to overall impact on health, diabetes is the leading cause of new cases of blindness, kidney failure, and non-traumatic lower-extremity amputations in the US. The total cost of diabetes in the US (in 2007 US dollars) is $174 billion annually [4]. The direct costs are estimated at $116 billion and indirect costs related to disability, work loss and premature death are $58 billion. In a study from the Kaiser Permanente health maintenance organization (HMO) in Oakland, California [6], the 1-year overall costs of medical

care for individuals with diabetes were 2.4 times higher than for age- and sex-matched non-diabetic controls. For those with diabetes, costs were 2.5 times greater for inpatient care, 1.7 times greater for outpatient care and 3.0 times greater for outside services and pharmacy costs. The largest proportion of the total excess costs was for hospitalizations (38.5%). Nearly 38% of the total excess expenditure for diabetes was spent treating the long-term complications of illness, predominantly coronary heart disease (CHD). In each case, the bulk of expenditures occurred in individuals >45 years of age, especially in those >65 years of age.

The impact of diabetes in older US adults in particular has been recently estimated through a national longitudinal analysis of Medicare claims [7]. The study examined participants ≥65 years of age who were first diagnosed with diabetes during 1994 (n = 33,164), 1999 (n = 31,722) or 2003 (n = 40,058). The presumption of the study was that almost all of those analyzed had the adult-onset type 2 form of diabetes. The cohorts were compared with two control groups of older adults of similar age who were not diagnosed as having diabetes during 1994, 1999 or 2003, or for the entire period from 1994 to 1999 or from 1999 to 2004. The analysis found that the annual incidence of diabetes increased by 23% between 1994–1995 and 2003–2004, and that the prevalence increased by 62%. At the same time, the mortality rate after diagnosis in older adults with diabetes decreased by 8.3% compared to the mortality rate in the control groups. From 1994 to 2004, complication rates among older adults with new diabetes increased or stayed the same compared to those in the control groups. From these trends, it follows that the cost and burden of providing medical care for diabetic older adults ≥65 years of age has risen rapidly in the first decade of the 2000s. This study was careful to point out that its estimates were for those with diagnosed diabetes. Estimates would have been even higher had consideration been given for those with undiagnosed diabetes.

The *relative* impact of older age on diabetes outcomes can be gleaned from the Emerging Risk Factors Collaboration [8] This collaboration undertook a meta-analysis of individual records of diabetes, fasting blood glucose concentration and other risk factors in individuals without known vascular disease from 102 population-based studies. Analyses included data for 698,782 individuals (52,765 non-fatal or fatal vascular outcomes; 8.49 million person-years at risk). Hazards ratios for CHD in those with diabetes vs. those without diabetes were higher at 40–59 years of age (Hazard Ratio [HR], 2.51; 95% Confidence Interval [CI], 2.25–2.80) and 60–69 years of age (HR, 2.01; 95% CI, 1.80–2.26) than at ≥70 years of age (HR, 1.78; 95% CI, 1.54, 2.05). Similar trends were seen for ischemic stroke ([HR, 3.74; 95% CI, 3.06–4.58], [HR, 2.06; 95% CI, 1.64–2.58], and [HR, 1.80; 95% CI 1.42–2.27], respectively). In other words, similar to other cardiovascular disease (CVD) risk factors, the impact of diabetes is attenuated with increasing age. However, it is important to note that the absolute rate of CVD outcomes is much higher in older adults than in younger adults, so that even a modest increase in relative risk has a large impact on the absolute numbers of outcomes.

26.4 The Impact of Diabetes on Cardiovascular Disease

26.4.1 Cardiovascular Disease and Coronary Heart Disease

Over the past several decades, CVD mortality has decreased in the US [9] while the prevalence of diabetes and its burden of CVD, specifically CHD, have increased [10]. It is uncertain whether individuals with diabetes have had a similar reduction in CVD mortality compared to individuals without diabetes. A report from the Framingham Heart Study showed that compared to mortality in the 1950s, absolute CVD mortality has decreased in individuals with diabetes, but the mortality risk relative to individuals without diabetes remains unchanged (~2-fold) [11]. A report from New York City likewise showed that CHD mortality associated with diabetes had

decreased to a similar degree to that of CHD without diabetes [12]. On the other hand, data from two other population studies suggested that CVD and CHD mortality in individuals who have diabetes has actually increased, especially for women [13, 14]. These four studies were done in predominantly middle-aged populations. The situation in older adults, in whom the incidence and prevalence of diabetes and CVD are highest [15], has been studied less fully. It is possible that the impact of diabetes is attenuated owing to the ubiquity of CVD and CHD in older age.

To examine these issues, we performed an analysis of the Cardiovascular Health Study (CHS) data set [16] from the years 1989–2001. Similar to other population-based diabetes mortality studies, we adjusted total and CVD mortality risk using traditional risk factors such as hypertension, age, sex and smoking status. In addition, we included other factors associated with diabetes that have been recently described as confounders, including low levels of attained education; high rates of disability, depression, frailty and subclinical CVD; and elevated levels of inflammation factors.

For older adults with diabetes (mean age ~72 years; ~32% were >74 years of age), we found that the adjusted relative risk of total mortality for those treated with oral hypoglycemic agents or insulin, relative to those without diabetes, was 1.33 (95% CI, 1.10–1.62) and 2.04 (95% CI, 1.62–2.57), respectively. The total mortality risk estimate for oral hypoglycemic agent users was lower than that found in prior studies, while the estimate for insulin users was in line with prior studies. For combined CVD mortality, adjusted mortality risks for participants treated with oral hypoglycemic agents or insulin were 1.99 (95% CI, 1.54–2.57) and 2.16 (95% CI, 1.54–3.03) times higher, respectively, than in participants without diabetes (Fig. 26.2). These estimates were similar to those from studies of older adults with diabetes from prior decades, which adjusted only for traditional CVD risk factors. Given the decreasing rate of CVD and CHD mortality in the general population, but the unvarying relative risk of mortality associated with diabetes, it follows that older adults with diabetes were experiencing the same rate of decline in CVD and CHD mortality as did individuals without diabetes.

With further stratification by age, participants with diabetes who were >75 years of age had similar relative mortality rates as those who were <75 years of age. This finding was consistent with a study based on 1990s Medicare claims data that demonstrated excess mortality risk from diabetes in every age group [17]. This last point should be emphasized. Mortality rates are highest in older adults. A relative risk of ~2.0–2.5 in the older adult population is of greater absolute public health impact than is a higher relative risk in a middle-aged population in which mortality is lower.

In the above study, women had a greater relative total mortality risk (diabetes vs. no diabetes) than did men ([HR, 2.28; 95% CI, 1.90–2.72] vs. [HR, 1.80; 95% CI, 1.53–2.11], respectively). When this risk was categorized by treatment type, women who were treated with oral hypoglycemic agents had a mortality risk similar to that of men so treated, but women treated with insulin had a much higher relative mortality than did men so treated (Fig. 26.3). Thus, the overall increased relative mortality in women with diabetes compared to men with diabetes was accounted for by insulin therapy. This last point is noteworthy. The increased relative mortality with insulin therapy for women with diabetes was due mainly to the lower risk of death in women without diabetes, since women and men with diabetes who were treated with insulin both had similarly high cumulative mortality (>75% at 12 years).

26.4.2 New-Onset Diabetes and CVD

We further examined the impact of diabetes on CVD outcomes in older adults who were recently diagnosed with diabetes [18]. We reasoned that if long-term diabetes-related hyperglycemia is a major contributor to cardiovascular morbidity and mortality in older adults with diabetes, then

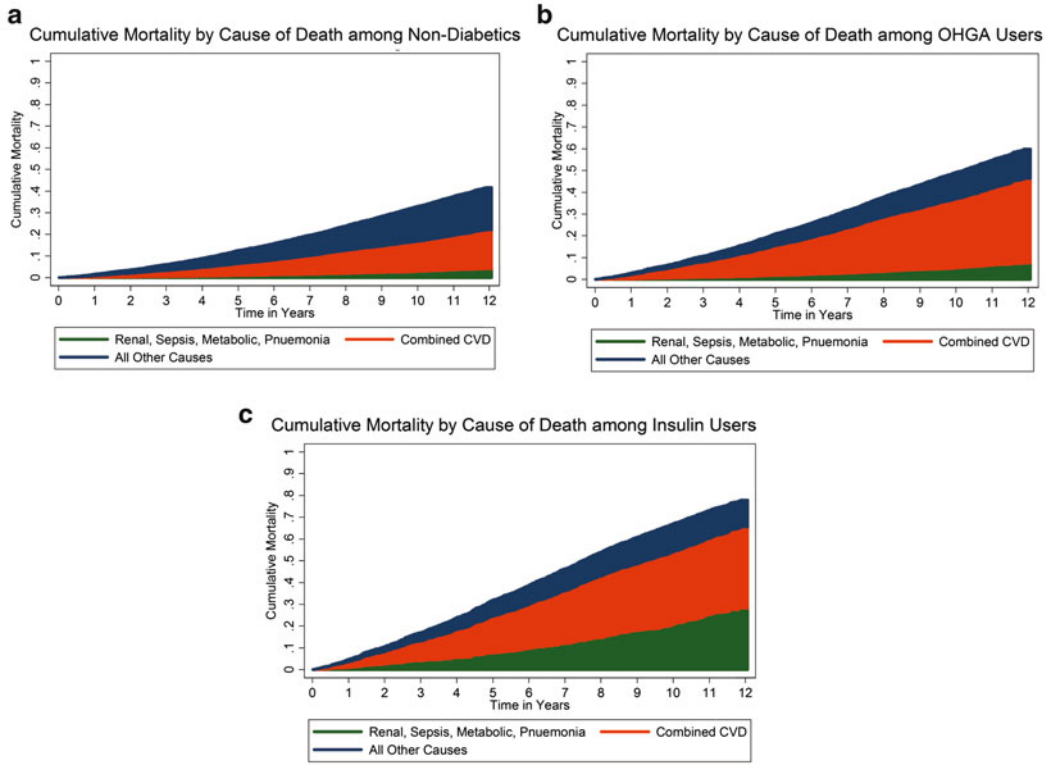

Fig. 26.2 Cumulative mortality by cause of death for non-diabetics, diabetics on oral hypoglycemic agents (OHGA) and diabetics on insulin [16]. A smooth estimate of the survival curve is computed for each of the three groups (non-diabetic, OHGA user, insulin user) and for each of the three causes of mortality shown in the figure (renal, sepsis, metabolic; cardiovascular; other). The *colored regions* shown in each graph were computed based on the estimated mortality for the three causes of death shown in the figure. For example, the curve that defines the *upper* boundary for the *red part* of the figure for the non-diabetic participants would be equal to the 1-the survival curve for the sepsis, renal, metabolic and pneumonia curve times the survival curve for the CVD endpoint. The *bottom* of the *red* section in the same figure is 1-survival curve for the sepsis, renal, metabolic and pneumonia. The *upper* boundary for the *blue* portion of the curve is 1-product for the three survival curves corresponding to the three causes of death for the non-diabetics. The figure for each of the other categories (OHGA and insulin users) is computed in the same fashion. These figures enable one to see at a glance the relative importance of each cause of death for the three groups. Abbreviation: *CVD* Cardiovascular disease

one would expect that the risk of all-cause and cardiovascular mortality would initially not differ greatly between individuals with a recent diagnosis of diabetes and those without diabetes. Over time, mortality risk associated with new-onset diabetes would be expected to increase, reflecting the detrimental vascular effects of prolonged exposure to hyperglycemia. Using data from the CHS, we found that new-onset diabetes (defined by the initiation of anti-diabetes medication or by a fasting plasma glucose >125 mg/dL) was associated with a 90% increase in the risk of all-cause mortality and a 120% increase in the risk of cardiovascular mortality compared to no diabetes. Contrary to our hypothesis, there was no increase in all-cause or cardiovascular morality risk over time. Instead, we found a significant, large increase in cardiovascular mortality in the first 2 years of follow-up which diminished over time, whereas all-cause mortality risk was similar and elevated throughout follow-up. The strong evidence of short-term mortality risk suggests two possible explanations: (1) that even limited exposure to a mildly

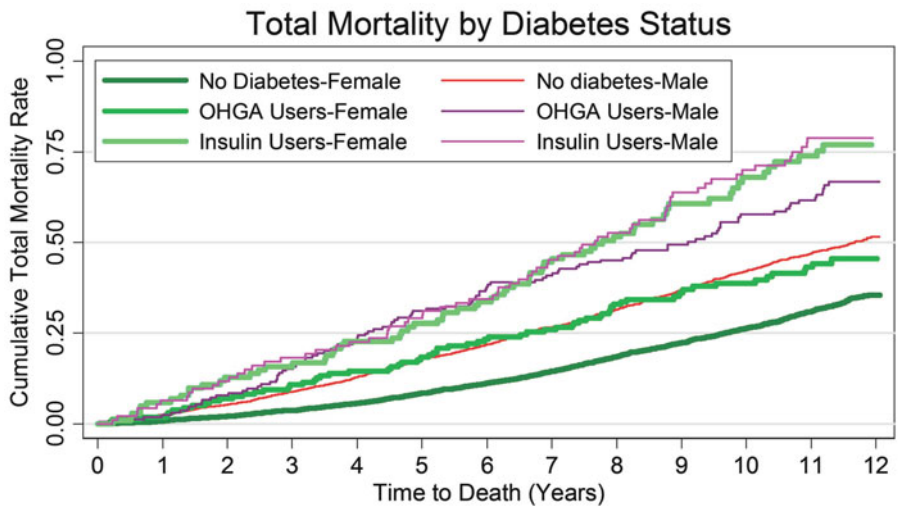

Fig. 26.3 Cumulative total mortality categorized by gender, diabetes status and type of antihyperglycemic treatment among 5,372 participants without diabetes, 322 with diabetes treated with oral hypoglycemic agents (OHGA) and 194 with diabetes treated with insulin with or without oral hypoglycemic agents, all followed 1989–2001 [16]

hyperglycemic environment—where fasting plasma glucose is elevated but <126 mg/dL—has detrimental effects, and (2) new-onset diabetes blood levels are associated with other unmeasured factors that are associated with CVD and non-CVD mortality.

26.4.3 Diabetes as a CHD Risk Equivalent

Type 2 diabetes has been described as a CHD "risk equivalent." In the CHS [19], we tested (over a mean of 12 years of follow-up) whether cardiovascular and all-cause mortality rates were similar between older adults with prevalent CHD (confirmed history of myocardial infarction, angina or coronary revascularization) and those with diabetes but no known clinical CHD (Fig. 26.4). The mean age was ~73 years. Following multivariable adjustment for other CVD risk factors and subclinical atherosclerosis, the risk of CHD mortality was similar between participants with CHD alone and those with diabetes alone (HR, 1.04; 95% CI, 0.83–1.30). In women, the proportion of mortality attributable to prevalent diabetes (population-attributable risk percent: 8.4%) and that attributable to prevalent CHD (6.7%) was similar. But in men, the proportion of mortality attributable to CHD (16.5%) was higher than that attributable to diabetes alone (6.4%). Patterns were similar for CVD mortality. In contrast, the adjusted relative hazard of total mortality was lower among participants with CHD alone (HR, 0.85; 95% CI, 0.75–0.96) compared to those with diabetes alone. We concluded that among older adults, diabetes by itself confers a risk for cardiovascular mortality similar to that of established clinical CHD.

26.4.4 Recurrent CVD

In a national study from Italy of diabetic patients who received usual care, 6.1% of the participants who had a prior CVD event developed a new major atherosclerotic complication [20]. This percentage is similar to that (5.9–6.0% per year) of other diabetic cohorts in secondary prevention studies such as the Prospective Pioglitazone Clinical Trial in Macrovascular Events

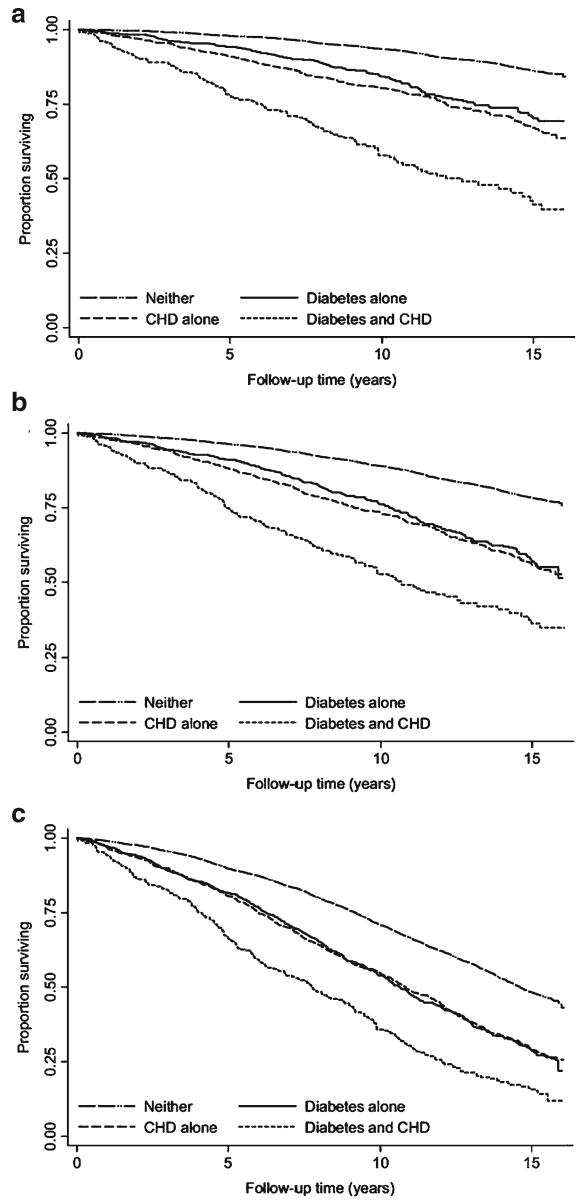

Fig. 26.4 Mortality risk with diabetes alone, coronary heart disease (CHD) alone or both, compared to neither condition in the Cardiovascular Health Study [19]

(PROactive) [21] study and the Scandinavian Simvastatin Survival Study (4S) [22]. In the Italian diabetic study, men had higher rates of recurrent CVD events than did women. Age played an important role as well, with a 10-year difference translating into a 26% risk increment. The use of insulin, alone or in combination with oral agents, was an independent risk factor for recurrence.

26.4.5 Heart Failure

Heart failure is a common disorder in older adults. This is especially so in older adults who have diabetes. It complicates acute myocardial infarction more often in individuals with diabetes than in those without diabetes. The increased percentage of participants with diabetes and heart failure in

clinical trials is in contrast to the total diabetic burden in the general population (6–8%). For example, in the Studies of Left Ventricular Dysfunction (SOLVD) [23], the Assessment Trial of Lisinopril and Survival (ATLAS) [24] study and the Vasodilator-Heart Failure Trial II (V-HeFT II) [25], the percentages of participants with diabetes and heart failure were 26, 19 and 20%, respectively.

In general, heart failure is due to CHD and/or hypertension, whether or not diabetes is present. CHD leads to impaired contractility whereas hypertension leads to left ventricular hypertrophy and poor ventricular distensibility. Among individuals with diabetes, there is a syndrome of heart failure that is independent of CHD, hypertension and other forms of atherosclerotic disease [26]. It is characterized by myocardial damage, hypertrophy, fibrosis, functional and structural changes in the small coronary blood vessels, autonomic impairment and altered metabolic substrate requirements. Perivascular fibrosis and capillary basement thickening are present. These impairments make the heart less able to withstand ischemic injuries. The thickened, stiff ventricle also makes the heart muscle less compliant. Less blood is able to enter the left ventricular chamber during diastole. Echocardiographic and angiographic assessments are required to distinguish this form of heart failure from the other types.

In the CHS, we examined the characteristics of individuals with heart failure and the relationship of heart failure to blood glucose levels [27]. Incident heart failure developed at a rate of 19.3/1,000 person-years, and diabetes was an independent risk factor for its development. We further examined a cohort of 829 diabetic participants ≥65 years of age who did not have prevalent heart failure, and followed the cohort for 5–8 years [28]. The Cox proportional hazards model was used to determine the risk of heart failure by fasting glucose levels. The cohort was further categorized by the presence or absence of prevalent CHD. For a 1-standard-deviation (60.6 mg/dL) increase in fasting glucose, the adjusted hazard ratios for incident heart failure among participants without CHD at baseline, with or without an incident myocardial infarction or CHD event on follow-up, was 1.41 (95% CI, 1.24–1.61; $p<0.0001$). Among those who had prevalent CHD at baseline, with or without another incident myocardial infarction or CHD event on follow-up, the corresponding adjusted hazard ratio was 1.27 (95% CI, 1.02–1.58; $p<0.05$). We concluded that among older adults with diabetes, elevated fasting glucose levels were a risk factor for incident heart failure. The risk was somewhat greater in the absence of prevalent CHD.

26.4.6 Cerebrovascular Disease

Diabetes is a risk factor for stroke as it contributes to the progression and destabilization of atherosclerostic vascular disease [7]. Population-based registries of stroke report a prevalence of diabetes ranging from 9.5 to 20% [29–31]. In addition, according to an oral glucose tolerance test performed 12 weeks after the stroke, 16 to 24% of patients who did not have a diagnosis of diabetes at the time of admission for acute stroke did in fact have diabetes [32]. In the Framingham Heart Study, the proportion of CVD—including stroke—attributable to diabetes increased from 5.4% in 1952 to 8.7% in 1998 [33].

The diagnosis of cerebrovascular disease by computerized tomography and magnetic resonance imaging (MRI) has led to an increased incidence of recognized stroke. This is especially so for older individuals who receive more frequent medical care. These technologies have made it apparent that there is a higher prevalence of "silent" cerebral infarction compared to clinical disease (i.e., stroke or transient ischemic attacks). Results conflict regarding whether diabetes is a risk factor for silent strokes. In the CHS [34], 3,660 participants ≥65 years of age, underwent cranial MRI. Of these, 2,529 (69%) were free of infarcts of any kind. Another 841 (23%) had one or more lacunar infarcts without other types present. Lacunes are defined as sub-cortical areas of infarction that measure 3–20 mm. For most of these 841, the lacunar infarcts were single (66%) and silent (89%) (i.e., without a history of transient ischemic attack or stroke). In

a multivariate analyses, participants with diabetes had an ~30% higher prevalence of lacunes than did those without diabetes (Odd Ratio [OR], 1.33; p < .05). In a follow-up study [35] of 1,433 CHS participants who underwent two MRI scans separated by 5 years and who had no infarcts on the initial MRI, 254 participants (17.7%) had one or more infarcts on the second MRI. Diabetes was not associated with these incident MRI-defined infarcts.

In the Rotterdam Scan Study, a population-based cohort study of 1,077 participants 60–90 years of age, participants underwent cerebral MRI. One or more infarcts on MRI were seen in 259 participants (24%); 217 had only silent and 42 had symptomatic infarcts [36]. The odds ratio of both silent and symptomatic infarcts increased with age by 8% per year (95% CI, 1.06–1.10 and 1.04–1.13, respectively). Silent infarcts were more frequent in women (age-adjusted OR, 1.4; 95% CI, 1.0–1.8) and were associated with hypertension (age- and sex-adjusted OR, 2.4; 95% CI, 1.7–3.3). Diabetes, however, was not associated with silent strokes (age and sex-adjusted OR, 1.0; 95% CI, 0.5–1.9). Thus, at present, there is no strong evidence regarding whether or not diabetes is a risk factor for silent lacunar infarcts.

26.4.7 Cardiovascular Autonomic Neuropathy (CAN)

Over time, the reduced heart rate variation (HRV) that is present in the pre-diabetic, insulin-resistant state (see the prior chapter) gives way to impaired parasympathetic control of the heart rate and vascular function. The prevalence of disorders related to impaired parasympathetic function increases with age, duration of diabetes, and poor glycemic control. The prevalence of CAN in population studies varies widely depending on the tests used to detect it [37].

CAN presents clinically in several different ways:

1. Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients who have parasympathetic (vagal) impairment [38, 39]. Resting heart rates of 90–100 beats per minute (bpm) occur and occasional heart rate increments up to 130 bpm occur. This autonomic dysfunction impairs exercise tolerance and blunts increases in cardiac output in response to exercise. http://circ.ahajournals.org/cgi/content/full/115/3/387—R12-180732#R12-180732
2. Reduced appreciation for ischemic pain can impair the recognition of myocardial ischemia or infarction. In a meta-analysis (n = 1,486 total participants) [40], estimates for the pooled prevalence rate risk for silent myocardial ischemia was 1.96 (95% CI, 1.53–2.51; p < 0.001). In a survey from the National Registry of Myocardial Infarction 2 (NRMI-2) [41], of 434,877 patients who presented with myocardial infarction, 33% did not have chest pain. Among those who presented without chest pain, 32% had diabetes, whereas 25.4% of those who presented with chest pain had diabetes.
3. Total mortality is increased. In a meta-analysis of 15 studies [24], based on follow-up of 1–15 years, the relative risk (with CAN vs. no CAN) was 2.14 (95% CI, 1.83–2.51; p < 0.0001) (Fig. 26.5). Death was especially increased in diabetic individuals with CAN. One potential cause may be severe but asymptomatic ischemia, which can induce lethal arrhythmias.
4. Echocardiographic studies have shown a significant correlation of the severity of CAN with reduced peak diastolic filling rate. This form of left ventricular diastolic dysfunction may progress to heart failure, mainly with preserved left ventricular systolic function (diastolic heart failure), which has a high morbidity and mortality rate [42].

26.4.8 Atrial Fibrillation

Atrial fibrillation http://www.springerlink.com.proxy.library.emory.edu/content/k79810012081241v/fulltext.html—CR9 is a common arrhythmia that confers significant risks for stroke and death in older adults. Many epidemiologic studies

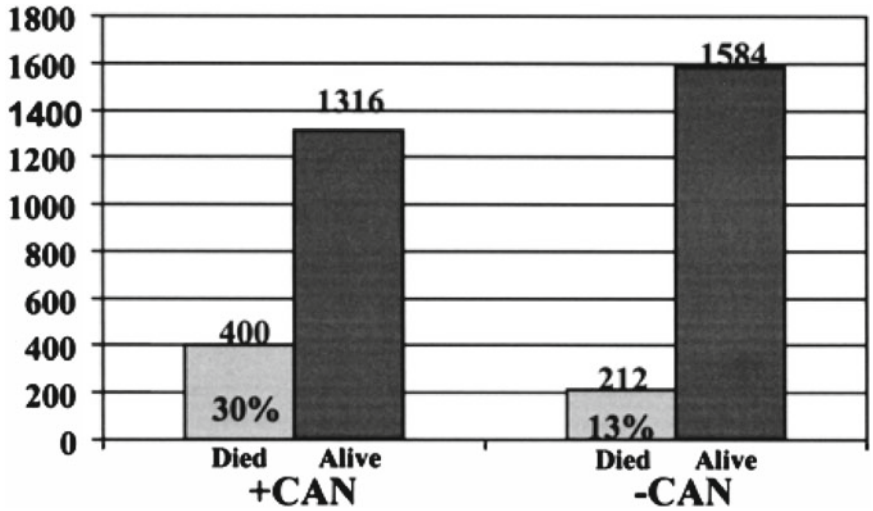

Fig. 26.5 Relative risks and 95% confidence intervals for the association between cardiovascular autonomic neuropathy and mortality in 15 studies [28]. Abbreviation: *CAN* Cardiovascular autonomic neuropathy

have examined atrial fibrillation risk in relation to diabetes or elevated blood glucose. In the CHS [43], 304 of 4,844 participants developed a first episode of atrial fibrillation during an average follow-up of 3.28 years, for an incidence of 19.2 per 1,000 person-years. For men, the incidences were 17.6 for ages 65–74 and 42.7 for ages 75–84. For women, incidences were 10.1 for ages 65–74 and 21.6 for ages 75–84. In a case–control study of newly-recognized atrial fibrillation [44], 17.9% (252/1,410) of cases had pharmacologically-treated diabetes compared to14.1% (311/2,203) of controls. The adjusted odds ratio for atrial fibrillation in those who had treated diabetes was 1.40 (95% CI, 1.15–1.71). Among those with treated diabetes, the risk of developing atrial fibrillation was 3% higher for each additional year of diabetes duration (95% CI, 1–6%). Compared to those without diabetes, the adjusted odds ratio for those with treated diabetes with an average HbA1c ≤7 was 1.06 (95% CI, 0.74–1.51); for those with HbA1c >7 but ≤8 it was 1.48 (95% CI, 1.09–2.01); for those with HbA1c >8 but ≤9 it was 1.46 (95% CI, 1.02–2.08); and for those with HbA1c >9 it was 1.96 (95% CI, 1.22–3.14).

The effect of diabetes on the risk of atrial fibrillation may differ by sex. A study from the Kaiser Permanente HMO [45] found that the prevalence of atrial fibrillation was significantly greater among patients who had diabetes (3.6 vs. 2.5%, $p<0.0001$). After full adjustment for other risk factors, diabetes was associated with a 26% increased risk of atrial fibrillation among women (HR, 1.26; 95% CI, 1.08–1.46), but diabetes was not a statistically significant factor among men (HR, 1.09; 95% CI, 0.96–1.24). Therefore, while diabetes appears to be associated with increased odds of atrial fibrillation, it is a stronger risk factor in women and in those with more poorly-controlled diabetes.

26.4.9 Peripheral Arterial Disease

The ankle-brachial index (ABI) reflects the ratio of the systolic arterial pressure in the posterior tibial or the dorsalis pedis arteries in the legs to that in the brachial artery. A low ABI is a valid, noninvasive indicator of lower extremity arterial disease (LEAD) [46]. In studies that use the ABI, the prevalence of LEAD in diabetic individuals ranges from 20 to 30% [47, 48]. The duration and severity of diabetes correlates with the incidence and extent of LEAD [49]. In addition, the risk for LEAD is higher in those of African-American or Hispanic descent compared to non-Hispanic white individuals [50], even after adjustment

for other known risk factors and the increased prevalence of diabetes in these populations.

Epidemiological studies report that a low ABI is associated with coexistent coronary artery disease and CVD, and it predicts future CVD and death [51]. In the CHS, over a 6-year follow up period, the percentage of participants who had a significant decline in ABI was 9.5% [35]. Independent predictors of ABI decline included diabetes, odds ratio 1.77 (95% CI, 1.14–2.76) [52].

Individuals who have diabetes are more likely than non-diabetic individuals to have symptomatic LEAD. In the Framingham study [53], the presence of abnormal glucose levels increased the risk of intermittent claudication (painful walking due to ischemia) by 3.5-fold in men and 8.6-fold in women. Furthermore, patients who have diabetes and LEAD are more likely to present with an ischemic ulcer than are patients without diabetes, a factor that increases the risk of lower-extremity amputation [54].

26.4.10 Advanced Glycation End Products (AGEs) and Hypertension

Up to 70–80% of individuals with diabetes have hypertension [55]. This is due in large part to the obesity that is present in most individuals who have diabetes in the US and to the insulin-resistant state that precedes diabetes. Hypertension underlies much of the CVD that is associated with diabetes [56]. Beyond this, increased glucose levels play a role in exacerbating hypertension by making the arterial wall stiff and less elastic.

The increased glucose levels of diabetes lead to the formation of chemical products called advanced glycation end products (AGEs). AGEs form at a constant but slow rate in the normal body and accumulate with time. However, their formation is markedly accelerated in diabetes due to the increased availability of glucose. AGEs are a heterogeneous group of molecules that are formed from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. The initial product of this reaction is called a Schiff base, which spontaneously rearranges itself into an Amadori product, as is the case of the well-known HbA1c. These initial reactions are reversible depending on the concentration of the reactants. A lowered glucose concentration will unhook the sugars from the amino groups to which they are attached; conversely, high glucose concentrations will have the opposite effect. A series of subsequent reactions, including successions of dehydrations, oxidation-reduction reactions and other arrangements lead to the irreversible formation of AGEs.

AGEs have two negative effects on the artery wall. First, the endothelial cells that line the inside of the artery have cell-surface receptors for AGEs. Endocytosis and degradation of AGEs by endothelial cells leads to pro-oxidant, pro-inflammatory events. These, in turn, lead to the formation and progression of atherosclerotic lesions. Increased AGE accumulation in the diabetic vascular tissues can modify LDL cholesterol in such a way that it tends to become easily oxidized and deposited within vessel walls, causing streak formation and atheroma. Second, AGEs have the ability for crosslink formation between proteins, which alters their structure and function, as in cellular matrix, basement membranes and vessel-wall components. This makes for stiff blood vessel walls. Stiffening of large arteries results in adverse hemodynamic consequences, such as a rise in pulse pressure and isolated systolic hypertension [57]. In addition, low diastolic pressure reduces coronary blood flow predisposing the individual to ischemia.

26.5 The Impact of Diabetes on Non-cardiovascular Outcomes

26.5.1 Cognitive Decline

Compared to non-diabetic individuals, those with diabetes have a greater rate of decline in cognitive function and a greater risk of cognitive decline. In a meta-analysis of 25 studies that assessed participants with diabetes at

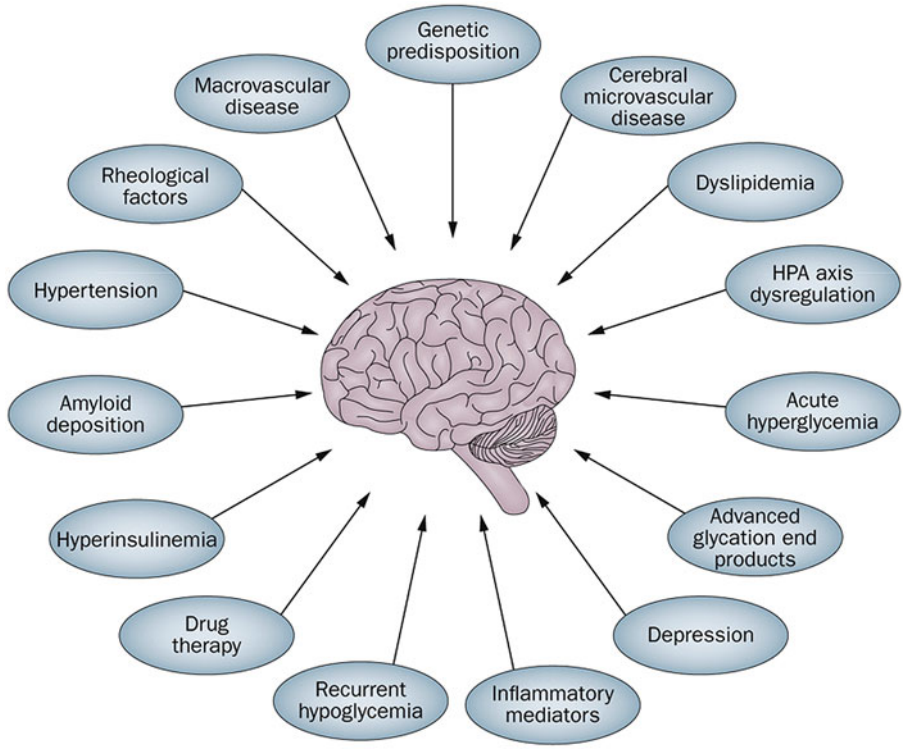

Fig. 26.6 Potential mechanisms for cognitive decline in diabetes [60]

baseline and at follow-up [58], participants with diabetes had a 1.2- to 1.5-fold greater change over time regarding measures of cognitive function than those without diabetes. When assessed by the Mini-Mental State Exam and the Digit Symbol Span tests, diabetes increased the odds of cognitive decline 1.2-fold (95% CI, 1.1–1.4) and 1.7-fold (95% CI, 1.3–2.3), respectively. The odds of future dementia increased 1.6-fold (95% CI, 1.4–1.8).

The mechanisms that underlie the association between diabetes and cognitive decline are multifactorial (Fig. 26.6). The related chapter on insulin resistance discussed oxidative stress and inflammatory proteins. Other considerations are micro- and macro-vascular cerebral disease. For example, in an MRI study of individuals with vascular disease [59], those with diabetes had more global and subcortical brain atrophy, larger white matter hyperintensities and more lacunar infarcts than did individuals without diabetes[60]. If vascular disease was the primary factor underlying cognitive decline in the context of diabetes, it is logical to assume that treating risk factors for vascular disease should reduce the incidence and progression of cognitive decline. The results of therapeutic trials have not confirmed this supposition. A Cochrane review [61] concluded that statin therapy given late in life to individuals at risk of vascular disease had no effect on preventing dementia. A review of observational studies and randomized trials found that angiotensin-converting-enzyme inhibitors or diuretics may reduce dementia risk [62], and two *post hoc* analyses confirmed this hypothesis [63, 64]. On the other hand, a Cochrane review found no strong evidence that antihypertensive agents prevent the development of dementia in hypertensive individuals who had no prior CVD [65]. Likewise, there is no evidence

that aspirin therapy reduces cognitive decline in healthy women >65 years of age who have asymptomatic atherosclerosis [66].

A prospective analysis [67] of 5,907 men in the Physicians' Health Study II and 6,326 women in the Women's Health Study (mean age 74.1 and 71.9 years, respectively, at baseline cognitive assessment) analyzed for cognitive change in relation to diabetes. Of those in the sample, 553 men and 405 women had diabetes. The primary outcomes were general cognition (the Telephone Interview for Cognitive Status [TICS] and a global score that averaged five tests) and verbal memory. All participants had second assessments approximately 2 years later; women had a third assessment an average of 4 years later. In adjusted linear regression models, participants with diabetes had significantly lower baseline scores for all outcomes. A longer duration of diabetes was associated with lower scores (p-trends < .001). Men with diabetes had significantly greater 2-year cognitive decline than men without diabetes, and a longer duration of diabetes was associated with greater decline (p-trends ≤ .01). In repeated-measures analyses of response profiles, women with diabetes had significantly greater 4-year cognitive decline in all outcomes than did women without diabetes. In women, as in men, there was a generally greater cognitive decline with a longer duration of diabetes (e.g., the adjusted mean difference in decline on the TICS associated with diabetes duration of ≥5 years was −0.74 (95% CI, −1.05 to 0.43) points (p-trend < .001)). There were no significant sex-diabetes interactions.

The baseline data from the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD–MIND) study (mean age 62.5 years) demonstrated a cross-sectional association between elevated levels of HbA1c and decreased measures of cognitive function in individuals with type 2 diabetes mellitus and at high risk for vascular disease [68]. Chronic hyperglycemia is associated with microvascular changes of the retinae and kidneys. Retinal and renal microvascular abnormalities are associated with cognitive impairment and dementia, possibly mirroring cerebral microvascular disease [53, 69]. On the other hand, the longitudinal analysis of the ACCORD-MIND study found no significant differences in cognitive scores between those whose glucose levels were treated intensively versus those not so treated (A1c 6.4 vs. 7.5%, respectively). There was no significant treatment difference in the mean 40-month Digit Symbol Substitution Test score (difference in mean 0.32, 95% CI −0.28 to 0.91; p = 0.29), the primary outcome of the study. The intensive-treatment group had, however, a greater mean total brain volume than the standard-treatment group (4·62, 2·0 to 7·3; p = 0·0007), the meaning of which is unclear [70].

Hypoglycemia resulting from diabetic treatment can also lead to decreased cognition. In a study from the Kaiser Permanente [71] HMO, a cohort of 16,667 diabetic patients with a mean age of 65 years was followed longitudinally from 1980 to 2007. Hypoglycemic events from 1980 to 2002 were collected and reviewed using hospital discharge and emergency department diagnoses. Cohort members who had no prior diagnoses of dementia, mild cognitive impairment or general memory complaints as of January 1, 2003 were followed up for a dementia diagnosis through January 15, 2007. During follow-up, at least one episode of hypoglycemia was diagnosed in 1,465 patients (8.8%) and dementia was diagnosed in 1,822 patients (11%); 250 patients had both dementia and at least one episode of hypoglycemia (16.95%). Compared to diabetic patients who had no hypoglycemia, those with single or multiple episodes had a graded increase in risk of cognitive impairment with fully adjusted hazard ratios: for one episode (HR, 1.26; 95% CI, 1.10–1.49); for two episodes (HR, 1.80; 95% CI, 1.37–2.36); and for three or more episodes (HR, 1.94; 95% CI, 1.42–2.64). Results were not attenuated when medical utilization rates, length of health plan membership, or time since initial diabetes diagnosis were added to the model. When examining hypoglycemia emergency department admissions for association with risk of dementia (535 episodes), results were similar (compared to patients who had no episodes) with fully adjusted hazard ratios: for one episode (HR, 1.42; 95%

CI, 1.12–1.78) and for two or more episodes (HR, 2.36; 95% CI, 1.57–3.55).

26.5.2 Liver

A 10-year study from the US Veterans Administration health system [72] of 173,643 men with diabetes and 650,620 men without diabetes found the incidence of chronic nonalcoholic liver disease to be significantly higher among patients with diabetes than among those without diabetes (incidence rate: 18.13 vs. 9.55 per 10,000 person-years, respectively; $p<0.001$). Similar results were obtained for hepato-cellular carcinoma (incidence rate: 2.39 vs. 0.87 per 10,000 person-years, respectively; $p<0.001$). Diabetes carried the highest risk among patients who had >10 years of follow-up. In a study from Denmark [73, 74], the standardized incidence ratio of hepato-cellular carcinoma was 4.0 (95% CI, 3.5–4.6) in men with diabetes and 2.1 (95% CI, 1.6–2.7) in women with diabetes. These ratios remained elevated with increasing years of follow-up and after the exclusion of patients who had reported risk factors (e.g., viral hepatitis) or patients whose cancers were diagnosed at autopsy. A study from Holland found that among patients with chronic hepatitis C, those with diabetes had a 3.28-fold increased risk (95% CI, 1.35–7.97; $p=0.009$) of developing hepato-cellular carcinoma compared to those without diabetes [75].

Liver disease is an important cause of death in diabetes [73]. In the population-based Verona Diabetes Study [76], cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes-related deaths. The standardized mortality ratio (SMR) (i.e., the relative rate of an event compared with the background rate) for cirrhosis was 2.52 compared with 1.34 for CVD. Diabetes is now assumed to be the most common cause of liver disease in the US. Cryptogenic cirrhosis, of which diabetes is the most common cause, has become the third leading indication for liver transplantation in the US [77].

It should be noted that chronic liver disease can itself give rise to insulin resistance and diabetes [78]. Up to 96% of patients who have cirrhosis may be glucose-intolerant and 30% may have diabetes.

26.5.3 Bone

Muscular stress stimulates bone growth. Given that most adults who have diabetes are overweight or obese—which puts stress on the bones—it is not surprising that individuals with diabetes have average-or-higher bone density compared to age-matched controls [79]. It is therefore paradoxical that individuals with diabetes have a higher risk of fractures. In the Study of Osteoporotic Fractures (of 9,654 women age ≥65 years of age), compared to women without diabetes, women with diabetes who were not using insulin had an increased risk of hip fracture (relative risk [RR], 1.82; 95% CI, 1.24–2.69) and proximal humerus fracture (RR, 1.94; 95% CI, 1.24–3.02) in multivariate models that controlled for age, body mass index, bone density and other factors associated with fractures and diabetes. Insulin-treated individuals with diabetes had more than twice the risk of foot fractures (multivariate adjusted RR, 2.66; 95% CI, 1.18–6.02) than did non-diabetic individuals. Data from the Women's Health Initiative Observational Study indicate that post-menopausal women who have diabetes are at an increased risk of hip, foot and spine fractures, as well as fractures overall [80].

The reasons for this paradox are unclear, though several explanations are possible. First, several diabetic complications predispose to falls, a necessary component of osteoporotic fractures. These include poor vision from diabetic eye disease and cataracts, poor coordination and strength in the leg muscles and peripheral neuropathy, making for gait unsteadiness [81]. Low blood glucose (hypoglycemia) as a result of treatment also predisposes to falls. The second reason may be due to poor collagen quality. Collagen serves as the scaffold on which bone mineralization takes place. The accumulation of AGEs in bone collagen is thought to contribute to the reduction in collagen strength for a given bone mineral density [82]. The prime targets of AGE accumulation are the structural components

of the connective tissue matrix. This accumulation can alter collagen function and thereby alter the strength and resilience of bone. Third, high glucose levels impair the ability of bone-building cells to synthesize osteocalcin, which is integral to bone formation [83]. Fourth, it should not be forgotten that renal disease, which is associated with diabetes, may also lead to bone disease.

26.5.4 Renal Disease

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure study recently reported the prevalence and impact of diabetes on renal disease in older adults (median age: 62 years) [84]. At baseline, approximately 68, 26 and 6% of participants had normo-, micro- and macro-albuminuria, respectively. Most participants retained their baseline albuminuria status on follow-up (83, 52, and 57%, respectively). During a mean follow-up of 4.7 years, 34 and 9% of those with micro- and macro- albuminuria, respectively, regressed to normo-albuminuria. Only 2.7 and 3.0% of these groups, respectively, developed end-stage renal disease requiring dialysis, transplantation or a creatinine level >3.3 mg/dL, of whom half had some degree of albuminuria at baseline and the other half had no albuminuria at baseline. Similar results were obtained when participants were categorized by randomization to intensive (systolic BP <120 mmHg) vs. standard (systolic BP <140 mmHg) blood pressure control. Likewise, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial and Telmisartan Randomized Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) studies of ~30,000 individuals at high risk for CVD (mean follow-up: ~4.6 years; mean age: 66 years), most participants maintained their albuminuria status on follow-up despite the use of medications that blocked the renin angiotensin system [63]. Dialysis or doubling of serum creatinine occurred in only 2.2% of those randomized to the angiotensin-converting enzyme (ACE) blocker ramipril, 2.0% of those on the ACE inhibitor telmisartan and 2.5% of those on combination therapy. There were no differences between those with or without diabetes (37% of the cohort had diabetes). It should be noted that it takes many years to develop end-stage renal disease. Thus, the relatively low rates of advanced renal disease in these studies are not surprising.

In the Antihypertensive Lipid Lowering Heart Attack Prevention Trial (ALLHAT) [85], more than 31,897 individuals 63–70 years of age who had hypertension and at least one other risk factor for coronary heart disease were stratified into three baseline-estimated glomerular filtration rate (eGFR) groups at baseline: normal (>90 mL/min/m^2), mildly reduced (60–89 mL/min/m^2) and moderately-to-markedly reduced (<60 mL/min/m^2). Of these participants, 11,498 (36%) had diabetes. While the relative risk for developing end-stage renal disease was higher than the risk of CHD or of CVD in the moderate-to-markedly decreased eGFR group, the absolute rates of CHD and CVD complications were many orders of magnitude greater than the rates of advanced renal disease (Table 26.1). These findings emphasize that advanced renal dysfunction in older adults who have diabetes is more strongly related to CVD than to renal disease.

26.5.5 Eye

In a community-based case control study [86], diabetes was found to increase the risk of poor eyesight or loss of vision by 50% among older adults (odds ratio, 1.50; 95% CI, 1.09–2.05; $p=0.013$). In participants with diabetes, duration of diabetes ($p=0.018$) and treatment with insulin ($p<0.001$) were significantly associated with visual impairment.

In westernized countries, diabetic retinopathy is the leading cause of visual impairment among individuals <60–65 years of age. On the other hand, among the older adults, diabetic retinopathy is a less common cause of visual impairment compared to age-related macular degeneration, cataracts and glaucoma. For example, in a

Table 26.1 Six-year event rates and hazard ratios compared across baseline glomerular filtration rate subgroupsa [85]

	End-stage renal disease				Coronary heart disease				Combined cardiovascular disease			
Variable	6-year rates per 100 ± SE	Events *n*	HR (95% CI)[b]	p-value	6-year rates per 100 ± SE	Events *n*	HR (95% CI)[b]	p-value	6-year rates per 100 ± SE	Events *n*	HR (95% CI)[b]	p-value
All participants												
GFR ≥90 mL/min per 1.73 m^2 (n = 8,126)	0.4 ± 0.1	27	–	–	8.5 ± 0.4	550	–	–	26.5 ± 0.6	1,816	–	–
GFR 60–89 mL/min per 1.73 m^2 (n = 18,109)	1.0 ± 0.1	125	2.90 (1.80–4.67)	<0.001	10.8 ± 0.3	1,588	1.09 (0.97–1.23)	0.136	30.5 ± 0.4	4,767	1.08 (1.01–1.15)	0.027
GFR <60 mL/min per 1.73 m^2 (n = 5,662)	6.0 ± 0.4	259	20.33 (12.74–32.42)	<0.001	15.4 ± 0.6	696	1.38 (1.20–1.59)	<0.001	40.0 ± 0.8	1,954	1.35 (1.24–1.46)	<0.001
Participants with diabetes at baseline												
GFR ≥90 mL/min per 1.73 m^2 (n = 3,674)	0.5 ± 0.2	15	–	–	9.7 ± 0.6	284	–	–	29.6 ± 0.9	915	–	–
GFR 60–89 mL/min per 1.73 m^2 (n = 5,944)	2.0 ± 0.2	78	4.18 (2.24–7.83)	<0.001	13.9 ± 0.6	655	1.15 (0.97–1.37)	0.105	34.8 ± 0.7	1,795	1.13 (1.02–1.24)	0.017
GFR <60 mL/min per 1.73 m^2 (n = 1,888)	10.8 ± 0.9	153	25.90 (14.01–47.86)	<0.001	19.6 ± 1.1	281	1.54 (1.25–1.90)	<0.001	45.5 ± 1.4	743	1.44 (1.27–1.63)	<0.001

Abbreviations: *GFR* Glomerular filtration rate, *HR* Hazard ratio

[a]GFR derived from application of the simplified Modification of Diet in Renal Disease equation based on serum creatinine level, age, race and sex

[b]Compared to the group with GFR ≥90 mL/min per 1.73 m^2; adjusted for age, ethnicity, sex, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, fasting triglyceride level, history of diabetes and cigarette smoking. Combined cardiovascular disease refers to death from coronary heart disease, nonfatal myocardial infarction, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization)

cross-sectional study of diabetic adults >70 years of age [87], ~28% had poor vision or legal blindness. In that group, less than 20% of the visual impairment was attributable to diabetic retinopathy. Of those who had vision impairment related to diabetic retinopathy, most had macular edema (a >30% increase in the thickness of the macula) due to ischemia. Intra-ocular hemorrhage as a cause of visual impairment was rare. The Eye Diseases Prevalence Research Group [88] estimated diabetic retinopathy prevalence in the US to be ~45% in older adults with diabetes who are 65–74 years of age, and ~42% in older adults with diabetes who are >75 years of age. Only 8 and 7%, respectively, had the more severe form of retinopathy associated with ischemia.

Cataract is a major cause of vision impairment in older adults, both for those with and without diabetes. Many cross-sectional and prospective studies have documented an association between diabetes and cataracts [89–91]. The risk of cataract development increases with increasing diabetes duration, age and severity of hyperglycemia [92]. Deposition of AGEs in the lens has been postulated as a mechanism for diabetic cataract development [93].

Epidemiological studies have reported an association between diabetes and glaucoma [94]. The risk of glaucoma has been reported to be 1.6–4.7 times higher in individuals with diabetes than in those without diabetes [95, 96]. Diabetes may impair the autoregulation of posterior ciliary circulation, which can exacerbate glaucoma. It is important to screen for glaucoma among individuals who have diabetes, as it can be asymptomatic until the late stages when decreased vision and/or constricted visual fields are noted.

26.5.6 Functional and Mobility Disorders

Many studies have documented that individuals with diabetes have decreased muscle strength, especially in the lower extremities. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [97]—a double-blind placebo–controlled trial of pravastatin for the prevention of vascular disease in individuals 70–82 years of age—functional capacity, as measured by activities of daily living and independent activities of daily living, was decreased with increasing age, female sex and the presence of diabetes. In a study of 1,560 Japanese individuals [98] ≥65 years of age, diabetes was a risk factor for mild functional disability in women. In a US study [99] of 2,802 independently-living older adults 65–94 years of age who were followed for 2 years, diabetes was associated with a faster decline on the 36-item Short Form Health Survey physical component score. In a 3-year longitudinal cohort study of a random sample of 729 physically impaired older women ≥65 years of age living in the community [100], the baseline prevalence of diabetes was 14.4%. After adjustment for age and compared to women without diabetes, those with diabetes had an RR of 1.8 (95% CI, 1.3–2.5) for incident mobility disability and 1.6 (95% CI, 1.2–2.1) for incident activity of daily living disability. The increased incidence of new disability associated with diabetes was paralleled by a greater decline in measures of lower-extremity function. Adjustment for multiple risk factors for disability did not significantly attenuate the risk for disability associated with diabetes. Data from The National Health and Nutrition Examination Survey (NHANES) show that diabetes among both men and women was associated with a 2- to 3-fold increased odds of not being able to walk one-fourth of a mile, climb stairs or do housework, and up to a 3.6-fold increased risk of not being able to do all three tasks. Given the high prevalence of diabetes, these deficits result in a major burden of physical disability in older US adults [101].

26.5.7 Cancer

The Emerging Risk Factors Collaboration [102] reported that diabetes is moderately associated with death from cancers of the liver, pancreas,

ovary, colo-rectum, lung, bladder and breast. Participants with diabetes who were >70 years of age had a somewhat lower hazards ratio for cancer death associated with diabetes (HR, 1.23; 95% CI, 1.07–1.41) compared to non-diabetic individuals than did those 40–59 years of age (HR, 1.51; 95% CI, 1.32–1.72) and 60–69 years of age (HR, 1.27; 95% CI, 1.11–1.45), but the interaction terms were not statistically significant. These results are consistent with other large cancer studies. An analysis of 15 studies [103], which included a total of 2,593,935 participants, found that diabetes was associated with an increased risk of colorectal cancer (summary RR of colorectal cancer incidence = 1.30; 95% CI, 1.20–1.40). In another meta-analysis [104], women with diabetes had a statistically significant 20% increased risk of breast cancer (RR, 1.20; 95% CI, 1.12–1.28), but only in older postmenopausal women. In the Nurses' Health Study [105], women with type 2 diabetes had a modestly elevated incidence of breast cancer (HR, 1.17; 95% CI, 1.01–1.35),independent of age, obesity, family history of breast cancer, history of benign breast disease, reproductive factors, physical activity, and alcohol consumption. The association was apparent in postmenopausal women only (HR, 1.16; 95% CI, 0.98–1.62). In the Whitehall study [106], a 25-year follow-up for mortality in 18,000 men (~51 years of age at baseline), showed that diabetes was positively associated with mortality from carcinoma of the pancreas and liver. In a large study of US veterans [107], men with diabetes had increased risks of cancers of the liver (RR, 1.95; 95% CI, 1.82–2.09), pancreas (RR, 1.50; 95% CI, 1.42–1.59), biliary tract (RR, 1.41; 95% CI, 1.22–1.62) and colon (RR, 1.20; 95% CI, 1.16–1.25) compared to men without diabetes. Overall, men with diabetes were 7% less likely to develop cancer than those without diabetes.

Although causality has not been established for the association of cancer and diabetes, hyperinsulinemia could favor cancer because insulin is a growth factor with mitogenic effects. Obesity, hyperglycemia and increased oxidative stress may also contribute to increased cancer risk in diabetes [108].

26.6 Summary

This chapter summarized many disparate effects that the diabetic state has on the health of older adults. The effects are pervasive and touch upon many different organ systems. With the aging of the population, the impact of diabetes will present an increasing challenge with regard to the resources of the medical community and to the rise in medical expenditures. The judicious use of medications and the implementation of lifestyle measures for treatment and prevention may attenuate this looming challenge.

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Chronic Kidney Disease

27

Stacy Andersen and Linda Fried

Abstract

Chronic kidney disease (CKD) is prevalent in 13% of US community-dwelling adults and over 46% of those >70 years of age. Improved recognition of this wide prevalence in the past 10–15 years has produced standardized staging of CKD, a platform for public health education and surveillance, ongoing research, and guidelines for secondary and tertiary prevention. Such measures are necessary in confronting an often subclinical disease that has massive public health consequences. The vast majority of CKD patients are older adults, due in most cases to decades of hypertension, diabetes and obesity. Many challenges remain in confronting the epidemic of CKD in older adults. Certain structural and functional reductions in the kidney are part of normal aging but mimic CKD, making distinction between routine renal senescence and renal pathology difficult. The most common serum markers and medical formulae for assessing renal function are at times inaccurate in older adults. Improved markers and equations are emerging, but are not yet widely available or perfected. The course of CKD, its risk factors and its associated morbidity and mortality risks are also increasingly recognized to diverge in older compared to younger CKD patients. More research and guidelines are needed to improve risk assessment and diagnosis, and to tailor the care of this largest CKD subpopulation.

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Abbreviations

AASK	African American Study of Kidney Disease
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin-Converting Enzyme Inhibitor
ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AKI	Acute Kidney Injury
ALLHAT	Antihypertesive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARBs	Angiotensin Receptor Blockers
BLSA	Baltimore Longitudinal Study of Aging
CKD	Chronic Kidney Disease
eGFR	Epidermal Growth Factor Receptor
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
ICD-9	International Statistical Classification of Diseases and Related Health Problems, Ninth Edition
MDRD	Modification of Diet in Renal Disease
NHANES	National Health and Nutrition Examination Survey
NKF-KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
SHARP	Study of Heart and Renal Protection
SPRINT	Systolic Blood Pressure Intervention Trial
UKPDS	UK Prospective Diabetes Study

27.1 Introduction

Chronic Kidney Disease (CKD) is increasingly understood as a disease of older adults, who have higher prevalence rates and a unique renal, cardiovascular and mortality risk profile compared to younger CKD patients. In this chapter, we will review how renal function changes with age, the methods for assessing renal function, and the definitions and prevalence of CKD stages. We will then review the risk factors for CKD and its progression in older adults. Last, we will review clinical trials and public-health strategies for the prevention and delay of CKD progression, and the non-renal outcomes that are associated with CKD.

27.2 How Renal Function Changes with Age

Kidneys keep the body in balance on a number of fronts at both the gross and molecular levels. They maintain electrolytes, pH, blood pressure, mineral balance and water balance within relatively tight ranges. They activate vitamin D, and help to maintain bone health and red blood cell counts through hormone secretion. They receive, filter and cleanse 20% of the blood flow coming out of the heart, excreting nitrogenous waste products, degrading small peptides and hormones, and clearing medications and many toxins.

The glomerular filtration rate (GFR) is a central marker of renal function, defined as the volume of plasma filtered each minute by the kidneys. When kidney function declines, so does the GFR. If the GFR gets low enough, waste products accumulate, and metabolic and hemodynamic complications develop which could lead

to the need for dialysis. Dialysis is a therapeutic medical procedure that removes some waste products and toxins from the blood, and corrects metabolic blood abnormalities and some hemodynamics. The treatment for ESRD is chronic dialysis, which costs over $34 billion annually in the US and comprises 6.6% of annual non-part-D Medicare costs. For an individual ≥80 years of age, the per-year Medicare cost for ESRD was over $80,000 in 2008 [1].

Expected age-related changes in renal structure and function mimic the pathologic changes of CKD. Renal mass peaks at 400 g or higher by age 30, then drops off to about 300 g by age 80 [2]. Glomerular sclerosis increases from affecting less than 5% of glomeruli (the filtering structure in the kidney) in individuals <40 years of age to affecting 30% of glomeruli in those >70 years of age [3]. The GFR generally peaks in the third and fourth decades of life at about 140 ml/min/1.73 m^2, then drops thereafter by about 8 ml/min/1.73 m^2 for every decade of life [4, 5]. That said, age-related decline in kidney function varies tremendously between individuals. Although the Baltimore Longitudinal Study of Aging (BLSA) showed a 0.75 ml/min/year mean decrease in creatinine clearance in 254 healthy men, over a third of participants (36%) had no decline in their renal function [4].

Most scholars agree that the GFR declines from one decade to the next as part of the normal aging process. But normal ranges for this decline have not been conclusively defined. In the BLSA, participants had no history of kidney disease or x-ray abnormalities of kidney disease, had a normal urinalysis and glucose tolerance test, and were not on medication for hypertension. They had no direct evidence of kidney disease at enrollment, though there was no criterion for exclusion based on blood pressure. As expected, older participants in the BLSA had higher blood pressure on average than younger participants. The kidneys of hypertensive participants worsened faster than those without hypertension. For example, the mean arterial blood pressure was 101 mmHg in individuals >70 years of age vs. 93 mmHg in individuals 30–39 years of age, with a mean rate of GFR decline of 0.87 ml/min/1.73 m^2/year [4]. Later analyses excluded individuals with a mean arterial blood pressure >107 mmHg [5]. In the remaining participants, the mean rate of GFR decline was 0.58 ml/min/1.73 m^2/year. Although higher blood pressure ranges had been secondarily excluded, this group could still include individuals with mild systolic hypertension. Therefore, the true age-related rate of decline in GFR is not entirely clear.

Age-related changes in renal tubular function also affect serum chemistry and medication handling. Older patients do not excrete a salt load as readily as younger patients, nor do they conserve sodium as well when sodium intake is limited [6]. Older individuals in general also have a lesser ability to excrete an acid load and to secrete potassium when necessary compared to younger individuals [2, 7]. These changes occur in the setting of increased rates of tubulointerstitial scarring from the glomerulosclerosis and tubular atrophy, which are seen more commonly in older patients and contribute to the higher rates of medication complications seen in older adults [6].

The kidney's endocrine functions likewise change with age, which affects the response to anemia, bone health, insulin metabolism and the regulation of the sympathetic nervous system. Erythropoietin, a hormone released by the kidney, is found at lower levels in older anemic participants compared to younger ones, which suggests that older patients have less renal responsiveness to anemia [6]. Insulin is not metabolized as well by older kidneys, which results in lower insulin requirements in older diabetics. In older patients, less renin and aldosterone are secreted. The kidneys also have a blunted response to these hormones and a decreased ability to concentrate the urine, which likely contributes to a greater susceptibility in older adults to complications from volume depletion [2, 7].

27.3 Assessment of Renal Function

In epidemiologic studies, the assessment of kidney function is usually made with a marker of kidney function (estimated GFR) and a

marker of glomerular damage (albuminuria). These two markers provide complementary information with regard to prognosis for mortality, cardiovascular disease, and progression of kidney dysfunction. To date, there is no widely-accepted paradigm for combining these complementary indicators into a single assessment of renal function, though collaborations are underway to create one.

GFR can be measured directly, but the procedures are cumbersome and not applicable to most epidemiologic studies or clinical practice. Instead, endogenous substances are used to estimate the GFR. The ideal endogenous marker would not be protein-bound, and would be freely filtered, excreted only by kidney filtration and generated at a constant rate. This ideal marker does not currently exist.

The most commonly used endogenous marker is serum creatinine, which is measurable via an inexpensive blood test. Creatinine is a breakdown product released with the routine physiologic turnover of skeletal muscle. When renal dysfunction occurs, the kidney filters less creatinine, which then builds up in the serum. But creatinine values may not adequately capture milder levels of kidney dysfunction due to differences in creatinine generation that result from differences in patient muscle mass. The distribution of normal creatinine values is lower in older individuals, due to generally lower muscle mass. Therefore, in older patients, a value in the high normal range may actually reflect an abnormal decline in kidney function. When done correctly, GFR can be accurately estimated from creatinine clearance by collecting urine over a 24-h period and measuring the serum and urine concentrations of creatinine, and sometimes urea, as well as the total volume of urine and protein. However, this collection is cumbersome and often incorrectly performed. In addition, it may be inaccurate in older individuals due to incomplete bladder emptying.

In the BLSA, 24-h creatinine clearance values declined with age. However, this was masked by the decline in creatinine generation, so that the mean serum creatinine values did not vary across age groups [5]. The various formulae used to estimate renal clearance (Table 27.1) attempt to account for the differences in muscle mass in certain populations, and attempt to make it easier to recognize high-normal creatinine levels that reflect decreased GFR.

27.3.1 The Cockcroft-Gault Equation

The Cockcroft-Gault equation was introduced in 1976 to estimate creatinine clearance based on serum creatinine values as well as patient age, sex and weight [8]. This was the first widely-accepted formula to estimate renal function both in populations and in individual patients. Of note, it was developed from a cohort of 249 men with creatinine clearances that ranged from 30 to 130 ml/min (i.e., from moderately diminished to normal renal clearance values). It was subsequently evaluated in numerous populations of different races, which included individuals who did and did not have diabetes and/or renal disease, as well as kidney transplant recipients and donors [9]. Unfortunately, due to the tubular secretion of creatinine (in addition to filtered creatinine), creatinine clearance overestimates GFR. The Cockcroft-Gault formula to estimate creatinine clearance is particularly age driven. While true creatinine clearance is higher than the GFR, in older individuals, the Cockcroft-Gault creatinine clearance estimate is actually lower than the GFR. The Cockcroft-Gault equation is also more inaccurate in obese patients or in those without CKD [12].

27.3.2 The Modification of Diet in Renal Disease Equation

A second equation, the Modification of Diet in Renal Disease (MDRD), remains the most widely used estimate of GFR since its introduction in 1999. This equation was developed from a cohort of 1,628 patients who were enrolled in the MDRD study, a multicenter controlled trial to assess the effects of restricted protein intake and tight blood pressure control on the progression of renal disease [9]. The formula incorporates creatinine, age, race (black or not) and gender. It reasonably estimates the GFR in

Table 27.1 Equations to estimate renal clearance

Name	Patient type	Equation
Cockcroft Gault [8]	All	$C_{Cr} = [(140\text{-age}) \times \text{weight}]/(72 \times S_{Cr}) \times 0.85$ (if patient is female)
MDRD [9]	All	$GFR = 186 \times (S_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if patient is female) or $\times 1.212$ (if patient is black)
MDRD adjusted[a]	All	$GFR = 175 \times (\text{standardized } S_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if patient is female) or $\times 1.212$ (if patient is black)
CKD-EPI [10]	Women: Creatinine level ≤0.7 mg/dl	
	White women	$eGFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	Black women	$eGFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	Women: Creatinine level >0.7 mg/dl	
	White women	$eGFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
	Black women	$eGFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
	Men: Creatinine level ≤0.9 mg/dl	
	White men	$eGFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	Black men	$eGFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	Women: Creatinine level >0.9 mg/dl	
	White men	$eGFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
	Black men	Black Man: $eGFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
Cystatin C [11]	Cystatin C alone	$eGFR = 76.7 \times \text{cysC}^{-1.18}$
	CKD EPI cystatin	$eGFR = 127.7 \times (\text{cystatin C})^{-1.17} \times (\text{age})^{-0.13} \times$ (0.91 if patient is female) $\times$ (1.06 if patient is black)
	Combined cystatin C and creatinine	$eGFR = 177.6 \times (\text{creatinine})^{-0.65} \times (\text{cystatin C in mg/l})^{-0.57} \times (\text{age})^{-0.20} \times$ (0.82 if patient is female) $\times$ (1.11 if patient is black)

For all formulas, creatinine is in mg/dl, cystatin C in mg/l
Abbreviations and units: creatinine clearance C_{Cr} in ml/min, age in years, weight in kg, serum creatinine S_{Cr} in mg/dl
[a]Adjusted for isotope dilution mass spectrometry traceable creatinine

nonhospitalized patients with CKD. It was evaluated in multiple populations and was found to be of either similar or, according to some studies, superior accuracy compared to Cockcroft-Gault, in older as well as younger patients [12]. But the MDRD tends to underestimate the GFR, potentially attributing renal dysfunction to patients with mild decrements of renal function but no frank renal disease. In other words, MDRD can give false-positive diagnoses of kidney disease for patients whose true GFR is above or near 60 ml/min/1.73 m^2 [13].

Creatinine values can vary from laboratory to laboratory, which can affect the accuracy of the MDRD formula. This typically does not matter with regard to advanced CKD, but it can lead to misclassification of CKD at milder levels [14]. This has led to efforts to standardize serum creatinine measures. Manufacturers of instruments that measure creatinine have been converting to this standard, known as the isotope dilution mass spectrometry traceable method. In general, the creatinine values reached through this statistic are lower than those reached prior to standardization, an important consideration when comparing values between one population study and another. There is an isotope dilution mass spectrometry traceable formula for the MDRD equation, though most other formulae have not yet been adapted.

It is also important to point out that the above formulae were developed in young and middle-aged populations. Although they account for age (and thereby indirectly account for this expected difference in creatinine), neither was developed in a cohort of older patients [15]. The more widely used formula, the MDRD, has not been validated in patients >75 years of age, despite the fact that this is a high-risk population for renal dysfunction with a high and increasing prevalence of CKD.

27.3.3 The Chronic Kidney Disease Epidemiology Collaboration Equation

The MDRD equation was developed in a CKD population and has bias and imprecision in patients who do not have kidney disease (e.g., when the GFR is >60 ml/min/m^2) [13]. It also diagnoses more women, more whites and more elders with Stage 3–4 CKD than would be expected. The Chronic Kidney Disease Epidemiology Collaboration developed a formula, the CKD-EPI, to lessen the systematic underestimation of GFR seen at higher levels of renal function with MDRD [10]. The group pooled data from 10 studies of patients who had kidney disease or were at risk for kidney disease (8,254 patients) to develop the equations and from 16 studies (3,896 patients) to validate them. They then used a subset of NHANES (16,032 patients) to estimate prevalence. The CKD-EPI introduces a spline term for creatinine values that reflects the weaker relationship between creatinine and GFR at lower creatinine values. It is based on creatinine measured with an isotope dilution mass spectrometry traceable method.

In comparing the performance of the two equations, CKD-EPI more accurately estimated GFR than did MDRD due to the lower bias of CKD-EPI with higher GFRs. Precision, however, is not much improved with the new equation [10]. Overall, US CKD prevalence was lower using CKD-EPI at 23.2 million (CI 21.3–25.0 million) or 11.5% of the population rather than the MDRD figure, which was about 3 million patients higher or 13.1% of the population. This formula has not been validated in older individuals. In contrast to the overall results for the general population, CKD-EPI does not find a lower prevalence of CKD in older adults.

27.3.4 The Cystatin C Equation

Due to limitations of creatinine-based estimates of renal function, particularly in populations that lose muscle mass with aging or disease, other renal function markers have been evaluated. Cystatin C, another endogenous marker of renal function, has been researched extensively as an alternative to serum creatinine. It is a low molecular weight cysteine protease inhibitor that is produced at near-constant levels regardless of an individual's lean body mass, and it is freely filtered at the glomerulus before being catabolized by the proximal tubules [16]. Cystatin C is not dependent on muscle mass and is less affected by race, gender and age than is creatinine, though its levels may be altered by fat mass, thyroid function and inflammation [17]. It is a stronger predictor of mortality and adverse cardiovascular and renal outcomes, particularly in older adults, than are creatinine-based estimates of GFR [18, 19].

Estimating CKD prevalence in the general population is difficult given the shortcomings of laboratory markers and renal function estimation formulae. The challenges are even greater when assessing the older adult population. Because it is independent of muscle mass, cystatin C is a more accurate marker of renal function in older adults than is creatinine. But it is only just becoming available for widespread use. More research is also needed on the non-renal determinants of cystatin C.

27.3.5 Testing for Albuminuria

Apart from reductions in estimated glomerular filtration rate (eGFR), the other common marker of kidney damage is albuminuria, the abnormal passage of albumin—even in small amounts—from the bloodstream to the urine through the basement membrane of the glomerulus. Microalbuminuria is defined as the presence of 30–299 mg/day of albumin, and overt albuminuria as ≥300 mg/day. As 24-h urine sampling and testing is not commonly performed, random urine samples are typically used to define microalbuminuria as 30–299 mg/g of urinary creatinine and albuminuria as ≥300 mg/g of urinary creatinine. The normalization to urine creatinine accounts for differences in urine concentration. Albuminuria >300 mg/g creatinine can be detected on a standard urinalysis with urine dipsticks, while the detection of microalbuminuria requires a radioimmunoassay.

It is controversial whether microalbuminuria always reflects kidney disease [20]. Microalbuminuria is the earliest stage of diabetic kidney disease, but not all patients with microalbuminuria progress to overt albuminuria (e.g., nephropathy). In many individuals, microalbuminuria may reflect endothelial dysfunction, vascular damage and an inflammatory state with coagulatory dysfunction rather than kidney disease *per se*. Data from the Cardiovascular Health Study show an independent and weakly-correlated mortality risk between microalbuminuria and reduced eGFR, which suggests the possibility that a different pathophysiologic process is driving the two diagnoses [21]. In contrast, overt proteinuria, a term frequently used interchangeably with albuminuria (>300 mg/day), always reflects kidney disease [20, 22].

27.4 Definitions and Prevalence of the Stages of CKD

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) issued standardized guidelines to define stages of CKD (Table 27.2) [23]. These NKF-KDOQI guidelines were part of a broader effort to make the public and the medical community more aware of renal disease, which can often be advanced before becoming symptomatic, and to standardize definitions within the renal community to improve research studies, risk stratification and quality of care. The NKF-KDOQI staging guidelines contain no age criteria: that is, an eGFR of 45 ml/min/1.73 m^2 in an 80-year-old is categorized at the same stage as that in a 30-year-old.

Clinically, CKD cannot be diagnosed based on a single lab value; by definition, persistent evidence of damage must be established over time. Transient or acute rises in creatinine are considered acute kidney injury, which is common in hospitalized patients and also portends an increased risk of mortality and increased length of hospital stay. Of note, however, most epidemiologic studies use a single eGFR to define CKD. NKF-KDOQI guidelines classify CKD into five stages which mark the progression of disease severity. Information on these stages is provided in Table 27.2 [23].

By the MDRD formula and these guidelines, the prevalence of CKD Stages 3 and 4 in the population >70 years of age according to NHANES (1988–1994) data is 24.6%, compared with only 7.1% prevalence in those from 60 to 69 years of age and 1.8% prevalence in those 40–59 years of age (Table 27.3). There is much controversy with regard to the meaning of these trends, since a lower GFR does not always equate with kidney disease, but the markedly higher prevalence rates for elders by NKF-KDOQI criteria are clear. Subsequent NHANES data (1999–2004) showed an increase in CKD preva-

Table 27.2 Stages of chronic kidney disease: a clinical action plan

Stage of CKD	Description	GFR (ml/min/17.3 m^2)	Action
–	At increased risk	≥60 with CKD risk factors	Screening, CKD risk reduction
1	Kidney damage with normal or increased GFR	>90	Diagnosis and treatment; Treatment of comorbid conditions; slowing progression, cardiovascular disease risk reduction for cardiovascular disease
2	Kidney damage with mild decrease in GFR	60–89	Estimating of progression
3	Moderate decrease in GFR	30–59	Evaluating and treating complications
4	Severe decrease in GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15	Replacement (if uremia present)

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Table 27.3 Prevalence of GFR categories in adults

	Age categories			
GFR (ml/min/1.73 m2)	20–39	40–59	60–69	≥70
≥90	86.0%	55.7%	38.5%	25.5%
60–89	13.7%	42.7%	53.8%	48.5%
30–59	–[a]	1.8%	7.1%	24.6%
15–29	–[a]	–[a]	–[a]	1.3%
N (millions)	82	55	20	20

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GFR estimated from serum creatinine using MDRD Study equation based on age, race, gender and calibration for serum creatinine. Data from NHANES III (1988–1994). N = 15,000. Based on one-time assessment of estimated GFR
[a]Fewer than 20 cases; data not considered reliable

lence among noninstitutionalized US adults who were >20 years of age, from 5.4 to 7.7% for CKD Stage 3 and from 0.21 to 0.35% for CKD Stage 4 [24]. The rate of increase was similar within age groups, suggesting that the upward prevalence trends were not due to age differences between the two NHANES populations. The prevalence of CKD is high for elders in other parts of the world as well, with a prevalence of 35 and 28% of the population >70 years of age in Europe and China, respectively [25].

It is important to note that Stage 3 CKD by NKF-KDOQI criteria is approximately 20 times more prevalent in the general population than Stage 4 CKD and is, by far, the CKD stage with the highest prevalence. Within Stage 3 CKD in particular (at least for older adults), a large difference in risk for mortality or morbidity, or for progression of renal dysfunction, exists between more severe and more moderate cases. Therefore, some researchers break Stage 3 into Stage 3A, defined as an eGFR from 45 to 59 ml/min/1.73 m^2, and Stage 3B, defined as an eGFR from 30 to 44 ml/min/1.73 m^2. Stage 3A CDK occurs three times more frequently than does the more advanced Stage 3B [24]. A study in a British cohort found that an older adult with a stable GFR in the Stage 3A range had no increased mortality risk compared to older adults without renal dysfunction, and these Stage 3A patients without significant elevation in mortality risk comprised 41% of the study population that had CKD Stage 3 or higher. They also comprised 14% of all study participants >75 years of age [26].

The metabolic consequences of kidney disease, such as anemia, abnormal bone and mineral metabolism, and difficulties with fluid and acid base balance also typically emerge with advanced Stage 3 CKD [27]. It has been argued that the current NKF-KDOQI classification system for CKD has the potential to mislabel large numbers of older adults as having kidney disease—for example, those with non-albuminuric Stage 3A CKD—when in fact their lab data simply represent physiologic age-related changes in renal function or changes that are not necessarily clinically significant [15]. An alternative explanation for the discrepancy in mortality rates within Stage 3 of CKD is that the MDRD formula is inaccurate in older individuals, which leads to the misclassification of a large number of individuals as having CKD.

The stages of CKD have different associations for ESRD at different ages. A younger patient with advanced Stage 4 CKD has a reasonably high likelihood of that renal disease progressing to the need for dialysis [28]. However, an older patient with CKD 4 has competing risks which make the progression of renal disease to ESRD relatively less likely than death (Figs. 27.1 and 27.2).

It has been postulated that this may reflect how CKD in older patients reflects overall health (and years of the effects of chronic health conditions such as diabetes, hypertension or being overweight), whereas in younger patients, CKD is more likely associated with a single specific pathology [28]. It is important to point out, however, that though an individual older CKD patient

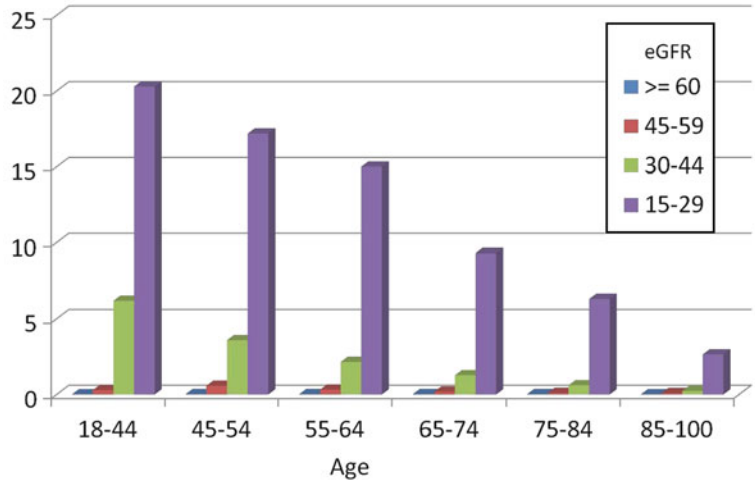

Fig. 27.1 Incidence of treated ESRD per 100 person years by age and baseline eGFR in US veterans (Adapted from: O'Hare et al. [28])

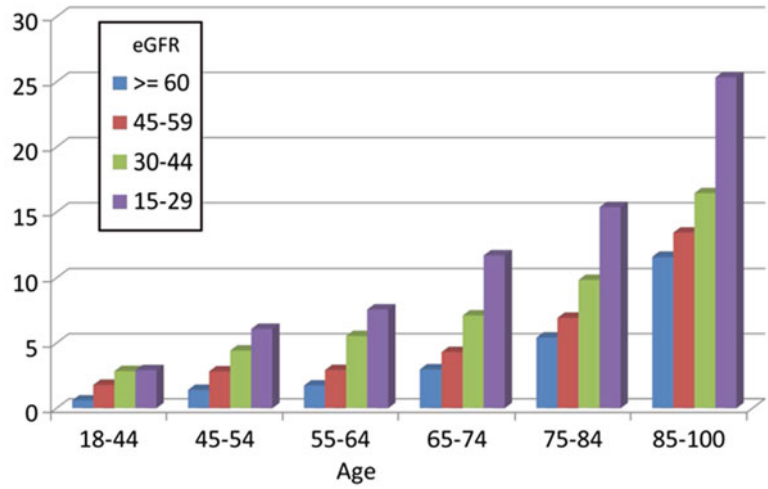

Fig. 27.2 Incidence of mortality per 100 person years by age and baseline eGFR in US veterans (Adapted from: O'Hare et al. (Table 2) [28])

is less likely to progress to ESRD than is a younger patient, the rate of ESRD is highest in older patients due to CKD being more common in older individuals [1].

Cystatin C may well prove useful for risk stratifying older adults who have CKD. Since it shows which older adults with early CKD carry excess mortality risk and which do not, cystatin C has been used to define what has been called 'preclinical kidney disease', which is defined as an eGFR >60 ml/min/1.73 m^2 with an elevated cystatin C >1.0 mg/l. In an analysis of Cardiovascular Health Study data, preclinical kidney disease or microalbuminuria alone was associated with a >50% increase in cardiovascular and all-cause mortality risk in older adults. If both were present, mortality risk increased 240% for these patients compared to other older adults in the cohort who had neither microalbuminuria nor CKD (Fig. 27.3) [29]. Heart failure risk also increases in graded fashion with increasing quintiles of cystatin C levels, starting with the

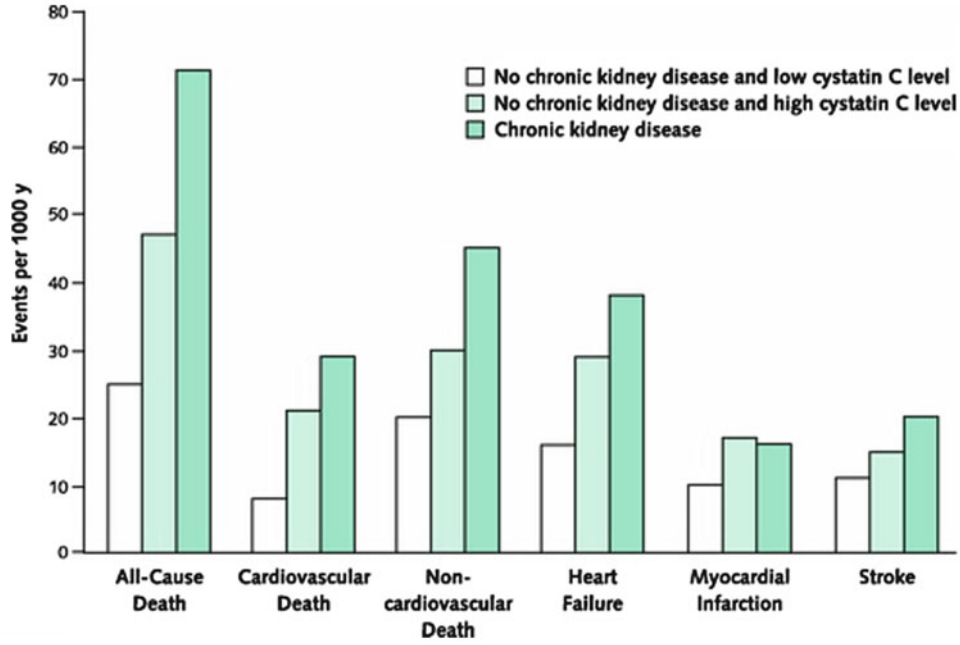

Fig. 27.3 Cardiovascular events and deaths per 1,000 years in the Cardiovascular Health Study (Reprinted from with permission from: Shlipak et al. [29])

second quintile. In contrast, the risk associated with creatinine-based eGFR did not begin until the eGFR was <60 ml/min/1.73 m^2 for these patients [19]. For older individuals, elevated levels of cystatin C also associate in more linear fashion with increased mortality risk than does the MDRD eGFR. In addition, very high eGFR due to very low creatinine was associated with increased risk (J-shaped curve), which likely reflected disease and poor muscle mass [19].

Epidemiologic work is also underway to incorporate both proteinuria/albuminuria and eGFR in a new classification so as to better stratify risk for different CKD subpopulations, including older adults. One recent study in this vein identified certain CKD subpopulations at low risk for adverse outcomes with greater accuracy than did current NKF-KDOQI guidelines [30]. Among subgroups that were more accurately reclassified were patients >60 years of age and diabetics of any age. In thus reclassifying CKD patients, the study estimated a >75% lower prevalence of Stage 3 CKD than do current NKF-KDOQI guidelines. Incorporating both eGFR and the level of albuminuria in classifying CKD—currently the subject of much ongoing research—may eventually prove pivotal in distinguishing between normal renal senescence and renal pathology in older populations.

27.5 Prevalence and Incidence of CKD in Older Adults

The 1999–2004 National Health and Nutrition Examination Survey (NHANES) tracked CKD in community-dwelling US adults >20 years of age and found that based on laboratory data, the prevalence of mild CKD (Stages 1 and 2) was 10% in individuals >70 years of age compared to only 3% in those 20–39 years of age. Prevalence for moderate to advanced CKD (Stages 3 and 4) was 37.8% in older adults (almost all in Stage 3) compared to only 0.7% in the younger age group [24]. According to this data, 13.1% of the adult population met criteria for CKD 1–4, including 46% of those >70 years of age. Medicare International Statistical Classification of Diseases and Related Health Problems, Ninth Edition (ICD-9) diagnostic codes have also been used to

track CKD prevalence and, unlike NHANES, tracked incidence in patients ≥65 years of age. CKD incidence in this older population has increased from 1.2% in 1995 to 4.3% in 2008. CKD prevalence in Medicare patients ≥65 years of age increased from 1.7% in 1995 to 7.6% in 2008 (4.6 times greater) [1]. Rates of CKD prevalence and incidence in Medicare patients have more than tripled in a 13-year period.

Incident CKD is difficult to define and study. Most—but certainly not all—CKD is subclinical, a marker of chronic disease burden both in individuals and in populations. Its presentation is usually slow and variable rather than dramatic, most often in the setting of years of hypertension, diabetes or obesity, three of the leading risk factors for CKD. To diagnose CKD, healthcare providers and researchers need lab values within a clinical context over a timeframe of at least 3 months. Even then, patients and healthcare providers miss this diagnosis all too often. Underdiagnosis of CKD by healthcare providers may explain why the Medicare prevalence rates are much lower than the NHANES estimates, with the rapid upward trend in CKD prevalence and incidence in Medicare databases reflecting both an increased occurrence and increased recognition of CKD. Uniform staging criteria for CKD were only introduced in 2002, and more precise ICD-9 billing codes were introduced in 2006. Of the 26 million Americans who have CKD, 10.1 million have Stages 1 and 2, while another 11 million are at early Stage 3, most without proteinuria [1, 4]. These CKD states generally have lower rates of renal disease progression and other complications. For those ≥70 years of age without proteinuria and at early Stage 3, the vast majority often have stable renal function for months at a time.

This combination of high prevalence and often subclinical disease can be controversial. Some argue that CKD is an under-recognized epidemic with increasing prevalence and incidence, particularly in older adults, which is associated with excess risk to their renal and cardiovascular health, physical functioning and mortality. Others claim that these relatively recent standardized definitions of CKD have had the unintended consequence of exaggerating this epidemic, since population data do not adequately separate CKD from normal renal senescence.

Regardless of this controversy, data show that even moderate CKD, as currently defined, is strongly associated with higher morbidity and mortality, particularly in older patients. Such patients are at higher risk particularly for cardiovascular disease and death, as well as for stroke, cognitive impairment, poorer physical functioning, bone disease, and all-cause mortality [31]. Medicare patients with CKD have been shown to have 2–5 times more disease burden than Medicare patients without CKD [1]. Medicare patients with CKD are more than twice as likely to die or to have cardiovascular events as are their counterparts who are free of CKD [1].

The disease trajectory of CKD in older individuals differs from that of younger patients: older individuals with CKD are much more likely than younger ones to die before progressing to end-stage renal disease [ESRD] in the setting of advanced CKD [28]. However, since more older than younger individuals have CKD, the numbers of patients that progress to ESRD are highest in older individuals. These opposing factors are illustrated in Figs. 27.1 and 27.4. Figure 27.4 shows that except for patients ≥85 years of age, there is a higher incidence of ESRD with older age. In contrast, Fig. 27.1 shows that for any given baseline level of kidney function, older individuals are less likely to progress to ESRD over time.

Despite its wide prevalence, many physicians do not diagnose CKD and most patients with CKD are not aware of their disease. The laboratory values for patients >65 years of age in the NHANES and Kidney Early Evaluation Program (National Kidney Foundation) databases indicated a 44% prevalence of CKD for this population (n = 5,538), despite the fact that CKD was diagnosed in only 7% of Medicare patients based on billing codes reported for 5% of the Medicare population [32]. For studies that use administrative or epidemiologic data, the diagnosis of kidney disease is insensitive, but specific. When participants in NHANES 1999–2004 were asked whether they had kidney problems, fewer than

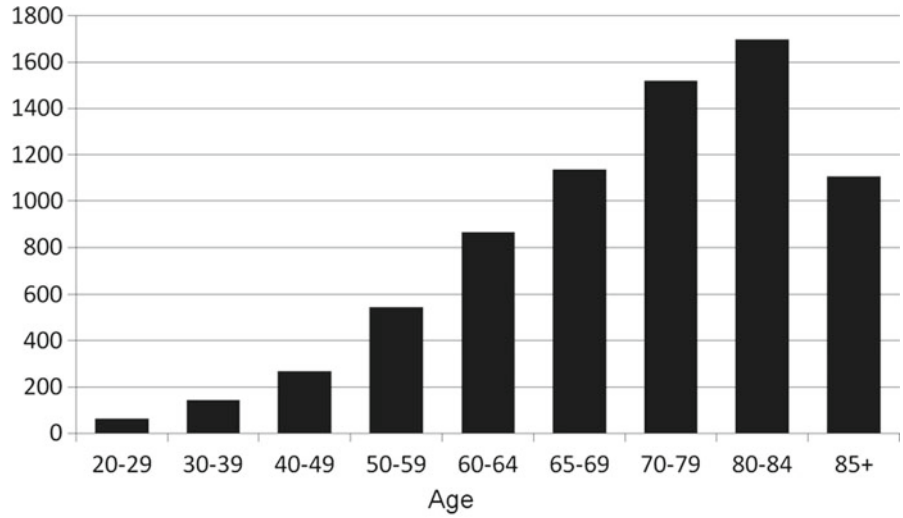

Fig. 27.4 Incident treated end-stage renal disease per million population by age [1]

15% of patients with Stage 3 CKD reported knowing that their kidneys were "weak" or "failing", and fewer than half of patients with Stage 4 CKD were aware of their renal problems [24]. Therefore, for epidemiologic studies, participant-reported history of kidney disease is not an accurate way to assess the prevalence of CKD.

27.6 Risk Factors for CKD and Its Progression in Older Adults

The most common risk factors for CKD are diabetes—the most common cause of CKD in the US—and hypertension [1]. Both of these conditions are more common in older populations than in younger ones. Longer duration and poorer control of either of these conditions incurs greater risk for CKD. In the Medicare population, 48.4% of individuals with a CKD diagnosis have diabetes and 91.4% have hypertension vs. 23.6 and 59.7% respectively in the general Medicare population [1].

In addition to its increased prevalence with age, CKD is also more common in African-Americans, Hispanics, Native Americans, and individuals of lower socioeconomic status. Other risk factors include obesity, smoking, hyperuricemia, dyslipidemia, cardiovascular disease and a family history of renal disease. Small studies in obesity show that weight loss leads to improvement in albuminuria [33], but no intervention studies have assessed whether it slows the loss of GFR. Certain conditions that are more prevalent in elders put individuals at risk for CKD, such as heart failure or cancers including blood dyscrasias. Frailty is not a risk factor *per se* for CKD; however, greater frailty correlates with higher CKD stages, particularly in women [34].

Two studies have developed prediction scores for incident CKD. One study developed a simplified score using eight clinical factors. This simplified score used a combined dataset from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study to predict incident Stage 3 CKD [35]. The risk factors are age (50–59: 1 point, 60–69: 2 points, ≥70: 3 points), female gender, anemia, hypertension, diabetes, cardiovascular disease, heart failure and peripheral vascular disease (each one point). The overall area under the curve was 0.70, with a score >3 having the best accuracy. The QKidney Score was developed in a cohort study in England of 3,574 individuals who were 35–74 years of age, did not have CKD and were seen in primary care to predict the development of the 5-year risk of incident moderate-severe CKD [36]. The risk factors in the

score are age, race/ethnicity, body mass index, smoking, comorbidity (diabetes, heart failure, peripheral vascular disease, cardiovascular disease, lupus, rheumatoid arthritis, kidney stones, hypertension), family history of kidney disease, systolic blood pressure and use of non-steroidal anti-inflammatory medications. The area under the curve (ROC) was 0.88. The score is available on-line at www.qkidney.org.

27.6.1 Hypertension

Hypertension, particularly systolic hypertension, is one of the strongest risk factors for CKD. African-Americans are six times more likely to develop ESRD from hypertension than are whites [1]. As with CKD, the prevalence of hypertension increases with increasing age. In the Systolic Hypertension in the Elderly Program, systolic blood pressure was the strongest blood pressure component that predicted a decline in kidney function, defined as a change in serum creatinine of 0.4 mg/dl at 5 years of follow-up [37]. The risk increased linearly across systolic blood pressure quartiles.

According to the National Kidney Foundation (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and the American Diabetes Association, the target blood pressure for prevention of CKD progression is <130/80. This is based more on expert opinion than on solid clinical evidence. Randomized studies have not yet proven that all patients with CKD, including older adults with CKD, should have this lower blood pressure target.

27.6.2 Albuminuria

Albuminuria has unique features as a risk factor for CKD progression, both in the general population and for older adults. The degree of albuminuria and its responsiveness to therapy correlates to risk of renal disease progression, and to cardiovascular risk and mortality [22, 38]. A secondary analysis of MDRD data showed that patients with greater baseline proteinuria lost GFR more quickly on average, and that both proteinuria and the rate of decline in the GFR could be lessened with tighter blood pressure control [39]. Lipid reduction has been associated with a decrease in proteinuria [40], but results of the Study of Heart and Renal Protection (SHARP) trial did not suggest that lipid reduction slowed the progression to dialysis [41].

27.6.3 Acute Kidney Injury

In addition to chronic decline in kidney function, individuals can experience an acute decline, not always reversible, in GFR with illness. Acute kidney injury (AKI) is increasingly recognized as a risk factor for both the development of chronic kidney disease and its progression in the older adult population. Among 233,803 Medicare patients with a mean age of 79.2 years who survived hospitalization in 2000, 3.1% developed AKI during their hospitalization and were found to be at markedly increased risk of CKD and ESRD during 2 years of follow up [42]. Among participants in this study who had AKI without preexisting CKD, 72% developed CKD during follow up. Patients with CKD who developed AKI during this hospital admission were 41.2 times more likely to have ESRD within 2 years of discharge than those who had neither preexisting CKD nor inpatient AKI. This study relied on ICD-9 codes, which are specific but not necessarily sensitive in identifying both AKI and CKD. The data are also not adjusted for the severity of either AKI or CKD. Nevertheless, the study suggests that AKI in older adults, especially those with preexisting CKD, may contribute to high incidence of ESRD in older patients among all age groups in the US. Older adults are at higher risk for AKI than younger adults due to their decreased functional and structural renal adaptive capacity (as part of the normal aging process), relative polypharmacy and higher rate of medication-related complications, as well as their higher rates of hospitalization, surgical procedures and other procedures.

27.7 Public Health Strategies and Clinical Trials to Prevent and Delay the Progression of CKD

27.7.1 Public Health Strategies

Public health efforts in kidney disease have focused on increasing awareness among care providers and the public, particularly among high-risk populations. The National Kidney Foundation sponsors an ongoing screening program for individuals at highest risk for CKD, the Kidney Early Evaluation Program. The program aims to identify individuals with CKD or with poorly-controlled risk factors for CKD such as hypertension and diabetes. It should be noted that the efficacy of primary CKD prevention through improved control of hypertension and diabetes has not been proven [43]. In addition, while kidney disease is primarily a disease of older individuals, randomized studies have not focused on older adults and most data on the prevention of kidney disease progression comes from middle-aged to younger older adults. Lifestyle modification has been shown to reduce the incidence of both diabetes and hypertension [44]. The prevention or delay of albuminuria has also been proven possible in patients who have diabetes by using tight glucose control and the use of angiotensin-converting enzyme inhibitor (ACEI) medications [45, 46].

If an individual has CKD, secondary prevention involves slowing the progression of CKD in Stages 3 and 4, particularly. Blood pressure continues to be a focus of clinical management, as well as volume status, bone health, electrolyte and acid base balance, and anemia. Many older individuals take renally-cleared medications that need to be dose-adjusted or discontinued to avoid adverse drug events. For any patient with Stage 4 disease, and particularly for older adults with Stage 4 disease, shared decision-making about whether and on what terms to initiate dialysis is also critically important so that appropriate preparations can be made before renal function deteriorates further.

27.7.2 The UK Prospective Diabetes Study

Many large studies have looked at whether glycemic control in individuals who have type 2 diabetes prevents microvascular outcomes, including nephropathy which is usually defined as albuminuria. The UK Prospective Diabetes Study (UKPDS) followed 3,867 patients newly diagnosed with type 2 diabetes (median age at enrollment: 54 years) for 10 years and compared aggregate endpoints, including both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (myocardial infarction, stroke, heart failure, angina, sudden death, and others) outcomes of intensive and conventional glycemic control. UKPDS patients with intensive glycemic control (median HgbA1c 7.0%) had a 25% reduction in microvascular complications compared to those with conventional control (median HgbA1c 7.9%), with a continuous reduction in the risk of microvascular complications—primarily retinopathy—for those patients who had better glycemic control [47]. Rates and progression of both microalbuminuria and proteinuria were reduced in the intensive-control arm, with a non-significant trend toward a lower rate of doubling of serum creatinine. The risk of macrovascular complications such as myocardial infarction, heart failure, or stroke did not differ between the groups.

27.7.3 The Action to Control Cardiovascular Risk in Diabetes Study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized over 10,000 diabetic patients (mean age: 62 years) to tighter glycemic control (median HgbA1c: 6.4% within 12 months of starting the study) vs. standard control (median HgbA1C: 7.5%) and followed them for 3.5 years. Concurrent blood pressure and lipid trials were also part of this large study [48]. At enrollment, the ACCORD study population had a mean duration of diabetes of 10 years, with 35% of participants using insulin

at baseline. The intensive glucose control arm of ACCORD was switched to standard therapy after 3.5 of 5 planned years after the safety monitoring committee noted higher mortality rates in the intensive glycemic control group relative to the standard therapy group, although the lipid and blood pressure arms of the study were continued. Intensive glycemic control lowered the incidence of microalbuminuria by 15% and macroalbuminuria by 28%, but showed no difference in change regarding eGFR or the incidence of ESRD [49].

27.7.4 The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Study

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study randomly assigned 11,140 patients who were at least 55 years of age and had type 2 diabetes to either standard or intensive glycemic control (mean age: 60 years), with a goal of a HgbA1c of 6.5% or less. Participants were followed for composite endpoints of both macrovascular and microvascular events for a median of 5 years. Fewer than 2% of participants were on insulin at trial initiation. The primary benefit associated with intensive glycemic control in ADVANCE was a 21% relative risk reduction in new or worsening nephropathy, defined as the development of macroalbuminuria, the doubling of baseline serum creatinine, the need for dialysis, or death from renal causes. No differences were seen between the treatment groups with regard to macrovascular events [50]. The reduced risk of nephropathy is comprised primarily of reduced risk for albuminuria, since the rate of change in eGFR did not differ between groups.

27.7.5 The Veterans Affairs Diabetes Trial

The Veterans Affairs Diabetes Trial followed 1,791 veterans with a mean age of 60.4 years for a median of 5.6 years with either intensive or standard glucose control. The tight-control group's HgbA1c was 6.9%, with the only significant difference between the groups being less risk for progression of albuminuria with tighter glucose control [51]. No changes in mortality risk or change in eGFR over time were apparent between groups.

In these studies of type 2 diabetes, tighter glucose control was associated with less frequent development or progression of microalbuminuria. However, none of these studies showed an association between tight glucose control and a lesser decline in GFR. It is not known whether this is due to different risk factors at different stages of both renal and diabetic disease, or to the study follow-up being of too short a duration for these differences to emerge. Also, the participants in the groups with tighter glycemic control frequently had more episodes of hypoglycemia and more weight gain than did those with more conventional control, which could in the long run raise the risk of cardiovascular disease.

27.7.6 The Modification of Diet in Renal Disease Study

Blood pressure control may become more difficult as disease advances but it remains important, particularly for proteinuric patients and in lowering cardiovascular risk. The MDRD study randomized 585 patients who had a GFR of 25–55 ml/min/1.73 m^2 and 255 patients who had a GFR of 13–24 ml/min/1.73 m^2 into higher and lower blood pressure target groups (mean arterial pressure ≤107 vs. ≤92 mmHg), then followed them for changes in GFR and proteinuria for up to 3.7 years. Forty-four percent of the study participants were >55 years of age. In the randomized study, there was no difference in GFR decline between participants randomized to low or standard blood pressure targets, but there did appear to be a benefit of lower blood pressure in individuals with proteinuria [39]. Despite the results of the randomized study, achieved blood pressure was associated with GFR decline, though this epidemiologic analysis may be confounded.

Of note, diabetics who required insulin and had kidney disease were excluded from this study.

27.7.7 The African American Study of Kidney Disease

The African American Study of Kidney Disease (AASK) randomized 1,094 African-Americans (18–70 years of age) who had Stage 3–4 CKD from hypertension to one of two mean arterial pressure goals: 102–107 mmHg or <92 mmHg. One of three different classes of antihypertensive was used to achieve this blood pressure goal, with follow-up ranging from 3 to 6.4 years. No difference was found in the progression of hypertensive nephropathy between participants of the higher and lower blood pressure target groups [52]. However, one class of antihypertensive medication, the ACEI, slowed the decline in eGFR compared to the others.

In both of these studies of hypertension control in patients with CKD, lower blood pressure targets did not in and of themselves slow decline in the GFR. However, in subgroup analyses, both studies suggested that lower blood pressure was beneficial for those with overt proteinuria. A recent follow-up study of individuals enrolled in AASK confirmed that there was no difference overall in progression in the two blood pressure groups, except for individuals with proteinuria [53].

Many of the studies of hypertension in CKD, including AASK, MDRD and UKPDS, did not enroll patients >75 years of age. Subgroup analyses of older patients in the ACCORD trial have not yet been released. The Systolic Blood Pressure Intervention Trial (SPRINT) will enroll about 7,500 nondiabetic participants ≥55 years of age and follow clinical outcomes after randomization to target systolic blood pressures of <140 mmHg and <120 mmHg. Hopefully, this study and others will improve our understanding of optimal management for hypertension in older adults with CKD. Careful medication review and frequent adjustments in the management of blood pressure and volume status are indicated for patients who have advanced CKD and particularly for older adults who have CKD.

In individuals who have proteinuria, medications that block the renin-angiotensin system—such as angiotensin receptor blockers (ARBs) or ACEIs—reduce proteinuria and slow the loss of kidney function. This has been shown for both diabetic kidney disease and non-diabetic kidney disease. ACEIs did not prevent progression to ESRD in patients with hypertension in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [54], but did prevent loss of GFR or progression to ESRD when used with a diuretic in the AASK study [52]. AASK also showed that the effectiveness of ACEI was greater in those with proteinuria. ARB therapy slowed the rate of CKD progression to ESRD in hypertensive diabetics with nephropathy and lessened proteinuria in the Irbesartan Diabetic Nephropathy Trial and Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study [55, 56]. Too frequently, care providers do not prescribe ACEIs or ARBs to older patients due to concern regarding complications from these medications, including hypotension and falls, increases in creatinine, and dangerous elevations in serum potassium [57]. However, multiple studies have shown that the complication rates from these medications are no higher for older than for younger populations [58–60].

27.8 Non-Renal-Associated Outcomes

Multiple non-renal-associated CKD outcomes assume greater prominence with worsening disease. For example, CKD patients carry marked associated cardiovascular and mortality risks. Due to the kidneys' role in sodium balance, kidney dysfunction tends to worsen hypertension, which increases the risk of cardiovascular disease. The prevalence of non-traditional risk factors such as inflammation and oxidative stress are also higher in patients with kidney disease [61], which may relate to the kidney's role in the clearance of some of these peptides.

27.8.1 Cardiovascular

In contrast to risk profiles for younger adults, in older patients, CKD may best be understood as a global risk marker for cardiovascular mortality more than a specific risk marker for ESRD. The 1-year mortality rate for Medicare patients who have a heart attack is 26%, whereas the 1-year mortality rate for Medicare patients who have Stage 3–5 CKD as well as a heart attack is 46% [1]. The incident stroke risk is over 30% higher in Medicare patients with CKD than in those without [1]. Patients with CKD are three times more likely than those without to be hospitalized for myocardial infarction, stroke or arrhythmia. In the Cardiovascular Health Study, patients with Stage 3 or more CKD had more than twice the prevalence of coronary artery disease and heart failure than did those without CKD, and they were over 50% more likely to have hypertension [62]. In the Cardiovascular Health Study, the risk for myocardial infarction for those with CKD and microalbuminuria was 2.5 times higher than for older adults who had neither of these comorbidities [21].

For patients who are ≥65 years of age, lower levels of renal function are an independent risk factor for *de novo* and progressive cardiovascular disease, as well as all-cause mortality over 3 years [62]. Even mildly elevated creatinine levels are prevalent in patients >65 years of age and can independently predict all-cause and cardiovascular mortality, cardiovascular disease and heart failure compared to older adults who don't have elevated creatinine [63]. When cystatin C-based calculations of eGFR were used to study longitudinal declines in kidney function, higher risks for heart failure, myocardial infarction and peripheral arterial disease were noted independent of demographics, baseline CKD stage or cardiovascular risk factors; however, creatinine-based calculations of the eGFR showed a higher risk only for heart failure [64].

Due to this very high cardiovascular risk, the American Heart Association has recommended that CKD be considered a coronary artery disease risk equivalent, as is diabetes [65]. The effectiveness of interventions to decrease this risk is not known due to the lack of treatment trials for cardiovascular disease in CKD. The recently published SHARP study showed that lipid reduction with simvastatin/ezetimibe reduced cardiovascular events in patients with CKD [41]. The SPRINT study will assess renal and cardiovascular outcomes with different degrees of blood pressure control. Outcomes from such studies will help to address whether these interventions prevent the progression of kidney disease and cardiovascular disease.

Albuminuria can also be used to risk-stratify individuals with CKD. While the current classification system considers albuminuria only in early CKD stages (Stage 1 and 2), recent studies have found that albuminuria and eGFR are independent risk factors for mortality, cardiovascular disease and progression to ESRD, as well as additive synergistic risk factors for cardiovascular mortality when both were considered in the same patient, especially in older patients [66]. The Second Nord-Trøndelag Health Study found that cardiovascular mortality risk associated with both lower eGFR and albuminuria was higher for patients >70 years of age than for younger patients, with this difference resulting in remarkably different excess risk. Comparing the number of cardiovascular deaths per 1,000 person-years between patients with an eGFR >75 ml/min/1.73 m^2 and no albuminuria vs. those with an eGFR <45 ml/min/1.73 m^2 and microalbuminuria, 4.1 more cardiovascular deaths occurred in patients <70 years of age compared with 63.6 more cardiovascular deaths in patients ≥70 years of age [66]. In this study, the combined data of albuminuria and eGFR when incorporated into traditional cardiovascular risk classification systems—which account for age, hypertension, diabetes, hyperlipidemia, and smoking—refined predictions of mortality risk among patients ≥70 years of age.

27.8.2 Cognitive and Physical Function

Individuals with ESRD have a high prevalence of cognitive impairment, which is likely due to vascular disease [67]. The risk begins earlier in CKD.

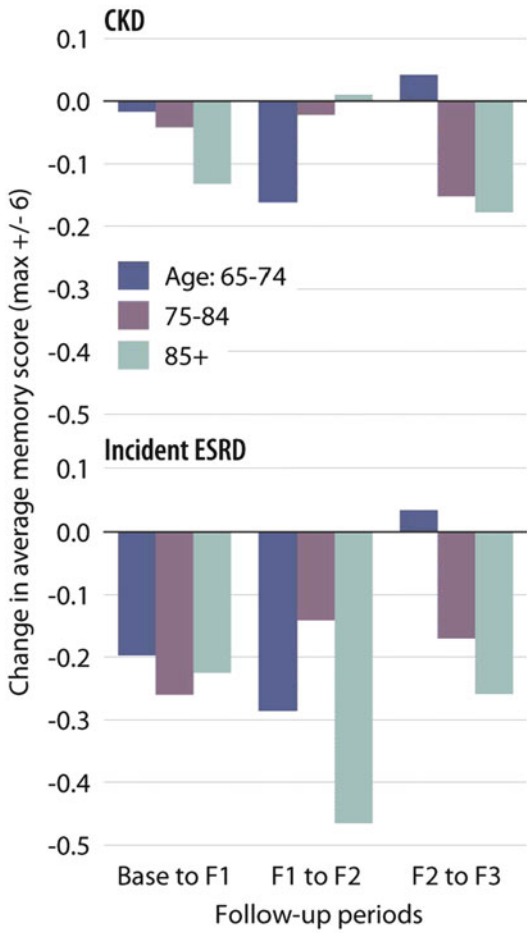

Fig. 27.5 Changes in average memory score in 2004–2006 nursing home residents in the minimal data set. Follow-up periods: F1≈2 months, F2≈6 months, F3≈12 months (Reprinted from: US Renal Data System (2010) [1])

Both albuminuria and low eGFR are associated with cognitive impairment, particularly on tests of attention and executive function [67, 68]. In nursing home patients, both CKD and ESRD are associated with declines in memory scores. The decline is greater with older age (Fig. 27.5) [1]. There have been few intervention studies on cognitive function in CKD. Despite the high homocysteine levels in this population, an ancillary study to the Homocysteine Study did not find an effect of B vitamins (which interact to control homocysteine) on cognitive function [69].

Individuals with CKD also have poorer physical function on tests of balance and gait speed [70]. They are more likely to be frail and to develop functional impairment on longitudinal studies [34, 71]. Individuals who are nursing home patients and develop ESRD are at particular risk for poor outcomes. In an analysis of the Minimum Data Set (a cohort of nursing home patients), Kurella Tamura et al. [72] found that the risk of mortality and decline in functional status as measured by the Minimum Data Set Activities of Daily Living score was very high in the first year after initiating dialysis. Within 3 months of starting dialysis, 61% had died and only 39% had the same functional status. At 1 year, 87% had died or had a decrease in functional status. The decline in physical function was greater with older age. Relative to individuals 65–74 years of age, the odds ratio of maintaining physical function at 12 months was 0.82 for those 75–84 years of age and 0.68 for those ≥85 years of age.

27.8.3 Bone Disease

As GFR declines, the kidney is less able to excrete phosphorus. The phosphorus retention leads to an increase in parathyroid hormone and fibroblast growth factor-23. At the same time, there is decreased α-1 hydroxylase activity, leading to decreased conversion of 25(OH) vitamin D to 1,25(OH)2 vitamin D, the active form. These factors lead to metabolic bone disease and possibly vascular calcification. While parathyroid hormone is used to treat osteoporosis, the constant elevation in CKD is associated with bone disease and treatments are directed at suppressing the hormone level. Due to the metabolic bone disease, individuals with CKD, and especially ESRD, are at increased risk for fracture [73].

27.9 Conclusion: Older Adults as a Unique CKD Subpopulation

In the past 10 years, CKD has been recognized as a public health threat and found to have 13% prevalence in the general US adult population. This disease is now the focus of intensive government,

research and clinical efforts to slow its increasing prevalence, high cost and unacceptably poor outcomes. With 46% of US adults >70 years of age carrying this often-unrecognized diagnosis, older adults are the largest and most complex CKD subpopulation.

The demographics of the aging population with CKD are changing the demographics of dialysis in the US. The fastest-growing group of US dialysis patients is >65 years of age, though only a small minority of older CKD patients actually survives long enough to develop ESRD [31]. However, more than half of the incident US dialysis patient population in 2006–2007 was ≥65 years of age and the incidence rate of patients ≥75 years of age who are initiating dialysis has increased 11% since 2000 [1].

Seniors with CKD have more chronic health conditions and poorer physical and cognitive functioning than those who do not. Some modifiable risk factors, such as obesity and physical functional status, are emerging as targets that may be especially relevant for older adults in addition to classical ones such as anemia, metabolic bone disease, blood pressure, and volume status. Optimal therapies even for these common CKD complications may be different for seniors, but much research needs to be done to explore this.

The physiology and structure of the aging kidney make detection and management of CKD in this population uniquely challenging. The equations used to develop criteria for CKD staging have not been validated in older populations. As currently formulated, staging criteria do not adequately offer renal or mortality prognoses for CKD patients, including the millions of older adults with CKD Stage 3, in part because they do not currently incorporate the degree of albuminuria. Older adults also face a uniquely elevated risk of acute kidney injury relative to younger adults, making AKI a particularly important risk factor for this population. There is a growing appreciation of the need for research uniquely focused on the kidney care of this older population. The time may come when guidelines for secondary and tertiary CKD prevention, such as blood pressure targets and optimal medication regimens, specifically address older adults.

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Osteoporosis

28

Jane A. Cauley

Abstract

Osteoporosis is a skeletal disorder that weakens bone and predisposes an individual to an increased risk of fracture. It has a major public health impact and current demographic trends point to an increasing number of individuals with osteoporosis worldwide. Current prevalence estimates using bone mineral density (BMD) criteria suggest that 50% of women and 32% of men have osteopenia (low bone mass) and 11% of women and 2% of men have osteoporosis. Hip fractures are the most devastating type of fracture, with major impacts on mortality, disability and institutionalism. Secular declines in hip fracture rates have been described for North America, but secular increases in hip fracture rates have been described for Asia. Age and low BMD are major risk factors for fracture in both men and women. Of importance, individuals who have the greatest number of risk factors have an increased risk of fracture. The World Health Organization has developed a fracture risk calculator (FRAX®) and many treatment guidelines incorporate FRAX® into their recommendation on who to treat. Future research needs include the identification of common genes that have large effects, the further understanding of the diabetes-bone-fat interface, and the identification of novel biomarkers of risk.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Osteoporosis • Hip fracture • Vertebral fracture • Risk factors • Prevention • Calcium • Vitamin D • Bisphosphonates • Dual energy x-ray absorptiometry • Bone architecture • Bone quality • Bone turnover

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Abbreviations

BMD	Bone Mineral Density
BMI	Body Mass Index
DALY	Disability Adjusted Life Years
DXA	Duel-energy X-ray Absorptiometry
FSH	Follicle-Stimulating Hormone
HR	Hazard Ratio
IGF	Insulin-like Growth Factor
IOF	International Osteoporosis Foundation
MrOS	Osteoporotic Fractures in Men Study
MSC	Mesenchymal Stem Cells
NHANES	National Health and Nutrition Examination Survey
NOF	National Osteoporosis Foundation
OPG	Osteoprotegerin
QCT	Quantitative Computed Tomography
RANKL	Receptor Activator of Nuclear factor κB Ligand
SD	Standard Deviation
SMR	Standardized Mortality Ratio
SWAN	Study of Women's Health Across the Nation
US	United States
vBMD	Volumetric Bone Mineral Density
WHI	Women's Health Initiative
WHO	World Health Organization
25(OH)D	25-hydroxyvitamin D

28.1 Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength which predisposes an individual to an increased risk of fracture [1]. Bone strength reflects the integration of two main features: (1) bone density, which accounts for an estimated 60–70% of bone strength and (2) bone quality, which reflects the rate of bone turnover, mineralization, material properties, microarchitecture (loss of horizontal struts, loss of connectivity) and geometry. Bone density can be easily quantified, while bone quality cannot. One issue regarding bone quality is that aging bone has deeper resorption cavities, which are spaces created when bone resorption by osteoclasts outpaces bone formation by osteoblasts. These cavities act to concentrate mechanical stress, and bones will tend to fracture at such sites.

In this chapter, we will review the pathophysiology of bone and the public health impact of osteoporosis. We will then review bone loss rates and patterns, fracture rates, and secular changes in hip fractures and other fractures. Finally we will review the prevalence of osteoporosis by bone mineral density, risk factors for fracture, and novel fracture risk factors that have been determined over the last decade.

28.2 Pathophysiology of Bone

Bone is constantly modified through resorption by osteoclasts and formation by osteoblasts. This remodeling process is triggered by osteocytes, which are osteoblast lineage cells that are embedded in bone. This process is an important repair function, enabling bone to repair micro-cracks and replace old bone.

In the 1990s, the discovery of receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) was a significant breakthrough that improved our understanding of bone remodeling. Up until this discovery, the presence of receptors on osteoblasts for most of the hormones, cytokines and growth factors that regulate osteoclast activity was a paradox [2] (Fig. 28.1). RANKL was found to be the osteoblast-derived factor, which is essential for osteoclast formation, function and survival. RANKL is expressed by bone-forming osteoblasts, bone marrow stromal cells and T and B lymphocytes that activate its receptor RANK, which is expressed on osteoblasts. After RANKL-induced RANK stimulation, several key regulating transcription factors, cytokines and enzymes are induced to promote the differentiation, proliferation, nucleation, activation and survival of osteoclasts. The result is a profound resorption of bone. OPG is a decoy receptor that binds to RANKL, which prevents RANKL/RANK from binding and activating osteoclastogenesis.

Although RANKL and RANK alone are not sufficient for bone resorption, the ratio of RANKL/

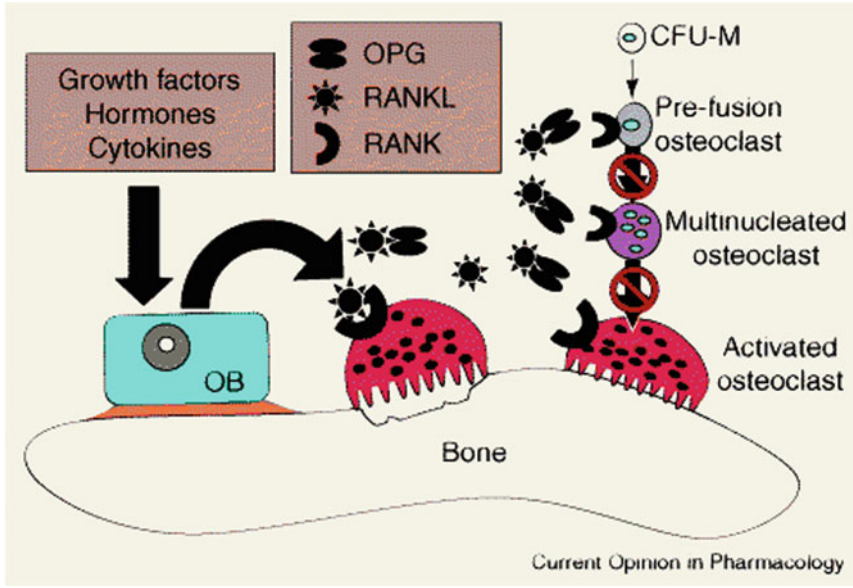

Fig. 28.1 Mechanism of action for OPG and RANKL [2]. Abbreviations: *OPG* Osteoprotegerin, *RANKL* Receptor activator of nuclear factor κB ligand (With permission: Kostenuik [2])

OPG may be the ultimate determinant of bone resorption. The over-expression of soluble RANKL in transgenic mice results in a skeletal phenotype with many similarities to post-menopausal osteoporosis, including low bone mineral density (BMD), increased porosity, increased bone resorption and skeletal fragility [3]. Each of these skeletal changes is also present in OPG knockout mice [4]. Estrogen deficiency increases RANKL, which leads to increased osteoclast recruitment and activation of osteoblasts and decreased osteoblast apoptosis. Estrogen suppresses RANKL production by osteoblastic cells and increases OPG production by osteoblastic cells [2]. Thus, with the onset of menopause, estrogen deficiency leads to an alteration in the ratio of RANKL to OPG which favors bone resorption and contributes to the accelerated rate of bone loss. However, several studies have demonstrated that estrogen deficiency plays a dominant role in mediating age-related bone loss in older men as well [5, 6].

Post-menopausal and age-related bone loss is not just due to accelerated bone resorption, but also to decreased bone formation. Decreased bone formation has been attributed to decreased paracrine production of growth factor and decreased levels of growth hormone and insulin-like growth factor (IGF) (reviewed in [7]).

28.3 Public Health Impact of Osteoporosis

The aging of the world's population is likely to lead to a greater worldwide prevalence of osteoporosis. In 2005, more than 2 million incident fractures were reported in the United States (US) alone, with a total cost of $17 billion [8]. Total costs including prevalent fractures exceeded $19 billion. Vertebral fractures account for 27% of all fractures; wrist fractures: 19%, hip fractures: 14% and pelvic fractures: 7%. Women account for 71% of all fractures and 75% of all fracture-related costs. Among women, whites account for the majority of all fractures (89%), followed by Blacks (4%), Hispanics (4%) and other women (3%). Even if rates stay the same, the aging of the world population is expected to increase the number of fractures and costs by 48%, to greater than 3 million fractures associated with a cost of $25.3 billion [8].

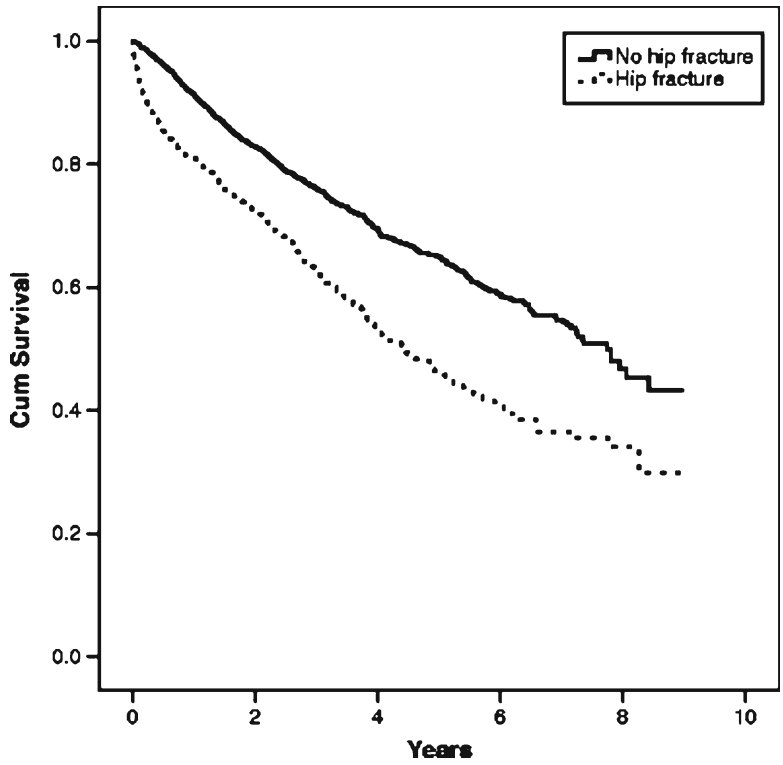

Fig. 28.2 Kaplan-Meier survival estimates for 781 women who sustained a hip fracture and 2,361 women without fracture [9] (With Permission: Gronskag et al. [9])

Hip fractures have a substantial impact on mortality. A recent study of older women from Norway showed that 10% of women who had a hip fracture died within 3 months of their hip fracture [9]. Excess mortality (death that occurs before average life expectancy) was highest a short time after the fracture, but persisted for several years after the fracture (Fig. 28.2). Of importance, the excess mortality in this study could not be explained by pre-fracture medical conditions. A recent meta-analysis found that women who had a hip fracture at 80 years of age had excess annual mortality rates of 8% at 1 year after the fracture, 11% at 2 years, 18% at 5 years and 22% at 10 years. The mortality risk following a hip fracture is greater in men. Men who had a hip fracture at 80 years of age had excess mortality rates of 18% at 1 year after the fracture, 22% at 2 years, 26% at 5 years and 20% at 10 years, and they had a nearly 3-fold increased mortality in the year after their hip fracture [10, 11]. Excess mortality decreased during the first 2 years after the fracture, but did not return to the rate of age-matched control participants during the 10-year follow-up. Stratification by health status suggested that hip fracture increases short-term mortality (1-year) but not long-term mortality in "healthy" (good to excellent health status) women ≥80 years of age [12]. Black women have a greater risk of mortality after a hip fracture than do White women [13].

A decline in hip fractures was observed from 1985 to 2005 in the Medicare sample (described below), and this was accompanied by declines in age and risk-adjusted mortality following hip fractures in women of 11.9% for 30-day mortality, 14.9% for 180-day mortality and 8.8% for 360-day mortality. In men, the accompanying declines were 21.8% for 30-day mortality, 24.5% for 180-day mortality and 20% for 360-day mortality [14].

The impact of osteoporotic fractures on mortality extends beyond hip fractures. In the Australian

Table 28.1 Age-adjusted standard mortality according to fracture type for the first 5 years after fracture [16]

Fracture type and age (years)	Women			Men		
	Deaths (n)	Person years	SMR (95% CI)	Deaths (n)	Person years	SMR (95% CI)
Hip						
All ages	89	509	2.53 (2.04–3.13)	41	147	3.52 (2.58–4.80)
60–74	12	84	8.28 (4.65–4.73)	5	55	2.43 (1.01–5.86)
≥75	77	425	2.24 (1.78–2.82)	36	92	3.65 (2.62–5.09)
Vertebral						
All ages	93	994	1.76 (1.43–2.17)	52	307	2.26 (1.72–2.98)
60–74	22	327	3.77 (2.45–5.81)	13	91	3.65 (2.42–1.27)
≥75	71	667	1.45 (1.14–1.84)	39	216	1.88 (1.37–2.59)
Major[a]						
All ages	48	591	1.60 (1.20–2.13)	28	209	2.01 (1.38–2.92)
60–74	13	227	3.23 (1.85–5.62)	7	105	2.22 (1.05–4.67)
≥75	35	364	1.31 (0.94–1.83)	21	104	1.80 (1.17–2.77)
Minor[a]						
All ages	76	1,349	1.38 (1.10–1.74)	33	400	1.64 (1.16–2.31)
60–74	17	732	1.43 (0.88–2.33)	6	225	0.94 (0.42–2.11)
≥75	59	617	1.37 (1.06–1.78)	27	175	1.82 (1.24–2.66)

With permission. Bliuc et al. [16]
Abbreviations: *CI* confidence interval
[a]Major fracture included pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus. Minor fractures included all remaining osteoporotic fractures

Dubbo cohort study, mortality increased in the first year after all major fractures. In women, age-standardized mortality ratios were 2.43 (95% confidence intervals [CI] 2.02–2.93) for hip fractures; 1.82 (95% CI 1.52–2.17) for vertebral fractures and 1.65 (1.31–2.08) (95% CI 1.70–2.14) for other major fractures [15]. In men, rates were 3.51 (95% CI 2.65–4.66) for proximal femur fractures, 2.12 (95% CI 1.66–2.72) for vertebral fractures and 1.70 (95% CI 1.23–2.36) for other major fractures [16]. All low trauma fractures were associated with an increased mortality risk for 5–10 years [16]. For both men and women, mortality was increased for all ages and for all fractures, except for minor fractures which showed increased mortality only in individuals ≥75 years of age (Table 28.1).

Both clinical and morphometric or radiographic vertebral fracture in women [17–19] and in men [20] are associated with an increased risk of mortality. This increased risk is due in large part to underlying conditions such as frailty, which are associated with both vertebral fracture and death.

Hip fractures are also associated with increased risks of disability, institutionalization and loss of independence [21]. Prevalent radiographic vertebral fractures are associated with back pain and health-related quality of life [22, 23]. The likelihood of back pain, reduced health-related quality of life, and a clinical diagnosis of vertebral fracture increase with the severity and number of fractures [22–24]. Incident radiographic vertebral fractures (i.e., not present on prior radiographs) were associated with an increased risk of back pain and back-related disability. The strength of these associations was greater among individuals who had a clinically-recognized vertebral fracture [25, 26]. Fracture-related disability may also be greater among patients who have lumbar fractures than among those who have thoracic fractures [23, 25]. Thus, both hip and vertebral fractures are associated with an increase in disability. Figure 28.3 shows the disability adjusted life years (DALYs) lost to osteoporotic fractures in Europe compared to DALYs lost to a selection of non-communicable diseases. The number of DALYs

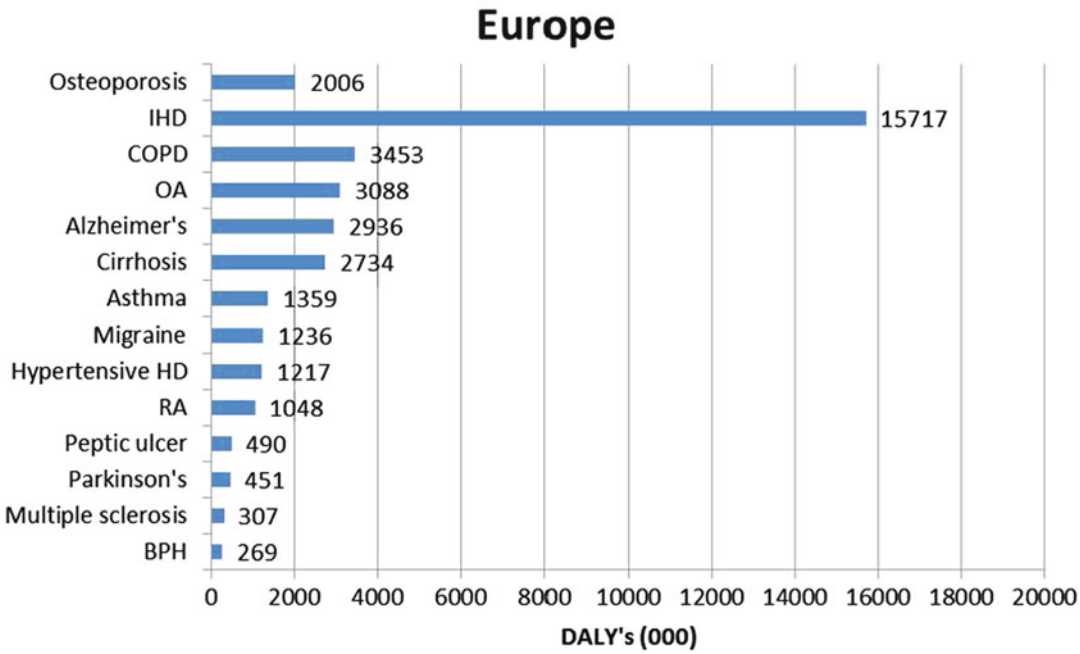

Fig. 28.3 Disability-adjusted life-years (DALYs) lost due to a selection of noncommunicable diseases in Europe [27]. Abbreviations: *BPH* benign prostatic hyperplasia, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *OA* osteoarthritis, *RA* rheumatoid arthritis (With permission: Johnell and Kanis [27])

lost to osteoporosis is slightly less than the number lost to Alzheimer's disease, but is greater than the numbers lost to many other conditions.

We recently showed that the impact of osteoporosis on disability extends to wrist fractures [28]. Women with incident wrist fractures had greater annual functional decline even after adjustment for age, body mass index and health status. The occurrence of a wrist fracture increased the odds of having a clinically-important functional decline by 48% (odds ratio: 1.48, 95% CI 1.04–2.12), even after adjustment for age, body mass index, health status, baseline functional status, lifestyle factors, comorbidities and neuromuscular function.

28.4 Rates and Patterns of Bone Loss

Peak bone mass is achieved in the third decade of life, and the timing may differ for cortical and trabecular bone. Peak bone mass is largely determined by genetic factors, but environmental (exercise/loading) and dietary (calcium/vitamin D, protein) factors influence whether or not an individual achieves their full genetic potential for skeletal mass [29]. Osteoporosis has been referred to as a pediatric condition with adult consequences because the amount and quality of a person's skeleton is dependent upon whether or not the individual achieved their full genetic potential for skeletal mass [29]. It is critical that we identify factors that determine peak skeletal mass to improve our understanding of an individual's risk of fragility fractures late in life. Age-related bone loss begins at a slow rate at about age 40 in both men and women, and it is accelerated at menopause in women.

Age-related loss in bone has been universally described in men and women of all ethnic groups. Bone mineral density (BMD) of the femoral neck was measured in the National Health and Nutrition Examination Survey (NHANES III) in 1988–1994 and NHANES 2005–2008 [30]. As shown in Fig. 28.4, femoral neck BMD was

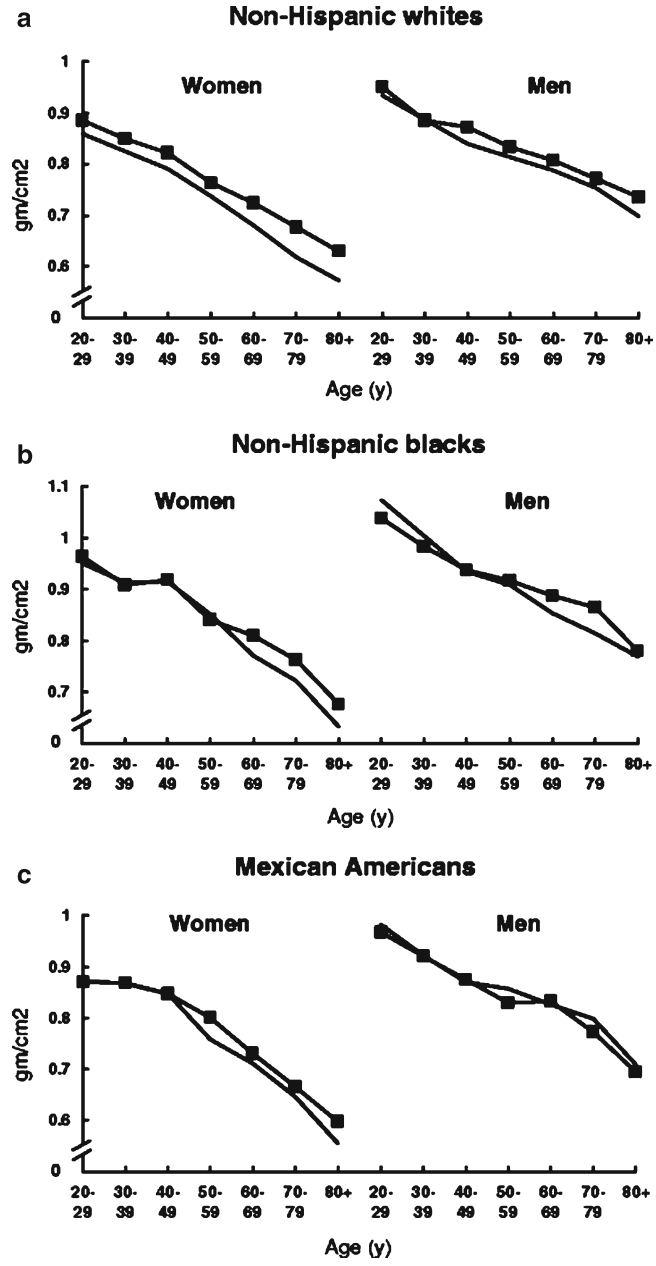

Fig. 28.4 Mean femoral neck BMD by age and sex in US adults between 1988–1994 and 2005–2008: demographic patterns and possible determinants: (**a**) Non-Hispanic Whites, (**b**) Non-Hispanic Blacks, (**c**) Mexican-Americans [30]. Mean femur neck BMD. – NHANES III (1988–1994), ■ NHANES 2005–2008. Abbreviations: *BMD* Bone mineral density, *NHANES* National Health and Nutrition Examination Survey (With permission: Looker et al. [30])

higher in NHANES 2005–2008 than in NHANES III: the age-adjusted mean for the total population ≥20 years of age was 0.839 gm/m^2 in NHANES 2005–2008 vs. 0.816 g/cm^2 in NHANES III [30]. BMD declined cross-sectionally across age groups in both men and women, as well as in Whites, Blacks and Mexican-Americans.

In the NHANES 2005–2008 data, differences in the patterns of lumbar spine BMD with age were evident between men and women [31]. Lumbar spine BMD declined significantly in each decade between 40–49 years of age and 70–79 years of age in women but not in men. These patterns, however, may be confounded by artifactural changes in the spine which are measured as bone mineral by dual-energy x-ray absorptiometry (DXA) (e.g., aortic calcification, osteophytes). These artifactural changes increase

with age, are more common in men and often result in falsely elevated BMD values.

28.4.1 Menopause

Menopause represents a vulnerable time in a woman's life for a number of reasons, but for her skeletal health in particular. The estrogen deficiency associated with menopause increases bone remodeling, which leads to an imbalance between bone formation and bone resorption [32, 33]. This increase in bone remodeling persists over several years and becomes associated with an increased rate of bone loss [34, 35]. Early cross-sectional studies compared BMD in pre-, peri- and post-menopausal women and generally reported lower BMD in the peri- and post-menopausal periods [36–38]. However, these cross-sectional studies cannot determine the point during the transition that bone loss begins, and cannot determine rates of bone loss during the various phases of the transition as the phases are outlined in the Stages of Reproductive Aging Framework [39].

To our knowledge, the first longitudinal study of bone loss during the menopausal transition was published in 1987 by Riggs et al. [40]. A total of 139 women were followed for a median of 2 years and were classified as post-menopausal if they had no menstrual periods for ≥6 months and had estradiol levels lower than 50 pg/ml. All other women were classified as pre-menopausal. BMD was measured using older methods (e.g., single and dual photon absorptiometry techniques), which have a lower precision. BMD at the mid-radius did not change before menopause, but it decreased by about 1% per year after menopause. For the lumbar spine, significant bone loss occurred both before (−1.32%/year) and after (−0.97%/year) menopause. These results suggested that bone mineral density at primarily trabecular bone sites (e.g., the vertebrae) decreases substantially before menopause.

Other earlier studies showed bone loss in the peri-menopausal period but not in the pre-menopausal period [41]. The first longitudinal study that used state-of-the-art DXA demonstrated significant change in femoral neck BMD but not lumbar spine BMD among peri-menopausal women [42]. A longitudinal study of 75 women (mean age 46 years at baseline) who were followed for 9.5 years showed that bone loss began about 2–3 years before menopause and ended 3–4 years after the last menses [43]. Over menopause, the total loss in the spine and femoral neck were 10.5 and 5.3%, respectively. Results suggested that menopausal bone loss in the hip is a composite of loss that is due to estrogen deprivation and age, but in the spine it is due to estrogen deprivation alone [43].

In summary, the initial longitudinal studies of bone loss at menopause had conflicting results regarding whether or not women experienced bone loss in the pre-menopausal period. Most showed loss in the peri- and post-menopausal period, with rates of loss slowing several years after the final menstrual period. However, most of these studies were limited by small sample sizes, short follow-up, variations in the definition of menopausal rates, use of older bone densitometers and/or changes in technology over the follow-up period.

The Study of Women's Health Across the Nation (SWAN) is a multicenter study designed to examine a wide range of issues for women who are traversing menopause. One of the foci is on the skeleton and BMD, which was measured annually in 1902 African-American, White, Chinese or Japanese women [44]. There was little change in lumbar spine or total hip BMD during pre- or early peri-menopause. However, bone loss accelerated markedly in the late peri-menopause, with an average loss of 0.018 g/cm^{2}year (1.6%) and 0.010 g/cm^{2}year (1.0%) from the spine and hip, respectively, ($p<0.001$ for both). In post-menopausal women, rates of spine and hip bone loss were 0.022 g/cm^{2}year (2.0%) and 0.013 g/cm^{2}year (1.4%) respectively ($p<0.001$ for both) (Fig. 28.5).

Regarding weight, bone loss during late peri- and post-menopause was approximately 35 to 55% slower, respectively, in women in the top tertile (kg >77.3) compared to those in the lowest tertiles (kg <60.7). Apparent ethnic differences in rates of spine bone loss were largely explained by differences in body weight. These results are for

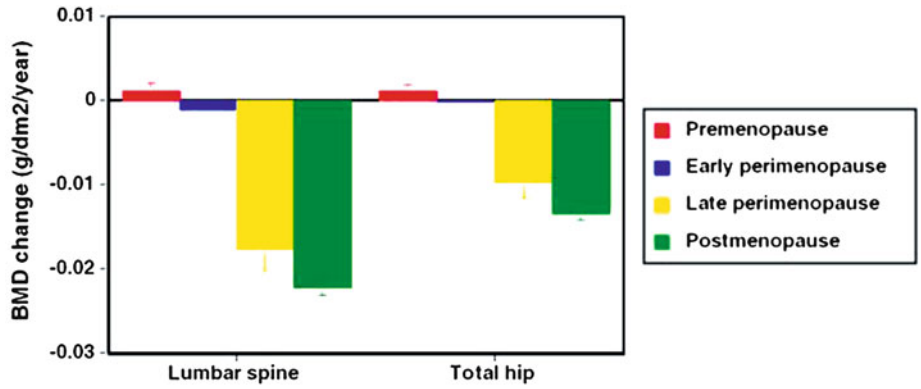

Fig. 28.5 Annual rate of change in BMD of the lumbar spine and total hip in premenopausal (*red bars*), early perimenopausal (*blue bars*), late perimenopausal (*yellow bars*), and postmenopausal (*green bars*) women (n = 1,902) [44]. Rates of change were estimated from multivariable linear mixed models and adjusted for multiple covariates. Error bars represent 95% confidence limits. Comparisons were made across status categories: early peri- vs. premenopausal, $p < 0.001$ (spine) and $p = 0.002$ (hip); late peri- vs. early perimenopausal, $p < 0.001$ (spine) and $p < 0.001$ (hip); and post- vs. late perimenopausal, $p = 0.002$ (spine) and $p < 0.001$ (hip). Abbreviation: *BMD* Bone mineral density (With permission: Finkelstein et al. [44])

follow-up over the first five annual follow-up visits. SWAN has continued to collect annual BMD measures over the first 12 annual follow-up visits. This will enable the description of BMD changes that occur from the pre-menopausal period through many years post-menopause, even into the seventh decade of life.

In SWAN, follicle-stimulating hormone (FSH) and increases in FSH were found to correlate strongly with transmenopausal changes in areal BMD [45]. Estradiol was shown to correlate with changes in BMD, with higher levels associated with slower rates of bone loss and inversely associated with changes in periosteal diameter [46].

Although BMD is a major determinant of bone strength, it does not capture important aspects of bone quality such as the microarchitecture and geometry of bone. Transmenopausal changes in trabecular bone structure were described in 38 women who underwent paired transilial biopsies pre-menopause and post-menopause (12 months after the final menstrual period). Analyses of these biopsies showed that bone volume/total volume and trabecular number decreased by almost 13% while trabecular spacing increased by 7%. There was an overall 10% decrease in apparent density.

Bone strength is also a function of bone size, with larger bones conferring greater strength. Changes in bone size were described in 108 women who were followed starting at the time of menopause and over a mean period of 15 years [46]. Medullary bone diameter and periosteal diameter increased while BMD decreased, all of which were correlated with serum estradiol levels. These results suggest that periosteal apposition may compensate in part for the decreased bone strength. Thus, focusing solely on bone density across menopause may miss important changes in bone strength that are reflected in trabecular architecture and bone size.

There are likely several mechanisms that underlie bone loss at menopause. Estrogen deficiency leads to T-cell activation, and studies in mice have shown that ovariectomy does not induce bone loss in mice that have been depleted of T-cells with T-cell antibodies [47]. The activation of T-cells by ovariectomy increases T-cell production of TNF, a cytokine that stimulates osteoclast formation by potentiating the activity of RANKL and by promoting the production of RANKL by osteoblast cells [48]. Gene expression also differs in pre- and post-menopausal women [49].

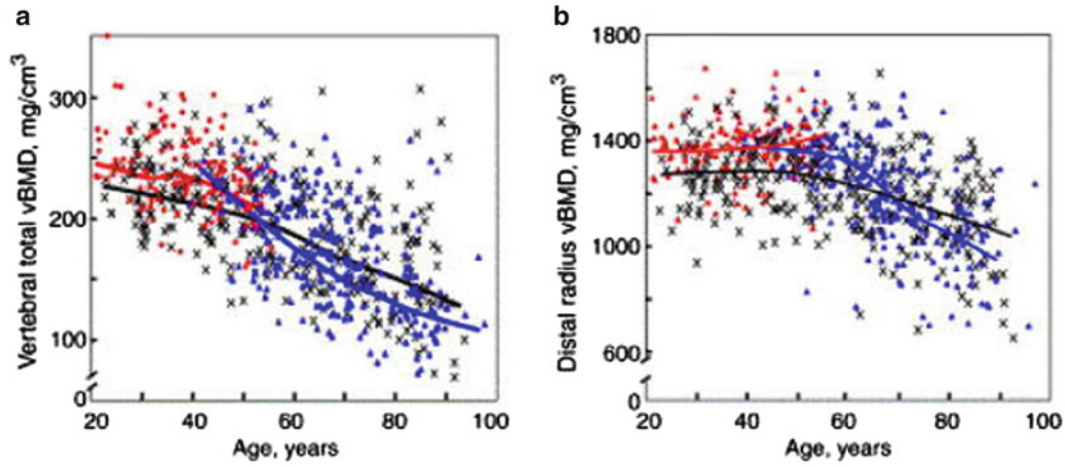

Fig. 28.6 Volumetric Bone Mineral Density (vBMD): (**a**) Values for vBMD (mg/cm^3) of the total vertebral body in a population sample of Rochester, Minnesota, women and men between 20 and 97 years of age. (**b**) Values for cortical vBMD at the distal radius in the same cohort [7]. Individual values and smoother lines are given for premenopausal women in *red*, for postmenopausal women in *blue*, and for men in *black*. All changes with age were significant ($p < .05$) (With permission: Clarke and Khosla [7])

28.4.2 Age

Although bone loss accelerates around menopause, most bone loss occurs after 65 years of age. Rates of areal BMD loss have been shown to increase at extreme ages in both men [50] and women [51]. In women, the rate of decline in total hip BMD steadily increased from 2.5 mg/cm^2/year in women 67–69 years of age to 10 mg/cm^2/year in those ≥85 years of age [51]. The average loss of bone in the total hip is sufficient to increase the risk of hip fracture by 21% every 5 years in women ≥80 years of age. In men, the loss of femoral neck BMD for men 85 years of age was 2.5 times greater than that observed in men 65 years of age. Such bone loss in 85-year-old men may be sufficient to increase the risk of hip fracture by 25% [50]. The etiology that underlies these patterns is multifactorial, but contributions are likely made by increased parathyroid hormone, vitamin D deficiency or insufficiency, increased inflammation, and declines in sex steroid hormones including estradiol and testosterone.

Most of the earlier studies used areal BMD as measured by DXA. More recent studies that use quantitative computed tomography (QCT) can distinguish trabecular and cortical volumetric BMD, and have shown different patterns of bone loss by type of bone. Trabecular volumetric bone loss appears to begin in the third decade of life, with decreases in lumbar spine volumetric BMD (vBMD) that are larger in women than in men (55 vs. 45%, $p < 0.001$) (Fig. 28.6) [52]. It was previously thought that trabecular bone loss was largely due to estrogen deficiency and cortical bone loss was due to age-related factors. The new paradigm suggests that trabecular vBMD loss is independent of estrogen deficiency because it begins in an estrogen-replete setting, while cortical bone loss is largely linked with estrogen deficiency since it appears to begin around the time of menopause. There is a need for a greater understanding of the factors that contribute to these patterns.

Until recently, the focus of much research was on trabecular bone loss because trabecular bone has a larger surface area and thus has higher remodeling rates. Vertebral fractures, a hallmark of osteoporosis, occur in bones that are largely comprised of trabecular bone. But cortical bone comprises 80% of the skeleton, and >70% of all fractures are non-vertebral in sites that are mainly cortical. Zebaze et al. [53] recently described patterns of bone loss using QCT in 122 women. Of the total bone lost with age, 68% was cortical

and 32% was trabecular. Sixteen percent of bone was lost from 50 to 64 years of age compared with 84% lost after 65 years of age. Micrographs from post-mortem specimens showed that with advancing age, much of the cortex is trabecularised by large and coalesced pores. Although this study was small and cross-sectional, results demonstrated the magnitude of intracortical remodeling. It also demonstrated the effect of intracortical porosity in producing most of the bone loss with age and the bone fragility that results from the concentration of mechanical stress at these pores. Further studies are needed to substantiate the role of cortical porosity in fracture etiology.

Geometric changes in bone also occur with advancing age. Aging has been associated with increased cross-sectional area at the femoral neck and radius due to continued periosteal apposition. The bone marrow space increased more rapidly than did the cross-sectional area due to continued endosteal bone resorption, but because the rate of periosteal apposition was slower than the rate of endosteal bone resorption, cortical area and thickness declined with aging. However, because periosteal apposition increases bone diameter, the ability of the bone to resist mechanical forces increased, offsetting the decrease in bone strength that resulted from decreased cortical area [7, 52].

28.4.3 Do All Women Lose Bone with Aging?

The landmark article by Rowe and Kahn [54] distinguished "successful" from "usual" aging, emphasizing that the physiologic, psychological and adaptive changes that promote chronic disease, disability and death are not the inevitable consequences of aging. Successful aging is multidimensional, and several definitions have been proposed. We hypothesized that there may be a subset of women who maintain their BMD, and that their fracture, disability and mortality rates will be lower and thus, the maintenance of BMD could be considered a biomarker of successful aging. We carried out these analyses in the Study of Osteoporotic Fractures, a cohort study of 9,704 women who were recruited from 1986 to 1988 in four clinics in the US [55]. Total hip BMD was measured in 8,224 women and we followed the women longitudinally for up to 15 years. Bone loss was not observed in all women: 9% of women (n = 724) maintained their BMD over the 15-year period. The mean age of study participants at the end of follow-up was 85 years, which indicates that these women maintained their BMD into old age. These women also experienced a 50% lower mortality rate. These associations were independent of weight loss or medication use (e.g., bisphosphonates [antiresorptive medications], estrogen). Our results suggest that bone loss is not an inevitable consequence of aging.

28.5 The Rates of Fracture

The incidence of fracture increases with age in both men and women (Table 28.2), but the patterns differ by the site of fracture [8]. Hip fracture rates increase exponentially with age, doubling from 65–69 to 70–74 years of age and doubling again at 75–79 years of age. After age 80, there is a further exponential increase in hip fracture rates. Vertebral fractures increase more linearly with age in both men and women. Wrist fractures are the most common fracture in women and men 50–54 years of age and the rate increases up to 60 years of age. There is a leveling off of rates after 60 years of age. Pelvic and other fractures are less common but follow linear patterns with age.

Worldwide, the frequency of hip fractures varies greatly by race and ethnicity [57]. The lifetime risk of hip fracture at 50 years of age in the US is 15.8% in women and 6.0% in men, compared to China which has rates of 2.4% in women and 1.9% men, and Latin America which has rates of 8.5% for women and 3.8% for men [57–59]. Rates of hip fracture are highest in Northern European countries, where the 10-year relative probability of hip fractures—averaged for age and sex, and adjusted to the probability of Sweden—is 1.24 in Norway compared to 0.62 in Singapore and 0.08 in Chile [57].

There is much less worldwide ethnic and racial variability in morphometric vertebral fractures

Table 28.2 United States fracture incidence rates [8]

	Fracture type				
Age (years)	Hip[a]	Vertebral[b]	Wrist[b]	Pelvis[b]	Other[b,c]
Per 10,000 white women					
50–54	3.8	22.5	42.3	1.3	51.6
55–59	6.5	21.5	57.9	1.7	89.3
60–64	11.2	34.9	90.0	5.5	73.4
65–69	20.6	68.2	92.2	20.0	70.0
70–74	41.0	116.7	96.1	13.7	114.5
75–79	88.7	156.6	101.8	60.0	128.7
80–84	180.1	257.9	96.7	64.5	174.1
85–100	324.7	313.2	96.6	108.3	199.1
Per 10,000 white men					
50–54	2.0	9.4	25.4	4.0	53.5
55–59	2.9	16.0	14.4	1.6	52.7
60–64	5.5	8.1	16.1	6.0	60.5
65–69	9.4	49.7	14.2	7.1	73.5
70–74	19.5	41.5	6.4	9.6	79.9
75–79	40.2	66.8	9.0	20.0	58.1
80–84	92.2	156.7	14.9	29.9	74.7
85–100	235.7	253.3	37.5	37.5	138.9

With permission. Burge et al. [8]
[a]Calculated from National Immunization Survey 2001
[b]Source: [56]
[c]Other includes clavicle, humerus (shaft/distal, proximal), leg (shaft/distal femur, patella, tibia/fibia), and hands/fingers

[58, 60, 61]. For example, the prevalence of vertebral fractures in women ≥65 years of age is 70% for White women, 68% for Japanese women, 55% for Mexican women and 50% for African-American women. This is surprising since both vertebral fracture and hip fracture are the hallmark of osteoporosis. The factors that contribute to the lower geographic and racial variability in vertebral fractures are unknown.

Sex is a strong determinant of the risk of fracture, depending on ethnicity and race. In general, White women experience hip fractures about twice as often as do White men at every age, especially in countries with high incidence rates, but the sex difference in hip fracture risk in Blacks and Asians is negligible. Rates of hip fracture are about 50% lower in Black women and Asian women than in US White women. Ethnic and race variability is much lower for men, although White men tend to have slightly higher hip fracture rates than do Asian men and Black men [58].

28.6 Secular Changes in Hip and Other Fractures

Hip fracture rates have declined in the US [14] and Canada [62]. In the US, the age-adjusted incidence of hip fractures increased from 1986 to 1995, then steadily declined from 1995 to 2005. In women, rates increased 9% from 1986 to 1995, then declined by almost 25% from 1995 to 2005. In men, rates increased 16% from 1986 to 1995, then declined by 19% from 1995 to 2005. These data are based on a 20% sample of Medicare enrollees and thus, should be generalizable to the US. The reason for the decline in hip fracture is unknown. Bisphosphonates were released in 1995 and their use could have contributed to the decline. Other factors that may have contributed to this decline include the epidemic of obesity, lifestyle changes such as use of calcium and vitamin D supplements, and increased physical activity.

Consistent with observations in the US and Canada, hip fracture rates in Europe and Oceania

have also either stabilized or decreased [63]. In contrast, rates of hip fracture in Asia appear to be increasing. In Beijing, between 1990–1992 and 2002–2006, hip fracture rates for those averaging 50 years of age has increased 2.76-fold (95% CI 2.68–2.84) in women and 1.61-fold (95% CI 1.56–1.66) in men. For those >70 years of age, the age-specific rates increased 3.37-fold (95% CI 3.28–3.43) in women and 2.01-fold (95% CI 1.95–2.07) in men. Even from 2002 to 2006, rates for those >50 years of age increased by 58% in women and 49% in men [64]. Secular increases have also been reported in Hong Kong, Singapore and Japan [63]. Cooper et al. [65] estimated that by the year 2050, 51% of the world's hip fractures would occur in Asia. However, these projections did not consider these secular increases and thus may have seriously underestimated the number of hip fractures in Asia.

Secular increases in hip fracture rates have been described for Hispanics in California [66]. There is little data from outside the US regarding hip fractures in Hispanics, but rates of hip fracture in Mexico have increased significantly for men and women by 1% per year from 2000 to 2006 [67]. Demographic changes estimated for Mexico indicate that the number of hip fractures will increase from about 30,000 in 2005 to an expected 155,000 in 2050. Thus, osteoporotic fractures will have an increasing public health impact on developing countries in Asia and Latin America.

28.7 Prevalence of Osteoporosis by BMD

The World Health Organization (WHO) defined osteopenia and osteoporosis on the basis of BMD: Osteopenia is BMD that is between one standard deviation (SD) and 2.5 SD below the mean of the young reference group, while osteoporosis is a BMD that is ≥2.5 SD below the mean of the young reference group [1]. As recommended more recently by the WHO, 20- to 29-year-old non-Hispanic White women from NHANES III were used as the reference group to derive these cutoff values for men and women [68].

The NHANES survey was carried out in a nationally representative sample of the US population in 1988–1994 and 2005–2006 [69]. The more recent data showed that 49% of older women and 30% of older men have osteopenia at the femoral neck, and that 10% of older women and 2% of older men have osteoporosis at the femoral neck (Fig. 28.7). This would translate to approximately 23 million women and 12 million

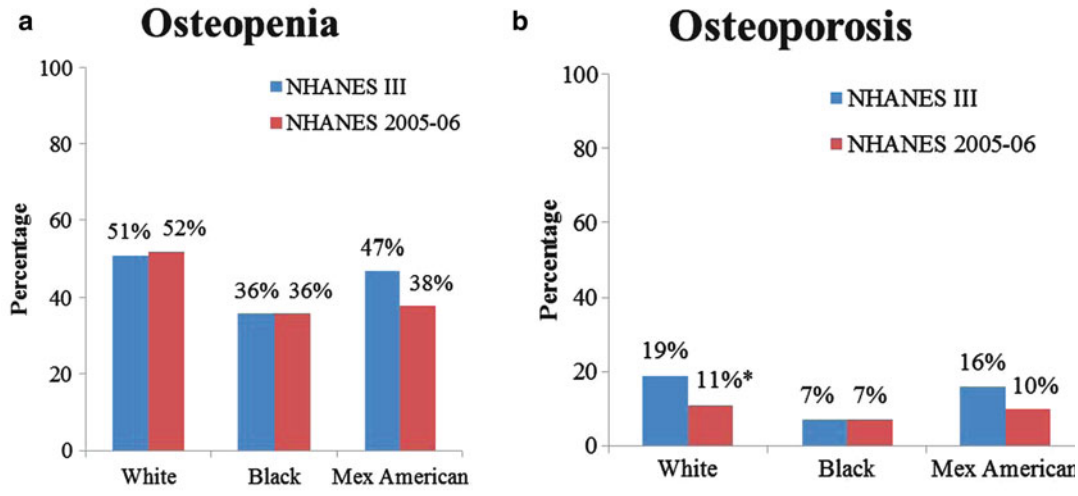

Fig. 28.7 Age-adjusted prevalence of (**a**) osteopenia and (**b**) osteoporosis at the femoral neck in US women ≥50 years of age by race/ethnicity: NHANES III compared with NHANES 2005–2006 [69]. *p < 0.05. Abbreviation: *NHANES*, National Health and Nutrition Examination Survey (With permission. Looker et al [69])

men with osteopenia, and 4.5 million women and 0.8 million men with osteoporosis.

From 1988–1994 to 2005–2006, the prevalence of osteoporosis at the femoral neck declined from 19 to 11% in White women, but the prevalence of osteoporosis was similar in Black women during the two time periods (Fig. 28.7) [69]. Among Hispanic women, prevalence declined from 16 to 10%, but this decline was not statistically significant. For men, the prevalence of osteoporosis at the femoral neck declined from 5 to 2% and osteopenia declined from 34 to 32%. The examination of ethnic-specific groups showed that rates of osteopenia declined in White men but increased to a non-significant degree in Black men and Hispanic men. Further adjustment for body mass index (BMI) and medication use had no effect on the results. In summary, the prevalence of osteoporosis declined and is consistent with secular decreases in hip fracture. Of importance, however, the number of women with osteoporosis is substantial and likely to increase due to the current demographic trends.

28.8 Risk Factors for Fracture

Most fractures occur in men and women due to low BMD [70]. Total hip BMD is strongly associated with the risk of hip fracture in men (a 3.2-fold increased risk per sex-specific SD decrease in BMD, 95% CI 2.4–4.1). This association was stronger than that observed in older women: 2.1 (95% CI 1.8–2.4) ($p < 0.001$ for interaction) [71]. The incidence of fracture decreases with increasing BMD in both men and women (Fig. 28.8). A 65–69-year-old White man with a T-score of −2.5 (using gender-specific norms) has a 7.6% (95% CI 5.6–10.2) cumulative 3-year risk of fracture, whereas a woman of same age and race has a 16.8% cumulative risk of non-vertebral fracture.

Other established risk factors for fracture include older age, White or Asian race, previous history of fracture, parental history of fracture, history of falls, low body weight or weight loss, poor self-reported health status, cigarette smoking, low physical activity and poor neuromuscular function. Inconsistent associations have been reported for caffeine intake and alcohol consumption. Most fractures occur due to a fall. Hence, many risk factors (e.g., long-acting benzodiazepines, visual impairment) may increase the risk of fracture due to an increased risk of falling. Prevention of osteoporotic fracture must include attention to the risk of falls and their prevention.

Vertebral fractures are the hallmark of osteoporosis. They are the most common osteoporotic fracture, with prevalence estimates of 35 to 50% among women >50 years of age [58]. The overall

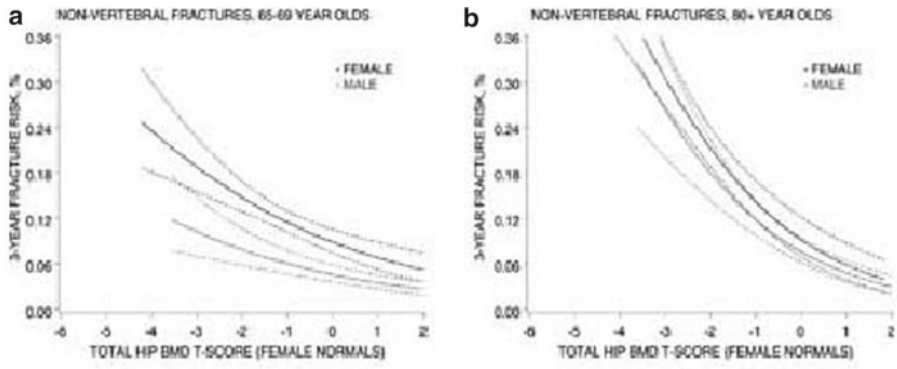

Fig. 28.8 Three-year risk of fracture (and 95% confidence limits) by sex-specific total hip BMD T-score and age in older women and men: (**a**) 65–69 years of age, (**b**) ≥80 years of age [71]. T-scores for both sexes using female normal values for the total hip are equivalent to the following BMD values: T-score of −2 = 0.698 g/cm^2; T-score of −1 = 0.820 g/cm^2; T-score of 0 = 0.942 g/cm^2. Abbreviation: *BMD* Bone mineral density (With permission. Cummings et al. [71])

prevalence of vertebral fractures in older men is about 20% [20]. About 700,000 vertebral fractures occur each year in the US. Only about one-third to one-quarter of vertebral fractures are clinically recognized [24, 72]. Prevalent vertebral fractures are one of the strongest risk factors for fracture. Women who had a prevalent vertebral fracture at enrollment into the Study of Osteoporotic Fractures had a 4-fold greater likelihood of having an incident vertebral fracture over the following 15 years [73]. Women who had two or more prevalent vertebral fractures had a 5-fold increased risk of fracture. These associations were independent of BMD, age and other risk factors. These results highlight the need for targeting women who have prevalent vertebral fractures for treatment.

What is certain is that women who have multiple risk factors and low BMD have an increased risk of fracture [74]. However, most studies have been carried out in White women. Fracture rates are lower in non-White women, but the consequences may be greater. In addition, the number of fractures is expected to increase in non-White women due to current demographic trends. There are limited prospective data on fracture risk factors in non-White women.

We studied 159,579 women 50–79 years of age who were enrolled into the Women's Health Initiative (WHI) [75]. Information on risk factors was obtained by questionnaire or examination. Non-spine fractures that occurred after study entry were identified over an average follow-up of 8 ± 2.6 (SD) years. Annualized rates of fracture were Whites: 2.0%, Blacks: 0.9%, Hispanics: 1.3%, Asians: 1.2%, and Native Americans: 2.0%. Significant predictors (hazard ratio [HR] and 95% CI) of fractures by ethnic group were as follows: Blacks: at least a high school education, 1.22 (1.0–1.5); (+) fracture history, 1.7 (1.4–2.2); and more than two falls, 1.7 (1.9–2.0); Hispanics: height (>162 cm), 1.6 (1.1–2.2); (+) fracture history, 1.9 (1.4–2.5); more than two falls, 1.8 (1.4–2.3); arthritis, 1.3 (1.1–1.6); corticosteroid use, 3.9 (1.9–8.0); and parental history of fracture, 1.3 (1.0–1.6); Asians: age (per 5 years), 1.2 (1.0–1.3); (+) fracture history, 1.5 (1.1–2.0); current hormone therapy, 0.7 (0.5–0.8); parity (at least five), 1.8 (1.1–3.0); more than two falls, 1.4 (1.1–1.9); Native American: (+) fracture history, 2.9 (1.5–5.7); current hormone therapy, 0.5 (0.3–0.9).

Of importance, women who had ≥8 risk factors had more than a 2-fold higher rate of fracture compared to women who had ≤4 risk factors (Fig. 28.9). Irrespective of their ethnicity, women who had multiple risk factors had a high risk of fracture. Targeting these high-risk women for screening and intervention could reduce fractures.

Low BMD was an important risk factor for fracture in both Whites and African-Americans, with a weaker association in Hispanics. The age-adjusted HR (95% CI) for clinical fractures per 1 SD decrease in total hip BMD was 1.30 (1.24–1.37) in White women; 1.31 (1.11–1.54) in Black women and 1.16 (0.90–1.50) in Hispanic women [75]. However, at every level of BMD, fracture rates were lower in Black women [76]. Adjustment for multiple risk factors and BMD attenuated the racial differences in fracture rates, but they remained significantly lower for Black women. This suggests that many other factors besides BMD and our traditional risk factors contribute to these ethnic differences in fracture rates.

Low BMD and age are the strongest risk factors for fracture. Risk of fracture is a function of both age and BMD (Fig. 28.10) [77]. At every age, women who have the lowest T-score have a higher risk of fracture. Axial measures of BMD at hip and spine are the gold standard, but lower BMD measured at appendicular sites using peripheral densitometers have also been linked with fracture [78].

There have been few prospective studies of fracture in men. From 2000 to 2002, the Osteoporosis Fractures in Men Study (MrOS) recruited nearly 6,000 men ≥65 years of age to address important gaps in our understanding of osteoporosis in men. After an average of 4 years, 275 (4.7%) men suffered an incident fracture [79]. The most common were ribs (18.6%), hip (16.4%), wrist (13.1%) and ankle (7.6%). The multivariate model identified six independent risk factors (HR: 95% CI): age ≥80 years, 2.06 (1.61–2.63); total hip BMD (per/SD decrease), 1.53 (1.35–1.74); fracture at ≥50 years of age,

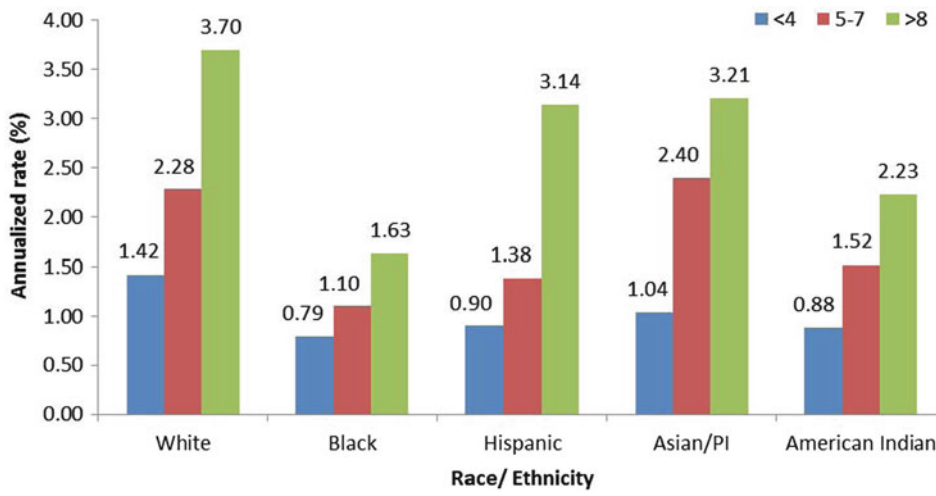

Fig. 28.9 Annualized (%) incidence rate of fracture by the total number of risk factors across ethnic groups [75]. Risk factors included: >65 years of age, height >161.9 cm, weight <70.5 kg, consumed >188 mg caffeine/day, >20 years since menopause, never used hormone therapy, higher than high school education, living without partner, current smoker, fair or poor health status, broke bone at ≥55 years of age, have any arthritis, use corticosteroids >2 years, depressed (CES-D or medication use), use sedatives/anxiolytic, parity (at least two), parental history of fracture, and greater than two falls during the last 12 months of follow-up or year before the fracture. The mean (SD) number of risk factors per group: White, 6.1 (1.9); Black, 5.8 (1.8); Hispanic, 5.4 (1.8); American Indian, 6.1 (2.0); Asians/PI, 5.3 (1.7). Abbreviation: *CES-D* Center for Epidemiologic Studies Depression scale, *PI* Pacific Islander (With permission. Cauley et al. [75])

2.06 (1.61–2.63); any fall in the past year, 1.58 (1.22–2.04); use of tricyclic antidepressant, 2.40 (1.27–2.37) and unable to complete narrow walk, 1.73 (1.26–2.37). Risk of fracture markedly increased with the number of risk factors (Fig. 28.11) [79]. The rate of non-spine fracture in men who had ≥3 risk factors and a BMD in the lowest tertile was nearly 15-fold higher than in men who had no risk factors and were in the highest BMD tertile.

28.8.1 FRAX®

Several risk calculators for fracture have been published [80, 81]. Recent efforts by the WHO Metabolic Bone Disease Group have focused on developing a risk assessment tool (FRAX®) using clinical risk factors with or without femoral neck BMD to enhance fracture prediction. To develop the Web-based FRAX® tool, Kanis et al. [82] used data from nine epidemiologic cohorts that had data on baseline BMD and common clinical risk factors that can be easily determined by primary care clinicians and were identified from previous meta-analyses. The performance characteristics of the FRAX® tool were then validated in 11 independent populated-based cohorts. The FRAX® algorithm is country-specific and uses clinical risk factor data (with or without consideration of femoral neck BMD measurement) and country-specific mortality rates to calculate an individual patient's 10-year probability of hip fracture and 10-year probability of major osteoporotic (hip, clinical vertebral, wrist, humerus) fracture. Risk factors included in FRAX® are summarized in Table 28.3. A recent consensus panel noted the strong association that falls and lower levels of physical performance had with fracture in men, and suggested that they be used in the assessment of fracture risk in men [83]. However, FRAX® does not include these risk factors and may, therefore, perform more poorly in men than in women.

The development of the FRAX® tool (http://www.sheffield.ac.uk/FRAX/) has been supported

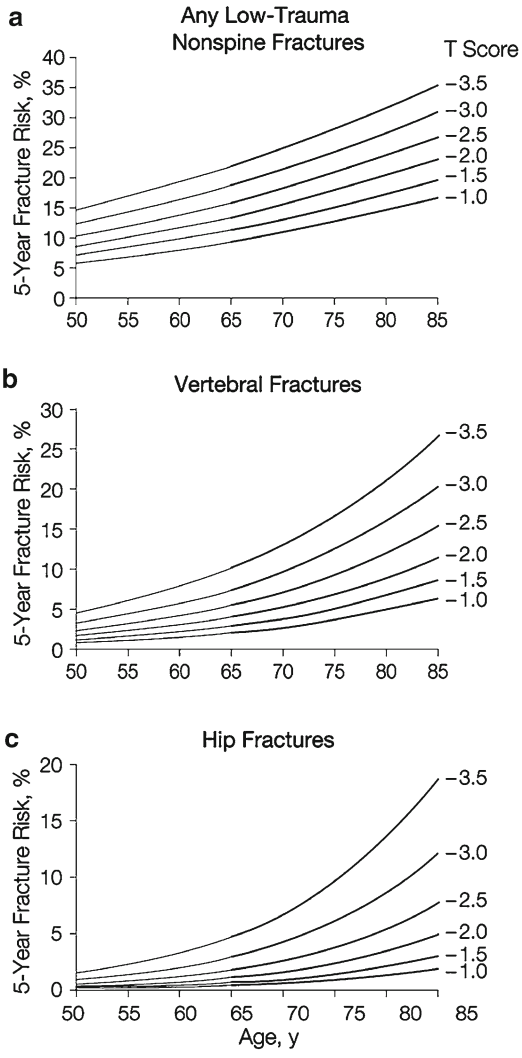

Fig. 28.10 Odds ratio (95% CI) of fracture by 25(OH)D level: (**a**) Any low-trauma non-spine fracture, (**b**) Vertebral fractures, (**c**) Hip fractures [77]. Multivariate adjusted (base-matched on age, ethnicity, blood draw date; multivariate adjusted for age, BMI, parental history of fracture, history of fracture, smoking, alcohol and total calcium intake). Abbreviations: *BMI* Body mass index, *25(OH)D* 25-hydroxyvitamin D (With permission. Cumming et al. [77])

by organizations, including the International Osteoporosis Foundation (IOF) and the National Osteoporosis Foundation (NOF) in the United States, which have strongly advocated its use in clinical decision-making. Of the primary cohorts used to develop FRAX®, 68% of the participants were women; of the validation cohorts, 100% of the participants were women. Nevertheless, guidelines promote the use of FRAX® in both men and women [84]. Based on the results of US-specific cost-effective analyses, the NOF recently modified its treatment guidelines to recommend pharmacologic therapy for adults ≥50 years of age who meet specific criteria, including those based on the presence of osteopenia (a BMD T-score from −1 to −2.5) and the level of 10-year absolute probability of hip fractures (≥3%) or major osteoporotic fractures (≥20%) as calculated by the FRAX® tool. Based on these criteria, 20% of men and 37% of women would be potential candidates for treatment to prevent fractures. As noted by the NOF, the widespread adoption of these new guidelines would shift the treatment approach from one based primarily on BMD measurement to a new approach based on the absolute risk of fracture [84]. The combination of both BMD and clinical risk factors had improved positive predictive value and lowered the number needed to treat more than did either risk factor alone [85].

28.9 Novel Risk Factors for Fracture in the Last Decade

28.9.1 Genetics

As reviewed by Ralston and Uitterlinden [86], twin and family studies have shown high heritability for BMD and bone geometry. Fractures are also heritable but this reduces with age, perhaps due to the importance of falls. Rare genetic variants with large effects, and common genetic variants with small effects, have been discovered. However, common genetic variants with large effects have yet to be discovered. In-depth discussions of these genetic variants are beyond the scope of this chapter (see review [86]). Several large genome-wide association studies have formed large consortia to increase sample size and statistical power. It is highly likely that these studies will identify genetic variants that regulate important osteoporosis phenotypes.

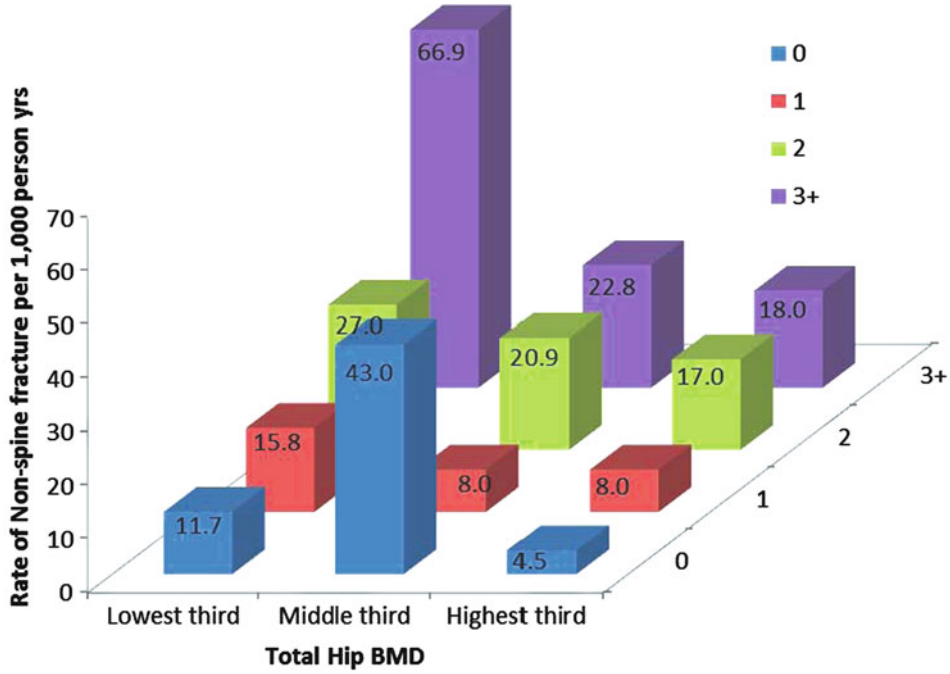

Fig. 28.11 Rate of non-spine fracture by number of clinical risk factors in tertile of BMD based on number of six risk factors from Table 2, model 1 [79]. The six risk factors include: ≥80 years of age, any fracture at ≥50 years of age, any fall in past year, tricyclic antidepressant use, unable to complete any narrow walk trial, depressed mood. Total hip BMD cut-points: <0.898; ≥0.898 and <1.013; and ≥1.013 g/cm^2. Abbreviation: *BMD* Bone mineral density (With permission. Lewis et al.[79])

28.9.2 Bone Marrow Fat, Osteoporosis and Diabetes

Type II diabetes affects an estimated 17% of older adults in the US [87]. It is increasingly recognized that individuals with type 2 diabetes have higher fracture rates. Two meta-analyses published in 2007 support this association [88, 89]. One of the studies concluded that type 2 diabetes mellitus was associated with a relative risk of hip fracture of 2.1 (95% CI 1.6–2.7) in women and 2.8 (95% CI 1.2–6.6) in men [89]. The increased risk is paradoxical because individuals who have type 2 diabetes tend to be obese and have higher BMD [88].

The higher fracture risk among individuals who have type 2 diabetes mellitus may reflect a higher risk of falling, perhaps due to peripheral neuropathy. However, a recent report from the Women's Health Initiative found a 1.2-fold increased risk of fracture among diabetic women that was not accounted for by a 38% greater likelihood of falling [90].

The higher fracture risk among diabetics, despite their higher areal BMD, may reflect poor bone quality. Melton et al. [91] showed that after adjusting for differences in BMI, trabecular volumetric BMD was higher in individuals who had diabetes mellitus but there was no difference in cortical volumetric BMD, which accounts for 80% of our skeleton. Bone cross-sectional area and cortical thickness were also similar between those with and without diabetes mellitus, and the authors concluded that load-to-strength ratios were similar in the two groups and thus, participants who have type 2 diabetes receive little benefit from their higher areal BMD.

The link between diabetes mellitus and higher fracture rates reflects recent interest in the fat-bone connection and whether osteoporosis reflects the obesity of bone [92]. Bone is a dynamic organ which is constantly being remodeled under the

Table 28.3 Clinical osteoporosis risk factors in FRAX® [82]

Risk factor level	Risk factor
Primary risk factors	Age
	Gender
	BMI
	Previous fragility fracture
	Glucocorticoid treatment
	>5 mg Prednisone daily, 3 month
	Current smoking
	Alcohol intake >3 drinks/day
	Rheumatoid arthritis
Secondary risk factors	Secondary osteoporosis
	Untreated hypogonadism in men and women
	Inflammatory bowel disease
	Prolonged immobility
	Organ transplant
	Type 1 diabetes mellitus
	Thyroid disease
	Chronic obstructive pulmonary disease

With permission: Kanis et al. [82]
Abbreviations: *BMI* Body mass index

actions of osteoclastic bone resorption and osteoblastic bone formation. When the bone formation rate cannot keep up with the bone resorption rate, spaces created by osteoclasts will not be refilled with new bone cells, which consequently results in the loss of bone mass. This coupling process is believed to be mediated by osteoblasts and cells in the osteogenic lineage [93]. Mesenchymal stem cells (MSCs), where osteoblasts originate, are also precursors for adipocytes. The differentiation of MSCs into either adipocytes or pre-osteoblasts is regulated by a complex process that involves many growth and transcription factors [92]. MSC differentiation is thought to be affected by the normal aging process favoring adipogenesis due to, in part, physiologic declines in growth factor secretion as well as declines in oxygen tension and blood supply within the bone marrow [94, 95]. As a result, more adipose tissue is stored in the bone cavity with advancing age.

This mechanism has been supported by histomorphometric studies on iliac crest biopsies in which a positive correlation was observed between bone marrow fat and age [96, 97]. However, it remains unclear whether marrow adipocytes induce the reduction in bone formation and the increase in bone resorption that leads to age-related bone loss in older adults, or whether bone marrow fat merely occupies the empty spaces created by the reduced osteoblast genesis process or by reduced bone marrow, white blood cells and red blood cell precursors. Further investigation is required to determine to what extent bone marrow fat actually affects bone metabolism, and whether higher bone marrow fat among diabetics accounts for their higher risk of fracture.

The infiltration of fat into muscle was higher in those who had diabetes or impaired fasting glucose than in those with normal glucose [98]. Fat infiltration into muscle was also associated with a 19% increased risk of clinical fracture, but did not attenuate the association between diabetes mellitus and fracture.

Adiponectin and leptin are adipokines that regulate fat metabolism and bone metabolism, and they may be important in the link between fat, bone and diabetes. Data is limited regarding the relationship of leptin [99, 100] and adiponectin [101–103] to fracture risk, and the results are conflicting. In the prospective Health Aging and Body Composition study, leptin was associated with a reduced risk of fracture, but this was explained by obesity. On the other hand, adiponectin was associated with a higher risk of fracture in men but not in women [104].

Given the increasing epidemic of type 2 diabetes mellitus and the aging of our population, there will likely be an increase in the attributable proportion of fractures due to diabetes. Thus, an important area of future research will be improving our understanding of the bone-fat-diabetes interface.

28.9.3 Vitamin D

Over the past decade, there has been an increasing focus on the relationship between vitamin D deficiency and the risk of osteoporotic fractures. Several large groups, including the Agency for

Healthcare Research and Quality and the Cochran Group, have released summary reports [105, 106]. There were few prospective studies on the relationship between 25-hydroxyvitamin D (25[OH]D, the primary circulating form of vitamin D) and fracture, and results were inconclusive. With respect to vitamin D supplementation and fracture risk, these reviews concluded that there was some evidence of an effect of vitamin D supplementation on hip fractures in participants who were institutionalized, but results were inconclusive for community settings [105, 106].

The WHI Calcium Vitamin D Trial examined 36,282 postmenopausal women who were randomized either to 1,000 mg calcium carbonate plus 400 IU vitamin D daily or to placebo. Results showed no overall significant benefit regarding hip fracture prevention [107]. Analyses of a subgroup of women who remained at least 80% adherent to supplementation showed a significant 29% reduction in hip fracture (HR: 0.71, 95% CI 0.52–0.97).

Many groups are advocating vitamin D supplementation, but the results of additional meta-analyses show conflicting results [108, 109]. The National Institute of Health Office of Dietary Supplements (2009) defined vitamin D "deficiency" as a 25(OH)D level of <10 ng/ml and "inadequacy" as a 25(OH)D level of 10–15 ng/ml. Other experts maintain that levels of 25(OH)D have to exceed 30 ng/ml to be adequate [110]. However, the 2010 Institute of Medicine report noted that a 25(OH)D level of 20 ng/ml is sufficient to ensure skeletal health for most individuals. The 20 ng/ml cutoff was chosen in part based upon recently published observational studies which showed that an elevated risk of fracture was confined to white women [111, 112] and men [113] with 25(OH)D levels <20 ng/ml. The Institute of Medicine recently revised the dietary reference intakes for calcium and vitamin D [114], recommending 1,200 mg calcium and 600 IU vitamin D for adults 51–70 years of age, and 1,200 mg calcium and 800 IU vitamin D for adults ≥71 years of age. Other benefits of vitamin D are emerging, including potential beneficial effects on cardiovascular disease and cancer. However, the Institute of Medicine committee noted that the evidence supporting these benefits remain inconclusive and are currently being studied in randomized trials.

28.10 Summary and Future Directions

Osteoporosis and its associated fractures are important public health problems that disproportionately affect women. Despite declines in hip fracture rates, the number of fractures and the numbers of men and women affected by osteoporosis are expected to increase due to current demographic trends. Many risk factors have been identified, including age, low BMD, and fracture history. Targeting individuals with multiple risk factors should facilitate the identification of individuals at high risk of fracture.

Future research is needed to further our understanding of the genetics of osteoporosis and the bone-fat-diabetes interface, and to identify the role of cortical porosity in fracture etiology. New techniques for measuring cortical porosity are needed. The identification of additional novel biomarkers of risk (e.g., renal function, sclerostin, serotonin, OPG, RANKL) will also help to identify individuals at the highest risk of fracture.

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Epidemiology of Osteoarthritis

29

C. Kent Kwoh

Abstract

Osteoarthritis (OA) is the most common type of arthritis and the most common cause of disability in the elderly. It is a disease process that affects the total joint. OA may occur as the consequence of a number of different pathways that ultimately result in joint failure. It is increasingly recognized that inflammation is an important component in the pathophysiology of OA. The main clinical feature of OA is pain that tends to be transient early in the disease course but becomes persistent with disease progression. Radiographic features of OA may precede the development of pain. OA is the most common reason for joint replacement, and there have been striking increases in the rates of knee and hip replacement. Important OA risk factors include age, obesity, genetic factors and joint injury/trauma. With the aging of the population and the epidemic of obesity, there have been dramatic increases in the public health impact of OA, and the incidence, prevalence and public impact of OA are expected to rise.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Osteoarthritis • Obesity • Magnetic resonance imaging • X-ray • Joint failure • Osteophytes • Risk factors • Obesity • Joint injury • Disability • Joint replacement

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Abbreviations

2C	Type II collagen
AC	Cartilage Surface
AGEs	Advanced Glycation End-products
bFGF	Basic Fibroblast Growth Factor
BMD	Bone Mineral Density
BML	Bone Marrow Lesions
BMI	Body Mass Index
C1	Type I collagen
C2C	Collagenase-generated neoepitope of type II collagen
cAB	Cartilage-covered subchondral bone
CDC	Centers for Disease Control
CPII	Type II collagen propeptide
CS846	Aggrecan chondroitin sulfate 846 epitope
CTX-I	Carboxy-telopeptide of type I collagen
CTX-II	Carboxy-telopeptide of type II collagen
dAB	Subchondral bone that is not covered by cartilage
DALYs	Disability-Adjusted Life Years
dGEMRIC	Delayed gadolinium-enhanced MR imaging of cartilage
DMOADs	Disease-Modifying OA Drugs
HA	Hyaluronan
IL	Interleukin
MMPs	Matrix Metalloproteases
MMP-3	Metalloproteinase of stormelysin
MRI	Magnetic Resonance Imaging
NTX-1	N-telopeptide of type I collagen
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PIIANP	Type IIA procollagen amino propeptide
PIICP	Type II collagen propeptide
RKOA	Radiographic Knee Osteoarthritis
ROS	Reactive Oxygen Species
tAB	Total area of subchondral bone
TGFα	Transforming Growth Factor Alpha
TGFβ	Transforming Growth Factor Beta
ThCtAB	Cartilage thickness over the total bone area
TNFα	Tumor Necrosis Factor Alpha
US	United States
VC	Cartilage Volume
WHO	World Health Organization
YLDs	Years Lived with Disability

29.1 Introduction

Osteoarthritis (OA), also known as degenerative joint disease, is the most common type of arthritis. OA is a disease of the synovial joints that encompasses the pathophysiologic changes that result from alterations in joint structure due to the failed repair of joint damage, as well as the individual's illness experience, which is most characteristically manifested by pain.

OA may occur as the consequence of a number of different pathways that ultimately result in joint failure, a disease process that affects the total joint, including the subchondral bone, ligaments, joint capsule, synovial membrane, periarticular muscles, peripheral nerves, menisci (when present) and articular cartilage [1]. These pathways may consist of abnormal intra- and extra-articular processes that involve a combination of biomechanical, biochemical and genetic factors which results in matrix destruction. The matrix destruction is, in turn, defined as the failure of the repair response and mechanical failure that ultimately lead to joint destruction and the manifestations of joint pain and disability. Examples of these pathways include bone trauma and repetitive injury; malalignment; joint instability due to muscle weakness and ligamentous laxity; nerve injury, neuronal sensitization and/or hyperexcitability; low grade systemic inflammation due to subacute metabolic syndrome; or local inflammation due to synovitis. The destruction of the joint, including the wearing away of articular cartilage, is therefore best viewed as the final product of a variety of possible etiologic factors.

In this chapter, we will review the clinical features and pathophysiology of OA, as well as the diagnosis and natural history of the disease. We will then review the descriptive epidemiology of OA, including prevalence and incidence, describe the impact of OA on the public, and review the non-modifiable and potentially modifiable risk

factors for OA. We will finish with a review of OA prevention and of the difficulties with and need for prevention clinical trials.

29.2 Clinical Features

The main clinical feature of OA is pain, though radiographic features of OA may be evident prior to the onset of the characteristic OA pain pattern. Pain is generally worse with activity and/or weight-bearing, and better with rest. Pain tends to be transient early in the course of the disease and more persistent with disease progression. In later stages, pain may also occur when at rest. Recent research has found that pain in OA may be reported as either a constant aching or as a more severe, intermittent pain [2]. OA pain tends to be localized to the specific joint involved, but may also be referred to a more distant site. A subset of individuals may experience neuropathic pain [3]. A number of patient-specific factors may modify pain reception and pain reporting. A patient's affective status (e.g., depression, anxiety, anger) may impact the level of pain reported. Similarly, a patient's cognitive status (e.g., pain beliefs, expectations, memories of past pain experiences, communication skills) may determine how pain is reported. Studies have shown that pain reporting may also be impacted by demographic factors such as age, sex, socio-economic status, race/ethnicity and cultural background [4].

The etiology of OA pain is unclear and is likely to be heterogeneous. OA pain may be the result of an interaction among the following factors: structural pathology; the motor, sensory and autonomic innervation of the joint; pain processing at both the spinal and cortical levels; and specific individual and environmental factors [4]. Cartilage is aneural, but the subchondral bone, periosteum, peri-articular ligaments, peri-articular muscle, synovium and joint capsule are all richly innervated and may be sources of nociceptive pain in OA. Sources of pain in subchondral bone include bone marrow lesions, perostitis with osteophyte formation, subchondral microfractures and bone ischemia due to decreased blood flow and/or elevated interosseous pressure [5], inflammation in the synovium and irritation of nerve endings by osteophytes. There may be peripheral sensitization as a result of hyperalgesia and central sensitization that leads to pain persistence. Allodynia may also be present. Pain in OA has been reported to be associated with the presence and size of bone marrow lesions seen on magnetic resonance imaging (MRI) [6]. A recent systematic review examined the associations of MRI findings (e.g., cartilage defects, bone marrow lesions [BML], osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition) with the presence of pain in patients with knee OA [7]. Only the presence of BMLs and effusion/synovitis were significantly associated with the presence of knee pain.

Stiffness in the affected joint may be present, particularly after prolonged inactivity, but it is not a major feature of OA and is of short duration, usually lasting for less than 30 minutes. In addition to loss of function, impaired quality of life, fatigue, sleep disturbance and mood disturbance may also be prominent features as the result of chronic pain [5]. Patients with knee OA may also complain of knee buckling.

Examination of an involved joint may reveal joint-line tenderness and bony enlargement of the joint. Joint effusion and/or soft-tissue swelling may be present, but tend to be intermittent. Crepitus with movement, limitation of joint motion, joint deformity and/or joint laxity may also be present. An involved joint does not generally show persistent inflammation with joint warmth, effusion and soft-tissue swelling.

Several subtypes of generalized OA have been identified. The nodal form of OA, involving primarily the distal interphalangeal joints, is most common in middle-aged women, typically those with a strong family history among first-degree relatives. Erosive, inflammatory OA is associated with prominent erosive and destructive changes, especially in the finger joints, and may suggest rheumatoid arthritis, though systemic inflammatory signs and other typical features of rheumatoid arthritis (e.g., nodules, proliferative synovitis, extra-articular features, rheumatoid factor) are absent.

The diagnosis of OA is based on history, physical examination and characteristic radiographic features. The physician must distinguish OA from other inflammatory joint diseases such as rheumatoid arthritis. Distinguishing OA from other inflammatory joint diseases involves identifying the characteristic pattern of joint involvement and the nature of the individual joint deformity. Joints commonly involved in OA include the distal interphalangeal joints, proximal interphalangeal joints, first carpometacarpal joints, first metatarsophalangeal joints, hips, knees and facet joints of the cervical and lumbar spine. Heberden's and Bouchard's nodes may be present in the hands. Involvement of the wrist, elbows, shoulders and ankles is uncommon except in the case of trauma, congenital disease, or endocrine or metabolic disease.

29.3 Pathophysiology

The causes of OA are complex and heterogeneous, but our understanding of its pathophysiology has increased over the years. The cardinal feature of OA is the progressive loss of articular cartilage with associated remodeling of subchondral bone. As noted previously, OA is ultimately joint failure due to a variety of pathways.

At the tissue level, normal cartilage exhibits a continuous extracellular matrix turnover with a balance of synthesis and degradation [8]. In OA, there is an imbalance of these two processes, with an excess of matrix degradation that exceeds the ongoing matrix synthesis. Excess degradation is the result of the overproduction of catabolic factors such as proinflammatory cytokines (e.g., interleukin [IL]-1, IL-6, IL-7, IL-8, and tumor necrosis factor alpha [TNFα]) and other catabolic factors such as transforming growth factor alpha (TGFα), nitric oxide and other reactive oxygen species (ROS), Oncostatin M, basic fibroblast growth factor (bFGF) and matrix fragments. These factors stimulate the chondrocyte to produce matrix metalloproteases (MMPs), aggrecanase and other proteases, which results in extracellular matrix degradation. At the same time, there is a decrease in the production of matrix and growth factors (e.g., bone morphogenic protein [BMP-7] and transforming growth factor beta [TGF- β]). An imbalance between tissue inhibitors of metalloproteases and the production of metalloproteases may be operative in OA.

Loeser [8] described a number of age-related changes that contribute to the susceptibility of OA. At the cellular level, decreased levels of growth factors and decreased growth factor responsiveness lead to reduced matrix synthesis and repair. There is an increased formation of advanced glycation end-products (AGEs), which leads to the increased cross-linking of collagen molecules, more brittle tissues and increased susceptibility to fatigue failure of cartilage. Decreased aggrecan size, increased cleavage of collagen and decreased cartilage hydration lead to the reduced tensile strength of cartilage. With aging, there is oxidative stress, an increase in ROS and an accumulation of oxidative damage that is manifested by reduced anabolic signaling and increased catabolic signaling, which ultimately result in decreased matrix synthesis and increased matrix degradation.

At the tissue level, an age-related decrease in the number of chondrocytes and an increase in chondrocyte senescence are manifested by telomere shortening. There is also the transformation of chondrocytes into the senescent secretory phenotype, which results in the increased production of inflammatory cytokines and MMPs that lead to matrix degradation. Aging chondrocytes are also less likely to respond to growth factors. Unlike in cartilage, within subchondral bone there is increased bone remolding with increased matrix calcification and the production of an abnormal bone matrix. This alters the mechanical properties of the bone, increasing its stiffness and making it less able to absorb loads, thereby transferring loadbearing to the cartilage. There are also age-related changes (e.g., sarcopenia) which result in decreased muscle strength and the resultant decreased ability of the muscles to act as internal shock absorbers to absorb the forces transmitted to the subchondral bone and cartilage. With aging, there is also loss of proprioception, and the degeneration and increased stiffness of ligaments and menisci.

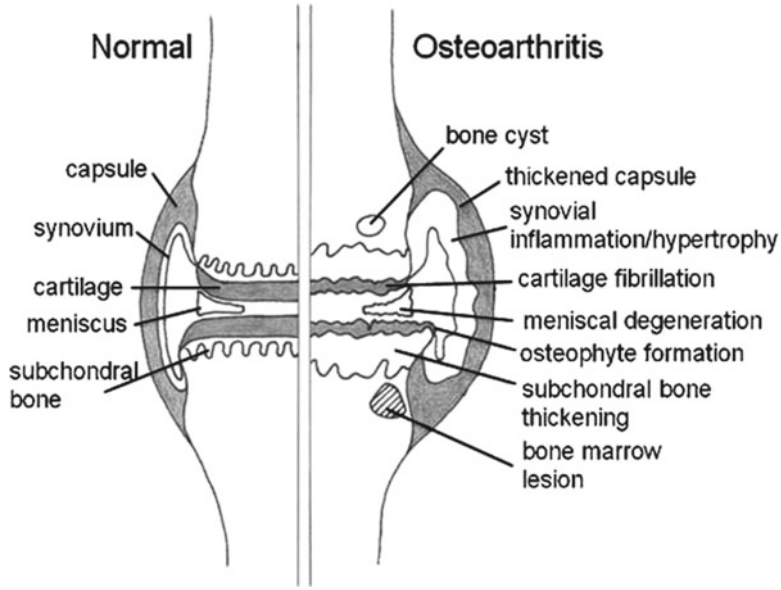

Fig. 29.1 Pathology of osteoarthritis. The osteoarthritic joint is characterized by degradation and loss of the articular cartilage, thickening of the subchondral bone accompanied by formation of bone marrow lesions and cysts, osteophytes at the joint margins, variable degrees of synovitis with synovial hypertrophy, meniscal degeneration (knee), and thickening of the joint capsule (Reprinted with permission from Loeser [8])

The pathology of OA is seen in Fig. 29.1. In OA, the entire joint is commonly involved. Cartilage degradation results in fibrillation, thinning and, ultimately, the loss of cartilage down to subchondral bone, leaving areas of denuded bone. There are changes in the subchondral bone with thickening; the development of BMLs which leads to subchondral bone cysts; the formation of marginal osteophytes; and bone remodeling, with bone attrition producing changes in bone curvature. There is often weakness of the bridging peri-articular muscles. If present, the menisci degenerate and may extrude beyond the bony margins. It is difficult to say which of these processes occurs first, but all of these features may be present in the later stages. Scanzello et al. [9] has described a number of changes in the synovium that occur in OA, including synovial hyperplasia, perivascular aggregates of small mononuclear cells, subintimal fibrosis, and increased vascularity.

In OA, the earliest finding is fibrillation of the most superficial layer of the articular cartilage. With time, the disruption of the articular surface becomes deeper, with extension of the fibrillations to subchondral bone, fragmentation of cartilage with release into the joint, matrix degradation, and eventually, the complete loss of cartilage, leaving only exposed bone. Early in this process, the cartilage matrix undergoes significant change, with increased water content and decreased proteoglycan content. This progression is in contrast to the dehydration of cartilage that occurs with aging. The *tidemark* zone, which separates the calcified cartilage from the radial zone, becomes invaded with capillaries. Chondrocytes are initially metabolically active and release a variety of cytokines and metalloproteases that contribute to the matrix degradation, which, in later stages, results in the penetration of fissures to the subchondral bone and the release of fibrillated cartilage into the joint space. Subchondral bone increases in density, and cyst-like bone cavities occur which contain myxoid, fibrous or cartilaginous tissue. Osteophytes (bony proliferations at the margin of joints at the site of bone-cartilage interface) may also form at capsule insertions. Osteophytes contribute to joint-motion restriction and are thought to be the result of new bone formed in response to the degeneration of articular cartilage; however the precise mechanism for their production remains unknown.

The diversity of risk factors that predispose an individual to OA suggests that a wide variety of insults to the joints (e.g., biomechanical trauma, chronic articular inflammation, and genetic and metabolic factors) can contribute to or trigger the cascade of events that results in the characteristic pathologic features of OA. At some point, the cartilage degradative process becomes irreversible, perhaps the result of an imbalance of regulatory molecules such as tissue inhibitors of metalloproteases. With progressive changes in articular cartilage, joint mechanics become altered which, in turn, perpetuates the degradative process.

29.4 Measurement of Clinical and Subclinical Disease: Diagnosis and Natural History

The diagnosis of OA is based on symptoms of pain, stiffness and/or poor sleep; the presence of characteristic radiographic features; or the presence of bony and intermittent soft tissue swelling in a joint commonly affected by OA such as distal interphalangeal joints, proximal interphalangeal joints, first carpometacarpal joints, first metatarsophalangeal joints, hips, knees, or facet joints of the cervical and lumbar spine.

The natural history of OA is depicted schematically in Fig. 29.2. Initially, one or more triggering event(s) initiates the disease process in a susceptible individual. Susceptibility may be increased by aging-related cellular and tissue changes that may occur either before or after the triggering events. Currently, clinically detectable OA is defined by the presence of abnormalities on plain radiographs. Unfortunately this stage occurs late in the disease course and is indicative of "joint failure." Depending on the joint and other circumstances, symptoms may precede or follow evidence of clinically detectable radiographic OA. Since there are no currently approved disease-modifying OA drugs (DMOADs) that slow disease progression, patients may progress to end-stage disease (i.e., joint death) where the only effective treatment is joint replacement. The challenge is to identify pre-clinical OA through morphologic changes in joint structures that are detectable by MRI, ultrasound or—at an even earlier stage—by molecular changes in joint structures that are detectable by MRI or other biomarkers.

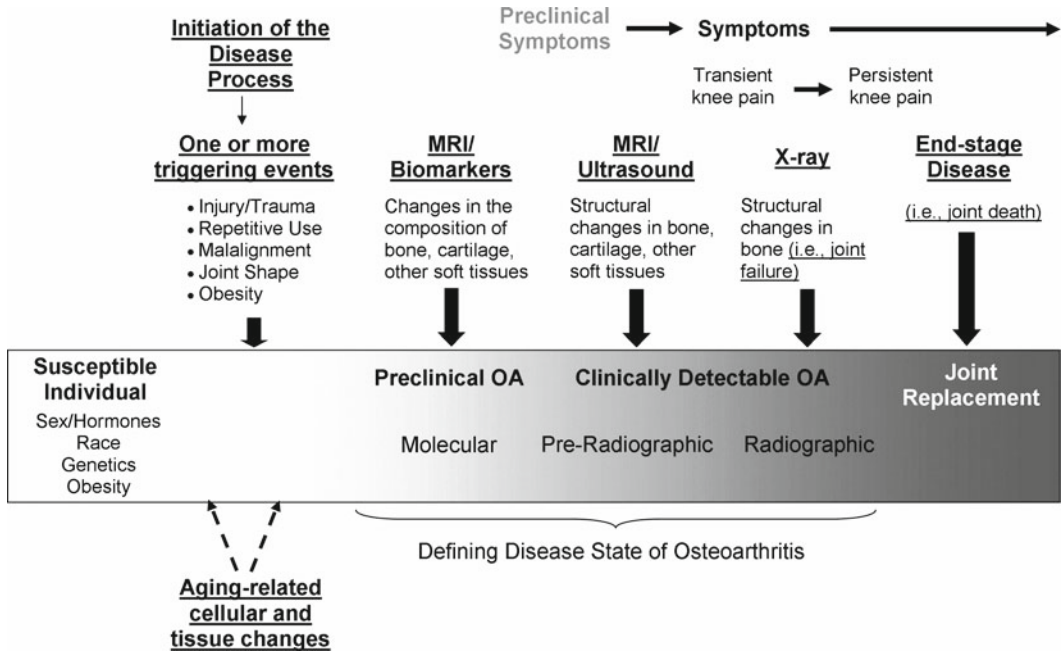

Fig. 29.2 The natural history of OA. Abbreviations: *MRI* magnetic resonance imaging, *OA* osteoarthritis

The characteristic radiographic features of OA are the result of pathologic changes. Joint space narrowing is felt to be a consequence of cartilage loss. Osteophytes may be a consequence of marginal lipping and outgrowths of bone. Subchondral bone cysts and sclerosis may be the result of osteonecrosis and the healing of microfractures. Altered bone contours may be due to bone attrition and the remodeling of bone surfaces.

The current definition of OA is based on the presence of features that are seen on conventional radiography. That is, osteophytes and joint space narrowing as a surrogate for the loss of cartilage. In most epidemiologic studies, the definition of OA is based on a combination of pain and the radiographic disease as assessed by the Kellgren-Lawrence grading system, which is scored using an ordinal scale from 0 to 4. On the scale, 0 indicates normal (i.e., no features of OA); 1 indicates "doubtful" and is characterized by the presence of a minute osteophyte of doubtful significance; 2 indicates the level most used to categorize "definite OA" and is characterized by the presence of a definite osteophyte without impairment of joint space; 3 indicates moderate OA and is characterized by the presence of multiple osteophytes and moderate diminution of joint space as a surrogate for cartilage loss; and 4 indicates severe OA and is characterized by the marked impairment of joint space, often bone on bone and with the presence of a sclerosis of subchondral bone [10]. These categories may often be difficult to assess and are based on the presumption of a progression of radiographic features with increasing severity, which may not always be the case. This has led to the development of an alternative scale developed by the Osteoarthritis Research Society International (OARSI), which provides an accompanying radiographic atlas that enables the separate scoring of features such as osteophytes, joint space narrowing and sclerosis [11]. Unfortunately, radiographs are limited in that they only provide images of bony structure and are two-dimensional projections of the three-dimensional joint(s) involved in OA.

The advent of MRI has greatly advanced our knowledge of OA and has enabled the visualization of pre-radiographic OA. MRI has demonstrated that additional morphologic abnormalities (e.g., BMLs, synovitis) may also be important features of OA [12]. MRI also has the advantage of greater resolution and the ability to visualize all of the joint tissues to assess their involvement. Other features of joint morphology that may be important in OA and can be assessed by MRI include subchondral cyst-like lesions; subchondral bone attrition; joint effusion; meniscal degeneration and/or subluxation; periarticular cysts and bursae; marginal and central osteophytes; and the integrity of the anterior cruciate, posterior cruciate, medial collateral and lateral collateral ligaments [13]. These features may be assessed using recently-developed semi-quantitative scoring systems [14, 15]. High resolution images have also enabled the quantitative assessment of joint structures through the manual segmentation of joint morphology, including cartilage volume (VC), total area of subchondral bone (tAB), the area of the cartilage surface (AC), the cartilage thickness over the total bone area (ThCtAB), the area of cartilage-covered subchondral bone (cAB) and the area of denuded subchondral bone that is not covered by cartilage (dAB) [16]. These parameters may be calculated for specific regions or subregions within a joint.

Advances in MRI have also enabled the development of non-contrast and contrast-enhanced imaging methods for assessing morphometric and compositional parameters that occur with degradation of the extracellular matrix as potential imaging biomarkers of preclinical OA. Examples include T2 mapping, T1 rho mapping, Ultrashort TE imaging, sodium imaging, diffusion-weighted imaging and delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) [17].

A recent review has recommended a panel of 12 OA-related biomarkers that have been validated for a variety of OA outcomes [18]. All 12 are commercially available and include the following: Urinary carboxy-telopeptide of type II collagen (CTX-II), Serum CTX-II, Serum hyaluronan (HA), Serum and urine collagenase-generated neoepitope of types I and II collagens (C1, 2C), Serum and urine collagenase-generated neoepitope of type II collagen (C2C), Serum and urine Coll2-1 and Coll2-1NO2, Serum type II collagen propeptide (CPII or PIICP), type IIA

procollagen amino propeptide (PIIANP), Urine/serum N-telopeptide of type I collagen (NTX-1), Urine/serum carboxy-telopeptide of type I collagen (CTX-1), Serum aggrecan chondroitin sulfate 846 epitope (CS846), and Serum metalloproteinase of stormelysin (MMP-3). The identification of these biomarkers and of changes in bone and cartilage composition is a step toward the classification of preclinical OA prior to morphologic changes in joint structure which may be apparent on conventional radiographs and MRI.

29.5 Descriptive Epidemiology

29.5.1 Prevalence

Over 26.9 million Americans >25 years of age have some form of OA, and the prevalence of OA increases with age. The prevalence of radiographic OA varies by the joint involved, with 27.2% of all adults and over 80% of those >65 years of age having evidence of hand OA (Table 29.1). With regard to knee OA, 37.4% of those ≥60 years of age have radiographic evidence of disease. The prevalence of symptomatic OA is lower, with 6.8% of all adults having evidence of symptomatic hand OA and 16.7% of those ≥45 years of age having evidence of symptomatic knee involvement. Hand and knee OA is more common among women, especially after age 50, and also more common among African-Americans. Nodal OA, involving the distal and proximal interphalangeal joints, is significantly more common in women and also more common among female first-degree relatives of those who have nodal OA.

In the Framingham study, radiographic evidence of knee OA increased from 27.4% in participants <70 years of age to 43.7% in those ≥80 years of age [20]. There was a slightly higher prevalence of radiographic changes of OA in women than in men (34 versus 31%); however, there was a significantly higher proportion of women with symptomatic disease (11% of all women versus 7% of all men; $p = 0.003$).

A meta-analysis of population-based studies of OA estimated that, compared to women, men have a decreased risk of prevalent hand and knee OA, but not hip OA [26]. The worldwide

Table 29.1 Prevalence of radiographic OA in the hands, knees and hips by age and sex, from population-based studies

Patient characteristics			% with mild, moderate or severe radiographic OA			% with mild, moderate or severe symptomatic OA		
Anatomic site	Age	Study sample	Male	Female	Total	Male	Female	Total
Hands	≥26	Framingham [19]	25.9	28.2	27.2	3.8	9.2	6.8
Knees	≥26	Framingham [20]	14.1	13.7	13.8	4.6	4.9	4.9
	≥45	Framingham [20]	18.6	19.3	19.2	5.9	7.2	6.7
	<70	Framingham [20]	30.4	25.1	27.4	6.2	7.6	7.0
	70–79	Framingham [20]	30.7	36.2	34.1	7.8	13.0	11.0
	≥80	Framingham [20]	32.6	52.6	43.7	5.4	15.8	11.2
	≥45	Johnston Co. [21]	24.3	30.1	27.8	13.5	18.7	16.7
	≥60	NHANES III [22]	31.2	42.1	37.4	10.0	13.6	12.1
Hips	≥45	Johnston Co. [23]	25.7	26.9	27.0	8.7	9.3	9.2
	60–74	NHANES I [24]	4.5	3.8	–	–	–	–
	65–89	Study of osteoporotic fractures [24]	–	5.5	–	–	2.2	–

Adapted from Lawrence et al. [25]
Abbreviations: *Co* county, *OA* osteoarthritis

age-standardized prevalence rates per 100,000 individuals of hip and knee OA are 426 and 1,170 in men, respectively, and 371 and 2,693 for women, respectively [24]. For hip OA in men and women, these estimated age-standardized prevalence rates per 100,000 individuals range from a low of 273 and 145, respectively, to a high of 700 and 601, respectively, across World Health Organization (WHO) epidemiologic subregions. For knee OA in men and women, these estimated age-standardized prevalence rates per 100,000 individuals range from a low of 1,163 and 1,773, respectively, to a high of 3,089 and 3,942, respectively.

29.5.2 Incidence

The age- and sex-standardized incidence rates of symptomatic OA are 100 per 100,000 person-years for hand OA, 240 per 100,000 person-years for knee OA, and 88 per 100,000 person-years for hip OA [27]. The rates in both sexes rise with increasing age, especially after age 50. The rate of incident symptomatic knee OA is estimated to be 1% per year, and the rate of incident radiographic knee OA is estimated to be 2% per year [28]. Men <55 years of age have a greater risk of incident cervical spine OA than do women of the same age group, whereas women have a greater risk of incident knee and hip OA than do men [26]. The lifetime risk of developing symptomatic knee OA is estimated to be about 40% in men and 47% in women [29]. The worldwide age-standardized incidence rates of hip and knee OA per 100,000 individuals are 35.0 and 119.7 in men, respectively, and 30.8 and 178.6 for women, respectively [24]. For hip OA in men and women, these estimated age-standardized incidence rates per 100,000 individuals range from a low of 22.2 and 12.8, respectively, to a high of 40.5 and 55.4, respectively, across WHO epidemiologic subregions. For knee OA in men and women, these estimated age-standardized incidence rates per 100,000 individuals range from a low of 67.7 and 136.8, respectively, to a high of 194.9 and 253.1, respectively.

29.6 Public Health Impact

OA is associated with major morbidity and is one of the top five causes of long-term disability in the United States (US) [30]. Lower extremity OA is the most common cause of difficulty with walking or climbing stairs, preventing an estimated 100,000 older US adults from independently walking from bed to bathroom. Overall loss of joint function as a result of OA is a major cause of work disability and reduced quality of life [31]. About 80% of patients with OA have some degree of movement limitation. About 40% of adults with knee OA report their health as "poor" or "fair." In 1997, a total of 4.9 million women and 2.2 million men had ambulatory medical care visits for OA, accounting for 19.5% of all arthritis-related ambulatory medical care visits [32].

In 1999, adults with knee OA reported more than 13 days of lost work due to health problems. In the year 2000, the years lived with disability (YLDs) [33] for men and women with OA were 5,549 and 8,667, respectively. In the year 2000, the disability-adjusted life years (DALYs) for men and women with OA were 5,554 and 8,675, respectively. These YLDs and DALYs rank high among chronic diseases, and both have increased since 1990.

The Centers for Disease Control (CDC) estimates that osteoarthritis and related arthritic conditions cost the US economy nearly $81 billion per year in direct medical care, with indirect expenses (including lost wages and lost production) of about $47 billion. CDC figures further estimate the total annual direct cost per person of OA and related conditions is approximately $1,752 [31]. A large proportion of these costs are associated with total joint replacement, with costs for total joint replacement in the US estimated to be $79 billion in 1997 [34]. The job-related costs of OA are estimated to be $3.4–$13.2 billion per year [35].

OA wields a large economic impact as the result of both direct medical costs (e.g., physician visits, laboratory tests, medications, surgical procedures) and indirect costs (e.g., lost wages,

home care, lost wage-earning opportunities). With the aging of the US population, the burden of OA is expected to increase throughout the coming years.

29.7 Risk Factors

OA is a complex disorder with identifiable risk factors that include biomechanical, metabolic or inflammatory processes; congenital or developmental deformities of the joint; and genetic factors. As noted above, age, sex and race are prominent risk factors for OA. Biomechanical contributors include repetitive or isolated joint trauma related to certain occupations or physical activities that involve repeated joint stress. These can predispose an individual to early OA. Obesity may contribute from a biomechanical perspective, or from a systemic perspective related to a subacute metabolic syndrome. Certain metabolic disorders (e.g., hemochromatosis, ochronosis) are also associated with OA. High bone mineral density (BMD) has been shown to be associated with hip or knee OA. Estrogen deficiency may also be a risk factor for hip or knee OA. Inflammatory joint diseases, such as rheumatoid arthritis, may result in cartilage degradation and biomechanical factors that lead to secondary OA. Candidate gene studies and genome-wide scans have identified a number of potential genetic markers of OA.

29.7.1 Non-Modifiable Risk Factors

29.7.1.1 Demographic Risk Factors

Prior studies have reported an increase in the risk of radiographic knee OA (RKOA) with advancing age, as well as an increased risk of RKOA in women compared to men. Data from the NHANES III and the Johnston County OA Study have reported an increased risk of RKOA among African-Americans compared to whites, particularly among African-American women [21, 22]. NHANES III did not find either education level or income to be associated with risk of RKOA [22].

29.7.1.2 OA in Other Joints

Studies have suggested that risk of knee OA might be related to the presence of hand OA [36–38]. In the Bristol cohort [36] the association was with Herberden's nodes. Data from the Rotterdam study [38] reported an increased risk of RKOA associated with radiographic hand OA of the metacarpophalangeal and carpometacarpal joints, with a higher risk among individuals who were overweight. In the Croatian study [37], the association was greater in women compared to men, and was greater for OA in the distal interphalangeal joints compared to the proximal interphalangeal joints. That study also found an increased risk of RKOA with carpometacarpal involvement in men. Radiographic hand OA has been reported to be associated with increased risk of RKOA in the both the index knee after menisectomy and in the contralateral knee [39].

29.7.2 Potentially Modifiable Risk Factors

29.7.2.1 Body Composition

In prior studies, obesity and increased body mass index (BMI) have been reported to increase the risk of RKOA. Data on more detailed measures of body composition are now available. Multiple studies have suggested that increased waist circumference and increased waist-to-hip ratio may be associated with increased risk of RKOA, but this increased risk was no longer significant after adjusting for BMI [40, 41]. In contrast, analysis of the NHANES III data suggested that waist circumference was still an important risk factor when analyzed by different strata of BMI, particularly in the medium and highest BMI tertiles [42]. Data from the Johnston County OA Study suggested that increasing fat mass and increasing lean mass are both associated with increased risk of radiographic knee OA, but neither were significant after adjusting for BMI [40]. Data from a study in Sweden suggest that the presence of metabolic syndrome may also be associated with increased risk of radiographic knee OA, but this association was also no longer significant after adjusting for

BMI [43]. Obesity also increases with increasing age, at least until reaching very old age when weight begins to decrease.

Data from a case–control study from southern Sweden suggest that changes in BMI from younger ages to older ages may be an important consideration [44]. Increasing BMI after age 30 was associated with increased risk of RKOA in both men and women. Decreasing BMI after age 30 helped to decrease the risk of RKOA. The highest risk of RKOA was seen in men and women who were already obese at a young age.

29.7.2.2 Bone Mineral Density

A number of prior studies, including some using data from the Framingham Study, have reported an association between increased BMD and increased risk of OA in a separate joint [45]. Data from the Johnston County OA Study reported that increased bone mass and lower percent bone mass were both associated with increased risk of RKOA, but this association was no longer significant after controlling for either BMI or weight [40]. The mechanisms behind this association are still unclear and require further investigation.

29.7.2.3 Malalignment

There is limited data on the association of the presence of malalignment with the risk of RKOA. A number of studies have demonstrated the importance of malalignment in the progression of RKOA, but few have looked at malalignment as a risk factor for the development of RKOA. Data from the Framingham Study was unable to demonstrate a relationship between various measures of alignment and increased risk of RKOA [46], whereas data from the Rotterdam Study indicated that varus malalignment was associated with an increased risk of RKOA, and that varus and valgus malalignment were both important in the development of RKOA in obese individuals [47]. It is important to note that both of these studies were based on the assessment of alignment using standing, fully-extended anteroposterior knee radiographs. These findings should be replicated using the measurement of alignment from full limb films, which may be more accurate in assessing the mechanical angle.

29.7.2.4 Physical Characteristics

A number of physical features have been associated with the risk of developing RKOA. Data from the Johnston County OA Study indicated that leg length inequality increased the risk of RKOA [48]. Data from the Beijing OA Study suggested that higher knee height was associated with increasing prevalence of both radiographic and symptomatic OA [49]. In addition, data from the Matsudai Knee Survey suggested that the presence of a round back also increased the risk of developing RKOA [50].

Data from Nottingham, UK suggested that the pattern of the second digit being shorter than the fourth digit is also associated with increased risk of knee OA [51]. The relationship between differences in joint shape (often related to congenital abnormalities of the hip) and the increased risk of hip OA has been clearly demonstrated. More work is needed to determine whether differences in joint shape and limb development may increase the risk of RKOA.

29.7.2.5 Knee Injury

Studies have shown a relationship and increased risk of RKOA with previous knee injury. The risk is increased in both men and women, and in both white women and African-American women [52]. With regard to knee surgery, the risk seems to be increased with subtotal or total menisectomy, as well as with degenerative tears of the meniscus [53]. Data from the Beijing OA Study indicated a trend toward increased quadriceps strength having a protective effect against the development of both tibiofemoral and patellofemoral RKOA, with the results becoming significant when both outcomes were considered together [54].

29.7.2.6 Recreational Activity

A number of studies have looked at the association of recreational activities and the risk of RKOA. It does not appear that the risk of RKOA is increased by walking for exercise, recreational walking or other levels of recreational activity such as working up a sweat or having a higher level of activity compared to peers [55, 56]. Regular sports participation may increase the risk

of RKOA, particularly specific types of activities such as soccer, ice hockey or tennis in men. However, the increased risk was more likely due to the occurrence of injury rather than to participation in these activities [36, 57]. The association with these activities was no longer significant after controlling for prior knee injury.

29.7.2.7 Occupational Activity

NHANES III demonstrated an increase in risk of RKOA in men with manual labor occupations [22]. Data from southern Sweden suggest that working in building construction increases the risk of RKOA in overweight men, and farm work increases the risk of RKOA in both men and women if they are overweight. Certain specific occupational activities (e.g., climbing more than 15 flights of stairs per day, lifting more than 10 kg ten times/week, squatting) seem to increase the risk of RKOA.

29.7.2.8 Hormone Therapy

Few studies have examined the relationship between the use of hormone therapy in women and the risk of radiographic OA. Previous data had been conflicting, depending on the joint of interest. Recent data from the Rotterdam study and the Melbourne Women's Life Study have not demonstrated an association of radiographic OA with the use of hormone therapy [56, 58]. Although the prevalence of radiographic OA was higher in the Rotterdam study among women who had previously used hormone therapy, this did not reach statistical significance (27 vs. 21%, $p=0.26$). Data from the Melbourne Women's Life Study suggested that women who had never used hormone therapy had an increased risk of 0.29, but this did not reach statistical significance (95% CI: 0.8–11.6, $p=0.12$).

29.8 Prevention, Including Prevention Clinical Trials

Possible targets of primary prevention, alone or in combination, include weight gain/obesity, joint injury related to recreational and/or occupational activities, or structural issues such as joint biomechanics. Secondary prevention in individuals with early disease could also be directed toward these targets, or directed toward other joints in individuals who already have OA in a joint.

It is difficult to design prevention trials in OA due to current definitions of the disease being based on radiographic changes, which are insensitive to detecting preclinical disease or changes early in the disease course [59]. With advances in biomarker technology (both imaging and biochemical markers), it will be possible to identify high-risk individuals with preclinical disease and to characterize changes early in the disease course. Such trials would likely involve large study samples with follow-up over several years, and would therefore be costly and complex to conduct. However, prevention studies are ultimately needed to decrease the large burden of disease due to OA.

29.9 Summary

OA is a disease of the whole joint, with alterations in joint structure due to the failed repair of joint damage. OA is a common disease and a leading cause of disability, particularly in older populations. Pain is the presenting symptom of the individual's illness experience, and the treatment for end-stage OA is joint replacement. With the aging of the population and the epidemic of obesity, the prevalence and public health impact of OA are expected to increase dramatically. Obesity and joint trauma have been identified as important modifiable risk factors and are potential targets for prevention studies.

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Stroke Epidemiology and Prevention

30

Lewis H. Kuller

Abstract

Stroke is the third leading cause of death and a leading cause of adult disability in the United States. Improvement in treating risk factors (especially blood pressure), better management at the time of the stroke, reduction of in-hospital case fatalities, and improvement in post-stroke rehabilitation have substantially reduced stroke incidence, mortality and disability. Unfortunately, substantial disparities in incidence and mortality by socioeconomic factors, region and race persist in the United States. Stroke is caused by several factors. Heart disease, especially atrial fibrillation and large vessel atherosclerotic disease in the carotid arteries and major intracranial and small intercerebral blood vessels, are important determinants of stroke. The association of hypertension with stroke and kidney disease results in a high prevalence of clinical kidney disease among older stroke patients. Small vessel intercerebral hypertensive vascular disease is an important cause of stroke, especially "lacunar infarctions," usually found in the basal ganglion. There is a high risk of recurrent stroke and further disability. Many older individuals who have incident stroke also have significant disease in other vascular beds, resulting in a high risk of coronary heart disease, congestive heart failure and peripheral vascular disease. Effective methods of stroke prevention include reducing high blood pressure and cholesterol, especially among older adults and individuals with diabetes, as well as smoking cessation and reduction of heavy alcohol use.

Keywords

Aging • Epidemiology • Geriatrics • Older adults • Longevity • Stroke epidemiology • Stroke prevention • Cerebrovascular disease • White matter hyperintensity • Lacunar infarction • Risk factor • Prevention • Rehabilitation • Disability

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Abbreviations

Aβ	Beta amyloid
ABCD^2	Age, Blood Pressure, Clinical features, Duration and Diabetes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AF	Atrial Fibrillation
ApoA1	Apolipoprotein-A1
ApoB	Apolipoprotein-B
ARIC	Atherosclerosis Risk in Communities
ASCO	Atherosclerosis, Small vessel, Cardiac and Other causes
BP	Blood Pressure
CAA	Cerebral Amyloid Angiopathy
CAD	Coronary Artery Disease
CHADS	Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and prior Stroke
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CHS	Cardiovascular Health Study
CL	Confidence Level
CT	Computed Tomography
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DALYs	Disability-Associated Life-Years
GWAS	Genome-Wide Association Studies
HDL	High Density Lipoprotein
IMT	Intima-Media Thickness
IVTPA	Intravenous Tissue Plasminogen Activator
LDL	Low Density Lipoprotein
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutrition Examination Survey
SPRINT	Systolic Blood Pressure Intervention study
TIA	Transient Ischemic Attack
TNAs	Transient Neurological Attacks
TOAST	The Trial of Acute Stroke Treatment
TPA	Tissue Plasmin Activator

30.1 Introduction

Stroke is the third leading cause of death and a leading cause of adult disability in the United States (US). Approximately 6.4 million individuals over the age of 20 living in the US have had a stroke: 2.5 million men and 3.9 million women. In the US, about 500,000 new strokes occur and 200,000 recurrent strokes occur each year. It is estimated that the direct and indirect cost of stroke in the US exceeds $53 billion. In 1990, the lifetime cost of an incident ischemic stroke for an individual was >$90,000.

Prior to around 1928, stroke was classified as "apoplexy." In 1928, the term *cerebrovascular accident* (CVA) was officially recognized and differentiated into hemorrhagic or ischemia [1]. In 1994, the term 'CVA' was replaced by the term 'stroke'. The formal definition of stroke was: a sudden impairment of brain function resulting from the interruption of circulation to one or other parts of the brain following either an occlusion (ischemic) or hemorrhage (hemorrhagic) of the artery supplying that area. In 2000, the Brain Attack Coalition recognized stroke as a medical emergency.

Advances in the prevention and treatment of strokes have been among the most important accomplishments in health care over the past 40 years. Improvement in treating risk factors (especially blood pressure [BP]), improved management at the time of the stroke, reduction of in-hospital case fatalities, and post-stroke rehabilitation have resulted in a substantial decline in stroke incidence, mortality and disability. However, in spite of these successes, a greater emphasis on prevention, treatment and rehabilitation is necessary to further substantially reduce disability due to stroke, especially in older individuals. Further, substantial disparities in stroke incidence and mortality in relation to socioeconomic factors, region and race persist in the US [2, 3].

Stroke is not caused by a single factor. Heart disease (especially atrial fibrillation [AF]) and large-vessel atherosclerotic disease in the carotid arteries, major intracranial and small intercerebral blood vessels are all important determinants of stroke. For example, a major determinant for stroke in older adults is embolization from the heart, which is often secondary to AF. Large-vessel atherosclerotic disease in extracranial arteries can cause stroke due to embolization from a plaque or carotid artery stenosis.

Small-vessel intercerebral hypertensive vascular disease is an important cause of stroke, especially "lacunar infarctions," usually found in the basal ganglion. Cerebral amyloid angiopathy, amyloid deposits in small arteries in the brain, can lead to intercerebral lobular hemorrhage which has a high case fatality rate among the elderly. Major advances in computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography scanning have led to a better understanding of both brain metabolism and vascular changes in the brain. Using brain MRI, large epidemiological studies such as Atherosclerosis Risk in Communities (ARIC) [4], the Cardiovascular Health Study (CHS) [5], the Framingham Heart Study [6] and the Rotterdam Study [7] have documented the high prevalence of asymptomatic brain infarction, white matter disease and abnormalities in cerebral blood flow secondary to hypertension. Silent brain infarction and white matter disease in the brain are important independent predictors of the risk of clinical stroke and probably dementia.

The development of stroke clinical centers for the specific care of stroke patients has resulted in effective care models that have substantially reduced hospital case fatality rates for post-stroke patients [2, 8]. However, stroke can also result in disability, including not only physical limitations but also increased risk of dementia and depression [1]. Many older individuals who have incident stroke also have significant disease in other vascular beds, resulting in a high risk of coronary heart disease (CHD), congestive heart failure (CHF) and peripheral vascular disease. Older stroke patients also have a high prevalence of clinical kidney disease due to the association of hypertension with both stroke and kidney disease. After an initial stroke, there is a very high risk of recurrent stroke and further disability.

In this chapter, we will review how strokes are classified as well as their incidence and mortality rates and risk to the population. We will then review events that could occur after a stroke, post-stroke survival and how stroke is treated. Last, we will review the risk factors for stroke, the physiological conditions that can contribute to a stroke, and methods of stroke prevention.

30.2 Classification of Stroke

The etiological classification of strokes by type is important for both patient care and stroke research. Classification of stroke can be difficult due to the variety of mechanisms that can lead to a stroke (Fig. 30.1). Across populations, about 87% of strokes are ischemic, 9% are due to intracerebral hemorrhage and 4% are due to subarachnoid hemorrhage. New classification systems based on etiology and clinical, epidemiological and diagnostic data classify stroke subtypes into five major categories: atherosclerosis, cardioaortic embolism, small arterial occlusion, other causes and undetermined causes. The Trial of Acute Stroke Treatment (TOAST) developed a classification system primarily for use in clinical trials that investigate nonhemorrhagic stroke. Recently, the TOAST Causative Classification System and two other classification systems—the Atherosclerosis, Small vessel, Cardiac and Other causes (ASCO) and the Causative Classification System—were compared using data from 381 first-ever strokes gathered by the North Dublin Population Stroke Study [10]. There was good agreement between the different classification systems. The study indicated that large-artery atherothrombosis accounts for about 9–13% of nonhemorrhagic strokes, cardioembolic or cardioaortic stroke account for about 33%, large artery atherothrombosis account for about 9–13%, small artery occlusive disease account for about 10–18%, other causes account for about 3–6%, and undetermined causes account for about 26–42%.

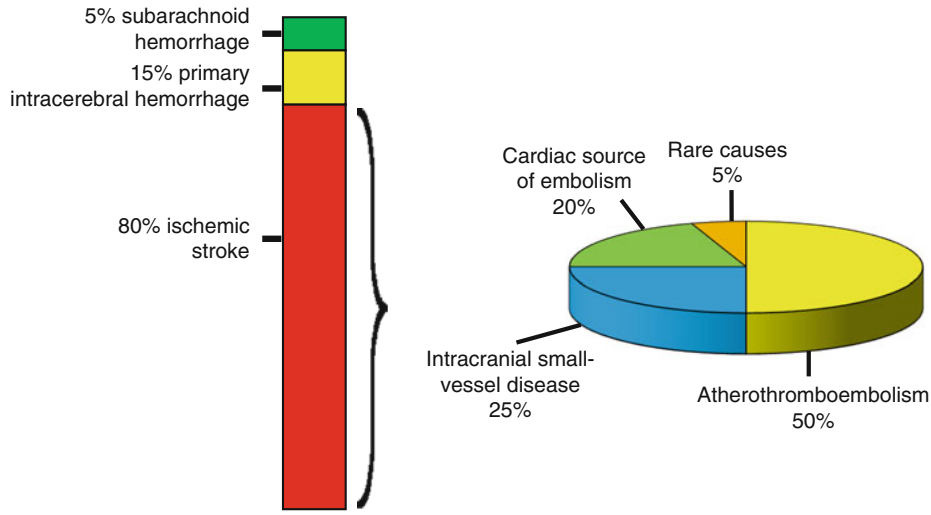

Fig. 30.1 Approximate frequency of three main pathological types of stroke (in white populations) and of main subtypes of ischemic stroke as shown by population-based study [9]

30.3 Incidence, Mortality and Risk

30.3.1 US and World Incidence and Mortality Rates

Since 1950, stroke death rates in the US and in many other countries have dramatically declined. In 1950, the age-adjusted death rate from stroke in the US was 180.7/100,000; by 2005, it had fallen to 46.6/100,000. In 1950, stroke mortality for ages 75–84 was approximately 1,500/100,000; by 2005, this had declined to 335/100,000 (Fig. 30.2) [12]. This decline in stroke mortality was consistent for sex in each racial and ethnic group in the US, and it is a function of a decrease in both the incidence of stroke and in short-term case fatality. Stroke death rates are a measure of deaths due to stroke in the short term (i.e., during hospitalization or within the first 6 months to a year after a stroke).The majority of individuals who survive their initial stroke subsequently die of other cardiovascular disease (CVD) or other causes.

The US has a low stroke mortality rate compared to other countries [13]. In 2002, the US ranked 186th in stroke mortality among 192 World Health Organization member countries. The median age-adjusted stroke mortality rate for the 192 member countries was 111/100,000 compared to 32/100,000 in the United States. Lower stroke mortality was also noted in Canada, France and Israel. Rates of stroke mortality were highest in Eastern Europe, Northern Asia, Central Africa and the South Pacific. There is a 10-fold variation in stroke mortality rates between the most-effected and least-effected countries.

In 2005, there was an estimated 16 million first-ever strokes worldwide and 5.7 million deaths attributed to stroke. In the absence of population-wide intervention, it is estimated that by 2015 the number of first-ever stroke cases will rise to 18 million and the number of stroke-attributed deaths will rise to 6.5 million. These numbers will further rise to 23 million first-ever strokes and 7.8 million deaths by 2030. Even if age-specific stroke death rates were to decline worldwide, the increase in the population of older individuals between 2005 and 2030 will result in a substantial increase in the number of deaths from stroke. In 2005, 87% of the worldwide deaths from stroke occurred in individuals living in low- and middle-income countries. It is estimated that the number of stroke deaths will be increasing in these countries, especially in the older age groups, due to the lack of effective preventive therapies [13].

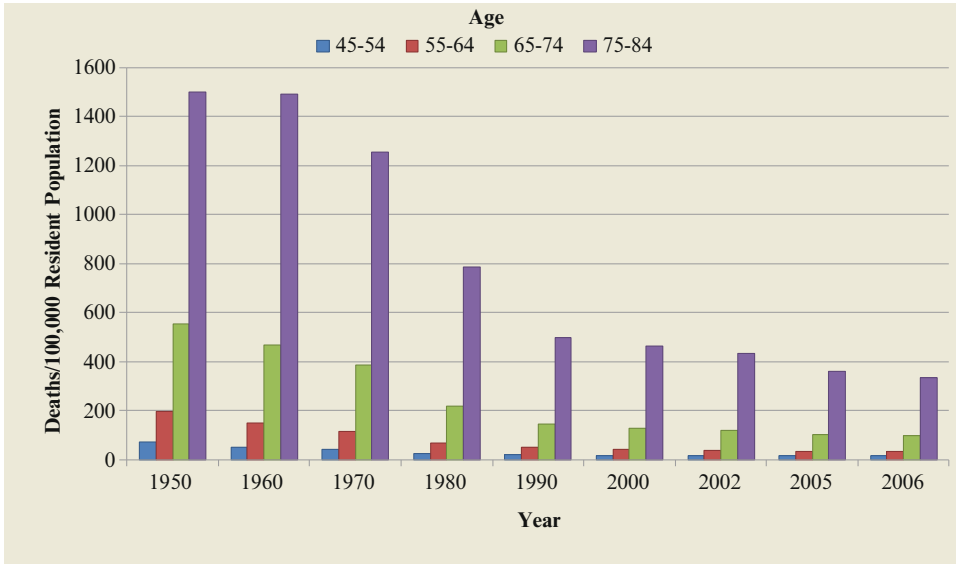

Fig. 30.2 Death rates for cerebrovascular diseases in the United States according to age (1950–2006) [11]

Among adults 45–69 years of age worldwide, heart disease and stroke are the leading causes of deaths and disability-associated life-years (DALYs) lost. One DALY is 1 year of healthy life lost, a measure of the burden of disease; a gap between the current health of a population and the ideal situation in which everyone in the population lives to old age in full health. Worldwide, the number of DALYs lost due to stroke increases with age. In 2005, the rate of DALYs lost for individuals >70 years of age was 54.8 per 1,000 individuals [13, 14].

30.3.1.1 US Incidence and Mortality by Region

In the United States, stroke incidence and mortality is much higher in both whites and African-Americans in the southeastern and south-central parts of the country, and very low in the Great Plains and Rocky Mountain areas [1, 15]. There is a >2-fold difference in stroke mortality rates between the highest and lowest states. There is also substantial variation in stroke mortality within states, primarily related to socioeconomic factors. Studies have evaluated the distribution of risk factors, environmental agents and treatment as a cause of this geographic variation. No single factor has been identified that accounts for the higher rates in the south or southeast, though they may, in part, be due to differences in socioeconomic factors [15]. Several studies have suggested that differences in the distribution of diabetes, or perhaps in abnormal glucose tolerance tests, might account for the variation in stroke incidence and mortality in these different regions [16]. A study of older participants in the CHS noted that geographic areas with higher stroke mortality had populations who had a greater extent of white matter abnormalities in the brain, which is a marker of long-term hypertensive disease and control [17]. This suggests that differences in duration or severity of hypertension, or in the treatment of hypertension, might explain these regional differences in stroke mortality, even though single measurements of BP at one or several time points did not account for these differences.

30.3.1.2 US Incidence and Mortality Rates by Race/Ethnicity

In the US, stroke incidence and death rates are much higher among African-Americans than among other ethnic groups, and the difference increases with age [11, 18]. The estimated age-adjusted incidence of stroke was 150/100,000 for white men and about 130/100,000 for white

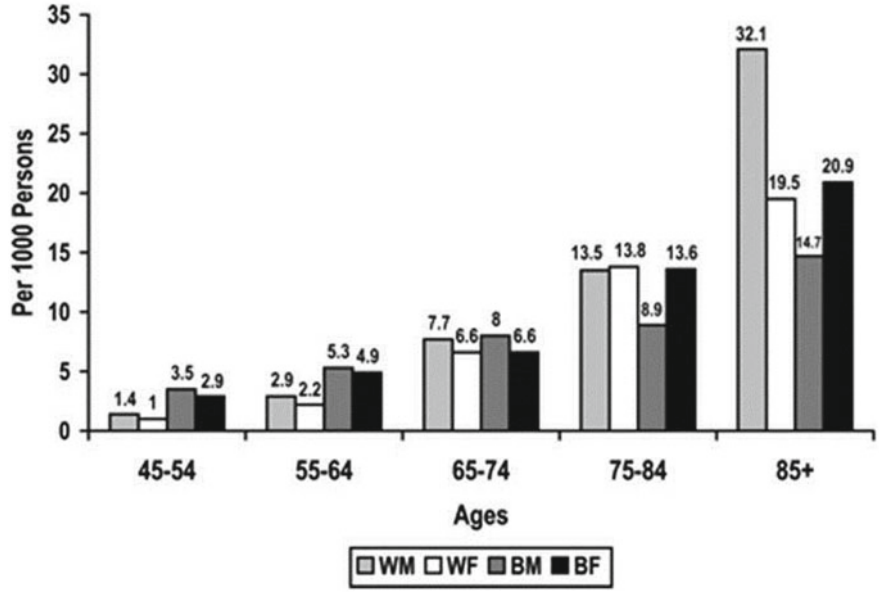

Fig. 30.3 Annual rates of first-ever strokes by age, sex and race [19, 20]

women compared to over 300/100,000 for African-American men and nearly 300/100,000 for African-American women. Incidence of first-ever stroke in the 75–84 age group are similar: per 1,000 individuals, incidence was 13.5 among white men, 13.8 among white women, 8.9 among African-American men and 13.6 among African-American women. Incidence is much higher among African-Americans than among Caucasians in the younger age groups (e.g., 55–64 years of age) (Fig. 30.3).

30.3.1.3 US Incidence by Age

Two-thirds of the burden of stroke occurs in people <70 years of age [13]. However, the prevalence of stroke increases dramatically with age. Approximately 8% of the population 60–79 years of age has had a stroke. For those ≥80 years of age, prevalence rises to 17% for men and 13% for women.

Age-adjusted annual stroke incidence rates have been declining in the US and in many western countries. In the Framingham Heart Study, age-adjusted annual incidence per 1,000 person-years declined from 1950–77 to 1992–94, from 7.6 to 5.3 in men and from 6.2 to 5.1 in women. Incidence of atherothrombotic brain infarction also decreased from 1950–77 to 1990–2004, from 4.9 to 3.6 in men and from 3.7 to 2.9 in women [21]. A recent population-based study from the Greater Cincinnati/Northern Kentucky Stroke Study reported that from 1993–1994 to 2005, first-ever stroke incidence declined in whites for all types of strokes, but not for African-Americans [18].

30.3.1.4 Non-US Incidence and Mortality

In recent years, the risk of stroke in China has seen a substantial increase. A recent report noted that the age-standardized rates of first-ever stroke in China (per 100,000 individuals) for ages 25–74 increased between 1984 and 2004, from 138 to 208 in men and from 121 to 150 in women. A much lower prevalence of cigarette smoking among women probably accounts for the differences in incidence between men and women. The majority of the strokes were ischemic. There has been a substantial decrease in hemorrhagic stroke incidence (per 100,000 individuals) in the Chinese population over the same time period, from 58.8 to 37.9 in men and from 53.2 to 14.2 in women. China has also seen a decrease in the case fatality rate and an increase in the age of onset of stroke [22].

Table 30.1 Age- and sex-specific, mortality-adjusted, 10-, 20- and 30-year and lifetime risk estimates for the development of stroke (all types) and ischemic stroke [21]

			Initial stroke, all types (875 events)			
			Short-term and intermediate-term risks			
Sex	Age (years)	Number: all strokes (and ischemic strokes)	10-year	20-year	30-year	Lifetime risk
Women	65	462 (400)	4.6 (3.8–5.5)	13.2 (11.8–14.5)	19.5 (17.8–21.1)	20.6 (19.0–22.3)
	75	347 (303)	10.5 (9.1–11.9)	18.3 (16.5–20.1)	–	19.7 (17.8–21.6)
	85	140 (123)	13.4 (11.1–15.6)	–	–	15.8 (13.3–18.2)
Men	65	293 (251)	7.0 (5.8–8.2)	14.1 (12.5–15.8)	16.5 (14.7–18.3)	16.8 (15.1–18.6)
	75	166 (145)	10.4 (8.6–12.1)	13.8 (11.8–15.8)	–	14.3 (12.2–16.4)
	85	38 (30)	8.5 (5.7–11.3)	–	–	9.8 (6.7–12.8)

In Japan, stroke mortality rates declined dramatically following World War II, though rates remained significantly higher than in the US [23]. As in the US, the incidence of stroke increases with age in Japan. In incidence per 100,000 individuals, incidence in men increases from 160 at 45–64 years of age to 1,363 at ≥85 years of age, and incidence in women from the same age groups increases from 63 to 1,203. Nonhemorrhagic stroke is the most common stroke type in Japan, and lacunar strokes are the most frequent ischemic stroke secondary to hypertension. This differs from the US and Europe, where cardioembolic and large-artery strokes are more common.

30.3.2 Lifetime Risk

Based on the Framingham Heart Study, the lifetime risk of stroke for men is 16.8% at 65 years of age (Table 30.1), 14.3% at 75 years of age and 9.8% at 85 years of age [21]. For women, lifetime risk is 20.6% at 65 years of age, 19.7% at 75 years of age and 15.8% at 85 years of age. The greater lifetime risk for women compared to men is due to the greater longevity among women. Thus, even at age 85, 13% of women and approximately 9% of men are predicted to have a stroke within 10 years. According to the Cardiovascular Lifetime Risk Pooling Project, the lifetime risk of fatal and nonfatal stroke beginning at age 55 is 10.5% for white men, 12.4% for white women, 11.7% for African-American men and 8.8% for African-American women. Lifetime risk of stroke was much higher among individuals who had prior myocardial infarction (MI) or higher BP [21].

In Japan, the lifetime risk of stroke at age 55 is 18.3% for men and 19.6% for women. Lifetime risk for cerebral infarction is 14.6% for men and 15.5% for women. The lifetime risk for cerebral hemorrhage is 2.4% for men and 1.4% for women. The lifetime risk of stroke at age 75 is about 19% for men and about 20% for women [23].

30.4 After a Stroke

30.4.1 Post-Stroke Events and Their Risk Factors/Predictors

The majority of individuals who survive their initial stroke subsequently die of other cardiovascular disease (CVD) or other causes. Case fatality during the first 30 days after a stroke is about 15–25%, with the stroke itself being the major cause of death [6, 10]. There is a very high risk of recurrent stroke and MI following an initial stroke, and the risk of dementia, depression and falls are also increased [24]. After a stroke, the risk of a recurrent cerebrovascular event is highest in the first month (4%) and within 1 year (12%). After the first year, the risk of a recurrent cerebrovascular event falls to about 5% per year, which is similar to the risk of a coronary event. During the first 5 years after a stroke, other CVD—especially CHD—becomes the major cause of death [12].

The risk of post-stroke death and disability increases with age, depending upon the type of

Table 30.2 Expected remaining lifetime (years) for 1-week survivors after stroke according to age at stroke onset and time period [12]

Sex, time period	50 years	60 years	70 years	80 years	90 years
Women					
1978–1981	14.2	9.5	5.4	2.6	1.1
1998–2001	17.6	13.5	8.8	4.9	2.3
Men					
1978–1981	13.2	8.5	4.8	2.4	1.0
1998–2001	17.2	12.5	7.8	4.3	2.1

Table 30.3 Adult 30-day case-fatality rates after first-ever stroke in 1993 to 1994, 1999 and 2005 by race and stroke subtype, inpatient plus out-of-hospital ascertainment [18]

	1993 to 1994 (%)			1999 (%)			2005 (%)		
Stroke subtypes	All	Black	White	All	Black	White	All	Black	White
All stroke subtypes	13.8	12.9	14.8	14.3	12.8	16.0	15.0	14.1	16.0
Ischemic	9.3	7.8	11.2	9.5	8.5	10.7	10.2	10.1	10.4
ICH	34.6	34.1	34.6	38.6	37.3	39.9	39.6	35.7	43.9
SAH	33.7	34.0	33.3	31.9	32.4	31.3	23.4	20.8	26.2

stroke, comorbidity, and disability prior to stroke [24]. The severity of a stroke is a key predictor of 30-day mortality. Other predictors include age, cardiac failure [12] and a history of previous stroke [12, 24]. The rate of 30-day disability also increases substantially following a recurrence of stroke [24]. Diabetes is one of the most powerful predictors for 5-year risk of subsequent stroke. Major long-term predictors of death after a stroke include increasing age, cardiac failure and renal disease. Lacunar strokes are associated with lower long-term case fatality.

30.4.2 Post-Stroke Survival

Five-year survival after a stroke is about 40%. About half of the patients who survive to 30 days after a stroke will live for 5 years [12]. The Perth Community Stroke Study examined 370 cases of first-ever stroke and found that 277 (83%) of the patients survived for 30 days, and 152 (55%) of the 30-day survivors were alive at 5 years. [24–26]

Longer term survival after a stroke is directly related to age. A study of Medicare patients found a 5-year survival rate of 48.3% in a population that averaged 80 years of age [27]. Post-stroke survival rates have increased for older adults in recent years. Boysen et al. [12] found that the average lifetime survival for women 70 years of age was 5.4 years in 1978–1981, and this improved to 8.8 years in 1998–2001. Similarly, the average lifetime survival for men was 4.8 years in 1978–1981, and this improved to 7.8 years in 1998–2001 (Table 30.2).

In the Greater Cincinnati/Northern Kentucky Stroke Study, the 30-day case fatality after all stroke subtypes was 15%; 14.1% in African-Americans and 16% in whites, probably due to the older age in whites. The 30-day case fatality for ischemic strokes was 10.2%, for intercerebral hemorrhage it was approximately 40% and for subarachnoid hemorrhage it was 23.4%. There has been little change in the 30-day case fatality rate from 1993 to 2005 (Table 30.3) [18].

The type of facility to which older adults are discharged after a stroke is also related to age. The American Heart Association Get with the Guidelines program in 2008 found that in a population of stroke patients with a mean age of 71 years, 35% were discharged home, 20.1% were discharged to a skilled nursing facility and 21% were discharged to an inpatient rehabilitation facility [28, 29]. In comparison, the afore-

mentioned study of Medicare patients found that in a population of stroke patients with a mean age of 80 years, 26.3% were discharged home, 15.7% were discharged to home care or organized home care, 43% were discharged to a skilled nursing facility or intermediate care, and 15% were discharged to 'other' [27].

30.4.3 Dementia After Stroke

There is a substantial increased risk of dementia after a stroke [30]. The risk of dementia appears to be substantially higher in studies that are based on hospitalized stroke cases as opposed to longitudinal follow-up studies. The risk 1 year after a stroke is about 20% based on hospitalized cases, but <10% based on the population-based studies. Risk factors for post-stroke dementia include lower education, AF, dysphasia, having multiple strokes, recurrent strokes after the first stroke during the follow-up period, white matter abnormalities in the brain, and ventricular brain atrophy on MRI. Women have a slightly higher risk for post-stroke dementia than men.

The Baltimore Longitudinal Study of Aging found that the majority of patients (mean age of 75 at entry) who had dementia after the initial stroke had mild cognitive impairment (MCI) prior to the stroke [31]. The risk of dementia (n = 15) among those with MCI was 41 (5.1–328), but was only 1.1 (0.3–3.3) (n = 18) for those who were cognitively normal prior to the stroke. Vascular disease did not affect the progression of dementia, but a new stroke was associated with a more rapid decline among dementia patients.

There is also an increased risk of dementia among older individuals with silent brain infarcts or high white matter abnormality scores. High white matter abnormalities are correlated with increasing ventricular size, which is a measure of global brain atrophy in the elderly. Atrial fibrillation has also been reported to be a risk factor for dementia. The relationship between vascular disease in the brain and Alzheimer's disease is controversial. In postmortem examination, older individuals often have a combination of both Alzheimer's disease pathology (amyloid plaques and neurofibrillary tangles) and vascular disease infarcts (white matter abnormalities, microhemorrhages, etc.). There is, however, only very limited clinical trial evidence that the treatment of hypertension reduces the risk of dementia.

30.5 Treatment of Stroke

30.5.1 Treatment at Onset

The administration of intravenous tissue plasminogen activator (IVTPA) [32] within 3 h of the onset of initial stroke symptoms will result in a substantial reduction in clinical stroke and disability. Older individuals are much less likely to be treated than younger individuals due to comorbidities that make them ineligible for therapy. There is a longer delay in time from the onset of symptoms to treatment and reluctance on the part of the physician and family to use IVTPA due to the risk of hemorrhagic complications, especially brain hemorrhage. Intravenous tissue plasminogen activator, however, is equally effective in older stroke patients and is very underutilized in older patients, even those who are at the highest risk of disability associated with stroke. There is little evidence of more adverse effects from the use of IVTPA in older individuals, even in those ≥80 years of age, than in younger individuals.

Many studies have attempted to decrease the time from symptomatology to treatment in the hospital and use of IVTPA [33]. Many of these studies have not been terribly successful. A major problem is the lack of recognition of early stroke symptomatology by the patient and their families, and even by physicians in the community. Specific criteria for thrombolysis have been published. The imaging of the brain (either CT or MRI) is required prior to thrombolysis with IVTPA to make sure that the diagnosis is not a cerebral hemorrhage. Recent programs have included the use of telemedicine to link hospitals in the community to stroke centers and to expertise in the use of IVTPA in the acute care of stroke patients.

30.5.2 Treatment in the Hospital

There is reasonably good evidence that patients treated at stroke centers have a reduced risk of morbidity and mortality [32]. In year 2000, the Brain Attack Coalition developed a concept of two types of stroke centers. A primary stroke center has the necessary staffing, infrastructure and programs to stabilize and treat most acute stroke patients [34]. A comprehensive stroke center is defined as a facility or system with the necessary personnel, infrastructure, expertise and programs to diagnose and treat stroke patients who require a high intensity of medical and surgical care, specialized tests or interventional therapies [8]. Recommendations for stroke performance measures in inpatient treatment have recently been reviewed based on the recommendations by different organizations. These include thrombolytic therapy administered prior to hospitalization or within the first 3 h, antithrombotic therapy in the hospital by the end of the second day, the management of deep vein thrombosis, prophylaxis, dysphasia screening, stroke education, smoking cessation, assessment for rehabilitation, discharge on antithrombotic therapy, discharge on anticoagulation for patients with AF, and discharge on cholesterol-reducing medications [1, 2].

30.5.3 Post-Stroke Care

Randomized trials have compared carotid endarterectomy vs. medical therapy alone and subsequent stroke and mortality for patients with both symptomatic and asymptomatic carotid artery stenosis. The value of carotid endarterectomy has been established from the results of three major randomized trials among symptomatic patients with either transient cerebral ischemia or strokes and high grade stenosis [35–37]. Individuals with symptomatic carotid stenosis >50% received benefit from surgical endarterectomy. In 2005, 66,698 endarterectomies were performed among patients >75 years of age [35–37].

Carotid endarterectomy for asymptomatic individuals with 60–99% stenosis has a small benefit for selected patients with good life expectancy [38]. The United States Preventive Services Task Force does not recommend screening for asymptomatic carotid stenosis [39].

Air pollution, acute infections and temperature changes may be important precipitants of stroke among older individuals and should be considered in post-stroke care. Also, there is suggestive evidence that vaccines for influenza and pneumonia will reduce the risk of incident stroke among older individuals by preventing incident influenza or pneumonia that may precipitate a stroke [40]. Finally, it is extremely important for the treatment of stroke that the high prevalence of disease in other vascular beds be considered in preventive therapies. The strong association of renal disease and brain vascular disease results in a high prevalence of renal disease among older stroke patients, especially those with diabetes and hypertension. Ideally, the prevention of stroke and reduction of morbidity after a stroke should be part of a broad-based vascular disease prevention and treatment strategy.

The development of new drug therapies to replace Coumadin anticoagulation may have a dramatic effect on preventive therapies for the elderly, especially those with AF. Similarly, the success of BP and lipid lowering, and of newer and better antiplatelet agents, may reduce the benefits of surgery versus medical therapies for patients who have carotid stenosis.

30.6 Risk Factors for Stroke

Risk factors for stroke vary in relationship to the pathophysiology of the stroke (thrombosis, embolism, hemorrhage, etc.), the location of the arterial pathology (extracranial and intracranial) and whether the stroke involves small or large vessels within the brain. Hypertension is the most important risk factor for stroke, both for infarction and for hemorrhage [41]. Small vessels in the brain are especially vulnerable to the effects of hypertension, which often results in lacunar-type strokes that affect the basal ganglion. Stroke mortality rate is linearly related to the level of systolic BP and, to a lesser degree, diastolic BP (Fig. 30.4).

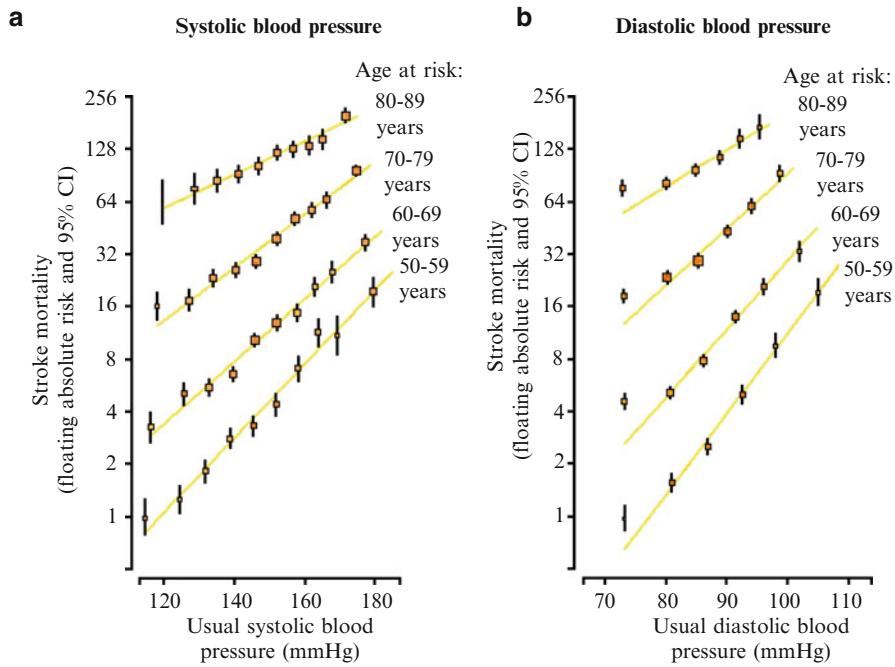

Fig. 30.4 Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade [42]

A single elevated BP measurement is a risk factor for stroke. BP, however, varies during the daytime and usually decreases at night. There are reports that failure of BP to decrease at night—so-called "nondipping"—may be associated with an increased risk of stroke and vascular disease [40]. Measures of the variability of BP over the daytime may provide better risk prediction.

Cigarette smoking is also an independent risk factor for stroke [43]. The prevalence of cigarette smoking decreases at older ages and becomes a less important attributable risk factor. Moderate alcohol intake has been reported to be associated with a lower risk of cerebral infarction in both men and women. However, heavier alcohol intake is associated with both higher BP and an increased risk of cerebral hemorrhage. In addition, there is a short-term increased risk of stroke in the hours after the ingestion of alcohol [44, 45].

The relationship of blood cholesterol and low density lipoprotein (LDL) cholesterol level to risk of stroke may be dependent, in part, on systolic BP levels. A large prospective collaborative study of blood cholesterol and vascular mortality by age, sex and BP (a meta-analysis of 61 prospective studies) showed that a higher cholesterol level is related to a higher risk of stroke for individuals with "normal" systolic BP (i.e., <145 mmHg [millimeters of mercury]), but individuals with a high systolic BP showed a relationship that was either inverse or inconsistent. The inverse relationship of high BP and serum cholesterol with stroke was stronger for hemorrhagic stroke than for ischemic stroke [46]. Lipoprotein levels are also closely related to large-artery atherosclerotic disease and risk of stroke.

Waist circumference or waist-hip ratio appears to be a stronger predictor of stroke than is a measurement of body mass index. The association of excess body weight and risk of stroke is, in part, determined by other risk factors such as BP, lipid levels, etc. [47].

Diabetes is a strong risk factor for both CHD and stroke [48]. The relationship is stronger for ischemic than it is for hemorrhagic or unclassified stroke, with the estimated hazards ratio for diabetic versus nondiabetic individuals for ischemic stroke at about 2.3, for hemorrhagic stroke at 1.5 and for unclassified stroke at 1.8. Risk among

Table 30.4 Comparison of the population-attributable risk (99% CI) for common risk factors in the INTERSTROKE and INTERHEART studies [49]

Common risk factors	INTERSTROKE (all stroke, 3,000 cases; 3,000 controls	INTERHEART (acute myocardial infarction; 15,152 cases; 14,820 controls
Hypertension	34.6% (30.4–39.1)	17.9% (15.7–20.4)
Smoking	18.9% (15.3–23.1)	35.7% (32.5–39.1)
Waist-to-hip ratio (abdominal obesity)	26.5% (18.8–36.0)	20.1% (15.3–26.0)
Diet		
Diet risk score	18.8% (11.2–29.7)	–
Fruits and vegetables daily	–	13.7% (9.9–18.6)
Regular physical activity	28.5% (14.5–48.5)	12.2% (5.5–25.1)
Diabetes	5.0% (2.6–9.5)	9.9% (8.5–11.5)
Alcohol intake	3.8% (0.9–14.4)	6.7% (2.0–20.2)
Psychosocial factors		
All psychosocial factors	–	32.5% (25.1–40.8)
Psychosocial stress	4.6% (2.1–9.6)	–
Depression	5.2% (2.7–9.8)	–
Cardiac causes	6.7% (4.8–9.1)	–
Ratio of apolipoproteins B to A1	24.9% (15.7–37.1)	49.2% (43.8–54.5)

individuals with diabetes is further increased by the presence of elevated BP, lipids and cigarette smoking.

A study of stroke patients and controls in different countries estimated the attributable risk of stroke from hypertension at about 35%, with smoking at 19%, waist-hip ratio (a measure of abdominal obesity) at 26%, physical activity at 28%, and diabetes at 5% (Table 30.4). Lipid levels, such as the ratio of apolipoprotein-B (ApoB) to apolipoprotein-A_1 ($ApoA_1$), are a much more important predictor of CHD than of stroke, while hypertension tends to be a more important risk factor for stroke [49]. Higher phospholipase A-2 and C-reactive protein are risk factors for stroke [50].

The CHS developed a stroke prediction score for older individuals [5]. Similar models have also been developed in the ARIC Study [51] and the 21-year follow up of the Israeli Ischemic Heart Disease Project [52]. All three risk scores are similar. The CHS model is based on systolic BP, time to walk 15 ft (a measure of physical functioning which is also highly correlated with white matter abnormalities in the brain), left ventricular hypertrophy by electrocardiogram, blood creatinine levels (a marker of kidney function), diabetes, age, AF and history of CHD. The model combined the measures of these factors into a total risk score. Regarding 5-year stroke risk, men with scores of 1–5 have a risk of 2.5%, while men with scores 41–45 have a risk of 59%. Women with scores of 1–5 have a risk of 3.5%, while women with scores of 41–45 have a risk of 39%.

Dietary sodium is a major determinant of BP levels. Studies have shown that in various populations, there is a strong relationship between dietary intake of sodium and both death rates and incidence of stroke [53]. Dietary and other risk factors for stroke were evaluated for women in the Nurses' Health Study and for men in the Health Professions Follow Up Study. Factors related to a low lifetime risk of stroke included no cigarette smoking; a body mass index <25 kg/m^2; ≥30 min of exercise per day; moderate alcohol intake (5–30 g in men and 5–15 g in women); a good health diet score from the Healthy Eating Index; a higher intake of fruits, vegetables, nuts, soy, and cereal fiber; a higher intake of chicken and fish and less red meat; a higher intake of polyunsaturated fat; and a lower intake of saturated fat and trans fat. Of those with this low risk pattern, the women had a hazard ratio of subsequent stroke of only 0.21 (0.12–0.36) and the men of only 0.31 (0.19–0.53) [44]. A study of metabolic risk factors for stroke followed 2,313 middle-aged men

for up to 32 years (mean age was 50 and there were 421 incident strokes). Dietary factors were evaluated using the measurement of cholesterol ester fatty acids, a marker of usual dietary intake in the past 2 weeks. A higher proportion of saturated and monosaturated fatty acids was associated with an increased risk of stroke, while a higher proportion of polyunsaturated fatty acids—especially linolenic acid—was associated with a reduced risk [54]. However, to date there has been no successful clinical trial to demonstrate that these dietary changes result in a reduction in the risk of stroke, especially in the elderly.

Depression and stroke are both very common in older age groups. A recent report noted that depression was associated with an increase in stroke over a 3-year period (hazard ratio 2.8 [confidence level {CL}: 1.5–4.7]). Among the symptoms of depression, only depressed mood was an independent predictor of incident first stroke in multivariate analysis [55]. Other studies have reported an increased risk of depression after stroke in the elderly [56].

30.7 Physiological Contributors to Stroke

Pathophysiological changes specifically associated with hypertension or elevated BP are important risk factors for stroke, including decreased kidney function [7], microvascular abnormalities in the eye [57], ventricular hypertrophy of the heart, white matter abnormalities and brain infarcts on MRI [58, 59] and increased carotid intima-media thickness (IMT) by ultrasound measurement. In the CHS, the prevalence of MRI infarcts was similar in men and women, and increased with age. The prevalence increased to almost 35–40% among men and women ≥85 years of age as compared to about 15% age 60–69. Among individuals with no prior history of stroke, MRI infarcts ≥3 mm were associated with systolic BP levels at baseline, lower scores in the digit symbol substitution test and a number of neurological abnormalities. Most of the silent infarcts were located in the basal ganglia area. The combination of higher systolic or diastolic BP and silent infarcts resulted in a striking increase in risk of stroke. Individuals with a systolic BP >146 mmHg and silent infarcts had a stroke incidence rate of 31.5/1,000 person-years versus only 8.1/1,000 person-years for those with a systolic BP <121 mmHg and no silent infarcts (Fig. 30.5) [58].

In a study in 2004, we found that white matter hyperintensities (a marker of hypertensive vascular disease) are also related to elevated BP and are correlated with silent infarcts in the brain. White matter abnormalities were graded from 0 to 9, with higher numbers indicating worse abnormalities. The prevalence of white matter abnormalities

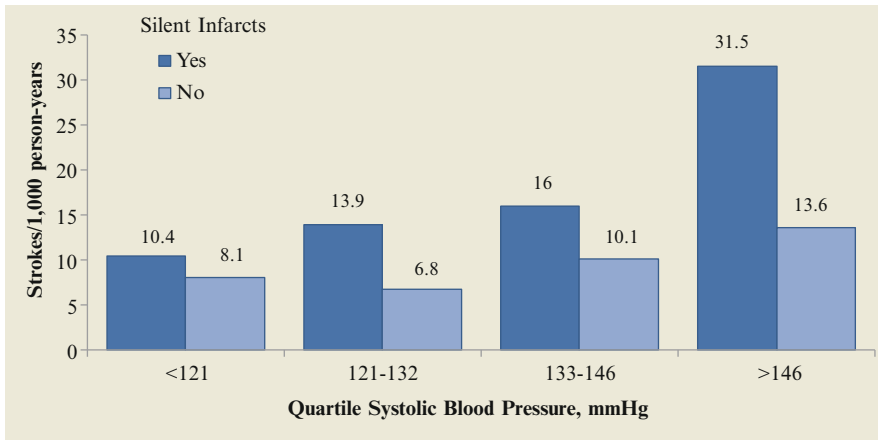

Fig. 30.5 Number of incident strokes as a function of systolic blood pressure and presence of silent infarcts [59]

increased with age and was associated with hypertension and diabetes. Incidence of stroke by white matter abnormalities increased from 6.0/1,000 person-years for individuals with a white matter grade of 1, to 39.4/1,000 person-years for those who had a white matter grade of 7. Individuals with higher white matter grades were at an increased risk of stroke, especially when in combination with hypertension and diabetes, a history of MI, or a history of CHF. The combination of a white matter abnormalities grade >5 and brain infarcts resulted in a 3.7-fold increase in risk of stroke [58].

Several studies have demonstrated that an increased IMT and carotid artery stenosis are important risk factors for stroke in the older age group. In the CHS, maximal IMT of the carotid artery was linearly related to the risk of stroke even after adjustment for age, sex and other risk factors. Relative risk was 2.13 when comparing the highest versus the lowest risk for the maximum carotid IMT, 2.35 when comparing with regard to the maximum internal carotid artery IMT, and 2.56 when comparing with regard to the combined measure [60].

Atherosclerotic plaque in the carotid artery is a risk factor for stroke. The characteristics of the plaque may be further associated with an increased risk of stroke. In the CHS, hypoechoic plaques were shown to increase the risk of stroke. Decreased ankle brachial index, a marker of lower extremity peripheral vascular disease, is a risk factor for both stroke and coronary artery disease (CAD). A declining ankle brachial index over time is also a risk factor for stroke. Lower extremity peripheral vascular disease is associated with a higher prevalence of carotid stenosis [61].

30.7.1 Amyloid Angiopathy and Cerebral Microbleeds

Intercerebral hemorrhage among older adults is usually due to hypertension and changes in small penetrating arteries in the brain, and it has a very high rate of case fatality [62]. A second type of hemorrhage in older individuals is related to cerebral amyloid angiopathy (CAA), characterized by deposition of beta amyloid (Aβ)—especially Aβ1-40—in the walls of the arteries [63]. Autopsy studies report a prevalence of CAA of about 5–9% in those 60–69 years of age to about 50% in those ≥90 years of age. Positron emission tomography imaging techniques can identify both the Aβ in plaques (Aβ1-42) and CAA Aβ1-40 in the arterial wall. CAA is an important determinant of lobular intracerebral hemorrhage in older adults and should be considered in older individuals with cerebral hemorrhage who do not have hypertensive-related risk factors, bleeding disorders, anticoagulation therapy or alcohol abuse.

Cerebral hemorrhage associated with CAA usually occurs in the cortex (i.e., lobular intracerebral hemorrhage). There is suggestive evidence that CAA in older populations is associated with an increased prevalence of ischemic brain lesions, possibly with cognitive impairment, and with a high prevalence of white matter lesions in the brain and recurrent stroke [64]. The diagnosis of CAA is based on the occurrence of singular or multiple lobular hemorrhages or "microbleeds" without evident cause. New MRI imaging techniques using gradient echo (GE) technology has improved the identification of cerebral microhemorrhages [64].

Microbleeds are usually asymptomatic and have been associated with an increased risk of stroke and with hemorrhagic changes within ischemic strokes. In the Rotterdam study of older individuals, the presence of cerebral microbleeds increased with age from 17.8% at 60–69 years of age to 38.3% at ≥80 years of age. Microbleeds were separated into lobular, which are most likely due to CAA, and deep or infratentorial, which are associated with lacunar infarcts and elevated cardiovascular risk factors, especially hypertension [65].

In patients' ≥age 65, lowering BP in patients with clinical cerebrovascular disease results in a significant decrease in CAA-related intracerebral hemorrhage by 77% (19–93%) and hypertensive-related intracerebral hemorrhage by 46% (4–69%). Thus, lowering BP predominantly protects against all types of intracerebral hemorrhage [66].

30.7.2 Genetics

There is evidence from twin and family studies, and data from many rare monogenic disorders, that there is an important genetic contribution to the risk of stroke. Genome-wide association studies (GWAS) have identified a few single nuclear polymorphisms that have an increased prevalence among stroke patients [67]. Generally, they have contributed little to our understanding of the genetics of stroke and have no clinical utility at the present time, especially among older individuals. For example, in eight recent GWAS reports on stroke, no single locus has been identified repeatedly with a high level of significance. The GWAS did not identify the loci that have been previously reported from candidate-gene studies of stroke. Variations on the 9P21.3 locus have been associated with ischemic stroke, especially large artery stroke. Similar associations of this specific locus are reported for coronary artery disease and MI. These inconsistent results are probably due to the failure to identify the specific subtype of stroke. Future genetic studies may be enhanced by evolving newer techniques for studying the genomics of stroke and better phenotyping of the specific type of stroke.

30.7.3 Atrial Fibrillation

AF increases the risk of embolization from the heart and is a major cause of stroke among older individuals [68]. AF is associated with nearly 45% of all embolic strokes. The prevalence of AF increases with age. It is estimated that 2.3 million adults in the US have AF, and 50% of AF patients are >80 years of age. AF is associated with a 4–5-fold increase in the risk of stroke, and approximately 15% of all strokes are caused by AF [69, 70]. This percentage increases dramatically with age. Approximately 40% of incident stroke patients >85 years of age have AF as compared to <20% of the controls without stroke. Similarly, in the 65–84 age group, close to 15–20% of incident stroke patients have a history of AF as compared to <10% of controls. The absence of AF symptoms does not rule out the risk of stroke. The attributable risk of stroke in older individuals due to AF is very high (36%). GWAS have identified 2 variants on chromosome 4 that are associated with an increased risk of AF. These variants are also associated with embolic stroke related to AF [71].

Atrial fibrillation is classified as either paroxysmal or chronic persistent, and both of these subtypes have similar stroke rates. The relative risk of stroke among patients with AF can be partially determined by the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and prior Stroke (CHADS) score, an index derived from large AF registries [72]. The CHADS score assigns points for risk factors: 1 point each for CHF, hypertension, age >70 and diabetes, and 2 points each for prior stroke and TIA. A CHADS score of 0 corresponds to a risk of stroke of <1% per year. A CHADS score of ≥2 corresponds to an increase in the risk of stroke to 4% per year. Most elderly individuals will have a CHADS score of at least 2 because 1 point is given for age (Table 30.5).

Less than 50% of older individuals who are candidates for anticoagulation therapy receive such therapy. This is unfortunate because even in the elderly, anticoagulation therapy is a highly effective method of preventing AF-related thromboembolism, including stroke. A recent study evaluated warfarin anticoagulation therapy among patients who were ≥65 years of age and had their warfarin carefully managed onsite. Of 473 patients, 32% were >80 years of age and 91% had >1 risk factor for stroke. The cumulative incidence of major hemorrhage for patients >80 years of age was 13%, as opposed to only 4.7% for those <80 years of age. Within the first year, 26% of patients >80 years of age had stopped taking warfarin, 81% of them due to safety concerns. Individuals with higher CHADS scores who were at highest risk were more likely to go off anticoagulation therapy.

Oral anticoagulation is superior to aspirin for the prevention of stroke among individuals with AF. Warfarin reduces the relative risk of stroke by 64% versus placebo, while aspirin reduces the risk by only 22% versus placebo [74]. Recently, new types of anticoagulants—which probably

Table 30.5 Risk of stroke in National Registry of Atrial Fibrillation (NRAF) participants, stratified by CHADS2 scorea [73]

$CHADS_2$ score	Number of patients (n = 1,733)	Number of strokes (n = 94)	NRAF crude stroke rate per 100 patient-years	NRAF adjusted stroke rate, (95% CI)[b]
0	120	2	1.2	1.9 (1.2–3.0)
1	463	17	2.8	2.8 (2.0–3.8)
2	523	23	3.6	4.0 (3.1–5.1)
3	337	25	6.4	5.9 (4.6–7.3)
4	220	19	8.0	8.5 (6.3–11.1)
5	65	6	7.7	12.5 (8.2–17.5)
6	5	2	44.0	18.2 (10.5–27.4)

Abbreviation: *CHADS* the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and prior Stroke score
[a] $CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval
[b]The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken

have less of the bleeding problem that is associated with warfarin—have become available, especially Factor X and direct thrombin inhibitors. It is likely that newer approaches to prevent embolization and stroke will replace current warfarin anticoagulation for older individuals. Also, new antiplatelet-aggregating agents are probably more effective than aspirin. These new therapies are much easier to manage, may be safer and are equal to warfarin in effectiveness. Hopefully, these new therapies will change the pattern of care for AF in the elderly and result in a decrease in stroke risk.

30.7.4 Transient Ischemic Attack

In 1975, a new classification of cerebrovascular disease defined transient ischemic attack (TIA) as temporary attacks (commonly 2–15 min in length, with a maximum of 24 h) with focal symptoms which are attributable to dysfunction of one of the brain areas supported by arterial trees of the brain. Transient neurological attacks (TNAs) were defined as diffuse, nonlocalizing cerebral symptoms, and are considered to be more benign [75].

The 90-day risk of stroke after a TIA is about 10.5%, and about half of these strokes will occur within the first 2 days after a TIA [48]. Prognostic risk scores predict the risk of stroke after a TIA, and these scores have been validated [75]. The risk score includes five factors: (1) one point for age >60, (2) one point BP elevation on first assessment after a TIA, (BP >140 or diastolic >90 mmHg), (3) two points for weakness or one point for speech impairment without weakness, (4) two points for duration of TIA >60 min or one point for duration of TIA 10–59 min, and (5) one point for having diabetes. These factors represent Age, Blood Pressure, Clinical features, Duration and Diabetes ($ABCD^2$ score) [75]. In an evaluation, 2-day stroke risk was 0% for an $ABCD^2$ score of 0 or 1, 1–2% for a score of 2, 3% for a score of 3, 3–5% for a score of 4, 3–7% for a score of 5, 4–14% for a score of 6, and up to 50% for a score of 7. The 'C' statistic for the $ABCD^2$ score varied across studies from 0.62 to 0.83. Stroke risk at 90 days was 9%, varied from 3% for those with a score of zero, to 21% for those with a score of 4. Only 3 strokes occurred among the 127 of the 544 with an $ABCD^2$ score of 0 or 1, while 48 strokes occurred among the 219 with scores of ≥3. The presence of brain infarcts on MRI or CT at the time of TIA independently increased the risk of clinical stroke [76].

Wijk et al. [77] conducted a long-term follow up of 8,447 patients with TIA in Holland. The mean length of follow-up was 10.1 years and age at entry to the study was ≥65 years. At the end of follow-up, 60% of the patients had died. The 10-year risk of death was 43%, much higher than

in the general population. The 10-year risk of a vascular event was 44%, and 54% had at least one vascular event. The risk of a vascular event fell for the first 3 years after a TIA and then increased over time.

The Rotterdam Study of older individuals has reported on the characteristics and outcomes of individuals classified as TIA and TNA [78]. Mean age of the participants was 67 years and 62% were women. Focal TIA occurred in 282 individuals, 228 had nonfocal TNA, and 38 were mixed. Symptoms of TIA included hemiparesis in approximately 50% of participants, hemianesthesia in 17%, dysarthria or dysphagia in about 40%, and amaurosis fugax or hemianopia in 18%. The nonfocal symptoms included such things as confusion, unconsciousness, decreased consciousness, amnesia, unsteadiness of gait, nonrotary dizziness, bilateral weakness, etc. Incidence of TIA varied from 1.8/1,000 person-years in those 55–64 of age to 10.5/1,000 person-years for those >85 years of age. Incidence in women ranged from 2.0 to 8.8/1,000 person-years. Nonfocal TNAs also increased with age with an incidence similar to TIA. Predictors of focal TIA included age, cholesterol level direct and HDL cholesterol indirect, cigarette smoking, AF and history of angina pectoris. Risk of stroke was increased 2-fold (1.5–2.91) for those with focal TNA and 1.56-fold (1.08–2.28) for those with nonfocal TNA. However, after adjustment for various risk factors, focal TIA was still associated with a 2.5-fold risk of ischemic stroke but there was no association with nonfocal TIA. Nonfocal TIA was strongly related to risk of dementia.

Recent imaging studies have shown that there are small brain infarcts among TIA patients [79]. Some now believe that TIA should be classified as mini-strokes. TIAs are a medical emergency, especially for older individuals. Antithrombotic medication, aspirin or other antithrombotic drugs (but not anticoagulants) should be given immediately after a TIA, as well as therapy to lower BP and probably blood lipids as well.

Unfortunately, symptoms of TIA are frequently ignored by patients and their relatives, and frequently go unrecognized by a doctor, which delays diagnosis and treatment and increases the risk of stroke. Specialized clinics to identify and treat TIA have been developed in some communities and have been associated with an improvement in treatment. It should be noted that TIA also carries a high risk of subsequent MI and other nonstroke vascular disease.

30.8 Stroke Prevention

Stroke prevention includes: (1) prevention of elevated risk factors, especially the reduction of high BP and high total and LDL cholesterol, not smoking cigarettes and treating diabetes; (2) treatment of elevated risk factors as above; (3) early recognition of TIA and appropriate antithrombotic therapy such as aspirin and similar newer drugs; (4) recognition of AF and appropriate anticoagulation therapy and/or antithrombotic therapy based on risk and/or potential rhythm control for the AF; (5) identification of high-grade carotid stenosis and endarterectomy for patients with a history of stroke and TIA, and selected asymptomatic older patients with good predicted survival; (6) early recognition of evolving stroke, and emergent treatment within 3–4 h of onset and treatment with tissue plasmin activator (TPA); (7) care of stroke patients within a stroke center or hospital that follows current guidelines; (8) post-stroke reduction of risk factors, especially BP and lipids, and antithrombotic therapy; (9) stroke rehabilitation; and (10) preventive therapies that reduce the risk of other CVD, falls and renal failure [24, 80].

30.8.1 Lowering Blood Pressure

Primary and secondary prevention of stroke is extremely effective in reducing stroke incidence and mortality [81]. Clinical trials have clearly documented that the reduction of BP decreases the risk of stroke [82, 83]. The reduction in the risk of stroke is directly related to the initial BP levels and decline in the BP levels via drug therapy. Antihypertensive therapy is effective even in

the oldest age groups. There is little evidence that any specific drug or drug combination is more effective than another in reducing the risk of stroke as long as BP reduction is the same. The choice of specific first-line and subsequent combined therapies to prevent stroke remains controversial. It often requires multiple drugs to substantially reduce systolic BP below 140 or 130 mmHg. In older age groups, there may be an increase in "orthostatic hypotension" and risk of falls and fracture among individuals on antihypertensive therapy. The basic problems with antihypertensive therapy are the lack of continued adherence to the drug therapy and the intensity of the drug therapy to reduce the BP.

The control of BP goes down with increasing age. For example, the National Health and Nutrition Examination Survey (NHANES) in 1999–2004 found that 77% of hypertensive women 70–79 years of age were aware of their elevated BP. Of these, 68% were being treated but only 45% had their BP controlled (defined as <140/90 for those without diabetes and <130/80 for those with diabetes). Similarly, in the ≥80 age group, 71% were aware, and of these 62% were treated and only 28% had their BP controlled. In contrast, among hypertensives 60–69 years of age, 45% had their BP controlled. Men had much better control of their BP than women. In men, 62% of the 60–69 age group, 45% of the 70–79 age group and 37% of the ≥80 age group had their BP controlled [84].

There is still controversy about how low the BP should be reduced in order to decrease the risk of stroke and CVD. A recently-completed Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by the National Heart, Lung and Blood Institute showed that lowering BP <130 mmHg was associated with little overall benefit, but was associated with a substantial reduction in the risk of stroke among individuals with type 2 diabetes [85, 86]. A new Systolic Blood Pressure Intervention study (SPRINT) by the National Heart, Lung and Blood Institute will evaluate lowering systolic BP to 120 mmHg among high-risk participants. Endpoints will include not only stroke, CHF and CVD, but also dementia.

The lowering of BP is also effective in reducing the risk of recurrent strokes and fatal strokes among individuals who already had an initial stroke. Lower BP is a cornerstone of the prevention of further strokes and disability among older individuals who have had a stroke. It is estimated that in the 70–79-year age group, a 20 mm/Hg reduction in systolic BP would result in about a 50% reduction in strokes, including cerebral ischemia, unknown types and cerebral hemorrhage. In the 80–89-year age group, a 20 mm/Hg reduction would result in about a 1/3 reduction in overall strokes, a 50% reduction in cerebral hemorrhage and a 25% reduction in cerebral ischemia. A 1 mm/Hg reduction in systolic BP generally transmits to about a 2% reduction in risk of stroke [83, 84].

30.8.2 Lowering Cholesterol

Although LDL or ApoB levels are not strongly related to the risk of stroke, reduction in blood cholesterol levels by statin drug therapy substantially reduces the risk of incident stroke and recurrent stroke. A recent meta-analysis suggested that for a 10% reduction in LDL, stroke incidence is reduced 15% among individuals with and without diabetes. This reduction in the risk of stroke is with regard to both initial strokes and recurrent strokes. The decrease in risk is directly related to the reduction in the blood LDL cholesterol level [40]. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) (mean age at entry: 65 years), a substantial reduction in LDL cholesterol with rosuvastatin resulted in about a 50% reduction in the risk of incident stroke over the approximate 2-year follow-up. There were 33 strokes among the 8,900 participants in the rosuvastatin treatment group and 64 strokes in the 8,901 that were on placebo. The reduction in stroke was consistent for nonfatal stroke, fatal stroke, hemorrhagic stroke and stroke of unknown type, but there was no reduction in TIA. The rate of stroke was substantially reduced for those individuals whose LDL cholesterol level was reduced below 70 mg% or who had a

>50% reduction in their LDL cholesterol. Reduction in C-reactive protein was also associated with a reduction in risk of stroke [87].

30.8.3 Glycemic Control

Diabetes is an important risk factor for stroke. Elevated blood glucose within the "normal" or pre-diabetic range may also be a risk factor for stroke. To date, however, there is no solid clinical trial evidence to indicate that a substantial lowering of blood glucose levels by drug therapy, or by nonpharmacological therapy such as exercise or weight loss, reduces the risk of stroke among individuals with diabetes. Among those with diabetes, the treatment of hypertension and high LDL cholesterol substantially reduces the risk of stroke and is an important component of preventive therapies, especially in the elderly [40].

30.8.4 Supplement Therapies

Observational studies have demonstrated a positive association between blood levels of homocysteine and the risk of stroke [88]. However, there is no evidence from clinical trials that an increased intake of vitamins B_{12}, B_6 or folic acid to reduce homocysteine levels is associated with a reduction in the risk of stroke. Similarly, clinical trials have not shown that increased doses of vitamin E or vitamin C reduce the risk of stroke. Multiple vitamin therapies are not recommended as a primary therapy for stroke prevention in the elderly [40].

30.8.5 Increased Physical Activity

Observational studies have found greater levels of physical activity to be associated with a decreased risk of both stroke and possibly dementia [40]. However, no clinical trials have documented that an increase in physical activity reduces the risk of stroke in the older age groups. The current Lifestyle Interventions and Independence for Elders (LIFE) study (www.thelifestudy.org/public/index.cfm) may provide further information on whether physical activity in an older at-risk population reduces the risk of stroke or dementia.

30.8.6 Prevention Guidelines

The American Stroke Association has provided guidelines for the prevention of recurrent strokes [81]. The recommendations include antihypertensive therapy and more rigorous control of BP and lipids in patients with diabetes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be more effective in those with diabetes, especially in preventing small vessel disease. Glucose control is recommended for preventing microvascular complications in patients who have both stroke and diabetes. Reducing glycohemoglobin levels to <7% is recommended. Though unproven to date, there is also some suggestion that raising high density lipoprotein (HDL) cholesterol with either niacin or a fibrate may be of benefit. Niacin therapy has resulted in the slowing of the progression of carotid IMT and may be indicated for patients with low HDL [43]. Similarly, there is some evidence that fibrates may be effective for selected patients with high triglycerides and low HDL cholesterol. Smoking cessation is strongly recommended. The reduction of heavy alcohol consumption is also important. High levels of alcohol intake may increase BP and the risk of stroke. Light alcohol consumption (i.e., 2 drinks per day for men and 1 for women) may be beneficial. Exercise is recommended, but there is no clinical trial evidence of benefit in reducing the risk of recurrent stroke with exercise. Physical exercise, however, may reduce post-stroke disability. Antiplatelet agents have been shown to reduce the risk of recurrent stroke or TIA and are currently approved and recommended. Antiplatelet therapy results in about a 28% reduction in nonfatal strokes and a 16% reduction in fatal strokes. Clopidogrel and similar drugs are also effective in preventing stroke among individuals who have TIA and stroke. At least four-fifths of the recurrent vascular events in patients with stroke

might be prevented by a multifactorial approach that includes exercise, aspirin, a statin and antihypertensive agents.

30.9 Conclusion

Rapid changes in the distribution of risk factors and aging among lower- and middle-income countries has resulted in an ever-increasing incidence of stroke and mortality due to stroke in these countries. The overall burden of stroke in these populations will significantly shift the worldwide burden of stroke to the lower- and middle-income countries, resulting in significant increases in disability, mortality and cost of care in these countries. Prevention of these increasing risk factors, especially smoking, high BP, high cholesterol, obesity and diabetes, as well as effective therapies should be high priorities in order to prevent epidemics of strokes in many of these countries.

The incidence of stroke and mortality caused by stroke has declined dramatically in the US and in many other countries due to better prevention and control of risk factors, as well as better treatment—both in and out of the hospital—after a stroke. Despite this, the number of strokes in the US is not likely to decline due to the aging and growth of the US population. There is a very high prevalence of silent or asymptomatic brain vascular disease (including infarction, white matter abnormalities and microhemorrhages) that may contribute to a subsequent increased risk of clinical stroke, dementia, depression and disability, especially among older individuals. A very important and unanswered question is whether an emphasis on treatment to prevent this burden of subclinical cerebrovascular disease (i.e., treatment of hypertension, lipids, diabetes, antiplatelet agents at younger ages) will reduce the incidence of stroke, dementia and disability among the elderly.

There is a continued need to improve the prevention, early treatment and follow–up of stroke in older patients. Adherence to effective therapies in older individuals remains poor, and early symptoms of stroke are often not recognized or treated. The prevention of stroke among older individuals with AF remains inadequate and stroke remains a major cause of disability among the elderly.

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Dementia and Alzheimer's Disease

31

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Abstract

Dementia is a general term that refers to a decline in cognitive function that is severe enough to affect a person's ability to perform usual daily activities. Alzheimer's disease (AD) is the most common cause of dementia in older adults, contributing to 50–80% of dementia cases, but there is growing recognition that many cases of dementia are likely to have mixed etiologies. New AD diagnostic criteria differentiate between three hypothesized phases: pre-clinical disease, mild cognitive impairment (MCI), and AD with biomarkers to help determine whether the cognitive symptoms are attributable to AD pathology. The most important risk factor for dementia is age, with a doubling in disease incidence every 5 years after 65 years of age. Given longer life expectancies and demographic changes, prevalence is expected to triple worldwide over the next 40 years. Many potentially modifiable risk factors have been identified, including medical conditions such as diabetes, hypertension and obesity; lifestyle factors such as physical inactivity, diet, smoking and low education; and psychosocial factors such as depression and lack of social support. Several randomized, controlled trials are examining the impact of risk factor modification strategies on cognitive decline and risk of dementia. If they are successful, large-scale public health interventions may help prevent the impending dementia epidemic.

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Abbreviations

Aβ	Amyloid-Beta
ACCORD-MIND	Action to Control Cardiovascular Risk in Diabetes - Memory in Diabetes
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's Disease
ADAMS	Aging, Demographics and Memory Study
ADVANCE	Action in Diabetes and Vascular Disease
AHEAD	Action for Health in Diabetes
ANDI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
CHAP	Chicago Health and Aging Project
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal Fluid
DHEA	Dehydroepiandrosterone
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBSHP	East Boston Senior Health Project
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FTD	Frontotemporal Dementia
HYVED-cog	Hypertension in the Very Elderly Trial cognitive function assessment
ICD-10	International Classification of Disease, 10th Edition
LBD	Lewy Body Dementia
LIFE	Lifestyle Interventions and Independence for Elders
MAPT	Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-Related Cognitive Decline
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging – Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NSAID	Nonsteroidal Anti-Inflammatory Drugs
PAR	Population Attributable Risk
PET	Positron Emission Tomography
PiB	Pittsburgh compound B
PS1	Presenilin 1
PS2	Presenilin 2
PSP	Progressive Supranuclear Palsy
P-Tau	Phosphorylated Tau
RCT	Randomized Controlled Trial
RR	Relative Risk
SOS	State-Of-the-Science
SPRINT	Systolic Blood Pressure Intervention Trial
US	United States
VaD	Vascular Dementia

31.1 Introduction

Dementia, which is most commonly caused by Alzheimer's disease (AD), takes a heavy toll on affected individuals and family members. The prevalence of dementia is expected to triple worldwide over the next 40 years. Currently, no treatments are available to prevent, stop or reverse this disease. However, researchers have developed new diagnostic criteria for earlier identification of dementia and AD and have identified numerous factors which may be useful in preventing or delaying the onset of symptoms.

In this chapter, we will review the various criteria that have been developed for the diagnosis of dementia and AD. We will also review the prevalence, incidence and public health significance of dementia and AD. Finally, we will review risk factors and prevention strategies, as well as current research efforts regarding prevention.

31.2 Diagnosis

31.2.1 Normal Cognitive Changes with Age and the Cognitive Continuum

Cognitive function is complex and refers broadly to the mental processes that are required to receive, analyze and act on information from the environment. These processes are defined in different ways by different disciplines. In epidemiologic studies, they are typically measured using neuropsychological tests to assess global cognitive function or specific cognitive abilities such as memory, executive function (the ability to plan and 'execute' activities), visuospatial function, language and processing speed. Some aspects of cognitive function remain relatively stable or improve throughout life, including wisdom/expert knowledge and language skills such as reading, writing and vocabulary. However, on average, most aspects of cognitive function decline throughout adulthood, with faster decline observed at older ages [1]. The rate of cognitive decline varies widely, and a substantial proportion of individuals experience no measurable cognitive deterioration even into very late life.

Cognitive function is currently viewed as a continuum in which some decline is to be expected as part of normal aging while other decline may reflect the earliest stages of dementia. Dementia refers to a decline in cognitive function that is severe enough to interfere with daily function. It is believed that most individuals who have neurodegenerative dementia will pass through a transition phase of mild cognitive impairment (MCI), in which cognitive function is lower than what would normally be expected with age but does not fulfill criteria for dementia. In some cases, MCI primarily affects memory function (amnestic MCI) whereas in other cases, MCI may affect other aspects of cognitive function (non-amnestic MCI) or multiple cognitive domains (multiple-domain MCI). It is hypothesized that amnestic MCI is more likely to progress to AD while non-amnestic MCI is more likely to progress to other types of dementia.

AD is the most common cause of dementia, accounting for 50–80% of cases [2]. Several diagnostic criteria for AD and dementia have been developed over the last 30 years that have allowed researchers to conduct pathological and clinical studies and compare incidence and prevalence rates across multiple populations. In addition, one of the most important advances in the knowledge of AD is that its pathological hallmarks (neurofibrillary tangles, amyloid plaques and neuronal loss) can be detected by cerebrospinal fluid (CSF), positron emission tomography (PET) and magnetic resonance imaging (MRI) studies. Consequently, a group of biomarkers has emerged. In this section of the chapter, we will describe the evolution of the concept of dementia and of the clinical diagnosis of AD, especially the recently published criteria for AD that incorporate the use of biomarkers (Table 31.1) [3–5].

31.2.2 Dementia

The term dementia "being out of one's mind" was found in the Latin works of Lucretius, and it appeared in the English language in the Oxford English Dictionary as early as 1644 [6]. During

Table 31.1 National Institute on Aging – Alzheimer's Association criteria

Label	Criteria
Dementia [3]	
All-cause dementia	Cognitive or behavioral (neuropsychiatric) symptoms that interfere with ability to perform usual activities, represent a decline from prior levels of function, are not explained by delirium or other major psychiatric disorder, evidence of cognitive impairment in at least two domains (memory, reasoning, visuospatial, language, personality)
Alzheimer's Disease (AD) Dementia [3]	
Probable AD	Dementia with insidious onset, clear evidence of worsening cognitive function over time, either amnestic or non-amnestic presentation, and lack of evidence for other types of dementia (substantial concomitant cerebrovascular disease or features of Dementia with Lewy bodies, frontotemporal dementia, primary progressive aphasia) or other medical conditions or medications that could have a substantial affect on cognition
Probable AD with increased certainty	Level of certainty for probable AD is increased with documented cognitive decline or causative genetic mutation (amyoid precursor protein [APP], presenilin1 [PS1] or presenilin2 [PS2]). Apolipoprotein-E (APOE) is not considered causative
Probable AD with pathophysiological evidence	Level of certainty that dementia is due to AD pathophysiological process is increased with biomarker evidence of brain amyloid-beta (Aβ) deposition:
	• Low cerebrospinal fluid (CSF) levels of $A\beta_{42}$
	• Positive positron emission tomography (PET) amyloid imaging or biomarker evidence of neuronal degeneration or injury
	• Elevated CSF total tau or phosphorylated tau (p-tau)
	• Decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in the tempoparietal cortex
	• Disproportionate atrophy on structural magnetic resonance imaging (MRI) in the medial, basal and lateral temporal lobe and medial parietal cortex
Possible AD	Dementia with atypical course or etiologically mixed presentation (evidence of concomitant cerebrovascular disease, features of dementia with Lewy bodies, or other neurological disease, medical condition or medication that could have a substantial effect on cognition)
Possible AD with pathophysiological evidence	Clinical evidence of non-AD dementia combined with biomarker evidence of AD pathophysiological process or meet neuropathological criteria for AD
Mild Cognitive Impairment (MCI) [4]	
All-cause MCI	Concern regarding change in cognition, performance lower than expected based on age and education in one or more cognitive domains typically including memory, preservation of independence in functional abilities, no dementia (no evidence of significant impairment in social or occupational functioning), lack of evidence that cognitive changes may be due to other factors such as vascular, traumatic or medical conditions
MCI due to AD	Level of certainty that MCI is due to AD pathophysiological process is increased with a positive Aβ biomarker combined with a positive biomarker of neuronal injury
Preclinical AD[5]	
Stage 1:	Positive Aβ biomarker, negative biomarker for neuronal injury, no evidence of cognitive change
Stage 2:	Positive Aβ biomarker, positive biomarker for neuronal injury, no evidence of cognitive change
Stage 3:	Positive Aβ biomarker, positive biomarker for neuronal injury, evidence of cognitive change

the 1700s, the term began acquiring medical connotations, and its use implied the presence of impaired psychosocial functions of multiple etiologies and occurring at any age. The concept of senile dementia started to emerge in the 1800s, especially the concept that it could be different than that seen in individuals who have a lifetime history of psychiatric illness. Over time, the central component of the syndrome shifted toward cognitive symptoms, and to the modern view that patients with dementia can have both cognitive and behavioral symptoms.

The modern concept of dementia has been based on the criteria proposed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [7]. These criteria currently state that a diagnosis of dementia requires impairments in memory and one additional cognitive domain (e.g., language, executive function) that cause significant impairment in social or occupational functioning and represent a significant decline from previous levels of functioning. These DSM criteria are still being used in clinical practice and research, although it is expected that there will be major modifications in the 5th edition, which is scheduled to be released in May 2013.

The 10th edition of the International Classification of Disease (ICD-10) has a more strict definition for dementia. These criteria require that memory and abstract thinking, judgment and problem solving all must be impaired, as well as impairment in one additional cognitive domain (e.g., language). Although these criteria have an increased specificity for dementia, they have low sensitivity because cases with mild disease are missed. In the Canadian Study of Health and Aging, Erkinjuntti et al. [8] examined the prevalence of dementia using several dementia criteria and found that the prevalence of dementia estimated using the DSM-IV was 13.7% and prevalence with the stringent ICD-10 criteria was 3.1%.

It has become increasingly recognized that dementia is a heterogeneous disorder and that not all patients first experience memory deficits. Therefore, the recently published criteria for all-cause dementia from the National Institute on Aging – Alzheimer's Association (NIA-AA) require deficits in at least two areas (e.g., memory, judgement/problem solving, visuospatial, language or behavior), but memory impairment is not required [3].

31.2.3 Alzheimer's Disease

AD was first described in 1906 by German psychiatrist and neuropathologist Alois Alzheimer and is characterized by the pathological hallmarks of amyloid plaques, neurofibrillary tangles and neuronal loss. Because these pathological changes can only be observed at autopsy, clinical criteria have been developed to indicate the extent to which dementia symptoms are likely to be attributable to AD pathology.

31.2.3.1 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria

The 1984 NINCDS-ADRDA criteria ranked AD diagnosis in terms of the certainty that the dementia was caused by AD pathology [9]. "Definite AD" was reserved for cases with neuropathological confirmation, "probable AD" was used to describe the clinical syndrome most likely expected in the context of AD, and "possible AD" was used when the patient had the core clinical symptoms for AD but there was evidence of other disease processes that in and of themselves could account for the cognitive deficits.

During the 1980s, the sensitivity and specificity of AD diagnosis varied widely. However, in the 1990s and early 2000s, there was a significant advance in the development of clinical criteria for other dementia syndromes that had a significant impact on the accuracy of AD diagnosis. Clinical criteria were developed for frontotemporal dementia (FTD), Lewy body dementia (LBD), progressive supranuclear palsy (PSP) and vascular dementia (VaD); standardized criteria for Creutzfeldt-Jakob disease and Parkinson's disease with dementia were intro-

duced more recently. Over the past several decades, the NINCDS-ADRDA criteria for AD have been widely used in clinical and research settings, and the probable AD diagnosis has been associated with good sensitivity (81%) and specificity (70%) [3].

31.2.3.2 Dubois Criteria

In 2007, Dubois et al. [10] proposed a modification of the NINCDS-ADRDA criteria for probable AD in order to incorporate the experience gained in the clinical characterization of the AD clinical syndrome and recent developments in biomarkers. These criteria required the presence of gradual and progressive change in memory function characterized by a specific pattern in which free recall performance should not improve with cueing or recognition testing. These criteria also elevated the importance of biomarkers and genotypes to support the diagnosis of AD, and they required that a diagnosis of probable AD must include the clinical AD-phenotype as well as one of the following supportive features: MRI evidence of atrophy in the medial temporal lobe structures, an abnormal CSF study, an "AD pattern" on PET studies, or the presence of proven AD autosomal dominant mutation in the immediate family. The term "definite AD" was used for patients who have pathology-proven AD and those who have clinical symptoms and genetic evidence of AD (mutations in chromosome 1, 14 or 21). These criteria did not revise the "possible AD" classification. This strict clinical definition made these criteria suitable for research purposes and drug trials where homogeneous groups are needed to test different scientific hypotheses.

31.2.3.3 National Institute on Aging – Alzheimer's Association (NIA-AA) Criteria

In 2011, the NIA-AA released new diagnostic criteria for AD (Table 31.1) [3]. These criteria retained the degrees of certainty that the clinical syndrome represented the neurodegenerative condition (i.e., probable and possible AD). Two key differences between the new criteria and the 1984 NINCDS-ADRDA criteria were the incorporation of biomarkers and the formalization of different stages of disease by also developing diagnostic criteria for MCI [4] and pre-clinical AD [5].

The NIA-AA criteria for "probable AD" are similar to the NINCDS-ADRDA criteria and require that the patient meet the clinical criteria for dementia and that symptoms have an insidious onset and clear-cut history of worsening without evidence of other causes such as cerebrovascular disease, other types of dementia (e.g., dementia with Lewy bodies, frontotemporal dementia, primary progressive aphasia) or other neurological or medical conditions or medications (Table 31.1). The level of certainty of the probable AD diagnosis may be increased with documented decline (e.g., based on repeated neuropsychological testing) or in the presence of a causative genetic mutation, specifically amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 (PS2). Notably, the presence of one or more apolipoprotein E (APOE) e4 alleles was *not* included as a causative genetic mutation.

Biomarkers are utilized in the NIA-AA criteria to indicate whether there is evidence of the AD pathophysiological process. Recent findings that AD is associated with low levels of amyloid-beta (Aβ) and high tau protein levels in CSF, decreased metabolism in specific brain regions in PET studies, decreased volume in mesial temporal and parietal lobes, and increased amyloid deposition in the brain with PET amyloid ligands have been replicated in multiple studies. The NIA-AA criteria take the position that these biomarkers measure two aspects of the disease: (1) amyloid deposition, including low CSF Aβ-42 levels and positive PET amyloid imaging, and (2) neuronal damage marked by high total or phosphorylated tau (p-tau) protein levels in CSF, decreased cerebral glucose metabolism, and disproportionate atrophy in the mesial temporal and parietal lobe cortices. In individuals who meet the core clinical criteria for probable AD, positive biomarker evidence may increase the level of certainty that dementia symptoms are attributable to the AD pathophysiological process. However, the authors cautioned that there is still a lack of standardization of the technologies and limited access to them by the medical community. For example, there is

a large standard deviation in CSF tau and Aβ-42 levels in cases with definite AD. Therefore, at present, biomarkers are most useful for research or clinical trial purposes, or in limited circumstances when deemed appropriate by clinicians.

The NIA-AA criteria also do not include age of onset as part of the criteria. The NINDCS-ADRDA stated that the age range for the onset of symptoms should be 40–90 years of age, and recommended that patients with an age of onset of <65 years should be considered a subgroup for research purposes. Subsequent research showed that neuropathology and clinical presentation of early- and late-onset AD was similar (onset at <65 years of age vs. >65 years of age), and that the central underlying pathology (i.e., abnormal amyloid metabolism) is similar in familial cases with early-onset (<40 years of age) and idiopathic late-onset AD. Furthermore, AD is the most prevalent form of dementia after 90 years of age.

The NINCDS-ADRDA criteria stated that *possible* AD should be used to define cases with atypical presentation or clinical course, the presence of other disease processes that could cause cognitive disorders, or progressive deficits in a single cognitive domain. The NIA-AA criteria have redefined this classification and considered possible AD when the patient has a sudden onset of symptoms, when there is insufficient historical detail to document the progression of symptoms, when there is evidence of concomitant neurological or non-neurological disorders, or when there is medication use that can affect cognition. That is, when there are factors present that lower the probability that AD is the sole cause of the dementia syndrome.

The use of the term "possible AD" by the NINDCS-ADRDA criteria to classify patients who have deficits in a single cognitive domain has also been revised by the NIA-AA criteria, and these patients are now classified as having MCI. This has been based on the findings of multiple longitudinal studies that have shown that some patients with MCI improved over time, some did not progress to dementia, and some progressed to other neurodegenerative dementias [11]. Nevertheless, the NIA-AA criteria state that when there is significant interference in the ability to function, clinicians should use their own judgment to distinguish MCI from an AD dementia syndrome with a single cognitive domain affected.

The possible AD diagnosis was also expanded to include cases in which individuals meet clinical criteria for non-AD dementia but have either biomarker evidence of an AD pathophysiological process or meet neuropathological criteria for AD.

31.2.4 Mild Cognitive Impairment

The recognition that there is cognitive decline with normal aging and that patients go through a mild cognitive deficit state during the progression to AD has been extensively described in the literature, and multiple diagnostic criteria have been proposed to characterize these patients. Amnestic MCI is the most closely-related syndrome to AD, and longitudinal studies have shown that these patients are the most likely to progress to AD [12]. However, epidemiological studies have shown that the "pure" amnestic MCI (i.e., idiopathic amnesia) has a low prevalence in the general population compared to patients who have a much wider range of cognitive impairments (i.e., multiple-domain MCI) [13], and that patients with relatively preserved memory function can also progress to AD. In 2004, the initial 1999 memory-based criteria for MCI [12] were expanded to include all of the possible cognitive manifestations of the syndrome (i.e., only memory impaired, memory + other cognitive domain, non-memory single domain, non-memory + other cognitive domain) [14].

The NIA-AA criteria for MCI were developed primarily to identify a syndrome that had a high likelihood of being caused by AD pathology [4]. The core clinical criteria are similar to prior criteria and require a concern about a change in cognition (based on individual, informant or clinician report); impairment in one or more cognitive domains below what would be expected for age and education, typically including memory; preservation of independence in functional abilities; and lack of dementia (i.e., not severe enough to impact social or occupational func-

tioning) (Table 31.1). The criteria maximize the likelihood that the syndrome is associated with AD by explicitly ruling out vascular, traumatic or other neurological or non-neurological causes of mild cognitive dysfunction.

The use of biomarkers in the diagnosis of MCI due to AD supports the presence of the AD pathology and increases the likelihood that the progression to dementia will occur within a relatively short period of time. The NIA-AA criteria for MCI use the biomarkers to help grade the likelihood of an underlying AD. The certainty that the MCI is due to AD is graded as: (1) high likelihood: when both beta amyloid and neuronal damage biomarkers are present; (2) intermediate likelihood: when the core clinical symptoms are present and there is a single positive biomarker, either amyloid deposition or neuronal damage; and (3) unlikely due to AD: neither type of biomarker is positive. However, the authors cautioned about the use of combination biomarkers in the diagnosis of MCI or as predictors of conversion to AD until more experience is gained in this respect. This position was supported by a recent study of the Alzheimer's Disease Neuroimaging Initiative which found that over a short term, single marker models were as effective as multiple marker models and their accuracy was only 64% [15].

31.2.5 Preclinical Alzheimer's Disorder

The pathology of AD starts several years—likely decades—before the onset of the clinical syndrome [5]. Pathological and *in vivo* amyloid ligand PET studies have shown that cognitively normal individuals can have AD neuropathological features, though to a lesser extent than that seen in patients who have dementia. The revised NINCDS-ADRDA proposed by Dubois et al. also addressed the issue of prodromal or preclinical AD and proposed that these mildly-affected patients should be classified as probable AD when they have an isolated memory deficit and at least one of the biomarkers described above.

The NIA-AA work group position is that AD is a pathological-clinical continuum that starts with amyloid deposition in cognitively normal individuals and gradually progresses to clinical dementia [5] (Table 31.1). Therefore, three stages were proposed: Stage 1: normal cognition with positive cerebral amyloidosis by CSF or amyloid ligand studies and with normal markers of neuronal damage; Stage 2: normal cognition with cerebral amyloidosis and markers of downstream neurodegeneration; and Stage 3: subtle cognitive change with cerebral amyloidosis and markers of neurodegeneration. The latter stage should include individuals who are in the borderzone between normal and MCI (i.e., "not normal" and "not MCI").

There are still many limitations in the staging of the pre-clinical phases of AD. Much has been learned over the past century, particularly over the last 20 years, but the fundamental etiology of the disease remains unclear. Although Aβ deposition and neuritic plaque formation are the pathological hallmarks of AD, and current evidence suggests that Aβ accumulates early in the disease process, the role of Aβ as an etiologic agent remains unproven. Furthermore, the recent failure of Aβ-lowering therapies highlights our limited understanding of AD etiology and the need for further research.

31.2.6 Future Research

The incorporation of biomarkers into clinical diagnostic criteria is a step forward in research and clinical practice, but also a substantial challenge. Studies are needed to validate the new criteria for AD, MCI and preclinical AD, but they will be difficult to perform due to the high cost of evaluating large numbers of participants with multiple biomarkers and following them until clinical symptoms develop and, ultimately, autopsy can be performed. Nevertheless, it is likely that biomarkers will be increasingly used to identify individuals who have pre-clinical and early-stage disease so that they can be targeted for prevention and early intervention.

31.3 Prevalence, Incidence, and Public Health Significance

31.3.1 Prevalence

Prevalence estimates for dementia and AD in the United States (US) have varied widely depending upon the study sample, diagnostic criteria and methodology used [16]. Higher prevalence estimates have been obtained when data from defined geographic regions are applied to US Census population data to make national projections. One of the earliest estimates used data from the East Boston Senior Health Project (EBSHP) to estimate that the national AD prevalence would increase from 2.9 million in 1980 to 10.2 million in 2050, and would be 5.1 million in 2010. Similar estimates were obtained using data from the Chicago Health and Aging Project (CHAP), in which national AD prevalence was projected to increase from 4.5 million in 2000 to 13.2 million in 2050, and to equal 5.1 million in 2010. The Alzheimer's Association estimates that AD prevalence in 2011 was 5.4 million, which translates into one in eight (13%) adults ≥65 years of age [2].

In contrast, lower prevalence estimates have been obtained when disease rates have been calculated by combining data from multiple studies or from a nationally representative sample. For example, estimates from Brookmeyer et al. [16] utilized statistical models in which transition rates from healthy to diseased states were determined from systematic literature reviews. Based on this approach, the estimated prevalence of AD in 2008 was 2.8 million, which is nearly half of previous estimates. Similar prevalence estimates were obtained in the Aging, Demographics and Memory Study (ADAMS), a nationally representative probability-based study of adults >70 years of age, in which the estimated prevalence of AD in 2008 was 2.6 million.

Regardless of how current prevalence is estimated, it is clear that prevalence is expected to increase dramatically over the next 40 years as a function of longer life expectancies and demographic shifts [17]. Using a current prevalence estimate of 5.4 million, the Alzheimer's Association projects that prevalence in the US will rise to 7.7 million by 2030 and 11 to 16 million by 2050. This translates into a new person developing AD every 69 s today and every 33 s by 2050 [2].

Global estimates of current dementia prevalence have been more consistent because similar methods have been used across studies. Ferri et al. [18] utilized a Delphi consensus process guided by a systematic review of the literature to estimate that the worldwide prevalence of dementia in 2001 was 24.3 million, with 4.6 million new cases each year, or one new case every 7 s. Furthermore, it was estimated that the number of people living with dementia would nearly double every 20 years to 42.3 million in 2020 and 81.1 million in 2040. Assuming a linear rate of increase from 2001 to 2020, this would suggest a prevalence of approximately 33.8 million in 2010. The majority of dementia cases were estimated to be in developing countries (60% in 2001, 65% in 2020 and 71% in 2040). When considering individual countries, the prevalence of dementia in 2001 was highest in China (5.0 million), the European Union (5.0 million), the US (2.9 million), India (1.5 million), Japan (1.1 million), Russia (1.1 million) and Indonesia (1.0 million). The rate at which dementia prevalence will increase will be greatest in Latin America (393%), North Africa/Middle East (385%), China (336%), Indonesia (325%) and India (314%), though increases also will be high in North America (172%) and Europe (102%).

Similarly, Brookmeyer et al. [17] used a statistical modeling approach and estimated that there were 26.6 million cases of AD worldwide in 2006, with a projected prevalence of 106.8 million in 2050. Assuming a linear rate of increase, this would suggest a prevalence of approximately 33.9 million in 2010. Using slightly different geographic definitions, nearly half (48%) of cases worldwide were in Asia, with 27% in Europe, 12% in North America, 8% in Latin America and 5% in Africa. By 2050, this distribution was projected to change to 59% in Asia, 16% in Europe, 10% in Latin America, 8% in North America and 6% in Africa.

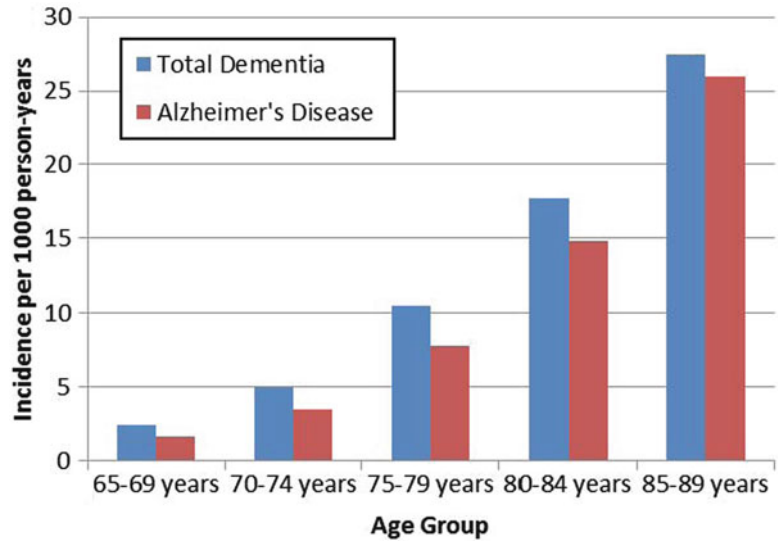

Fig. 31.1 Incidence of dementia and Alzheimer's disease in the US by age group [20]

31.3.2 Incidence

The incidence of AD and dementia rises exponentially with age, with an approximate doubling in incidence every 5–6 years after the age of 65 [19]. An early meta-analysis found that the age-specific incidence of dementia per 1,000 person-years in the US was approximately 2.4, 5.0, 10.5, 17.7 and 27.5 for the age groups of 65–69, 70–74, 75–79, 80–84 and 85–89 years, respectively [20]. For AD, the age-specific incidence rates were 1.6, 3.5, 7.8, 14.8 and 26.0, respectively, for the same age groups (Fig. 31.1).

A recent study found that the doubling rate was similar throughout the world and did not differ by gender [19]. However, there was substantial variability in the incidence rates themselves, with age-specific incidence higher in North America and Europe than in other regions, and higher in women than in men. Similarly, the study by Ferri et al. [18] found that the annual dementia incidence per 1,000 individuals ≥60 years of age was highest in North America (10.5), Latin America (9.2) and Western Europe (8.8), and lowest in Africa (3.5), India (4.3) and Indonesia (5.9). It remains unclear whether these differences are due to genetics, risk factor profiles or diagnostic criteria. However, one study found substantially lower dementia incidence among Africans in Ibadan, Nigeria than in African-Americans in Indianapolis, Indiana using nearly identical study methodology. This suggests that diagnostic criteria do not explain all of the geographic differences [21]. It is important to note that increased mortality in patients with dementia may affect the prevalence of the disease; regions with high mortality rates after the diagnosis may exhibit low prevalence rates.

31.3.3 Public Health Significance

Because dementia incidence increases exponentially with age, it is expected that longer life expectancies and demographic changes will result in a worldwide epidemic of dementia and AD over the next 40 years [17]. If a treatment or cure is not developed, it is anticipated that dementia prevalence will be three to four times higher in 2050, when 1 in 85 (more than 100 million) individuals will be living with the disease.

The average per-person costs of health care and long-term services are more than three times higher for older adults who have AD and other dementias ($42,072) than for those who do not ($13,515) [2]. Total dementia-related payments in 2011 are expected to be $183 billion in the US, about 70% of which will be paid for by Medicare

and Medicaid. In addition, there are approximately 15 million family members and friends in the US who provide unpaid care to individuals with dementia. In 2010, 17 billion hours of unpaid care were provided with an estimated value of $202 billion. Caregiving is often associated with further hidden costs, including high levels of stress and depression, adverse health outcomes, loss or reduction of employment, and greater financial insecurity. As dementia prevalence rises over the next 40 years, there will be a corresponding increase in the paid, unpaid and hidden costs of care.

Despite these grim projections, there is hope that interventions to delay the onset of disease may be able to dramatically reduce prevalence over time. One study estimated that delaying AD onset by 1 year would result in 12 million fewer cases worldwide in 2050, while delaying AD onset by 2 years would result in 23 million fewer cases [17]. Furthermore, many risk factors for dementia are potentially modifiable. Another study estimated that more than half of AD cases may be attributable to modifiable risk factors, and that a 10% reduction in risk factor prevalence worldwide could potentially lower AD prevalence by 1.1 million cases, while a 25% reduction in risk factor prevalence could potentially lower AD prevalence by 3.1 million cases [22].

31.4 Risk Factors and Prevention Strategies

Currently approved treatments for dementia and AD include cholinesterase inhibitors (i.e., donepezil, rivastigmine and galantamine) in the mild-to-moderate stages of disease and memantine in the moderate-to-severe stages of disease. These medications are effective for alleviating some of the symptoms but do not appear to alter the course of the disease. Therefore, there has been growing interest in identifying strategies for prevention. In fact, because the incidence of dementia increases exponentially with age, delaying the onset of symptoms by as little as a year or two could dramatically lower prevalence over time [17].

In 2010, the National Institutes of Health convened a state-of-the-science (SOS) conference on preventing AD and cognitive decline [23, 24]. The scientific committee listened to presentations by experts, and reviewed 25 systematic reviews and 250 primary research articles related to a wide range of risk factors and prevention strategies, and concluded that the current evidence is insufficient to recommend specific interventions to prevent cognitive decline or AD. Nonetheless, several factors were identified as being ineffective and potentially harmful while others were identified as having more consistent evidence than others. In this section, we review the evidence regarding risk factors—with an emphasis on those which are potentially modifiable—and strategies for prevention (Table 31.2).

31.4.1 Vascular Risk Factors

Although AD and vascular dementia have traditionally been viewed as distinct disorders, the two rarely occur in isolation and both types of dementia share many risk factors [50]. In addition, the presence and severity of cerebrovascular pathology appears to increase the risk and stage of AD for any given level of AD pathology. Thus, the modification of vascular risk factors might reduce the risk of dementia for both AD and vascular dementia, the two most common forms of dementia.

31.4.1.1 Diabetes and Diabetes Treatments

A recent meta-analysis found that older adults with diabetes have approximately a 50% increase in the risk of developing AD or dementia (relative risk [RR], 1.54; 95% confidence interval [CI]: 1.33, 1.79) [25]. Initial observations suggested that diabetes was most strongly associated with the risk of vascular dementia, but more recent research indicates that individuals with diabetes also have an increased risk of developing AD. There is also a growing body of work that suggests a direct link between insulin and AD pathology, with *in vitro* studies indicating that insulin influences extracellular β-amyloid

Table 31.2 Summary of risk factors and potential prevention strategies for dementia

Risk factor	Observational studies	Randomized, Controlled Trials (RCTs)
Vascular risk factors		
Diabetes [25, 26]	Increased risk	No effect of treatment on dementia incidence (intensive vs. standard glucose control, 1 RCT)
Hypertension [27–29]	Mid-life hypertension – increased risk	Mixed effect of treatment on dementia incidence (6 RCTs)
	Late-life hypertension – inconsistent	
	Late-life hypotension – increased risk	
Hypercholesterolemia [30, 31]	Mid-life – increased risk	No effect of treatment on dementia incidence (statins, 2 RCTs)
	Late-life – inconsistent	
Obesity [22, 25, 32]	Mid-life obesity – increased risk	No RCTs
	Late-life obesity – inconsistent	
	Late-life underweight – increased risk	
Lifestyle		
Physical inactivity [33–37]	Increased risk	Improved cognitive function (limited domains); increased hippocampal volume; no RCTs on dementia incidence
Cognitive inactivity [38–40]	Increased risk	Improved cognitive function (domain-specific); no RCTs on dementia incidence
Smoking [41]	Increased risk	No RCTs
Diet [42–44]	Inconsistent	No RCTs
Psychosocial		
Depression [45, 46]	Increased risk	Improved cognitive function but below normal levels; no RCTs on dementia incidence
Social Isolation [47]	Inconsistent	No RCTs
Pills and supplements		
Postmenopausal hormone therapy [24]	Reduced risk/inconsistent	No effect/harmful (2 RCTs)
Non-steroidal anti-inflammatory drugs (NSAIDs) [24]	Reduced risk/inconsistent	No effect/harmful (2 RCTs)
Vitamin supplements [43, 44, 48, 49]	Inconsistent	No effect/inconclusive (Vitamin E: 1 RCT on dementia incidence; Omega-3: 4 RCTs on cognitive decline; Vitamin B/folate: 8 RCTs on cognitive decline)
Gingko biloba [24]	None	No effect (1 RCT)
Cholinesterase inhibitors [24]	None	No effect (8 RCTs)

levels. Consequently, individuals with insulin resistance or diabetes may have increases in β-amyloid levels and, in turn, an increased risk for AD pathology.

Findings from randomized controlled trials (RCTs) have been less consistent. Preliminary trials of diabetes medications—including insulin—have indicated that these drugs may be beneficial to cognition in patients who have AD and mild cognitive impairment. However, the Action in Diabetes and Vascular Disease (ADVANCE) trial found no difference in the risk of dementia or cognitive decline in 11,140 individuals ≥55 years of age with diabetes who were randomly assigned to standard or intensive glucose control [26]. Therefore, although diabetes is associated with an increased risk of dementia, it appears that intensive glucose control does not lower dementia risk. This may reflect in part the increased risk of hypoglycemia with

intensive glucose control, which also may increase dementia risk.

31.4.1.2 Hypertension and Antihypertensive Treatments

Several comprehensive reviews have found that midlife hypertension is consistently associated with an increased risk of AD and all-cause dementia in observational studies [27]. In contrast, the association between late-life hypertension and dementia is more controversial. Both very high systolic blood pressure and very low diastolic blood pressure in late life have been associated with an increased risk of dementia and AD in some studies. However, other studies have found no relationship between late-life hypertension and the risk of dementia. Several studies indicate that people who receive treatment for hypertension, both in midlife and late-life, have a reduced risk of developing cognitive impairment compared to those with untreated hypertension. However, other studies have not confirmed this. Hypotension in late life has been consistently associated with an increased risk of dementia and AD, particularly in individuals who take antihypertensives. Thus, the association between blood pressure and dementia appears to be complex and age-dependent.

RCTs that examined the effects of antihypertensive medication on cognition outcomes have had inconsistent results [28]. Five of six RCTs performed found no significant effect of hypertension treatment on dementia incidence. The most recent trial, the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-cog), suggested a non-significant beneficial effect of hypertension treatment that was significant when combined in a meta-analysis with three of the other trials (hazard ratio [HR], 0.87; 95% CI, 0.76–1.00). However, a Cochrane systematic review that included HYVET-cog with a different subset of trials found a non-significant association (HR, 0.89; 95% CI, 0.74–1.07) [29]. Ongoing studies, such as the Systolic Blood Pressure Intervention Trial (SPRINT), should help to clarify whether treatment of hypertension in late life will lower the risk of dementia.

31.4.1.3 Hyperlipidemia and Statins

Observational studies have consistently found that hyperlipidemia, particularly in mid-life, is associated with an increased risk of AD and dementia, while the use of statins is associated with a reduced risk [30]. In addition, several smaller trials have suggested that statin use improves cognitive outcomes in individuals who have hypercholesterolemia. However, two large RCTs have now found that statins given in late life to individuals at risk of vascular disease did not reduce the risk of cognitive decline or dementia [31]. Therefore, despite some initially promising findings, the available evidence suggests that statins are unlikely to be effective for preventing AD or dementia.

31.4.1.4 Obesity

A recent meta-analysis found that people who are obese in mid-life have approximately a 60% increased risk of developing AD and dementia (odds ratio [OR], 1.60; 95% CI: 1.34, 1.92) [22]. However, as with hypertension, there is evidence that the association between body weight and risk of dementia changes with age. One study found that while obesity in mid-life was associated with an *increased* risk of dementia (HR, 1.39; 95% CI: 1.03, 1.87), obesity in late-life was associated with a *reduced* risk of dementia (HR, 0.63; 0.44, 0.91). In fact, in late-life, being underweight was associated with an increased risk of developing dementia (HR, 1.62; 95% CI: 1.02, 2.64), although late-life underweight could also be a marker of preclinical disease rather than a true risk factor 32.

There are several potential mechanisms by which obesity, particularly in mid-life, could increase the risk of AD and dementia [51]. Obesity is associated with an increased risk of other conditions that have been associated with dementia including diabetes and hypertension. In addition, adipose tissue secretes both metabolic and inflammatory factors, and the secretion of inflammatory adipocytokines may be involved in neurodegenerative pathways. However, it is unclear whether adipose tissue is directly linked to cognitive impairment or whether the adipose

tissue is a marker of insulin resistance and hyperinsulinemia.

31.4.1.5 Multiple Vascular Risk Factors

Given the relationship of individual vascular risk factors with dementia and the frequency with which they co-occur, it is not surprising that studies that have evaluated the effect of multiple or composite vascular risk factors on the risk of dementia have found that patients who had diabetes, hypertension, high cholesterol or were smokers at mid-life were more likely to develop dementia later in life [52]. Similarly, the 'metabolic syndrome', which is a clustering of disorders that include abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, hypertension and/or hyperglycemia, has been associated with an increased risk of cognitive impairment and cognitive decline, especially in patients who have high levels of inflammation [53].

There is a consensus that patients who have vascular risk factors are at a higher risk for dementia compared to those who do not have these risk factors. As a result, clinicians who are treating individuals who have vascular risk factors should be aware of and screen for symptoms of cognitive impairment. RCTs are needed to examine the impact of potential preventive strategies—which may include lifestyle management and medications that target dementia pathologic features—in this high-risk group.

31.4.2 Lifestyle Risk Factors

31.4.2.1 Physical Inactivity

The role of physical activity as a potentially protective factor against the risk of dementia and cognitive decline has received much recent attention. In observational studies, individuals who are physically active often demonstrate less cognitive decline and a lower risk of dementia than do individuals who are sedentary [33]. A meta-analysis found a relative risk (RR) of 0.72 (95% CI: 0.60, 0.80) for dementia and 0.55 (95% CI: 0.36, 0.84) for Alzheimer' disease when comparing the highest to lowest physical activity groups [34]. Although fewer studies have investigated the association between mid-life physical activity and cognitive impairment, most have found that mid-life activity is associated with a lower incidence of both AD and all-cause dementia.

The mechanisms by which physical activity affects cognition are also complex and likely multi-factorial [33]. Physical activity is associated with a reduced risk of vascular risk factors such as diabetes, hypertension and obesity and, as discussed above, these vascular risk factors are associated not only with an increased risk of vascular dementia but also of AD. In addition, individuals who exercise have higher levels of brain neurotrophic factors, which are implicated in neurogenesis and neurological repair. In addition, rodents with high levels of voluntary physical activity also have less β-amyloid plaque formation.

Controlled trials have confirmed that exercise training can improve some aspects of cognitive performance in older adults. A recent Cochrane review suggested that the strongest effects appear to be for motor and auditory function [35]. In contrast, an earlier meta-analysis suggested that the strongest effects were for executive function [36]. Furthermore, recent studies have found that sedentary older adults who engage in aerobic exercise experience increases in hippocampal volume as well as improvements in memory [37]. Larger trials are needed to investigate the role of physical activity in relation to cognitive performance and the incidence of dementia in sedentary and high-risk older adults.

31.4.2.2 Cognitive Inactivity

The strong and consistent association between higher education and lower incidence of dementia has promoted the hypothesis that cognitive activity may reduce the risk of developing cognitive decline and dementia [54]. A meta-analysis of 22 prospective observational studies that included more than 21,000 participants and 1,700 cases of dementia found that the risk of dementia was lower for those who had higher education (odds ratio [OR] 0.53; 95% CI: 0.45, 0.62), higher occupational attainment (OR, 0.56; 95% CI: 0.49, 0.65), higher intelligence or IQ (OR, 0.57; 95% CI: 0.44, 0.77), or more mentally

stimulating leisure activities (OR, 0.50, 95% CI: 0.42, 0.61) with a combined estimate of 0.54 (95% CI: 0.49, 0.59) [38]. Furthermore, compared to older adults who do not engage in cognitively stimulating activity, those who are cognitively active may have a greater extent of AD neuropathology without exhibiting the symptoms of dementia [54]. This phenomenon is referred to as "cognitive reserve," a concept that arose from the initial observation that individuals with higher levels of education had a sparing of cognitive performance in the setting of AD pathology. However, the relationship between education level and neurodegeneration is still controversial. There are autopsy-based studies that have found no association between AD pathology and education level, and a study from the Alzheimer's Disease Neuroimaging Initiative (ADNI) showed no association between Pittsburgh compound B (PiB) levels and IQ.

Nonetheless, recent trials have demonstrated that cognitive interventions improve cognitive function, and they may reduce the risk of cognitive impairment and slow cognitive decline [39]. However, benefit from cognitive training seems to be domain-specific. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial found that while cognitive training can improve memory, reasoning and mental processing speed in older adults, cognitive training did not generalize across domains and did not affect everyday functioning [40]. Future trials should investigate whether adapted multi-domain cognitive interventions designed to mimic daily life might be effective in improving global cognition and daily functioning.

31.4.2.3 Diet

Many of the vascular risk factors for dementia (e.g., hypertension, diabetes, obesity) may be modified by diet. In addition, a diet high in antioxidants may reduce inflammation, which is associated with the risk of dementia. Thus, it is reasonable to suggest that the risk of dementia itself could be modified by diet. Several observational studies support this hypothesis [42]. For example, older adults who consume a Mediterranean diet and a higher fruit and vegetable intake may have a lower risk of developing dementia. Other studies found that individuals with a high consumption of fish have a lower risk of dementia and cognitive decline.

The association between diets high in fish, fruit and vegetables and a lower risk of dementia has largely been attributed to antioxidants and polyunsaturated fatty acids. The interest in antioxidants in relation to dementia stemmed from the observation that oxidative stress may contribute to AD pathology. This has led to the hypothesis that a high dietary intake of antioxidants might slow cognitive decline and lower the risk of dementia. Indeed, in some studies, individuals with a higher intake of vitamin E and C (both antioxidants)—either through diet or supplements—have slower cognitive decline and a lower risk of AD in old age [42]. However, the relationship has not been consistent and other large, prospective observational studies found no association between vitamin intake and dementia risk. Furthermore, RCT evidence has been inconsistent at best, with most studies finding no relationship between vitamin E supplementation and cognitive performance [24]. Therefore, it remains unclear whether the observed association between antioxidant use and dementia is causal or is due to uncontrolled confounding or other biases.

The investigations regarding polyunsaturated fatty acid consumption in relation to cognitive outcomes have been similarly inconclusive [43, 44]. Several observational studies—though not all—have reported that individuals with high polyunsaturated fatty acid consumption had lower risk of dementia and AD, but RCTs have not confirmed the results. Furthermore, polyunsaturated fatty acid supplementation had no effect on memory and attention in cognitively healthy older adults. As a result of these trials, the relationship between polyunsaturated fatty acids and cognition has come under question, though further study is still warranted. Moreover, given that adherence to a Mediterranean diet and a high consumption of anti-oxidants and polyunsaturated fatty acids are associated with a reduced risk of cardiovascular disease, individuals who adopt healthy diets are likely to have positive health outcomes regardless of the effect on cog-

nitive functioning and without any adverse effects.

Increasing attention has recently been paid to vitamin D supplementation as a strategy to prevent dementia [48]. Although evidence is very preliminary and generally from cross-sectional studies, some suggest that higher serum 25-hydroxyvitamin D may be associated with better global cognition. Vitamin D is also associated with a number of risk factors for dementia, including diabetes, cerebrovascular disease and depression. Future prospective observational and controlled trials should examine vitamin D intake in relation to cognition, particularly in institutionalize older adults who are likely to be deficient in Vitamin D.

31.4.2.4 Smoking

Although several early case-control studies found that smokers had a reduced risk of AD, this may have been explained by participation or survival bias (e.g., individuals who were smokers may have been less likely to participate in the study or more likely to die early in the course of their disease). More recent population-based, prospective studies have found that the incidence of AD is increased in older adults who are current smokers. A meta-analysis of 19 prospective studies found that current smoking was associated with an increased risk of developing all-cause dementia (RR, 1.27; 95% CI: 1.02, 1.60) and AD (RR, 1.79; 95% CI: 1.43, 2.23) [41]. There are a variety of potential mechanisms by which smoking could contribute to dementia risk, including vascular disease, neurotoxic effects, oxidative stress or inflammatory processes. Given how common smoking is worldwide, smoking cessation interventions could potentially prevent AD in a large number of individuals.

31.4.2.5 Alcohol

Several studies have found that light-to-moderate drinkers have a reduced risk of dementia and AD, though the definition of light-to-moderate drinking has varied substantially between the studies (from <1 drink/day to 1–3 drinks/day). A recent meta-analysis that included 23 longitudinal studies found that alcohol consumption was associated with a reduced risk of all-cause dementia (RR, 0.63; 95% CI: 0.53, 0.75) and AD, (RR, 0.57; 95% CI: 0.44, 0.74), but not VaD (RR, 0.82; 95% CI: 0.50, 1.35) or cognitive decline (RR, 0.89; 95% CI: 0.67, 1.17) [55]. However, it remains unclear whether this reflects a true protective effect of alcohol or uncontrolled confounding or other biases.

31.4.3 Psychosocial and Other Risk Factors

31.4.3.1 Depression

It is well known that individuals—especially older adults—with depression have reduced cognitive performance. In addition, many individuals with dementia also have concurrent depression. However, it is unclear whether depression is risk factor for dementia or whether it is a prodromal symptom. Some observational studies have found that older adults with depressive symptoms were more likely to have dementia at follow up compared to those without these symptoms, whereas others have found that depressive symptoms coincided with or followed dementia onset rather than preceded it. A meta-analysis of prospective cohort studies found that the risk of dementia was approximately doubled in older adults who had a history of depression (OR, 1.90; 95 % CI: 1.55, 2.33) [45].

There are several hypotheses that have been proposed to explain the relationships between depression and dementia: (1) depression may sometimes be an early symptom or prodrome of dementia; (2) the clinical examination required for the diagnosis of depression may make dementia more likely to be detected, especially at an earlier stage; and (3) those who have early cognitive deficits may be more likely to become depressed due to the earliest cognitive symptoms [45]. Mechanistically, depression is associated with elevated cortisol levels, which may directly damage the hippocampus and increase the risk of dementia. Furthermore, recent studies have suggested that individuals with depression have an enhanced deposition of β-amyloid plaques. This area is still under investigation. Although it seems that depressive symptoms are increased around

the time that individuals develop dementia, less is known about those who have had a lifetime history of major depression.

The treatment of depression also seems to improve cognitive function in individuals who are depressed, but it may not return cognition to normal levels [46]. In addition, it has not yet been resolved whether the treatment of depression decreases the risk of dementia among individuals who have depressive symptoms.

31.4.3.2 Social Engagement

Individuals who have limited social networks and low social engagement may be more likely to develop dementia compared to those who have socially rich lives [47]. Social engagement through visits with friends and relatives; going to movies, clubs, centers and churchs/synagogues; and volunteering may be protective against developing cognitive impairment. Some have proposed that social activity, similar to cognitive and physical activity, might reduce the risk of dementia by increasing cognitive reserve so that individuals can better maintain their cognitive performance even with neuropathology. However, another study found that the relationship between low social engagement and the risk of dementia was restricted to those participants who experienced a decline in social engagement from mid-life to late-life [56]. This suggests that rather than being a risk factor, low social engagement may be an early symptom of cognitive impairment. Further studies are needed to determine whether social interventions might curb cognitive decline.

There are few controlled trials that have investigated the effect of social engagement on risk of dementia or on cognitive outcomes. As a result, the importance of social engagement in a successful prevention strategy is still unclear. However, older adults who participated in Experience Corp—a program that involves helping elementary school children with reading achievement, library support and classroom behavior—showed a trend towards improved cognition compared to a waitlist control group.

The interaction between social activity, cognitive activity and physical activity is also difficult to disengage. Many leisure activities contain all three components. By evaluating each leisure activity for cognitive, social and physical components, several studies have concluded that each component is equally important in the protection against dementia [47]. As a result, interventions that include cognitive, social and physical components might be the best strategy to reduce the risk of cognitive impairment, and research should investigate this possibility.

31.4.4 Medications

31.4.4.1 Postmenopausal Hormone Therapy

Many observational studies had initially suggested that women who took postmenopausal hormone therapy were less likely to develop AD and dementia, and these studies were supported by biological studies that suggested plausible biological mechanisms and the possibility that estrogen may have neuroprotective effects. However, two large RCTs (N = 7,479) subsequently found that older women randomized to receive estrogen alone did not have a lower risk of AD than those in the placebo group. Furthermore, women who received estrogen plus progestin actually had a twofold increase in the risk of developing AD. Other RCTs have found that estrogen, raloxifene (a selective estrogen reuptake modulator) and dehydroepiandrosterone (DHEA), an endogenous steroid hormone, are not associated with rate of cognitive decline in older women [24].

Taken together, these studies suggest that postmenopausal hormone therapy is unlikely to prevent cognitive decline or AD in older women and that some formulations may increase the risk of AD. It remains possible that different formulations or doses of estrogens or other sex hormones may be beneficial. It also has been hypothesized that there is a 'critical window' in which postmenopausal hormone therapy may have protective effects if administered during

mid-life and harmful effects if administered during late-life [57].

31.4.4.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Several observational studies have found that older adults who used NSAIDs had a reduced risk of AD and dementia, although the association was not consistent across studies [24]. In addition, there is considerable evidence that AD is associated with inflammatory and immune changes in the brain, including acute-phase proteins and activated microglial cells in and around amyloid plaques and complement proteins around tangles. However, two RCTs have now found that older adults randomized to receive NSAIDs were more likely to develop AD than those in the placebo group, and several selective cyclooxygenase-2 (COX-2) inhibitors, which are types of NSAIDs, have recently been withdrawn from the market due to an increased risk of cardiovascular events. Therefore, NSAIDs are likely to be ineffective for the prevention of AD and appear to increase risk.

31.4.4.3 Vitamins C, E and Beta-Carotene

Observational studies that have included nearly 20,000 participants have found no consistent association between vitamin C, vitamin E or beta-carotene and the risk of developing AD or cognitive decline [24]. In addition, an RCT that included 769 participants who had MCI showed that vitamin E did not slow progression to AD. Other RCTs have found that vitamin E and multivitamins are also not associated with the maintenance of cognitive function in older adults without dementia. Therefore, it is likely that vitamin supplements are ineffective for the prevention of AD or dementia.

31.4.4.4 Ginkgo Biloba

Ginkgo biloba is widely used as an herbal supplement for its purported effects on memory and cognitive function. However, a recent RCT that included more than 3,000 participants found that gingko biloba did not slow progression to AD in older adults who had normal cognitive function or MCI [24].Gingko biloba is likely to be ineffective for the prevention of AD.

31.4.4.5 Cholinesterase Inhibitors

Cholinesterase inhibitors have been shown to be effective for the treatment of symptoms in AD and dementia. However, eight RCTs that have included more than 4,000 participants have found no difference between treatment and control groups regarding the rate of conversion from MCI to AD/dementia [24]. In addition, participants treated with cholinesterase inhibitors experienced higher drop-out rates due to adverse events. Therefore, cholinesterase inhibitors are probably ineffective for the prevention of cognitive decline or AD and may increase the risk of other adverse consequences.

31.4.5 US National Institutes of Health Report

In 2010, the US National Institutes of Health released a consensus statement [23] and a comprehensive technical report [24] on the existing evidence for the prevention of dementia and cognitive decline. The report concluded that although a number of promising risk factors have been identified, no conclusive evidence exists to recommend interventions. The data supporting these potential modifiable risk factors ranges from moderate to poor, and there is a need for both expanded observational studies and RCTs before appropriate prevention strategies can be implemented.

31.5 Current Prevention Efforts

31.5.1 The Projected Impact of Risk Factor Reduction

Because the optimal strategies for the prevention of AD and dementia remain unclear, a recent study sought to help determine which potential prevention strategies might have the greatest impact if found to be effective [22]. This was accomplished by calculating population attributable risks (PARs) to estimate the potential impact of risk factor reduction for seven potentially modifiable risk factors: diabetes, mid-life hyper-

tension, mid-life obesity, depression, physical inactivity, low education and smoking. PARs are estimates of the proportion of cases of a disease in a population that can be 'attributed' to, or caused by, a given risk factor assuming that there is a causal relationship. They take into account the prevalence of the risk factor as well as the strength of the association between the risk factor and disease, thereby providing an important public health perspective on which risk factors are likely to be contributing to the largest proportion of cases on a societal level.

The strength of the association was similar for all of the risk factors examined, ranging from a relative risk of 1.4 for diabetes to 1.9 for depression. However, the global prevalence of the risk factors varied widely, ranging from 3% for mid-life obesity to 40% for low education. For this reason, a larger proportion of AD cases worldwide were attributable to factors such as low education (19%), smoking (14%), physical inactivity (13%) and depression (11%), while a smaller proportion of cases were attributable to cardiovascular risk factors such as mid-life hypertension (5%), diabetes (2%) and mid-life obesity (2%). In the US, the proportions were different due to differences in risk factor prevalence, with the largest proportion of cases attributable to physical inactivity (21%), depression (15%) and smoking (11%), and smaller proportions attributable to mid-life hypertension (8%), mid-life obesity (7%), low education (7%) and diabetes (3%). Together, these seven risk factors contributed to as many as half of Alzheimer's cases (worldwide: 51%, 17.2 million; US: 54%, 2.9 million). Furthermore, it was estimated that a 25% reduction in all seven risk factors could potentially prevent up to three million cases worldwide and nearly 500,000 cases in the US.

31.5.2 Current Randomized, Controlled Prevention Trials

Several large-scale RCTs are currently underway or being planned to directly test the impact of risk reduction strategies on cognitive decline or risk of dementia. If these studies are successful, it may be possible to mitigate the impending dementia epidemic through large-scale public health interventions. The studies currently underway include the following:

- The Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes (ACCORD-MIND) study is comparing the effects of intensive glucose, blood pressure or lipid management to standard care on cardiovascular outcomes and cognitive decline in nearly 3,000 older participants who have diabetes (ClinicalTrials.gov: NCT00182910).
- SPRINT is comparing the effects of intensive vs. standard systolic blood pressure control on several outcomes including cognitive decline in over 9,000 older adults (ClinicalTrials.gov: NCT01206062).
- The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is comparing the effects of a multidomain intervention that includes cardiovascular risk reduction combined with physical and mental activity to a health education control condition on rate of cognitive decline in 1,200 older adults who have an elevated dementia risk (ClinicalTrials.gov: NCT01041989).
- The Lifestyle Interventions and Independence for Elders (LIFE) study is examining the effects of exercise in 1,600 frail, sedentary older adults, and cognitive decline is included as a secondary outcome (ClinicalTrials.gov: NCT01072500).
- The Look AHEAD (Action for Health in Diabetes) study is examining the long-term cognitive effects of a 4-year lifestyle intervention that is designed to achieve and maintain weight loss in 5,000 men and women 45–74 years of age who are overweight/obese and have type 2 diabetes (ClinicalTrials.gov: NCT00017953).
- The Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-Related Cognitive Decline (MAPT) is utilizing a factorial design to study the effects of omega-3 supplementation alone, a multi-domain behavioral intervention (nutrition, physical exercise, cognitive stimulation, social activities) alone, and a combined omega-3 plus multi-domain

intervention vs. placebo on cognitive decline in 1,680 frail older adults ≥70 years of age (ClinicalTrials.gov: NCT00672685).
- The Testosterone Trial in Older Men is examining the effects of testosterone gel in older men with low testosterone levels and symptoms potentially attributable to low testosterone, including cognition (ClinicalTrials.gov: NCT00799617).

31.6 Conclusion

Dementia, which is most commonly caused by AD, is a devastating disease that takes a tremendous toll on affected individuals and family members. The prevalence of dementia is expected to triple worldwide over the next 40 years, and there are currently no treatments available to prevent, stop or reverse the disease. New diagnostic criteria have been developed in which biomarkers are utilized to help identify cases of AD and dementia earlier in the pathophysiologic process. In addition, observational studies have identified a large number of factors that may prevent or delay the onset of symptoms. These include cardiovascular risk factors (e.g., diabetes, mid-life hypertension and mid-life obesity), behavioral risk factors (e.g., physical inactivity, lack of mental stimulation, smoking and diet), and psychosocial risk factors (e.g., depressive symptoms and lack of social engagement). However, it remains unclear whether the treatment of these conditions or lifestyle changes will result in lower dementia incidence. RCTs are critically needed to determine whether risk reduction strategies can effectively prevent or delay the onset of dementia symptoms, thereby lowering prevalence over time and preventing or mitigating the anticipated dementia epidemic.

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Depression and Other Common Mental Health Disorders in Old Age

32

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Abstract

Mental health disorders are common in older adults and seriously affect their quality of life. This chapter mainly focuses on the most prevalent mental health disorders among older adults: depressive and anxiety disorders. Their prevalences range from around 2% (for full-blown psychiatric disorders) to 15% (for subclinical forms) in community-dwelling older adults. Although half of affected older adults have an early onset disorder with a chronic or remittent course into later life, many older adults experience their first onset of mental disorder in later life. Comorbidity with other mental health disorders, and also with physical illnesses, is common. For example, individuals who have somatic diseases and impairments have a greater onset rate of both depression and anxiety, and having depression or anxiety increases the risk of subsequent morbidity, cognitive impairment, physical decline and mortality. The overlap with other mental and somatic conditions complicates the detection and treatment of mental health disorders in older adults. However, there is evidence for the effective prevention of depression and anxiety in older adults, as well as effective psychological and pharmacological treatments.

Keywords

Aging • Epidemiology • Geriatrics • Older Adults • Longevity • Depression • Mood disorder • Bipolar disorder • Suicide • Risk factors • Prevention • Disability • Cognitive function • Dementia

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Abbreviations

DSM-IV-TR	Diagnostic and Statistical Manual 4th edition, Text Revision
ECT	Electroconvulsive therapy
HPA	Hypothalamus-pituitary-adrenal
IDO	Indoleamine-2,3-dioxygenase
IL	Interleukin
US	United States

32.1 Introduction

Aging has a profound impact on the individual. It is generally associated with adverse changes in human anatomy and physiology that result in the development of degenerative and chronic conditions. In addition, aging involves various transitions, both social (e.g., retirement, loss of intimate persons) and behavioral (e.g., physical inactivity, disability). Some of these transitions are entered into voluntarily and some are imposed by circumstances. All of these age-related changes may affect the mental health of older adults.

This chapter will describe mental health aspects of the older population. Since the most common and best-examined mental problems in old age are depression and anxiety, the main focus will be on these conditions. However, bipolar disorder and alcohol use disorders will also be briefly discussed. Mental health disorders that have a very low prevalence in older age (e.g., drug addiction, schizophrenia) fall outside the scope of this chapter.

32.2 Mental Health Problems in Older Adults

32.2.1 Depressive Disorders

Depressive disorders include major depressive disorder, dysthymia and bipolar disorder. According to the American Psychiatric Association's Diagnostic and Statistical Manual, 4th edition, Text Revision (DSM-IV-TR) [1], a *major depressive disorder* is diagnosed when a person exhibits five or more out of the following nine symptoms: depressed mood, lack of interest, feelings of worthlessness or inappropriate guilt, diminished ability to concentrate or make decisions, fatigue, psychomotor agitation or retardation, insomnia or hypersomnia, significant decrease or increase in weight or appetite, and recurrent thoughts of death or suicidal ideation. The identified symptoms should include at least one of the two core symptoms (depressed mood and lack of interest), should be present for most of the day for at least 2 weeks and should be severe enough to cause disruptions in an individual's daily functioning. *Dysthymia* is a chronic long-lasting form of depression that shares many of the characteristic symptoms of major depressive disorder, though these symptoms tend to be less severe. To be diagnosed, an individual must experience two or more of the depressive symptoms (including at least one of the two core symptoms) for at least 2 years. The diagnosis of depressive disorders can be established using a psychiatric interview, such as the Structured Clinical Interview for DSM-IV. Various valid and reliable instruments that apply DSM criteria to diagnose major depressive disorder and dysthymia are available for research and clinical purposes.

In addition to a 'full-blown' diagnosis, it is possible to suffer from substantial depressive symptomatology without meeting the diagnostic criteria for a depressive disorder. This condition is often referred to as 'subthreshold depression', 'significant depressive symptoms' or 'minor depression'. These milder forms of depression are commonly assessed using depressive symptom questionnaires that ask about the presence, intensity and/or frequency of a series of symptoms. Some examples of symptom checklists that are commonly used in older populations are the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. These instruments are well-validated and have been proven to be valid and reliable instruments in older populations.

Half or more of the depressive disorders in older adults represent a new condition arising in old age (late-onset depression). Late- and

early-onset depression have partly distinctive risk factors (see Sect. 32.4), and may also have a different course, though studies in this field are still limited. There is an ongoing discussion regarding differences in symptom profiles between depressed older adults and depressed younger adults. Some studies have indicated that depressive symptoms presented to the clinician are rather similar across older adults and individuals in midlife. However, some subtle differences in symptom experience across age groups have been described. Apathy (symptoms of non-interactiveness) appears to be more frequent in older age than in younger age, with psychomotor disturbances also being more obvious in older adults [2].

Bipolar disorder, also known as manic-depressive disorder, is a mood disorder that is defined by the presence of one or more episodes of abnormal shifts in mood, energy and activity levels. It can be described as extreme ups and downs, in which individuals experience periods of overactivity and irresponsible behaviors that alternate with depressive episodes. The elevated moods are referred to as mania or, if milder, hypomania. These manic and depressive episodes are usually separated by periods of normal mood. Bipolar disorder usually starts before 30 years of age and commonly lasts throughout the individual's lifetime. However, bipolar disorder can have a late onset. The diagnosis of bipolar disorder can also be established using a psychiatric interview. To satisfy the clinical diagnosis of bipolar disorder, the abnormal mood should have a detrimental effect on the individual's daily functioning. To assess the presence of depressive symptoms, the same lists can be used as mentioned above. Mania symptoms can be assessed using the Young Mania Rating Scale.

32.2.2 Anxiety Disorders

Anxiety disorders are mainly characterized by a distinctive fear experience and related physical symptoms. However, anxiety disorders are heterogeneous and several disorders are currently being differentiated. The most prevalent anxiety disorders among older adults are panic disorder, agoraphobia, generalized anxiety disorder and social phobia. *Panic disorder* is characterized by sudden anxiety attacks that are attended with bodily symptoms like gasping for breath, cardiac palpitation, chest pain, nausea, dizziness, shivering, trembling, sweating, cold tremors or tinglings. Patients with panic disorder often have feelings of derealization (the outer world is unreal) and depersonalization (living outside of the body/mind or as in a dream), and they sometimes avoid situations or places in which they have had previous attacks or that make them anxious (this avoidance is also known as *agoraphobia*). *Generalized anxiety disorder* is depicted by the continuous pondering about daily worries such as work, finance, health and shelter without any concrete immediate cause. Among the bodily symptoms are fatigue, concentration problems, irritability, dry mouth, cardiac palpitations, aching muscles, sweating, swallow-complaints and diarrhea *Social phobia* is the fear of eating and speaking in public or of being at the center of attention in general. It is often accompanied by panic-like bodily symptoms. As with depression, 'subthreshold' forms of anxiety also exist. These are often identified using anxiety checklists such as the Beck Anxiety Inventory or the Hospital Anxiety and Depression Scale – Anxiety subscale. The diagnosis of anxiety disorders can be established using validated psychiatric interviews that apply DSM criteria to identify the anxiety disorder diagnosis. The clinical presentation of anxiety disorders appears rather similar in younger and older adults.

32.2.3 Alcohol Use Disorders

Alcohol consumption among older adults is not uncommon and has increased in the past 10 years [3]. Alcohol use exists on a spectrum from abstention to dependency. The National Institute on Alcohol Abuse and Alcoholism recommends no more than one drink per day for individuals who are ≥65 years of age. This is less than is usually recommended for younger adults (no more than two drinks per day for women and no more than

three drinks per day for men). This adaptation for older adults is necessary because the adverse effects of alcohol use are believed to be stronger in older adults due to less efficient liver metabolism, greater use of contraindicated medications, and decreases in lean body mass and total body water [4]. Whereas mild alcohol use seems to have a beneficial effect on physical health, severe or excessive use (more than one drink per day) and binge drinking (drinking large amounts of alcohol within a short period of time) have adverse effects on both physical and mental health [5].

The DSM-IV psychiatric classification includes two types of alcohol use disorders: problem use or abuse, and dependency. Problem use or alcohol abuse is defined as drinking at a level at which adverse medical, psychological or social consequences may occur [6]. Alcohol dependency is defined as an alcohol use disorder with clinically significant distress or impairment, and with preoccupation with alcohol, loss of control, continued use despite adverse consequences and/or physiological symptoms such as tolerance and withdrawal. According to the DSM criteria for alcohol dependence, at least three of the following seven criteria must be manifest: tolerance; withdrawal symptoms or clinically-defined alcohol withdrawal syndrome; use in larger amounts or for longer periods than intended; persistent desire or unsuccessful efforts to cut down on alcohol use; time is spent obtaining alcohol or recovering from its effects; social, occupational and recreational pursuits are given up or reduced due to alcohol use; and use is continued despite knowledge of alcohol-related harm [1].

Alcohol abuse and dependency can also be diagnosed using a structured psychiatric interview that applies DSM criteria. There are also self-report screening instruments that can be used to assess alcohol use and detect alcohol problems in older adults (e.g., the CAGE questionnaire, the Alcohol Use Disorders Identification Test). When assessing alcohol use, it is important to take into account that individuals generally tend to underreport their alcohol intake in self-reports and in face-to-face interviews.

32.2.4 Comorbidity Between Mental Health Problems

Comorbidity between mental health problems is extensive. For example, about 60% of individuals who have depression or anxiety disorders appear to have a second diagnosis of depression or anxiety as well [7]. Anxiety disorders often precede a depression diagnosis; however, this does not necessarily imply a causal relationship. Alcohol disorders are associated with both anxiety and depressive disorders [5]. The expected prognosis for individuals who have comorbid mental health disorders is poorer than for those who have a single disorder. Patients with comorbidity have an increased severity of symptoms, increased risk of suicidality, a more chronic course and more somatic complaints. As a consequence, these patients tend to have more hospital admissions, are more difficult to treat, need a longer time to remit and need higher doses of medication [8, 9].

32.3 Prevalence of Mental Health Problems in Older Adults

Prevalence rates of mental health disorders in older adults vary considerably depending on the sample studied and methods used. Studies in long-term care or clinical settings generally find higher prevalences than studies in community settings, and studies that apply psychiatric diagnostic criteria for mental health disorders find much lower prevalences than studies that use symptom checklists to identify subthreshold symptoms.

As confirmed in several aging studies, major depressive disorder affects about 2 to 3% of the older community-dwelling population, which appears to be a robust finding across Western countries [10]. Contrary to what might be expected, psychiatrically-defined depressive disorders appear to be less prevalent among older adults in the community than among young and middle-aged adults in the community. However, the most frail and vulnerable older adults live in long-term care facilities.

Table 32.1 Prevalence of mental health problems in men and women across different age groups in the Longitudinal Aging Study Amsterdam

	Men			Women		
Mental health problems	55–65 years (n=490)	65–75 years (n=456)	75–85 years (n=560)	55–65 years (n=526)	65–75 years (n=517)	75–85 years (n=558)
Psychiatric disorders[a]						
Major depressive disorder	1.2%	1.1%	0.5%	3.4%	3.5%	2.0%
Panic disorder	0.4%	0.2%	0.2%	1.5%	1.5%	0.4%
Social phobia	1.2%	0.4%	1.1%	2.1%	1.5%	1.8%
Generalized anxiety disorder	1.8%	2.0%	2.1%	4.6%	5.2%	4.1%
Subthreshold symptoms						
Subthreshold depression[b]	8.2%	8.1%	13.2%	9.7%	14.1%	21.0%
Subthreshold anxiety[c]	5.3%	4.2%	4.5%	6.7%	7.7%	7.2%
Excessive alcohol use (≥3 drinks/day)	12.5%	7.8%	4.2%	1.7%	1.1%	0.2%

[a] 1-Year prevalence rates based on diagnostic DSM-criteria using the Diagnostic Interview Schedule
[b] Indicated by Center for Epidemiologic Studies Depression Scale score ≥16, but no major depression diagnosis
[c] Indicated by Hospital Anxiety and Depression Scale – Anxiety subscale score ≥8, but no anxiety disorder diagnosis

The prevalence of depression in these facilities is considerably higher: about 10% [11]. The prevalence of bipolar disorder in the community is also lower in older adults (up to 0.1%) compared to younger adults (about 1%).

The 12-month prevalence of anxiety disorders in the older community range around 7% [7, 12, 13], which is slightly lower than the estimated prevalence of anxiety disorders in younger adults. The prevalence of anxiety disorders in long-term care facilities has been shown to be somewhat lower, and is estimated to be around 5.7% [11]. Anxiety disorders often have an early onset, and have the same clinical presentation in younger and older adults. However, late-onset anxiety is not as rare as it has long been assumed to be. It is present in 30–40% of late-life anxiety disorder [12, 14].

Table 32.1 shows the 1-year prevalence rates of major depressive disorder and the most prevalent anxiety disorders among participants of the community-based Longitudinal Aging Study Amsterdam (n=3,107, www.lasa-vu.nl). These prevalence rates are rather comparable to those found in older populations in the United States (US) [7, 13]. Consistent with other studies, these data also indicate that as is seen in younger age groups, women in older age groups generally show much higher rates of depressive and anxiety disorders than do men. Above the age of 55 years, there is no increase in the prevalence of psychiatric diagnoses of depression or anxiety; there might even be a slightly decreasing trend. This has also been indicated in aging studies that have been conducted in other countries and cultures [7, 13].

Some have suggested that part of this declining prevalence of depression and anxiety with older age could be due to bias, since those with mental problems may die earlier and therefore not survive to old age. It could also be due to the fact that older adults may underreport depression compared to younger adults. However, not much evidence exists for the latter. Overall, research findings do indicate that the prevalence of psychiatric depressive and anxiety disorders in old age is not as high as in earlier age.

A completely different picture arises when we look at sub-threshold depressive and anxiety symptoms. These symptoms are more prevalent among older adults than among younger adults. Even within the older population, rates of subthreshold symptoms steadily increase with increasing age (Table 32.1). Again, women clearly show higher rates of significant depressive symptoms than do men. In a literature review that compared prevalence rates across various

cultures and countries, prevalences of clinically significant levels of depressed mood in older community-based populations ranged from 12 to 20% [10]. Such a literature review does not exist for anxiety symptoms, but when using symptom checklists such as the Beck Anxiety Inventory, reported prevalences are in the same range as those of depressive symptoms. Again, the prevalence of both depressive symptoms and anxiety symptoms is much higher in long-term-care facilities, estimated to be at a mean of 29% for both [11].

Suicide is a very severe symptom of depression. Comorbid anxiety disorders and other mental health disorders have been shown to further increase the risk for suicide. In 2004, 14.3 of every 100,000 American adults ≥65 years of age died by suicide (according to the Centers for Disease Control and Prevention, National Center for Injury Prevention and Control). This proportion is higher than the 11 per 100,000 found in the general population. These patterns are in line with observations from the World Health Organization: in year 2000, an estimated 40 out of every 100,000 men ≥65 years of age and 12 out of every 100,000 women ≥65 years of age committed suicide. Both of these statistics were higher in older age than in younger age, though there appears to be a recent trend of suicide rates increasing among the young adult group (World Health Organization, www.who.org). Although depressive and anxiety disorders are more prevalent among older women than among older men, about 80% of those who commit suicide are male. This is in line with other observations that although suicidal intentions are higher among women, it is men who are more likely to turn these intentions into successful suicide attempts.

Alcohol use, abuse and dependency have long been less frequent among older adults relative to younger adults. However, the frequency of alcohol use and alcohol disorders in older adults is increasing [3, 15]. The National Survey on Drug Use and Health showed that in men ≥65 years of age, the prevalence of at-risk alcohol use was 13% and of binge drinking was 14%. In women of this age group, these prevalences were 8 and 3%, respectively [15]. A recent study on the large-scale US National Survey on Drug Use and Health, which was conducted among more than 16,000 older adults, found 1-year prevalence rates of 1.9% for alcohol dependence and 2.3% for alcohol abuse among older adults 50–65 years of age. Prevalence rates were lower (0.6% for alcohol dependence and 0.9% for alcohol abuse) among adults ≥65 years of age [16].

32.4 Pathophysiology and Risk Factors of Mental Health Problems in Older Adults

The etiology of mental health disorders is complex because many different risk factors can contribute to the onset of mental health disorders. The etiological model for mental health disorders is often described in terms of the 'stress-vulnerability' model [17], in which both the extent of the stressor experienced and an individual's biological, genetical and psychological vulnerability determine whether or not mental health disorders develop. In this section, we will first describe these pathophysiological and etiological domains of depressive and anxiety disorders, since these have much commonality. Specific aspects of the etiological background for bipolar and alcohol disorders will be briefly described at the end of this section.

32.4.1 Biological Mechanisms Involved in Depressive and Anxiety Disorders

There is a central belief that distinct pathophysiological mechanisms interplay in the etiology of depression, some of which have also been implicated in anxiety disorders. One of the most central mechanisms is dysregulation of the monoamine system, which results in a different neurotransmitter balance in the brain. For example, a down-regulation of serotonin receptors, an increased monoamine oxidase activity and deficits in norepinephrine functioning have been implicated in depression [18]. That is why the most commonly used treatment option to date,

antidepressant medication, targets serotonergic and/or noradrenergic pathways in order to improve the neurotransmitter balance in the brain. A similar monoamine disbalance has been observed in various anxiety disorders and in line with this, antidepressant medication is also the treatment of choice for anxiety. Although most evidence for a monoamine system disbalance comes from younger samples, there is evidence that this pathophysiological mechanism also plays a role in older adults.

Additional age-related physiological and brain structure changes have been suggested as pathophysiological mechanisms for depression and anxiety. Magnetic resonance imaging of older patients who have depression has revealed structural abnormalities in areas related to the cortical-stratial-pallidal-thalamus-cortical pathway. Some of these abnormalities may be specific in an older sample, and may have a vascular basis. In fact, studies suggest that vascular lesions in selected regions of the brain may contribute to a unique variety of late-life depression [19]. These '*vascular depression'* impairments resemble impairments exhibited in frontal lobe syndromes.

Other central physiological mechanisms that have shown dysregulations in patients with depression or anxiety concern the body's central stress systems. The hypothalamus-pituitary-adrenal (HPA) axis is believed to function hyperactively, resulting in an increased release of the stress hormone cortisol. Hyperactivity of the HPA axis is caused by a corticotrophin-releasing hormone overdrive, a strong corticotrophin-releasing hormone response to adrenocorticotrophic hormone release and/or a blunted feedback control by central glucocorticoid receptors. Several studies have shown that major depression and panic disorder are associated with hyperactivity of the HPA axis, as illustrated by elevated basal cortisol levels in the evening, an excess of cortisol after awakening in the morning or an associated finding of non-suppression to a dexamethasone suppression test. However, some recent evidence suggests that especially in an older population, frailty could actually exhaust the body's responses to stress, potentially resulting in hypoactivity of the HPA axis. This may explain why some studies among older adults have observed not only hyper- but also hypoactivity of the HPA axis among individuals who have depression [20, 21]. It has not yet been widely studied whether similar patterns of both hypo- and hyperactivity of the HPA axis can be observed among older adults.

Other endocrine changes have also been associated with late-life depression. Low levels of sex steroid hormones, such as testosterone, estradiol and dehydroepiandrosterone sulfate, which are especially apparent in older adults, particularly after menopause, have been associated with an increased risk of late-life depression [22]. This is in contrast to younger age groups, where high levels of sex hormones have sometimes been associated with greater depression. Growth hormones and factors have been also implicated in the pathophysiology of depression. A recent meta-analysis showed that a low level of the brain-derived neurotrophic factor (a neurotrophin that has been linked to the viability and differentiation of neurons in brain circuits that regulate emotion, memory, learning, sleep and appetite) has been consistently observed among individuals who have depression [23]. This pattern appears to occur in younger as well as in older populations.

A final pathophysiological mechanism involved in depression and anxiety is inflammation. Inflammation is characterized by a chronic mild elevated activity of the immune system illustrated by higher levels of, for example, C-reactive protein and cytokines such as interleukin (IL)-6 or tumor necrosis factor-alpha. With aging, inflammation levels generally increase steadily over time, thereby reaching levels that are closer to critical levels at which adverse health impact could occur. High levels of inflammatory markers have been observed in older populations that have a range of disease conditions, including cardiovascular disease, lung disease, cancer, frailty or physical disability. However, growing evidence suggests that immune dysregulation may also be involved in depression. For example, the

administration of pro-inflammatory cytokines (as is done in treatment for cancer or hepatitis C) has consistently been shown to induce depression in about one-third of patients. A recent meta-analysis that summarized evidence from large-scale cohort studies confirmed that inflammatory marker levels are increased in individuals who have depression compared to those who do not [24].

The above described pathophysiological dysregulations in monoamine, endocrine, inflammatory and brain mechanisms that are observed among individuals who have depression, or sometimes those who have anxiety, do not stand alone but are strongly intercorrelated. For example, prolonged hyperactivity of the HPA axis could result in blunted anti-inflammatory responses to glucocorticoids, which can result in increased inflammation. Furthermore, proinflammatory cytokines, low levels of brain-derived growth factor and high cortisol levels might inhibit hippocampal neurogenesis, which could lead to a reduced hippocampal volume which is also seen in depression. Also, several inflammatory markers have been shown to promote indoleamine-2,3-dioxygenase (IDO) activation, which catalyzes tryptophan to kynurenine, thereby reducing the availability of serotonin. Consequently, the pathophysiological dysregulations described above should be seen as a complex interaction of multiple biological processes that often occur in combination and may stimulate other processes. It should be pointed out, though, that these physiological abnormalities are not seen in all patients who have depression or anxiety.

32.4.2 Early Life Risk Factors for Depressive and Anxiety Disorders

It is important to realize that a large proportion (an estimated 50%) of older adults who have a depressive or anxiety disorder have had prior episodes during earlier phases of their lives. Thus, depressive and anxiety disorders in old age often represent recurring episodes of early-onset disorders. Consequently, a personal history of depressive disorder is one of the strongest risk factors for a major depressive disorder in old age. This also strongly indicates that disruptive events that occurred much earlier in life (e.g., childhood abuse, trauma, severe negative life events) can have enduring effects and still constitute significant risk factors for depression and anxiety in later life [25]. Intermediate pathways between childhood adversity and late-life poor mental health might include alcohol or illicit drug use, difficulties in forming and maintaining social relationships, and lower educational attainment. Simultaneously, traumatic childhood experiences might produce long-lasting psychobiological changes, such as disturbances in the HPA axis, which continue to impact mental health throughout life.

In recent years, a great interest has arisen to search for genetic susceptibility to mental health disorders across the life cycle. Longstanding vulnerability factors, such as personality and heredity, are more important factors for major depressive disorder than for the milder type of depressive symptoms. In community samples of older adult twins, genetic influences accounted for 30 to 40% of the variance in depression and anxiety [26, 27]. A study that examined both older and middle-aged twins found no age or sex difference in the magnitude of heritable influence [28]. However, a recent twin study conducted by Kendler et al. [29] indicated that depression in the early life of one twin was associated with a higher genetic risk of depression in the other twin, whereas depression in the late life of one twin was associated a higher genetic risk of cardiovascular disease in the other twin. This suggests that even though genetic factors remain important for depression in late life, the underlying genetic variants differ for early-life versus late-life depression. There may be a shared genetic vulnerability for depression and somatic conditions, especially in late-life depression. Such a shared vulnerability could be due to genes that affect biological pathways (e.g., inflammation, endocrine factors), thereby impacting on both mental and somatic health.

32.4.3 Behavioral and Psychosocial Risk Factors for Depression and Anxiety

In general, aging tends to be associated with relationship losses due to retirement, widowhood, or the death of age-peers such as siblings or friends. Increasing age also brings changes in relationship needs, such as those that result from increasing physical impairment. Older adults may become more dependent on others when they lose the ability to fulfill social or instrumental tasks. The existing balance in their relationships may be disrupted, introducing strain and discomfort. However, it has been mentioned that specific stressors, such as the loss of a partner or other intimates, are more normative in old age and more typical in that part of the life cycle than in younger age, and are therefore less disruptive. Older individuals have had the opportunity to learn how to cope with stressful circumstances and how to adjust their expectations so as to have fewer feelings of failure. On the basis of age and experience, older adults have developed more effective skills with which to manage stressful life events and reduce emotional distress. Nevertheless, although their impact in old age might be smaller than in younger age, social circumstances still have a significant impact on the presence of depressive and anxiety symptoms in later life. For example, negative life events and the loss of a partner have consistently been associated with more feelings of depression and anxiety among older adults [30]. The search for restitution secondary to the inevitable losses in late life is a major developmental task for aging individuals, and depression may appear when this task is not accomplished successfully. In line with the social disengagement theory [31], it appears that older adults who are less socially engaged are more depressed.

Personality is strongly linked to depression and anxiety in older adults. For example, feelings of high neuroticism, low internal locus of control and low extraversion have been associated with greater depressive and anxiety symptoms [30]. The link between neuroticism and depression or anxiety appears to be especially strong, and neuroticism is therefore one of the best indices of a person's underlying vulnerability to mood disorders.

32.4.4 Somatic Health Risk Factors for Depressive and Anxiety Disorders

The importance of somatic health for the presence of late-life depression and anxiety is undisputed. Chronic physical illnesses are consistently among the strongest risk factors of depression and anxiety in old age. For example, depression is more frequent in the presence of the following diseases: lung disease, arthritis, cancer, diabetes, stroke, coronary heart disease and other cardiac illnesses [32]. In addition to specific diseases, depression is also more prevalent in the presence of certain impairments, such us hearing and vision problems and cognitive impairment. Somatic health risk factors such as poor health, poor vision and hearing loss have also been shown to be important predictors of anxiety symptoms in older adults [33].

Several explanations can be given for the higher prevalence of depression and anxiety with the presence of chronic diseases and impairments. Depression can occur as an outcome of certain somatic illnesses or medications, reflecting a biologically mediated process. For example, the structural and neurochemical changes that are involved in stroke and Parkinsonism can lead to depression and anxiety. Diseases and their specific symptoms also have several adverse psychosocial and physical consequences. For example, the loss of function, role and independence; negative body image and sense of identity; pain and a promoted sense of helplessness can be a reaction to being ill, and then consequently cause increased feelings of depression and anxiety. The development of chronic conditions and impairments has a large impact on the physical functioning of older adults. The extent of physical disability is an important factor in the development of psychological stress. Several studies among older adults have shown that depression and anxiety are more strongly predicted by the level of physical disability than by the number or specific types of chronic conditions. This indicates that the effect of chronic conditions on depressive symptomatology is mediated through the level of existing physical disability.

However, it must also be noted that some symptoms of depression and anxiety, especially the somatic ones such as low energy level and sleeping problems, may partly be a manifestation of somatic disease. Consequently, it is sometimes difficult to distinguish the 'pure' emotional consequences of a somatic condition from depression, especially among older adults who have many somatic conditions. According to psychiatric criteria, depressive and anxiety disorders are only present when not all symptoms are clearly the consequence of one somatic condition or the use of a certain pharmacological drug. So this distinction—though not always easy to make—must be considered when evaluating the presence of mental health disorders.

32.4.5 Specific Additional Risk Factors for Bipolar Disorders

Little is known regarding the etiology and risk factors of bipolar disorders in older adults. Early-onset bipolar disorders have a high family rate—much higher than for other depressive and anxiety disorders—which suggests a rather large genetic influence. However, late-onset bipolar disorder seems to be mainly associated with medical and neurological conditions [34]. Upon neuroimaging, brain white matter hyperintensities have been found in older patients who have bipolar disorder [35]. The etiology may be the consequence of deficits in vascular perfusion in the brain. Since no longitudinal studies on this topic have yet been published, it is not known whether this is a progressive process over a period of time.

32.4.6 Specific Additional Risk Factors for Alcohol Abuse and Dependence

The risk factors for alcohol abuse and alcohol dependence in older adults are understudied. The National Survey on Drug Use and Health showed that high income and smoking were risk factors for high-risk alcohol use in men. Among women, a higher level of education was associated with at-risk drinking [15]. High income and education may form specific risk factors for alcohol use disorders since they partly reflect the availability of funds to purchase alcohol. The risk factors for binge drinking in older men include being divorced or widowed, smoking and illicit drug use. The risk factors for binge drinking in older women include being African-American, having lower education, smoking and the nonmedical use of prescription drugs [15].

32.5 Consequences of Mental Health Problems in the Older Adults

Not only is somatic health an important risk factor for the development of mental health problems, it is clear that mental health problems themselves are risk factors for various types of unfavorable health outcomes. Consequently, the interaction between somatic and mental health should be seen as a downward spiral in which somatic and mental health could bidirectionally impact on each other.

32.5.1 Impact of Mental Health Disorders on Morbidity and Mortality

Most of the conducted scientific studies regarding the impact of depression on morbidity and mortality are in the area of cardiovascular disease. In reviewing these studies, it is clear that depression has a significant impact on the cardiovascular health of patients [36]. For example, among individuals who do not have initial cardiovascular disease, depression increases the risk of developing coronary heart disease by a factor of 1.8. The effect of depression on cardiovascular disease is greater for major depressive disorder than for depressive symptoms [37], which suggest that there is a dose-response association between severity of depressive symptoms and risk for developing cardiovascular disease. A similarly increased risk has been found in meta-analyses that examined the adverse effect of depression on overall mortality [38].

Mental health disorders are strongly related to suicide in older adults. A literature review of references that referred to a period from 1980 to 2008 found that of older adults who committed suicide, 71–95% had been diagnosed with some mental disorder, mainly a depressive disorder [39]. Although suicide occurs much more frequently among older adults who have mental health disorders, most mortality outcome studies have focused on non-suicidal mortality, so increased suicide does not explain the observed link between late-life depression, anxiety and mortality.

The results for increased cardiovascular morbidity and mortality are not specific for depression but have been confirmed for the presence of anxiety symptoms [40, 41]. The associations between depression and anxiety as predictors of mortality and cardiovascular morbidity hold across many of the published studies, despite the addition of potentially confounding variables such as baseline lifestyle or disease status. In addition to overall mortality and morbidity, additional studies confirm that depression also increases the onset of diabetes [42], stroke [43] and obesity [44]. Explanations for the negative health effects of depression and anxiety include—among others—underlying biological dysregulations (see Sect. 32.4.2), underlying (health) behavioral differences (see Sect. 32.4.3) and poorer adherence to treatment and health regimens.

32.5.2 Impact of Mental Health Disorders on Physical Function

Depression and anxiety have also been shown to affect functional status and disability over time. In one study, depression increased the risk (over 6 years) for activities of daily living disability and mobility disability by 67 and 73%, respectively [45]. Even when physical function is objectively assessed through timed physical performance tests such as a walking and balance test, older adults with depression showed a significantly greater decline in performance over 4 years than did older adults without depression [45]. The presence of depression has been shown to accelerate the transition from physical impairments to disability [46]. In other words, depression appears to accelerate the disablement process in older adults. In addition, various cross-sectional reports have linked depressive symptoms to aspects of frailty. However, these associations are hard to interpret since frailty status itself could result in increased feelings of depression and mood changes. For certain aspects of the frailty syndrome, longitudinal associations with depression have been confirmed as well. Individuals who have a high level of depressive symptoms have been shown to have a larger 4-year decline in walking speed [45] and a larger decline in muscle strength [47]. In line with this, depression has also been shown to increase the risk of falls, and both vertebral and non-vertebral fractures, in the older population [48]. Although some have suggested that depression and/or the use of selective serotonin reuptake inhibitor antidepressants may decrease bone mineral density, this has not consistently been indicated and cannot therefore be assumed to be a mediating mechanism [49].

Older adults who suffer from anxiety symptoms or disorders also have increased disability [50], but there has been less examination of other physical consequences in relation to anxiety symptoms. For older adults who have alcohol use disorders, adverse physical health outcomes have been reported as well, which may arise from alcohol-induced somatic conditions such as liver diseases, neuropathy, diabetes, cancer and cardiac arrhythmias [5].

32.5.3 Impact of Mental Health Disorders on Cognitive Function

Another health consequence of mental health disorders is in the cognitive domain. Cognitive problems (i.e., memory and concentration problems) are part of the depression syndrome. These cognitive problems often disappear when the depression is treated, though a meta-analysis [51] showed that cognitive problems may remain after the depression is successfully treated, especially in late-onset depression. This is probably due to

underlying white matter abnormalities in the brain. Early depressive symptoms among individuals who have minimal cognitive impairment may also represent a preclinical sign of Alzheimer's disease or vascular dementia. Depression has been shown to be a risk factor for the onset of Alzheimer's disease and cognitive decline [52]. Depression further complicates the course of Alzheimer's disease by increasing disability and physical aggression, and leading to greater caregiver depression and burden.

The association between anxiety and cognition depends on the severity of the anxiety symptoms. There has been evidence that mild anxiety symptoms lead to better cognitive function in older adults [53], which suggests that the symptoms may have an arousing impact on the brain and thus improve cognitive function. However, severe anxiety symptoms and anxiety with comorbid depression are associated with poor cognitive outcome and larger cognitive decline over time [53].

The effect of alcohol disorders on cognition is well known. Brain damage can occur as a consequence of the toxic effects of alcohol metabolism and a deficiency of thiamine (vitamin B1). Cognitive impairment includes memory problems and impaired executive functioning. In the worst case, alcohol disorders can lead to the Wernicke-Korsakoff syndrome, a severe condition with predominantly severe memory problems, which makes independent living for most patients impossible.

32.6 Treatment and Prevention of Mental Health Problems in Older Adults

32.6.1 Treatment of Mental Health Disorders

Although most studies regarding efficacy in the treatment of mental health disorders are performed in younger adults, numerous studies have shown that the use of various forms of psychotherapy as well as pharmacological treatment are also effective in older adults who have mental health disorders. Various evidence-based psychological treatments for depressive and anxiety disorders are available. Examples are cognitive behavioral therapy, problem-solving therapy, bibliotherapy and life review therapy. Most of these treatments have been slightly adapted for older adults (e.g., smaller treatment steps or less homework). Only life review therapy, a technique in which events of one's life are reviewed and integrated in order to cope with the final stages of life, has been especially developed for older adults.

In most countries, these psychotherapy treatments are the first choice treatment in case of mild depression or anxiety disorders. In severe disorders, the best options are pharmacological treatment or a combination of psychological and pharmacological treatments. The pharmacological treatment options for older adults who have depression or anxiety disorder is very much comparable to those in younger adults. Randomized controlled trials have demonstrated similar efficacy in younger and older adults for selective serotonin re-uptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors [54]. However, it has been shown that certain side effects which may arise when taking antidepressants may be more pronounced among older adults or constitute a larger risk in this population. For example, tricyclic antidepressants are known to increase autonomic tone dysregulations, which could result in elevated heart rate and blood pressure [55]. Such side effects in older adults may be more detrimental due to their often already-increased cardiovascular risk, and consequently warrant monitoring. Nevertheless, in older adults, care must be taken in contributing all physical complaints to a side effect of the medication, because most side effects disappear during the treatment.

For the most severe mental health disorders, which do not respond to the standard psychological and pharmacological treatments, another evidence-based treatment is available: electroconvulsive therapy (ECT). ECT has shown impressive results, including in older adults. ECT may have cognitive side effects that may be transient in most but not all cases [54, 56].

Patients with bipolar depression are often treated with additional medications that stabilize their mood. Thus far, research on effective pharmacological and psychological treatments comes from younger bipolar patients. Treatment guidelines are therefore based upon evidence from younger adults and from clinical experience [34]. There is a clear lack of randomized clinical treatment trials to indicate whether treatments work as well in older bipolar patients.

The treatment for alcohol disorder is complex. It is often organized in specialized centers for addiction, and requires a comprehensive treatment plan that includes biological, psychological and family interventions [5]. The type of treatment depends on the severity of the problem and the possibilities and motivation of the patient. Again, there has been no systematic examination of whether available treatments that have been mainly developed and tested among younger adults work equally well in older adults.

32.6.2 Prevention of Mental Health Disorders

Prevention strategies are important to prevent the incidence or recurrence of mental health problems, or to reduce their adverse outcomes [54]. Preventive efforts with respect to mental health are commonly directed at individuals who are at risk of a disorder. A recent randomized controlled trial showed that a 'stepped care program' for individuals ≥75 years of age who had subthreshold depression or anxiety symptoms halved the incidence of depressive and anxiety disorders [57]. This 'stepped care program' consisted of four consecutive steps that each lasted for 3 months and were conducted by trained nurses. From an initial watchful waiting step (to see whether symptoms disappear spontaneously), older adults underwent subsequent steps (cognitive behavioral therapy, problem-solving therapy, referral to physician to discuss pharmacological treatment or specialized mental health care referral) when symptoms persisted in prior steps. This stepped-care program is a so-called indicated prevention program, and it appears to be a cost-effective form of prevention among older adults [58].

Another prevention strategy that might be considered is approaches that help to educate professionals in recognizing mental health disorders in older adults. Depressive and anxiety symptoms and disorders, and also excessive alcohol use, often remain unrecognized due to a lack of knowledge or experience among professionals, and also sometimes due to a specific presentation by the patient. For example, older patients complain less easily about their mood, but instead report physical complaints or nervousness. They more often attribute mood symptoms to their somatic conditions. As a consequence, a large proportion of older adults who have mental health disorders do not receive the treatment they need. Although mental health care for older adults has improved considerably over the past decades, there are various opportunities for improvement. This improvement could be stimulated through more research that focuses on mental health disorders in older adults.

32.7 Concluding Remarks About the Importance of Common Mental Health Disorders in Epidemiological Studies on Aging

This chapter has indicated that subclinical mental health disorders are common in older adults and seriously affect their quality of life. Moreover, many common mental health disorders (e.g., depressive and anxiety disorders) increase the risk of subsequent morbidity, cognitive impairment, physical decline and mortality. The high prevalence of mental health conditions and their impact on somatic health outcomes are clear indicators that such conditions cannot be ignored in general aging studies. Even if depression and anxiety are not the primary variables of interest, it remains important to include depression and anxiety assessment instruments in epidemiological aging studies in order to account for their impact.

Various questions in the area of late-life mental health disorders have yet to be addressed. First, although there is evidence for effective prevention as well as treatment options for older adults who have mental health problems, there is a severe lack of randomized controlled trial data in the oldest old age group. More studies on innovative interventions to prevent and treat late-life psychopathology are warranted. Second, epidemiologic research into less prevalent mental disorders (e.g., bipolar disorders, schizophrenia, specific anxiety disorders) in older adults is scarce, and requires further attention in order to better understand their prevalence, phenomenology and global health impact. Since alcohol use among older adults is increasing, the prevalence and impact of alcohol use disorders in old age also needs to be further followed-up using large-scale epidemiological studies. Finally, novel epidemiological designs need to be extended and integrated with adequate imaging, genetic and biological research techniques. These will further contribute to a better understanding of the neuropathological mechanisms that contribute to late-life mental health disorders and explain their impact on other somatic health outcomes.

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