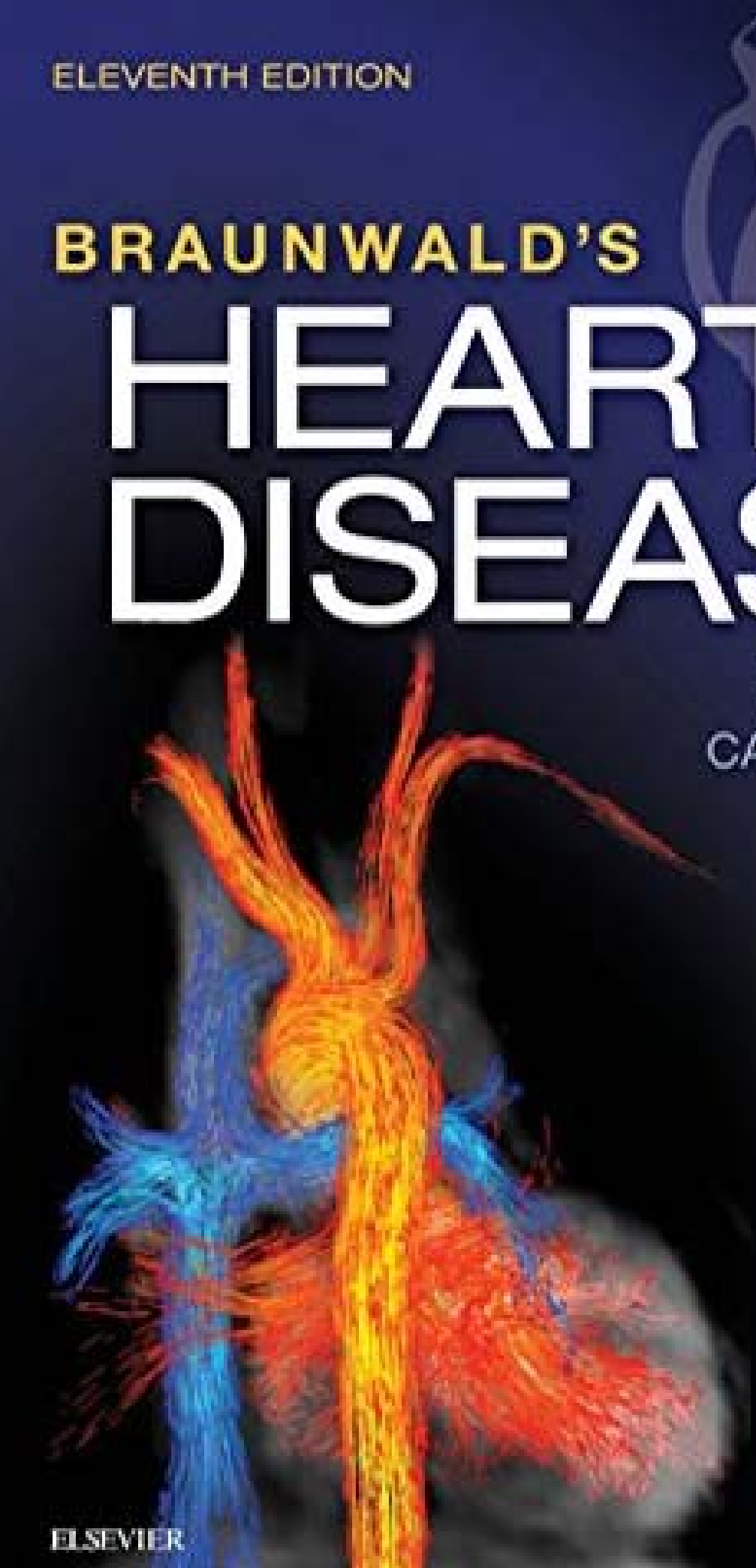
ELEVENTH EDITION

BRAUNWALD'S HEART DISEASE

A TEXTBOOK OF CARDIOVASCULAR MEDICINE



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Bradyarrhythmias and Atrioventricular Block
Pacemakers and Implantable Cardioverter-Defibrillators
Hypotension and Syncope
Neurologic Disorders and Cardiovascular Disease

Preface

This is the 11th edition of the classic textbook, *Heart Disease: A Textbook Of Cardiovascular Medicine,* that Dr. Eugene Braunwald began almost 40 years ago. The editors are pleased and honored to dedicate this edition to him for his extraordinary contributions to the discipline of cardiology, especially this textbook and its companions, and for his unique concept of creating a "living textbook."

In the past several decades, cardiology has advanced at a breakneck pace on many fronts. Knowledge of the diagnosis and management of patients with heart disease, as well as understanding of responsible mechanisms and preventive approaches, advance daily. Genetics, molecular biology and pharmacology, imaging, catheter-based therapy, and cardiac repair are only a sampling of what we encounter daily.

This constant flow of innovative research has generated a proliferation of new cardiovascular journals, cumulatively publishing an unprecedented amount of information. With the rapidly changing cardiovascular knowledge base, an authoritative textbook like *Heart Disease* to which readers can turn, confident that the statements are as accurate and up-to-date as possible, offers even greater value.

As with each edition of this reference work, international experts — household names to many readers — have totally revised *every* chapter. In addition, 14 new chapters have been added to recognize the ever-expanding role of cardiology into areas such as oncology, chronic lung disease, environmental toxins, catheter-based treatments of congenital heart disease, and other topics. Some sections have been revised for clarity, such as arrhythmias; some have been expanded, such as diseases of heart valves; others have had a shift of emphasis, such as congenital heart disease in the adult. Finally, to maintain vitality of standard topics, new authors have replaced more than a third of those who have tirelessly written for previous editions, in chapters on ethics, personalized and precision medicine, imaging, obesity, diabetes, sleep-disordered breathing, autonomic nervous system, and other areas.

In the preface for the 10th edition of *Heart Disease,* we emphasized that the online version contained audio, video, and written information not available in the print edition. We have continued and expanded this practice. To put this 11th edition in perspective, it contains more than 2700 illustrations and 565 tables, while maintaining the number of printed pages near 2000. The eBook includes an additional 400 illustrations, 60 tables, and 300 videos.

We have divided the book into 11 sections, including fundamentals of cardiovascular disease; genetics and personalized medicine; evaluation of the patient; heart failure; arrhythmias, sudden death, and syncope; preventive cardiology; atherosclerotic cardiovascular disease; diseases of heart valves; diseases of the myocardium, pericardium, and pulmonary vasculature bed; cardiovascular disease in special populations; and cardiovascular disease and disorders of other organs.

We have continued the tradition of including practice guidelines, and have written the text for all levels of learners and for all specialties in cardiology. As before, information not directly relevant to practicing clinicians is presented in smaller font. More detailed information on many topics can be found in the companions to this book:

Cardiovascular Intervention by Deepak L. Bhatt
Cardiovascular Therapeutics by Elliott Antman and Marc Sabatine
Chronic Coronary Artery Disease by James DeLemos and Torbjorn Omland
Clinical Arrhythmology and Electrophysiology by Ziad Issa, John Miller, and Douglas Zipes
Clinical Lipidology by Christie Ballantyne
Diabetes in Cardiovascular Medicine by Darren McGuire and Nikolaus Marx
Heart Failure by Michael Felker and Douglas Mann
Hypertension by George Bakris and Matthew Sorrentino
Mechanical Circulatory Support by Robert Kormos and Leslie Miller
Myocardial Infarction by David Morrow
Preventive Cardiology by Roger Blumenthal, JoAnn Foody, and Nathan Wong
Valvular Heart Disease by Catherine Otto and Robert Bonow
Vascular Medicine by Marc Creager, Joshua Beckman, and Joseph Loscalzo
Braunwald's Heart Disease Review and Assessment by Leonard Lilly
Atlas of Cardiovascular CT by Allen Taylor
Atlas of Cardiovascular MR by Christopher Kramer and W Greg Hundley
Atlas of Nuclear Cardiology by Amil Iskandrian and Ernest Garcia

In keeping with the revitalization theme noted above, one of us (DPZ) will be leaving after this edition. Beginning with the 2nd edition of Heart Disease in 1984, Dr. Zipes has written the arrhythmia section and, in more recent editions, with co-authors, and has co-edited *Heart Disease* since the 6th edition. Gordon F. Tomaselli will be his very capable replacement.

The editors and authors, along with the Elsevier staff, have endeavored to make *Heart Disease* the go-to source for current cardiology knowledge, maintaining the high standards Dr. Braunwald set many years ago. We hope readers will enjoy reading this edition and learn from it, as we all strive to improve patient care, our ultimate goal.

Douglas P. Zipes
Peter Libby
Robert O. Bonow
Douglas L. Mann
Gordon F. Tomaselli

Preface to the First Edition

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous scourges — bubonic plague, yellow fever, and small pox — cardiovascular disease not only strikes down a significant fraction of the population without warning but also causes prolonged suffering and disability in an even larger number. In the United States alone, despite recent encouraging declines, cardiovascular disease is still responsible for almost 1 million fatalities each year and more than half of all deaths; almost 5 million persons afflicted with cardiovascular disease are hospitalized each year. The cost of these diseases in terms of human suffering and material resources is almost incalculable.

Fortunately, research focusing on the prevention, causes, diagnosis, and treatment of heart disease is moving ahead rapidly. Since the early part of the twentieth century, clinical cardiology has had a particularly strong foundation in the basic sciences of physiology and pharmacology. More recently, the disciplines of molecular biology, genetics, developmental biology, biophysics, biochemistry, experimental pathology and bioengineering have also begun to provide critically important information about cardiac function and malfunction.

In the past 25 years, in particular, we have witnessed an explosive expansion of our understanding of the structure and function of the cardiovascular system—both normal and abnormal—and of our ability to evaluate these parameters in the living patient, sometimes by means of techniques that require penetration of the skin but also with increasing accuracy, by noninvasive methods. Simultaneously, remarkable progress has been made in preventing and treating cardiovascular disease by medical and surgical means. Indeed, in the United States, a steady reduction in mortality from cardiovascular disease during the past decade suggests that the effective application of this increased knowledge is beginning to prolong human life span, the most valued resource on earth.

To provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I enlisted the aid of a number of able colleagues. However, I hoped that my personal involvement in the writing of about half of the book would make it possible to minimize the fragmentation, gaps, inconsistencies, organizational difficulties, and impersonal tone that sometimes plague multiauthored texts. Although *Heart Disease: A Textbook of Cardiovascular Medicine* is primarily a clinical treatise and not a textbook of fundamental cardiovascular science, an effort has been made to explain, in some detail, the scientific bases of cardiovascular diseases.

To the extent that this book proves useful to those who wish to broaden their knowledge of cardiovascular medicine and thereby aids in the care of patients afflicted with heart disease, credit must be given to the many talented and dedicated persons involved in its preparation. I offer my deepest appreciation to my fellow contributors for their professional expertise, knowledge, and devoted scholarship, which has so enriched this book. I am deeply indebted to them for their cooperation and willingness to deal with a demanding editor.

Eugene Braunwald
1980

Video Contents

VIDEO CONTENTS

PART I

FUNDAMENTALS OF CARDIOVASCULAR DISEASE

1

Global Burden of Cardiovascular Disease

THOMAS A. GAZIANO, DORAIRAJ PRABHAKARAN, AND J. MICHAEL GAZIANO

Over the last decade, cardiovascular disease (CVD) has become the leading cause of death worldwide. In 2013, CVD caused an estimated 17.3 million deaths and led to 330 million disability-adjusted life-years (DALYs) lost[1]—about 32% of all deaths and 13% of all DALYs lost that year. Overall, these data represent increases in both absolute numbers and percentages of deaths and DALYs compared with 2010 estimates. As with many high-income countries during the last century, low- and middle-income countries are now experiencing an alarming and accelerating increase in CVD.

This chapter reviews the features of the epidemiologic transitions underlying this shift in CVD morbidity and mortality and evaluates the transition in different regions of the world. A survey of the current burden of risk factors and behaviors associated with CVD includes regional variations and trends. A review of the economic impact of CVD highlights the cost-effectiveness of various strategies to reduce it. The chapter ends with a discussion of the diverse challenges that the increasing burden of CVD poses for various regions of the world, along with potential solutions to this global problem.

SHIFTING BURDEN

Between 1990 and 2013, deaths from CVD increased from 26% to 32% of all deaths globally, a reflection of the rapid epidemiologic transition, particularly in low- and middle-income countries (LMICs). Although the net percentage of deaths caused by CVD overall has increased, this results from an increase in LMICs and a decline in high-income countries (HICs) (**Fig. 1.1**). CVD now causes the most deaths in all low- and middle-income regions, with the exception of sub-Saharan Africa, where it is the leading cause of death in those older than 45 years. In absolute numbers, CVD causes four to five times as many deaths in LMICs as in HICs. Within the six World Bank–defined low- and middle-income regions, the CVD burden differs vastly (**Fig. 1.2**), with CVD death rates as high as 59% in Eastern Europe and as low as 12% in sub-Saharan Africa. The CVD mortality rate is 38% in HICs.

EPIDEMIOLOGIC TRANSITIONS

The overall increase in the global burden of CVD and the distinct regional patterns result in part from the "epidemiologic transition," which includes four basic stages (**Table 1.1**): Pestilence and Famine, Receding Pandemics, Degenerative and Man-Made Diseases, and Delayed Degenerative Diseases.[2,3] Movement through these stages has dramatically shifted the causes of death over the last two centuries, from infectious diseases and malnutrition in the first stage to CVD and cancer in the third and fourth stages. Although the transition through the age of Pestilence and Famine has occurred much later in LMICs, it has also occurred more rapidly, driven largely by the transfer of low-cost agricultural technologies, the overall globalization of world economies, and public health advances.

Humans evolved during the age of **Pestilence and Famine** and have lived with epidemics and hunger for most of recorded history. Before 1900, infectious diseases and malnutrition constituted the most common causes of death in virtually every part of the world, with tuberculosis, pneumonia, and diarrheal diseases accounting for a majority of deaths. These conditions, along with high infant and child mortality rates, resulted in a mean life expectancy of approximately 30 years.

Per capita income and life expectancy increase during the age of **Receding Pandemics** as the emergence of public health systems, cleaner water supplies, and improved food production and distribution combine to reduce deaths from infectious disease and malnutrition. Improvements in medical education follow, and along with other public health changes, contribute to dramatic declines in infectious disease mortality rates. Rheumatic valvular disease, hypertension, and cerebrovascular accident (stroke) cause most CVD. Coronary heart disease (CHD) often occurs at a lower prevalence rate than stroke, and CVD accounts for 10% to 35% of deaths.

During the stage of **Degenerative and Man-Made Diseases,** continued improvements in economic circumstances, combined with urbanization and radical changes in the nature of work-related activities, led to dramatic changes in diet, activity levels, and behaviors such

FIGURE 1.1 Changing pattern of mortality, 1990 to 2013. *CVD,* Cardiovascular disease; *ONC,* other noncommunicable diseases; *CMNN,* communicable, maternal, neonatal, and nutritional diseases; *INJ,* injury. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013, Seattle: Institute for Health Metrics and Evaluation; 2014.)

as smoking. For example, in the United States, deaths from infectious diseases decreased to fewer than 50 per 100,000 people per year, and life expectancy increased to almost 70 years. The increased availability of foods high in calories, coupled with decreased physical activity, contributes to an increase in atherosclerosis. In this stage, CHD and stroke predominate, and between 35% and 65% of all deaths are related to CVD. Typically, the ratio of CHD to stroke is 2:1 to 3:1.

In the age of **Delayed Degenerative Diseases**, CVD and cancer remain the major causes of morbidity and mortality, but CVD age-adjusted mortality rates decline by almost half, accounting for 25% to 40% of all deaths. Two significant advances have contributed to the decline in CVD mortality rates: new therapeutic approaches and prevention measures targeted at people with or at risk for CVD.[4]

Treatments once considered advanced—including the establishment of emergency medical systems, coronary care units, and the widespread use of new diagnostic and therapeutic technologies such as echocardiography, cardiac catheterization, percutaneous coronary intervention (PCI), bypass surgery, and implantation of pacemakers and defibrillators—have now become the standard of care. Advances in drug development have also yielded major benefits on both acute and chronic outcomes. Efforts to improve the acute management of myocardial infarction (MI) led to the application of lifesaving interventions such as beta-adrenergic blocking agents (beta blockers), PCI, thrombolytics, statins, and angiotensin-converting enzyme (ACE) inhibitors (**see Chapters 58 and 59**). The widespread use of an "old" drug, aspirin, has also reduced the risk of dying of acute or secondary coronary events. Low-cost pharmacologic treatment for hypertension (**see Chapter 47**) and the development of highly effective cholesterol-lowering drugs such as statins have also made major contributions to both primary and secondary prevention by reducing CVD deaths (**see Chapter 48**).

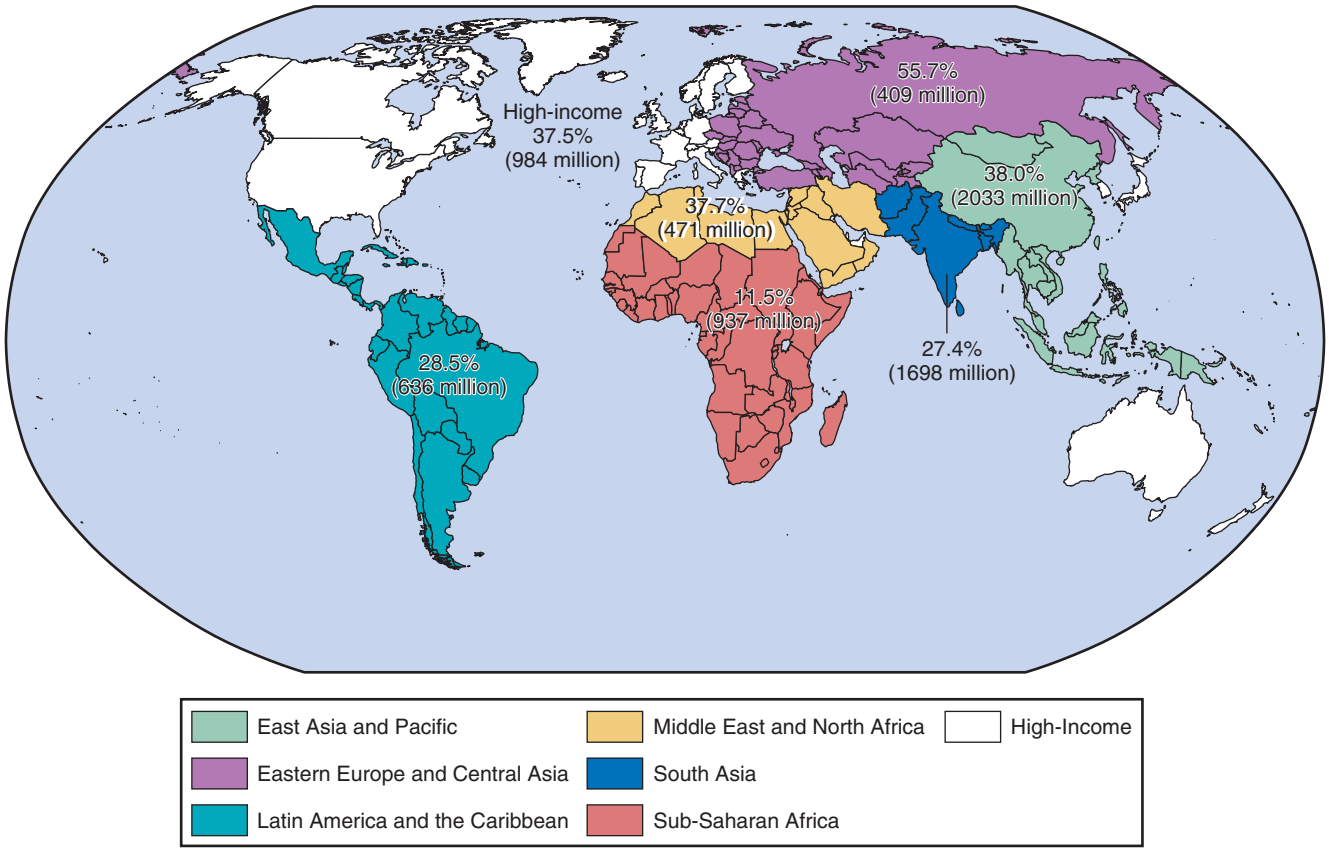

FIGURE 1.2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2013. (From Global Burden of Disease Study 2013: Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014; and World Health Organization. Global Health Observatory Data Repository. Demographic and socioeconomic statistics: population data by country. http://apps.who.int/gho/data/view.main.POP2040?lang=en.)

TABLE 1.1 Five Typical Stages of Epidemiologic Transition in CVD Mortality and Types

STAGE	DESCRIPTION	TYPICAL PROPORTION OF DEATHS CAUSED BY CVD (%)	PREDOMINANT TYPES OF CVD
Pestilence and Famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy.	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding Pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths caused by malnutrition and infection; precipitous decline in infant and child mortality rates.	10-35	Rheumatic valvular disease, hypertension, CHD, stroke
Degenerative and Man-Made Diseases	Increased fat and caloric intake and decreased physical activity lead to emergency of hypertension and atherosclerosis; with increased life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious diseases.	35-65	CHD, stroke
Delayed Degenerative Diseases	CVDs and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events. Age-adjusted CVD mortality declines; CVD affects older and older individuals.	40-50	CHD, stroke, congestive heart failure
Inactivity and Obesity	Increasing prevalence of obesity and diabetes; some slowing of CVD mortality rates in women.	38	

CVD, Cardiovascular disease; *CHD,* coronary heart disease.
Modified from Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Mem Fund Q 1981;49:509; and Olshanksy SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. Milbank Q 1986;64:355.

In concert with these advances, public health campaigns have conveyed that certain behaviors increase the risk of CVD and that lifestyle modifications can reduce risk. In this regard, smoking cessation furnishes a model of success. In the United States, for example, 57% of men smoked cigarettes in 1955; in 2012, 20.5% of men smoked. The prevalence of smoking among U.S. women has fallen from 34% in 1965 to 15.8% in 2012.[5] Campaigns beginning in the 1970s dramatically improved the detection and treatment of hypertension in the United States. This intervention likely had an immediate and profound effect on stroke rates and a subtler effect on CHD rates. Public health messages concerning saturated fat and cholesterol had a similar impact on fat consumption and cholesterol levels. Population mean cholesterol levels also declined, from 220 mg/dL in the early 1960s to 192 mg/dL by 2014,[6] with a simultaneous decrease in the prevalence of elevated low-density lipoprotein (LDL) cholesterol.

Age of Inactivity and Obesity: a Fifth Phase?

Troubling trends in certain risk behaviors and risk factors may foreshadow a new phase of epidemiologic transition, the age of **Inactivity and Obesity**[7] (see Chapters 49 and 50). In many parts of the industrialized world, physical activity continues to decline while total caloric intake increases at alarming rates, resulting in an epidemic of overweight and obesity. Consequently, rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are rising—a particularly evident trend in children.[6] These changes are occurring while measurable improvements in other risk behaviors and risk factors, such as smoking, have slowed. If these trends continue, age-adjusted CVD mortality rates, which have declined over the past several decades in HICs, could plateau, as they have for young women in the United States, or even increase in the coming years. This trend pertains particularly to age-adjusted stroke death rates. This concerning increase in obesity also applies to LMICs.[8]

Fortunately, recent trends in the first decade of this century suggest a tapering in the increases in obesity among adults, although the rates remain alarmingly high at almost 34%.[9] Furthermore, continued progress in the development and application of therapeutic advances and other secular changes appear to have offset the effects from the changes in obesity and diabetes; cholesterol levels, for example, continue to decline. Overall, in this decade, age-adjusted mortality has continued to decline at about 3% per year, from a rate of 341 per 100,000 population in 2000 to 223 per 100,000 in 2013.[10]

Different Patterns of Epidemiologic Transition

The HICs have followed different patterns of the CVD transition, which differ in both peak death rate from CHD and time of transition. Three patterns emerge that rely on data from countries with an established death certification system[11] (**Fig. 1.3**). One pattern, followed by the United States and Canada, showed a rapid rise and peak in the 1960s and 1970s, followed by a relatively rapid decline through the end of the 2000s. The peak was 300 to 700 CHD deaths per 100,000 population, with current rates between 100 and 200 per 100,000. This pattern also occurred in the Scandinavian countries, the United Kingdom, Ireland, Australia, and New Zealand. A second pattern showed a peak in the same period but a peak CHD death rate of only 100 to 300 per 100,000. Countries such as Portugal, Spain, Italy, France, Greece, and Japan followed this pattern. Some countries did not have the same rapid rate of decline, with slower rates in central European countries (Austria, Belgium, Germany) compared to northern European countries (Finland, Sweden, Denmark, Norway), but with lower peaks of 300 to 350 per 100,000 in the 1960s and 1970s. Some countries appear to display a third pattern of continued rise (particularly many components of the former Soviet Union), and others have yet to see any significant increase, such as many countries in sub-Saharan Africa (excluding South Africa). Latin America has less longitudinal data, but limited data suggest that many of the countries follow the pattern of either Mediterranean or Southern European countries, with peaks between 50 and 300 deaths per 100,000. Whether other LMICs will follow a "classic" pattern of significant increases then rapidly declining rates (as happened in North America, Australia, and northwestern European HICs), a more gradual rise and fall (as in the southern and central European countries), or some other pattern will depend in part on cultural differences, secular trends, and responses at the country level with regard to both public health and treatment infrastructures.

CURRENT VARIATIONS IN THE GLOBAL BURDEN

Three phenomena impact the various metrics for disease burden. First, population growth increases the overall number of deaths caused by CVD globally. Second, a trend in general aging of the population has shifted the proportion of deaths caused by CVD in most regions as a result of better control of many communicable diseases that

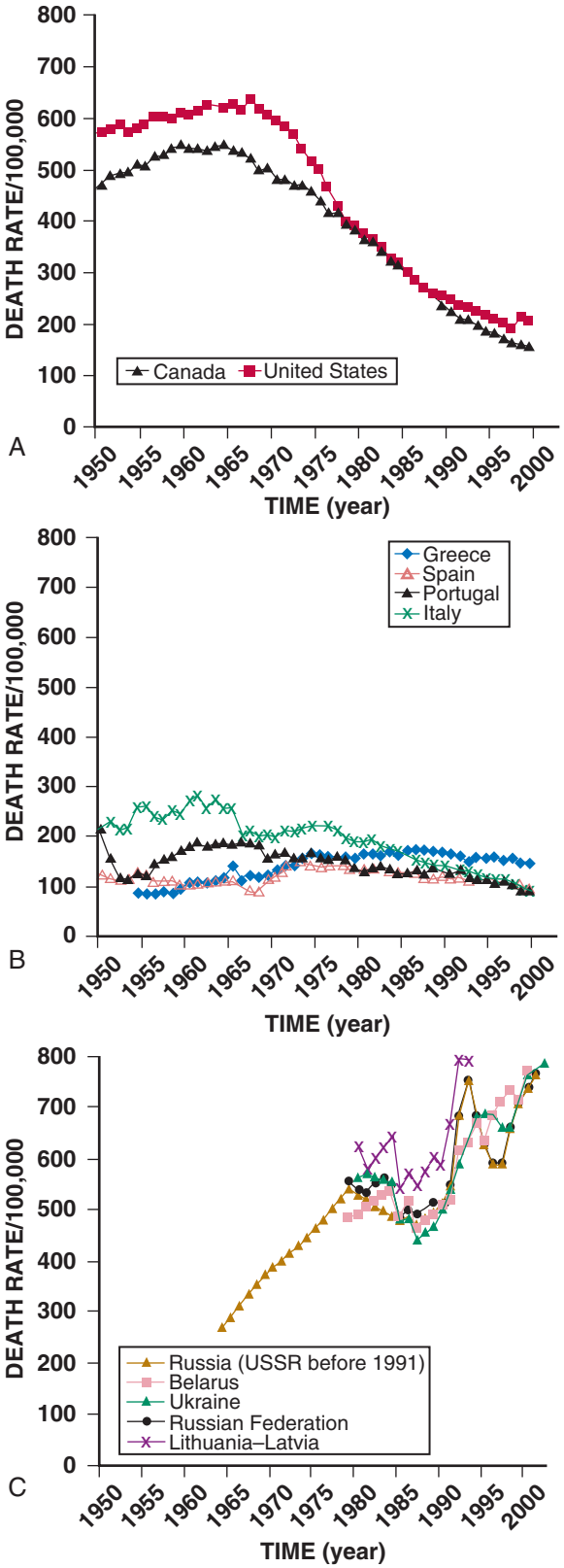

FIGURE 1.3 Differing coronary heart disease mortality patterns. **A,** Rapid rise and decline. **B,** Mild rise and decline. **C,** Continuing rapid rise. (From Mirzaei M, Truswell A, Taylor R, Leeder SR: Coronary heart disease epidemics: not all the same. Heart 2009;95(9):740-6.)

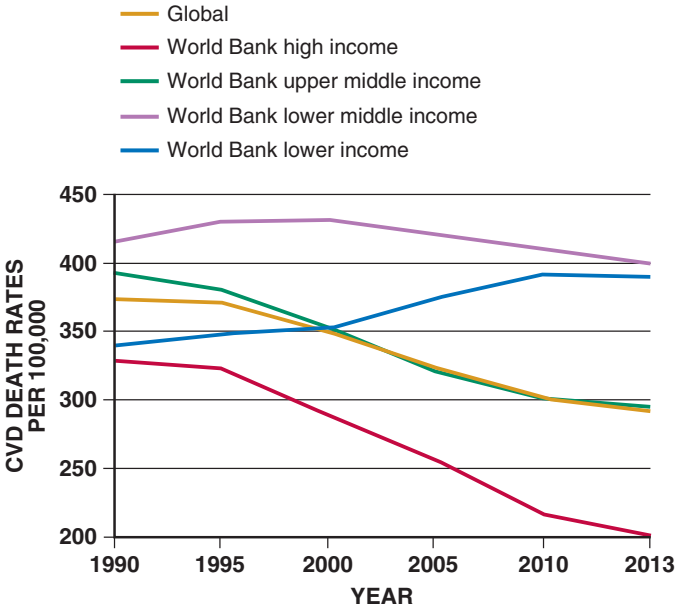

FIGURE 1.4 Cardiovascular disease death rates per 100,000 population from 1990 to 2013, by World Bank income categories. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

strike those at early ages. Third, prevention of CVD and treatment for those with CVD have both improved, which reduces age-adjusted mortality rates. We rely on data from the Global Burden of Disease (GBD) study data from 2013. Although extensive, data from GBD 2013 has limitations. The availability and reliability of data on cause of death, especially in LMICs without standardized protocols, are uncertain.

Globally, CVD deaths increased by 46% between 1990 and 2013. The increase in overall CVD deaths results from both increases in CHD and stroke-related deaths. In 2013, CHD accounted for 15% of all deaths worldwide. The second-ranking cause of death was stroke, at 12% (equally split between ischemic stroke and hemorrhagic stroke). An estimated 14.5 million people died from CHD and stroke, which together accounted for almost a quarter of all deaths worldwide in 2013.[1]

Although still substantial, deaths from communicable, neonatal, and maternal diseases are decreasing worldwide,[1,12] with a 27% decrease between 1990 and 2013. Deaths from noncommunicable diseases increased in the same period. In 2013, CHD accounted for the largest portion of global years of life lost (YLLs) and DALYs. Stroke was the third-ranking contributor to global YLLs and DALYs. On the other hand, in 1990, communicable diseases accounted for the largest portion of both YLLs and DALYs.

Despite the increase in overall CVD deaths, age-adjusted death rates decreased by 21.9% in the same period, from 374 to 292 per 100,000 population, suggesting significant delays in age of occurrence and/or improvements in case-fatality rates. Unfortunately, not all countries appear to share in the reductions. Examination of regional trends is helpful in estimating global trends in the burden of disease, particularly CVD. Because 85% of the world's population lives in LMICs, these countries largely drive global CVD rates. These estimates depend on modeling mortality rates in areas where established death certification–based vital registration systems do not cover an entire country. Even as age-adjusted rates have been falling globally, the pattern is different when assessed by income (**Fig. 1.4**) or by region (**Fig. 1.5**).

The magnitude of the peak of the CVD epidemic, and whether the peak has arrived at all, has a great range. Here we describe and highlight trends in the seven regions of the world as defined by the GBD project, which includes HICs as one grouping and divides the remaining LMICs into six geographic regions with a variety of subregions. The East Asia and Pacific, Europe and Central Asia, Latin America and Caribbean, and Middle East and North Africa Regions all saw declines in age-adjusted CVD mortality from 1990 to 2013. Sub-Saharan Africa had little change in its age-adjusted CVD mortality rates. South Asia was the only region that experienced a significant increase in the age-adjusted mortality rates.

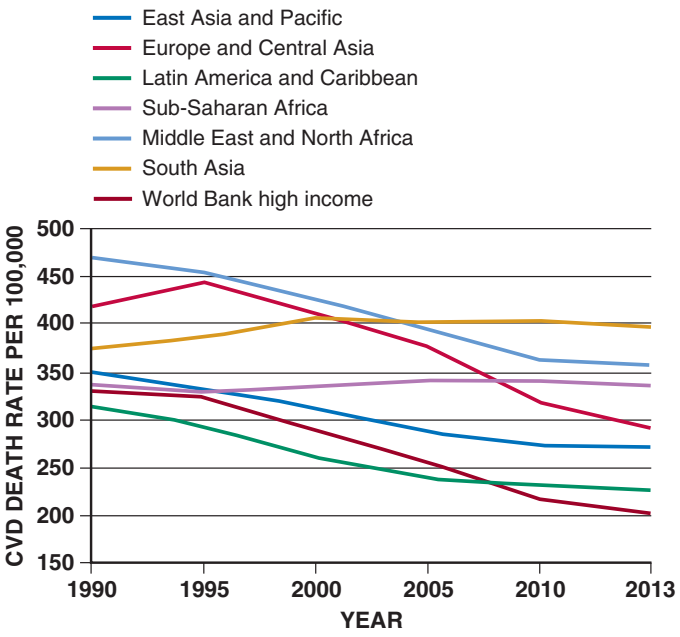

FIGURE 1.5 Cardiovascular disease death rates per 100,000 population from 1990 to 2013 in low- and middle-income countries by region, compared to World Bank high-income countries. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

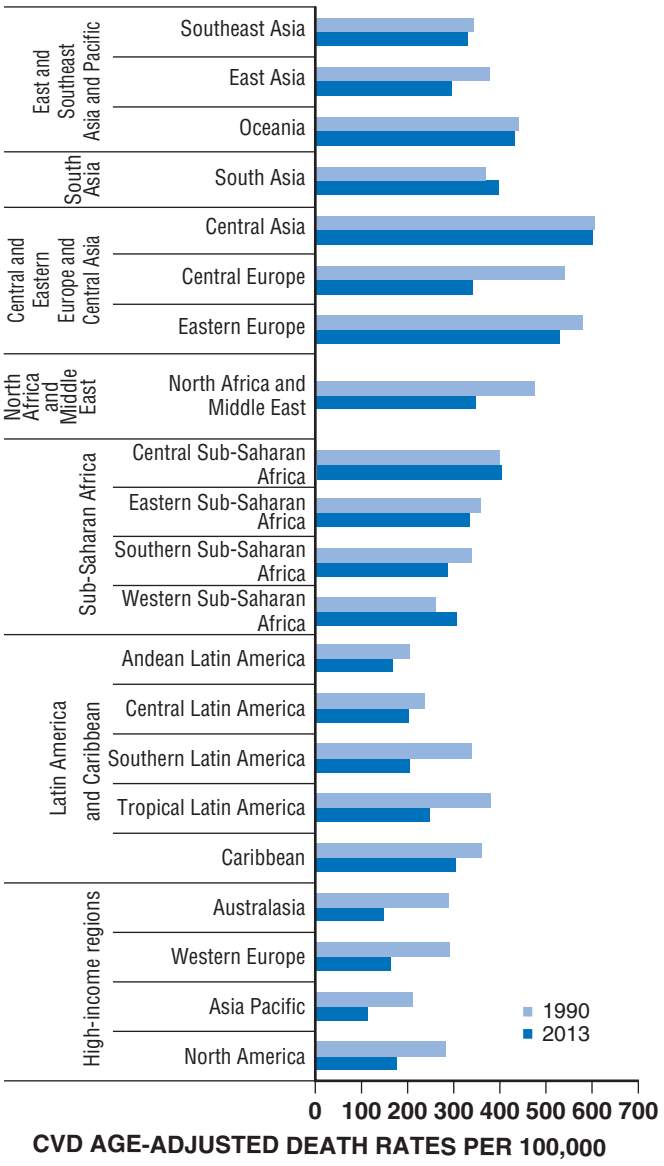

FIGURE 1.6 Age-adjusted death rates per 100,000 population for cardiovascular disease, 1990 and 2013. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

Much of the variation appears to relate to income, which is one proxy for the stages of the epidemiologic transition. Looking at age-adjusted CVD death rates by income reveals the different trends over the last two decades. In lower-income regions the death rates have increased from 340 per 100,000 in 1990 to 390 per 100,000 in 2013. Lower middle-income countries saw a small increase (416 to 432 per 100,000 deaths), followed by a decline to 400 per 100,000 population. Upper middle-income countries saw a 25% decline, from 392 per 100,000 in 1990 to 296 per 100,000. High-income countries had a nearly 37% decline, from 330 to 202 CVD deaths per 100,000.

The LMICs have a high degree of heterogeneity with respect to the phase of the epidemiologic transition. First, LMIC subregions differ by age-adjusted CVD death rates, as well as by trends over the last 20 years (**Fig. 1.6**). CVD mortality rates are increasing in most LMICs but are decreasing in HICs. Next, low- and middle-income subregions are unique, as illustrated by the different CVD disease rates by cause in each region (**Fig. 1.7**). Lastly, in the East Asia and Pacific and sub-Saharan Africa regions, stroke still exceeds CHD as a cause of CVD death. Hypertensive heart disease is the largest single contributor among remaining causes of CVD morbidity and mortality.

Variability in disease prevalence among various regions likely results from multiple factors. First, the countries are in various phases of the epidemiologic transition described earlier. Second, the regions may have cultural and genetic differences that lead to varying levels of CVD risk. For example, per capita consumption of dairy products (and thus consumption of saturated fat) is much higher in India than in China, although it is rising in both countries. Third, certain additional competing pressures exist in some regions, such as war or infectious diseases (HIV/AIDS) in sub-Saharan Africa.

Because CHD affects a younger population in LMICs, the number of deaths is increased in the working population. For some LMICs, the severity of the epidemiologic transition has appeared to follow a reverse social gradient, with members of lower socioeconomic groups having the greatest rates of CHD and the highest levels of various risk factors. Unfortunately, reductions in risk factors do not follow the same trend. Compared with people in the upper and middle socioeconomic strata, those in the lowest stratum are less likely to acquire and apply information on risk factors and behavior modifications or to have access to advanced treatment. Consequently, CVD mortality rates decline later among those of lower socioeconomic status.

High-Income Countries

In 2013, CVD accounted for almost 38% of all deaths in high-income regions, and CHD caused more than half of these deaths (**see Fig. 1.7**). The movement of most HICs through the epidemiologic transition, with rising levels of risk factors and CVD death rates until the 1970s and then declines in both over the next 40 years, resembles what occurred in the United States. CHD is the dominant form, with rates that tend to be twofold to fivefold higher than stroke rates. Two notable exceptions are Portugal, where stroke rates for both men and women exceed CHD rates, and Japan, where stroke causes many more fatalities than CHD. In both these countries, however, the pattern seems to be moving toward that seen in other HICs, with more rapid declines in stroke rates than in CHD rates.

Age-adjusted mortality for CVD declined in all HICs. This age-adjusted decline results largely from preventive interventions that allow people to avert disease, treatments to prevent death during an acute manifestation of disease (particularly stroke or MI), and interventions that prolong survival once CVD is manifest. Thus the average age at death from CVD continues to climb, and as a result, CVD affects a larger retired population.

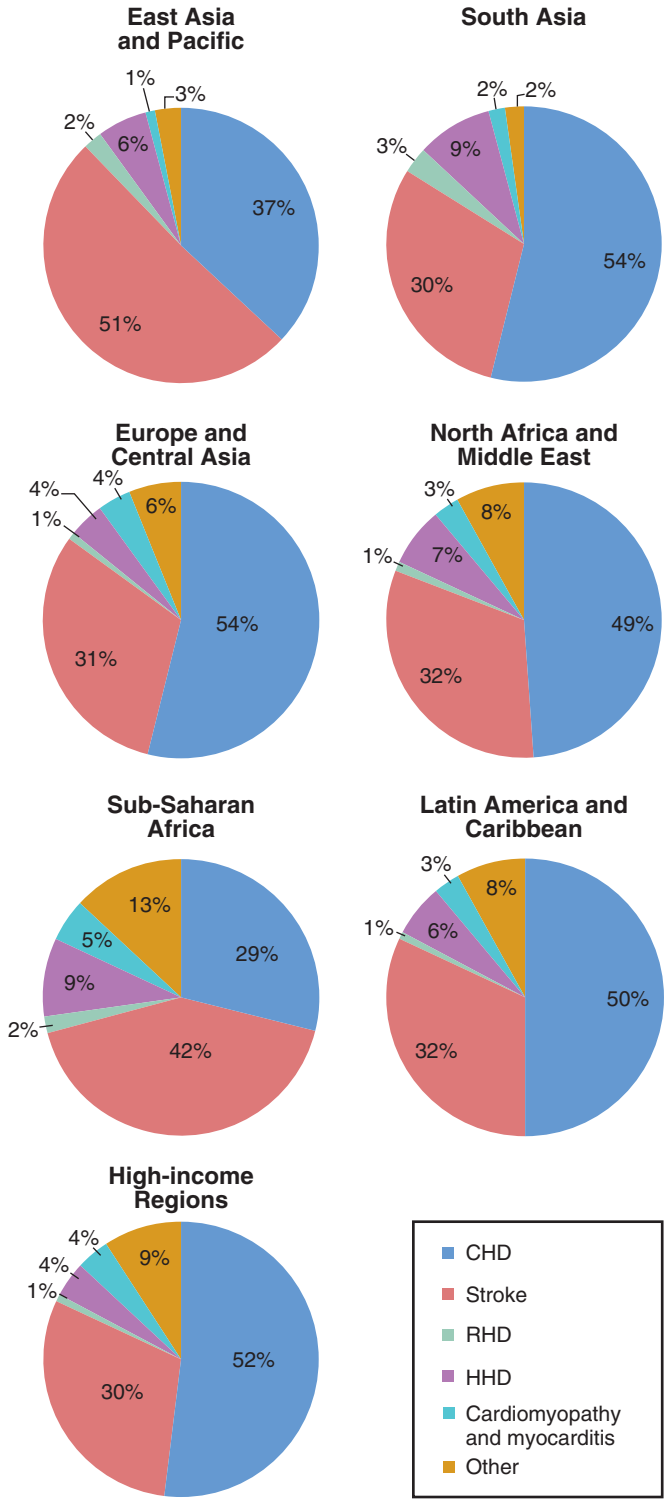

FIGURE 1.7 Cardiovascular disease death by specific cause and region. *CHD,* Coronary heart disease; *RHD,* rheumatic heart disease; *HHD,* hypertensive heart disease. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

Western Europe, with an overall CVD mortality rate of 344 per 100,000 in 2013 and an age-standardized rate of 163 per 100,000, had the highest mortality rates, whereas Australasia had the lowest overall (234/100,000) rate, and Japan had the lowest age-adjusted rate (110/100,000). As mentioned, high-income regions have higher mortality rates for CHD than for stroke. The exception is the East Asia and Pacific region, where overall death rates for stroke and CHD are 132 per 100,000 and 88 per 100,000, respectively. Mortality rates and number of deaths attributable to stroke and CHD increased in this region between 1990 and 2010; stroke rates increased by approximately 18%, whereas CHD rates increased by almost 40%.[12] Japan is unique among HICs; as its communicable disease rates fell in the early 20th century, its stroke rates increased dramatically. CHD rates, however, did not rise as sharply in Japan as in other industrialized nations and have remained lower than in any other industrialized country. Overall, CVD rates have fallen 60% in Japan since the 1960s, largely because of a decrease in age-adjusted stroke rates. Japanese men and women currently have the highest life expectancy in the world: 86.4 years for women and 79.6 years for men. The difference between Japan and other industrialized countries may stem in part from genetic factors, although the traditional Japanese fish- and plant-based, low-fat diet and resultant low cholesterol levels may have also contributed. Nevertheless, as in many other countries, dietary habits in Japan are undergoing substantial changes. Since the late 1950s, cholesterol levels have progressively increased in both urban and rural populations. Although the prevalence of CVD risk factors is increasing in the Japanese population, the incidence of coronary artery disease remains low and even declined.[13] This situation could change, however, because there seems to be a long lag phase before dietary changes manifest as CHD events.

East Asia and Pacific

Demographic and Social Indices

The East Asia and Pacific (EAP) region is the most populated low-income and middle-income region in the world, with almost 2 billion people; approximately 49% of the region is urban. The gross national income (GNI) per capita is $4243, ranging from $4420 in Thailand to $1130 in Laos. In 2004, total health expenditure was 4.8% of total gross domestic product (GDP), or $183 per capita.[14] The region is divided into three distinct subregions: Southeast Asia, East Asia, and Oceania. China is by far the most populated country, representing almost 70% of the region. Life expectancy has risen quickly across the EAP region in past decades, up to an average of 72 years. In China the increase has been dramatic: from 37 years in the mid-1950s to 73 years in 2010.[14] This increase associates with a large rural to urban migration pattern, rapid urban modernization, aging of the population, decreased birth rates, major dietary changes, increasing tobacco use, and a transition to work requiring low levels of physical activity.

Burden of Disease

CVD caused more than 5.2 million deaths in the EAP region in 2013, accounting for 38% of all deaths in the region. More than half of these deaths resulted from stroke, whereas only 31% were caused by CHD (**see Fig. 1.7**). CVD death rates differed significantly between subregions, most notably in Oceania. Age-adjusted mortality rates were highest in Oceania, at 439 per 100,000 in 2010, even though overall mortality for CVD was 205 per 100,000, suggesting that many premature deaths from CVD are occurring in Oceania.

Stroke and CHD lead as causes of death in the East Asia and Southeast Asia subregions. In Oceania, however, lower respiratory infections and diabetes account for the largest proportion of deaths. Whereas stroke and CHD rates increased in both East Asia and Southeast Asia, stroke rates decreased slightly in Oceania, from 40 to 36 per 100,000.[12] China appears to be straddling the second and third stages of a Japanese-like epidemiologic transition. Men in China age 50 to 69 have stroke death rates of 190 per 100,000, versus CHD death rates of 123 per 100,000.[1]

Central and Eastern Europe and Central Asia

Demographic and Social Indices

Of the three subregions that constitute this region—Central Asia, Central Europe, and Eastern Europe—Eastern Europe is the most populated. Russia alone accounts for more than 30% of the region's 404 million inhabitants. Sixty-five percent of the population in the region is urban, with an average life expectancy of 71 years. The average GNI per

capita for the region ranges from $870 in Tajikistan to $23,610 in Slovenia. Russia has a GNI of $10,400. On average, the region spends more than 6% of total GDP on public and private health care. Health expenditure per capita ranges from $49 per capita in Tajikistan to $2154 in Hungary. Russia spends about $525 per capita, or 5.1% of its GDP.[14]

Burden of Disease

The highest rates of CVD mortality occur in this region. Overall CVD mortality rates are 793 per 100,000 in Eastern Europe and 547 per 100,000 in Central Europe. Overall rates resemble or exceed those seen in the United States in the 1960s, when CVD peaked. CHD is generally more common than stroke, which suggests that the countries that constitute Eastern Europe and Central Asia remain largely in the third phase of the epidemiologic transition. As expected in this phase, people who develop and die of CVD have a lower average age than that in HICs. In 2013, CVD accounted for almost 60% of all deaths in the region, 55% of which resulted from CHD and 33% from stroke.

A country-level analysis reveals important differences in CHD profiles within the Central and Eastern Europe and Central Asia region (**see Fig. 1.3**). Since the dissolution of the Soviet Union, CVD rates have increased surprisingly in some of these countries, with the highest rates (almost 800 per 100,000 for men) in Ukraine, Bulgaria, Belarus, and Russia.[11] By 2013, this region had the highest CVD mortality rates in the world. Of note, deaths resulting from CHD in these countries affect not only older adults; the GBD study estimates that working-age populations (15 to 69 years) have a significant CHD burden. Almost one third of all deaths in persons age 45 to 49, for example, result from CVD. For people age 60 to 64, CVD accounts for half of all deaths, 27% of which are caused by CHD.[12]

Latin America and the Caribbean

Demographic and Social Indices

The Latin America and Caribbean (LAM) region comprises Andean Latin America, Central Latin America, Southern Latin America, Tropical Latin America, and the Caribbean. The region has a total population of 589 million, 79% of which is urban.[14] Brazil, the region's most populous country, represents one third of the population, with Argentina, Colombia, Mexico, Peru, and Venezuela making up another third. The Caribbean nations, including the Dominican Republic, Jamaica, and Haiti, account for less than 10% of the population in the region. Life expectancy in the LAM region is approximately 74 years but varies greatly. In 2010, for example, Haiti and Cuba had life expectancies of 64 years and 79 years, respectively. Average GNI per capita in the region is about $8544 (purchasing power parity [PPP] of $11,587). The region spends an average of 7.7% of its GDP on health care. This level of spending translates into health care expenditures that range from $46 per capita in Haiti to $1003 per capita in Barbados.[14]

Burden of Disease

The LAM region bears a substantial CVD burden. In 2013, CVD caused 29% of all deaths in the region. As in HICs, CHD dominates among circulatory diseases (**see Fig. 1.7**). Mortality rates vary significantly by subregion. The Caribbean has the highest age-standardized mortality rates for CHD and stroke: 150 deaths per 100,000 and 110 per 100,000, respectively. As with other global trends, overall mortality increased between 1990 and 2013, but age-adjusted mortality declined for this region. Death rates also increased in Central Latin America and Andean Latin America; similar increases in mortality occurred in Tropical Latin America. Together, CHD (14%), stroke (6.9%), and hypertensive heart disease (2.1%) accounted for almost one quarter of all deaths in Central Latin America in 2010. Southern Latin America, which includes Argentina, Chile, and Uruguay, was the only subregion to have declines in both overall and age-adjusted CVD mortality rates. Overall CVD, CHD, and stroke mortality rates decreased in this subregion between 1990 and 2010, but to a lesser extent than for global changes.[12] The lower reductions in the LAM region may result from rapid lifestyle changes: unfavorable dietary changes, increased smoking, increased obesity, and less exercise.

North Africa and the Middle East

Demographic and Social Indices

The 19 countries of the North Africa and Middle East region represent approximately 5% of the world's population (337 million people). Egypt and Iran are the two most populous countries in the region, with Egypt representing 24% of total inhabitants and Iran, 22%. Approximately 59% of the population is urban, with an average life expectancy of 72 years. The average GNI per capita for the region is $3869, ranging from $1070 in Yemen to $48,900 in Kuwait. Approximately 5.3% of the GDP, or approximately $203 per capita, is expended for health in the region. The per capita health expenditure ranges from $63 in Yemen to $1450 in the United Arab Emirates.[14]

Burden of Disease

Forty-two percent of all deaths in the North Africa and Middle East region result from CVD: 9% from CHD and 32% from stroke. The region has lower CVD mortality rates than global averages. In 2013 the overall death rate per 100,000 for CHD, stroke, and overall CVD were 89, 57, and 180, respectively. The mortality rate for CHD only declined marginally in the region since 1990, when the rates were 88, 62, and 192 deaths per 100,000 population, respectively. However, age-adjusted mortality rates for CVD declined by almost 25% across the region. In 2013, CVD accounted for 20 million DALYs lost, or 21% of all DALYs lost in the region. The DALYs lost were split differently between CHD and stroke, at 9.7 million and 5.7 million, respectively.[12]

South Asia

Demographic and Social Indices

The South Asia region (SAR), one of the world's most densely populated regions, accounts for about 24% of the world's population, with more than 1.6 billion residents. India, home to almost 75% of the region's inhabitants, is the largest country in the region. Only 31% of the region is urban, and life expectancy is approximately 65 years. Average GNI per capita for the region is $1299, ranging from $540 in Nepal to $6530 in Maldives. India's GNI per capita of $1410 sits near the regional average. Countries in the SAR spend an average of 3.9% of their total GDP, or $47 per capita, on health care. Maldives spends the most per capita at $208, and India spends $31, or 5% of its GDP. The lowest expenditures for health care are $22 per capita in Pakistan and $23 in Bangladesh.[14]

Burden of Disease

CVD accounts for 27% of all deaths in the SAR. CHD led causes of mortality in 2013—responsible for 15% of total reported fatalities, or 2 million deaths, and more than half of CVD mortality. Cerebrovascular disease accounted for 6.8% of all deaths and 30% of CVD deaths. The region loses almost 60.5 million DALYs from CVD, accounting for 10% of the total. CHD contributes 4.6% of the DALYs lost because of CVD, nearly twice as high as for stroke.[12] Mortality rates for CVD are increasing in the region.

CVD probably represents 31% of all deaths in India, the largest country in the SAR. Studies also show a higher CHD prevalence in men and in urban residents. The rise in CHD mortality contributes to the economic burden in the Indian subcontinent. Data indicate that symptoms of CHD arise 5 to 10 years earlier in this region than in Western European and Latin American countries.[15]

Sub-Saharan Africa

Demographic and Social Indices

The GBD study divides sub-Saharan Africa into four subregions: Central Africa, East Africa, Southern Africa, and Western Africa. Approximately 875 million people live in these four regions, with Nigeria being the most populous (163 million) and Cape Verde being the least populous (500,600). Only 36% of the population in the region is urban. The average GNI per capita is $1255, ranging from $250 in Burundi to $7480 in Botswana. Overall, the region also has the lowest average life expectancy—54 years.[14] Average public and private health care

expenditures for the region are 6.5% of the total GDP, or $84 per capita. The range of health care expenditures per capita for sub-Saharan Africa is similar to the GDP range for this region, from $3 in Burundi to $511 in Seychelles. Nigeria spends $23 per capita, or 4.6% of the total GDP.[14]

Burden of Disease

In Western Africa, CVD accounts for 7.5% of all deaths. The highest portion of CVD-caused deaths occurred in Southern Africa, where 13% of all deaths were caused by CVD. Mortality rates in the region are lower than global averages and are decreasing, in line with global trends. The exception is Southern Africa, where rates increased from 129 to 136 per 100,000. Communicable, neonatal, and maternal disorders still dominate causes of death in sub-Saharan Africa. Malaria and HIV/AIDS lead as causes of death, accounting for almost half of all deaths in the region.[12]

RISK FACTORS

Worldwide, CVD is largely driven by modifiable risk factors, such as smoking, lack of physical activity, and diets high in fat and salt (**see also Chapters 45 to 47 and 49 and 50**). Elevated levels of blood pressure (BP) and cholesterol remain the leading causes of CHD; tobacco, obesity, and physical inactivity remain important contributors as well. The GBD project estimated that the population-attributable fraction (PAF) for individual risk factors for CHD in LMICs in 2013 were as follows: high BP, 54%; high cholesterol, 32%; overweight and obesity, 18%; dietary intake, 67%; and smoking, 18%. Because factors may contribute to similar disease mechanisms, the sum exceeds 100%. Unique features regarding some CHD risk factors in LMICs are described next.

Tobacco

By many accounts, tobacco use is the most preventable cause of death in the world. More than 1.3 billion people use tobacco worldwide, with 5.8 trillion cigarettes smoked globally in 2014.[16] More than 80% of tobacco use occurs in LMICs, and if current trends continue unabated, tobacco will cause more than 1 billion deaths during the 21st century.

Tobacco use varies greatly across the world, as do deaths attributable to smoking in both sexes (**Fig. 1.8**). Although historically greatest in HICs, tobacco consumption has shifted dramatically to LMICs in recent decades; some of the highest tobacco use now occurs in the EAP region. Kiribati has the highest prevalence of age-adjusted tobacco use in the world: 71.0% in men and 42.9% in women. Indonesia has similarly high rates (>60% prevalence in men). China is the largest consumer of tobacco in the world, with an estimated 301 million smokers in 2010 (>50% prevalence in men). Smoking rates have increased in China by 50% since 1980. Several countries in the Central and Eastern Europe regions also have alarmingly high prevalence rates, including Russia (approximately 60.0% in men and 24.3% in women), Ukraine (>50% prevalence in men), and Albania (60% prevalence in men). Latin America, the Middle East, and North Africa have high rates as well, although smoking is not as common among women in these regions as it is in the Pacific region. Countries in sub-Saharan Africa have some of the lowest prevalence rates; Niger and Ethiopia, for example, have less than 10% and 1% prevalence in men and women, respectively.

Women also have a high—and increasing— smoking prevalence in several countries, including Kiribati (42.9%), Austria (45.1%), Nauru (50%), and Greece (41.4%). In general, however, considerably more men than women smoke. Exceptions to this pattern include Nauru and Greece, which have comparable tobacco use prevalence in men and in women. Where they do occur, variations by sex can be substantial. In China, for example, tobacco use prevalence is 50% in men but only 2.2% in women. Indonesia has similarly diverging trends: prevalence in men is 61.3% and only 5.1% in women. Significant variations also occur in North Africa, the Middle East, and some countries in sub-Saharan Africa. Tobacco use is generally less than 1% in women in these regions but is much higher in men.

Other forms of tobacco use increase risk for CHD. Bidis (hand-rolled cigarettes common in South Asia), kreteks (clove and tobacco cigarettes), hookah pipes (water pipes used for smoking flavored tobacco), and smokeless tobacco all link to increased CHD risk.[17] The combined use of different forms of tobacco associates with a higher risk of MI than using one type.

Secondhand smoke also contributes to CHD risk. In 2011, approximately 600,000 nonsmokers died as a consequence of exposure to secondhand smoke. A retrospective analysis of 192 countries found that the largest portion of secondhand smoke–related deaths in 2004 resulted from ischemic heart disease.[18] Smoking bans have both immediate and long-term effects in reducing admissions for acute coronary syndrome (ACS). In Ireland, implementation of a country-wide smoking ban in workplaces decreased ACS-related hospital admissions promptly by 12%, and after 2 years, such admissions decreased by an additional 13%.[19]

Hypertension

Elevated BP is an early indicator of epidemiologic transition. Rising mean population BP occurs as populations industrialize and move from rural to urban settings. Worldwide, approximately 62% of strokes and 49% of CHD cases are attributable to suboptimal (>115 mm Hg systolic) BP, a factor thought to account for more than 7 million deaths annually. The GBD project estimates that 19% of deaths and 9% of DALYs lost globally result from nonoptimal levels of BP.[20] The high rate of undetected, and therefore untreated, hypertension presents a major concern in LMICs. The high prevalence of undetected and untreated hypertension probably drives the elevated rates of hemorrhagic stroke throughout Asia.

The most recent update of the GBD study analyzed mean systolic BP between 1980 and 2008 using multiple published and unpublished health surveys and epidemiologic studies. The analysis, which applied a bayesian hierarchical model to each sex by age, country, and year, found a global decrease in mean systolic BP between 1980 and 2008 in both men and women.[21] Worldwide, the age-standardized prevalence of uncontrolled hypertension has decreased from 33% to 29% in men and from 29% to 25% in women. However, the number of people with uncontrolled hypertension (systolic BP ≥140 mm Hg) has increased; in 1980, 605 million had uncontrolled hypertension, and by 2008, the number increased to 978 million. The trend results largely from population growth and aging. Globally, mean systolic BP has decreased by 0.8 mm Hg per decade among men and by 1.0 mm Hg per decade among women. In 2008, age-standardized mean systolic BP values worldwide were 128.1 mm Hg in men and 124.4 mm Hg in women.

The proportion of CVD deaths attributable to BP by country in 2013 varied by gender (**Fig. 1.9**). The highest mean systolic BP in 2013 occurred in East and West African countries, where both men and women had systolic BP levels that were significantly higher than global averages. In Mozambique and in São Tomé and Príncipe, for example, mean systolic BP in women was 135.4 mm Hg and 136.3 mm Hg, respectively. In men, mean systolic BP was as high as 137.5 mm Hg in Mozambique and 139.4 mm Hg in Niger. Men in Eastern Europe had mean systolic BP levels comparable to those in East and West Africa. Mean systolic BP was lowest in high-income regions such as Australasia (117.4 mm Hg in Australian women) and North America (123.3 mm Hg in U.S. men).

The most significant decreases occurred in high-income regions, where mean systolic BP decreased by 2.4 mm Hg per decade in men and 3.1 mm Hg per decade in women. The decrease in men ranged from 1.7 to 2.8 mm Hg per decade, with the greatest decrease occurring in the North America subregion. The decrease in mean systolic BP in women ranged from 2.3 mm Hg per decade in North America to 3.9 mm Hg per decade in Australasia.

Mean systolic BP increased in several regions. In South Asia, systolic BP increased by 0.8 mm Hg per decade in men and 1.0 mm Hg per decade in women. Southeast Asia saw similar increases: 0.9 mm Hg per decade in men and 1.3 mm Hg per decade in women. In East

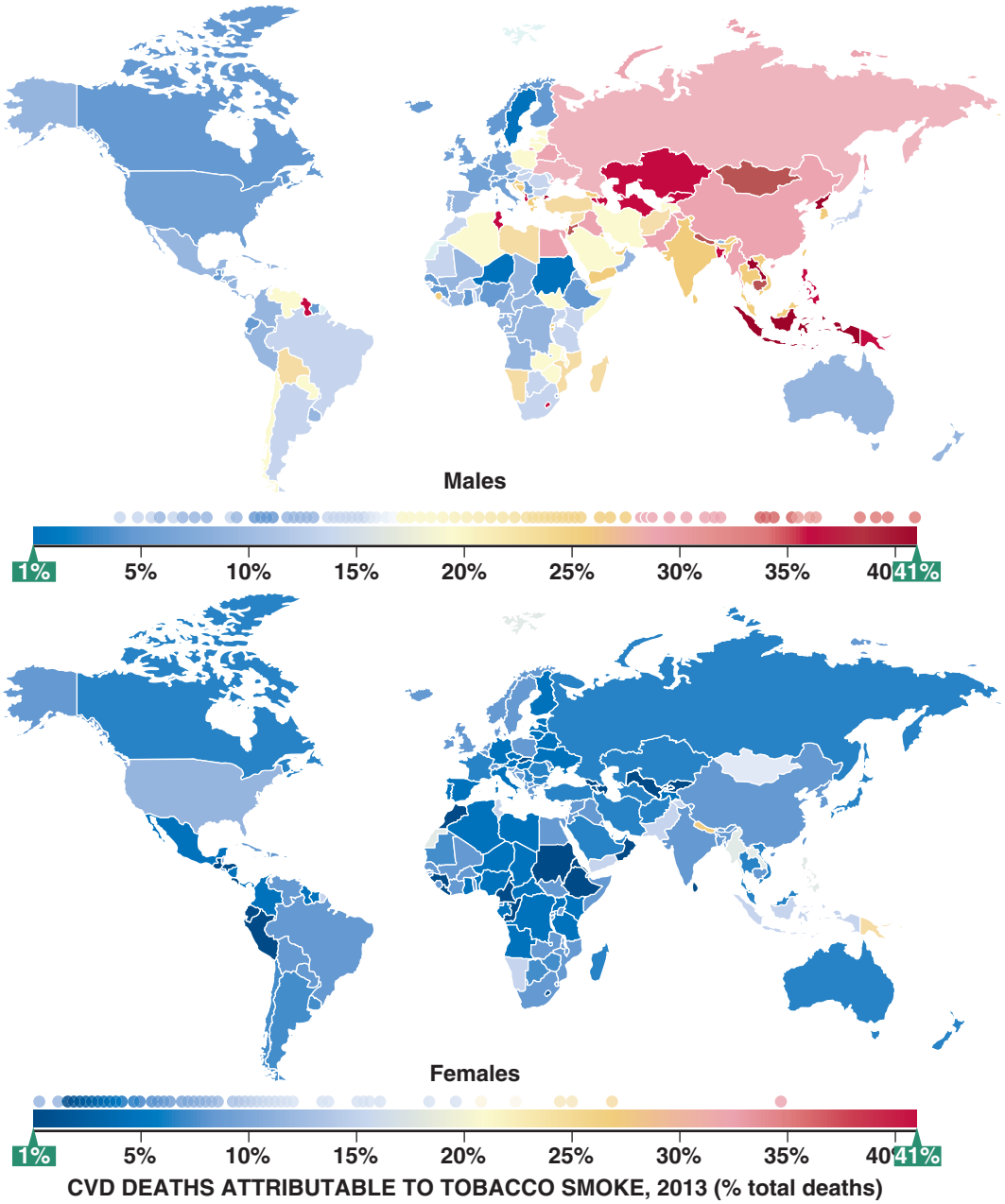

FIGURE 1.8 Cardiovascular disease mortality attributable to tobacco smoke in 2013, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

Africa, mean systolic BP increased by 1.6 mm Hg per decade in men and 2.5 mm Hg per decade in women. The most significant increases in men occurred in East Africa (1.6 mm Hg per decade). In women, mean systolic BP increased the most in Oceania (2.7 mm Hg per decade).

Notable sex differences occurred in Oceania and West Africa. In Oceania, mean systolic BP in women increased by 2.7 mm Hg per decade, the largest increase in any female cohort in the world. In men in this region, however, mean systolic BP increased by only 1.2 mm Hg per decade. Data from West Africa show diverging trends in men and women: although mean systolic BP in men decreased by 0.4 mm Hg per decade, it decreased in women by 2.5 mm Hg.

Lipids

Worldwide, high cholesterol causes about 56% of ischemic heart disease and 18% of strokes, accounting for 4.4 million deaths annually. Unfortunately, most LMICs have limited data on cholesterol levels (often only total cholesterol). In HICs, mean population cholesterol levels are generally decreasing, but in LMICs, these levels vary widely. As countries move through epidemiologic transition, mean population plasma cholesterol levels typically rise. Changes accompanying urbanization clearly play a role, because urban residents tend to have higher plasma cholesterol levels than rural residents. This shift results largely from greater consumption of dietary fats, primarily from animal products and processed vegetable oils, and decreased physical activity.

Globally, mean serum total cholesterol levels have decreased.[22] The GBD study analyzed data between 1980 and 2008 using a bayesian model to estimate mean total cholesterol by age, country, and year. Age-standardized mean total cholesterol was 4.64 mmol/L (179.6 mg/dL) in men and 4.76 mmol/L in women in 2008 (184.2 mg/dL). CVD death rates attributable to cholesterol have changed between 1990 to 2013, with most of the larger LMICs (China, India, Brazil) worsening and most HICs improving (**Fig. 1.10**). In 2008 the combined regions of Australasia, North America, and Western Europe had a mean total

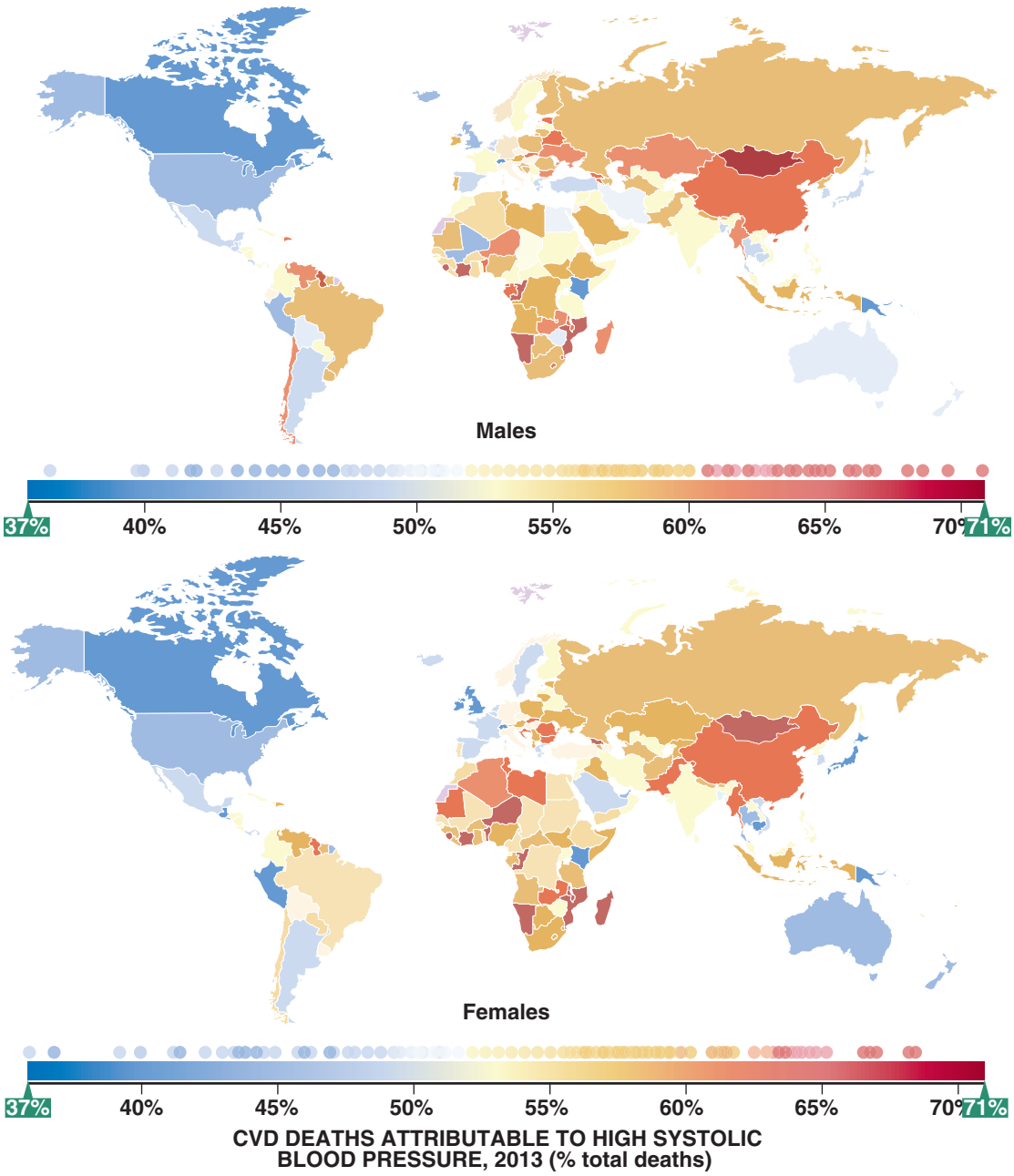

FIGURE 1.9 Cardiovascular disease mortality attributable to high systolic blood pressure in 2013, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

cholesterol of 5.24 mmol/L in men and 5.23 mmol/L in women. In Greenland, mean total cholesterol was as high as 5.7 mmol/L for both sexes. Sub-Saharan Africa had the lowest levels for both sexes. Some cohorts, primarily men in Southern African countries such as Liberia, Nigeria, and Burkina Faso, had levels less than 4.0 mmol/L.

Between 1980 and 2008, mean total cholesterol levels decreased by 0.08 mmol/L per decade in men and by 0.07 mmol/L per decade in women. The most significant decreases in cholesterol levels occurred in the Central Europe, Eastern Europe, and Central Asia regions: 0.23 mmol/L per decade in men and 0.24 mmol/L per decade in women. The high-income regions of Australasia, North America, and Western Europe had similarly large decreases in cholesterol levels: 0.19 mmol/L per decade in men and 0.21 mmol/L per decade in women. Countries such as Finland and Sweden had notably faster decreases in cholesterol levels than other Western European countries.

Several exceptions to the worldwide downward trend in cholesterol levels occurred. In the EAP region, levels increased by 0.08 mmol/L per decade in men and by 0.09 mmol/L per decade in women. The high-income Asia-Pacific subregion showed a similar trend, but the increase was more moderate (≤0.1 mmol/L per decade). South Korea demonstrated no change in cholesterol levels. Singapore data were also notable: In the 1980s, cholesterol levels decreased for both men and women, but beginning in 2000, the downward trend ended in men. In women the trend reversed, increasing from 4.7 mmol/L in 2000 to 5.3 mmol/L in 2008. Several regions, including North Africa and Middle East, sub-Saharan Africa, and South Asia, showed no notable change in cholesterol levels, in part because of a lack of available historical data. In general, women in LMIC subregions had higher total cholesterol than their counterparts in HICs.

Diabetes

Diabetes prevalence has grown rapidly worldwide in the past 30 years. As a result, death rates for CVD attributable to diabetes have increased

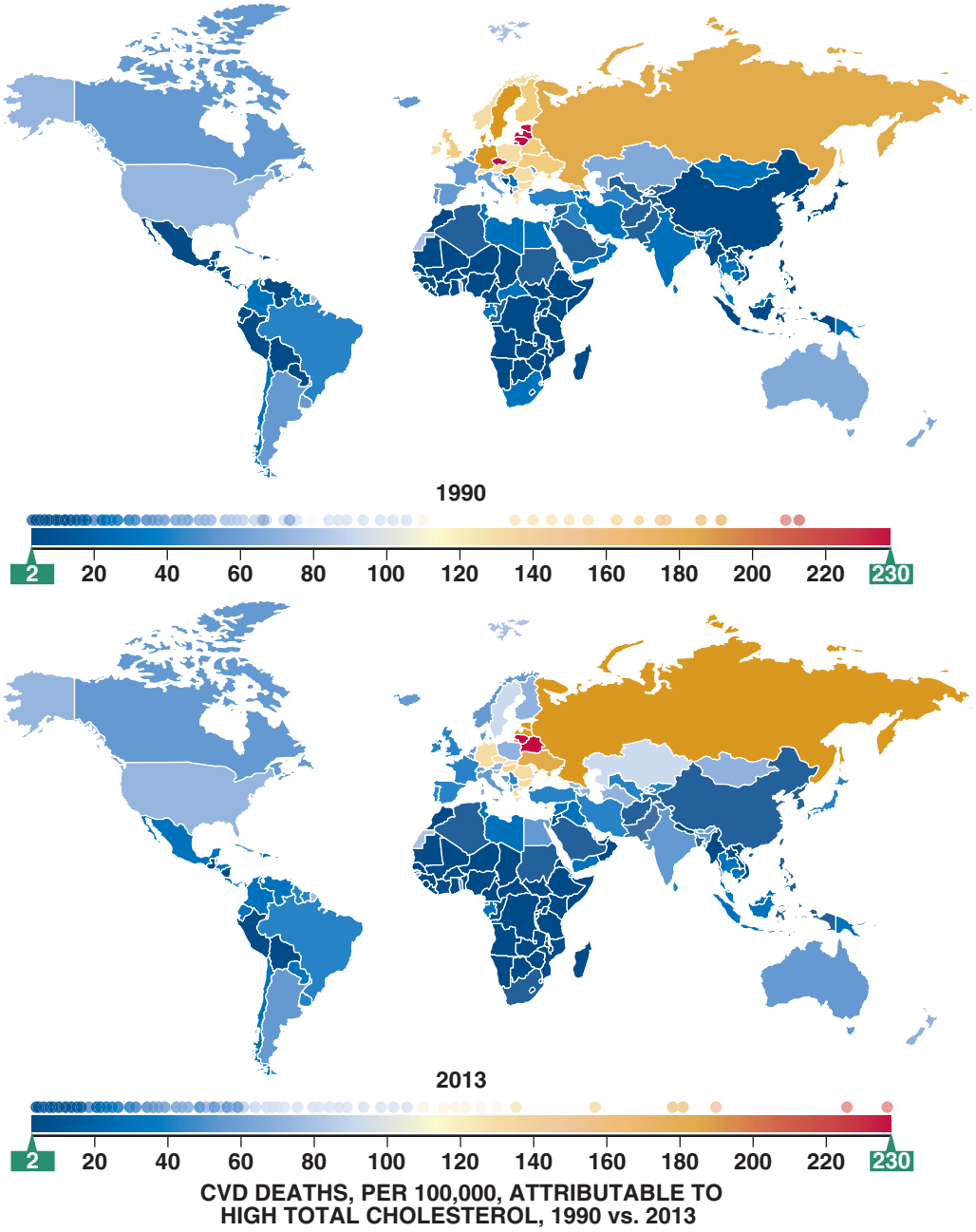

FIGURE 1.10 Cardiovascular disease mortality attributable to high total cholesterol, deaths per 100,000, 1990 versus 2013. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

for many LMICs, particularly in East Asia, South Asia, and Eastern Europe and Central Asia (**Fig. 1.11**). According to the GBD study, an estimated 346 million people worldwide have diabetes.[23] The more expansive International Diabetes Foundation (IDF) definition—which, in addition to fasting plasma glucose (FPG) as in the GBD study, includes oral glucose tolerance and hemoglobin A_{1c} tests—found that 366 million people had diabetes in 2011. Almost 50% of these cases were undiagnosed. By 2030 the number of people with diabetes is expected to increase to 522 million. This rise is estimated to occur at 2.7% annually, a higher growth rate than that of the total world adult population.

Eighty percent of people with diabetes live in LMICs. The highest regional prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 12.5% of the adult population (20 to 79 years of age) has diabetes. Pacific island and Middle Eastern countries have the highest prevalence, with age-adjusted prevalence ranging from 18.8% to 25.4%. Future growth will be concentrated in LMICs, especially in regions such as sub-Saharan Africa, Middle East and North Africa, and Southeast Asia.[24] In addition, a majority of cases will remain within those age 45 to 64 in LMICs, whereas those older than 65 are most affected in HICs. Rising rates of obesity, aging, and urbanization of the population are likely related to the diabetes epidemic. Almost 90% of type 2 diabetes cases are associated with obesity, and diabetes and its related complications are the costliest consequence of obesity. Mortality from diabetes is also increasing, with approximately 4.6 million deaths in 2011.

Asian countries face a relatively larger burden of diabetes compared with the Europe and Central Asia or Latin America and Caribbean regions. India and China, for example, have the largest numbers of people with diabetes in the world: 61.3 million and 90 million, respectively. Asian populations may have a higher risk for developing diabetes even at a lower body mass index (BMI), because of a greater tendency toward visceral obesity. In addition, this population may experience both undernutrition (during the perinatal period) and rapid weight gain (during childhood), a combination that increases the risk for insulin resistance.[25]

The most recent GBD study found a global increase in mean FPG. The study analyzed multiple published and unpublished health surveys and epidemiologic studies by applying a bayesian hierarchical model for each sex by age, country, and year. Between 1980 and 2008, mean FPG increased by 0.07 mmol/L (1.26 mg/dL) per decade in men and 0.08 mmol/L (1.44 mg/dL) per decade in women. The upward trend in FPG was nearly universal.[23] In almost every region worldwide, mean FPG increased or remained unchanged; regions that displayed apparent decreases (e.g., men in the East Asia and Southeast Asia region) were not statistically different from flat trends (posterior probabilities ≤0.80).

Although some regions had unchanging mean FPG levels, other regions, including southern and tropical Latin America, Oceania, and high-income regions, experienced significant increases. The most notable region is Oceania; between 1980 and 2008, mean FPG increased by 0.22 mmol/L per decade in men and 0.32 mmol/L per decade in women. By 2008, Oceania had the highest mean FPG for both sexes (6.09 mmol/L for men, 6.09 mmol/L for women) and the highest prevalence of diabetes (15.5% in men, 15.9% in women) in the world.

In addition to Oceania, the Caribbean and North Africa and the Middle East have the highest mean FPG levels worldwide: 21% to 25% of men and 21% to 32% of women in these countries have diabetes. By contrast, men in sub-Saharan Africa and women in Asia-Pacific

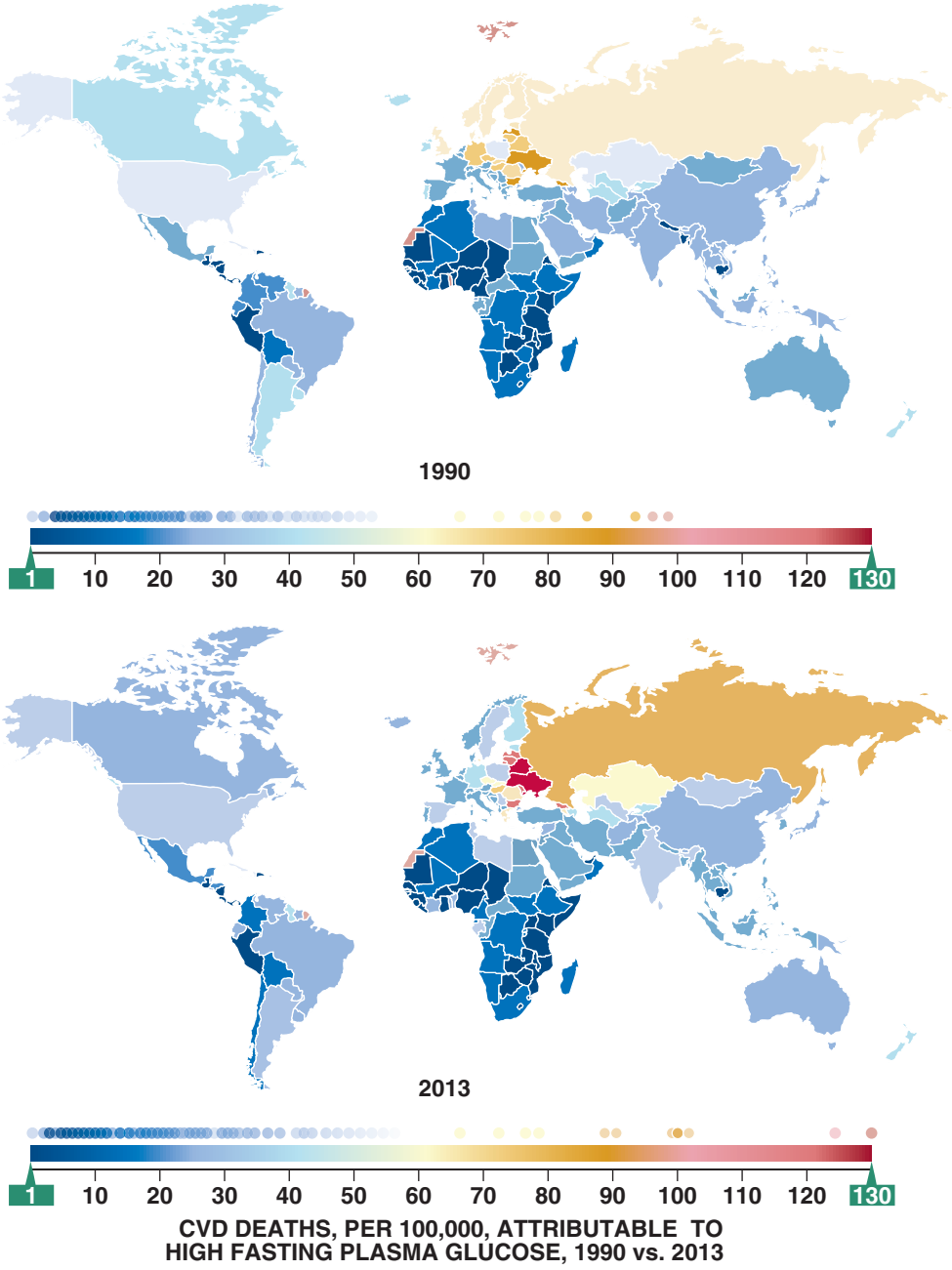

FIGURE 1.11 Cardiovascular disease mortality attributable to high fasting plasma glucose, deaths per 100,000, 1990 versus 2013. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

HICs had the lowest mean FPG in 2008: 5.27 mmol/L and 5.17 mmol/L, respectively. The only significant decrease in mean FPG occurred in women in Singapore, where levels fell by 0.21 mmol/L per decade.

Trends in mean FPG also varied by sex. In sub-Saharan Africa, for example, mean FPG increased by 0.05 mmol/L per decade in men, but by 0.13 mmol/L per decade in women. The Central Asia, North Africa, and Middle East region had similar differences in sex: mean FPG increased by 0.06 mmol/L per decade in men and by 0.16 mmol/L per decade in women.

Obesity

Obesity is increasing throughout the world and particularly in LMICs, which have steeper trajectories than in HICs. According to the latest GBD study, almost 1.46 billion adults were overweight (BMI ≥25 kg/m^2) in 2008; of these, approximately 502 million were obese (BMI ≥30 kg/m^2).[26] Explanations for this rapid rise include changes in dietary patterns, physical activity, and urbanization. Popkin and colleagues[27] report that the use of edible oils, caloric sweeteners, and animal-source foods is increasing. Annual animal food consumption tripled in China from the 1950s to 1990s. Physical activity declines as urbanization leads to increased use of motorized vehicles and a change to more sedentary occupations.

Unlike data from the 1980s, which showed that obesity affected predominantly the higher-income group in LMICs, a recent analysis shows a shift to the poor in the burden of overweight and obesity. Although higher-income groups still have the highest prevalence of overweight and obesity, rates are increasing faster in lower-income groups.[28] The poor are relatively more susceptible to obesity as a developing country's GNP approaches the middle-income range.[28,29] Higher GDP is also associated with faster rates of increase in the prevalence of overweight and obesity in lower-income groups.[28]

Women are more affected than men, with overweight women generally outnumbering underweight women, as indicated by data from LMICs.[26] In the same survey, prevalence of overweight women exceeded 20% in more than 90% of surveyed countries. Even rural areas in half the countries surveyed exhibited such rates. Adolescents are at particular risk: 19% of U.S. adolescents are obese.[30] The number of overweight children is increasing in countries as diverse as China, Brazil, India, Mexico, and Nigeria. According to the most recent World Health Organization (WHO) estimates, 40 million children younger than 5 years are overweight. Brazil saw an alarming rise, from 4% to 14% over a two-decade period. In 1980 the worldwide obesity prevalence rate was 4.8% in men and 7.9% in women. By 2008, prevalence rates had almost doubled, to 9.8% in men and 13.8% in women.

Globally, BMI rose in both men and women. The GBD study analyzed published and unpublished health examination surveys and epidemiologic studies (linear regressions were developed to estimate mean BMI from overweight or obesity prevalence, when available) and found that between 1980 and 2008, global BMI rose by 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women.

BMI varied substantially between regions and by sex and over time. In more than two thirds of the countries, the contribution of obesity to attributable burden of CVD death rates worsened. The majority of countries that improved were from HICs, although some were from each of the LMICs that saw improvements except from South Asia (**Fig. 1.12**). In 2008 the age-standardized mean BMI in the United States was 28.5 kg/m^2 in men and 28.3 kg/m^2 in women. In contrast with the United States and other HICs with similarly high BMIs, the sub-Saharan Africa and Asia regions have some of the lowest mean BMIs. Men in Ethiopia, for example, have a mean BMI of 20.2 kg/m^2, and women in Bangladesh have a mean BMI of 20.5 kg/m^2.