BRAUNWALD'S HEART DISEASE

A Textbook of Cardiovascular Medicine

VOLUME I

NINTH EDITION

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Dedication

We are proud to dedicate the ninth edition of *Braunwald's Heart Disease* to its founder, Eugene Braunwald, MD. The first edition of this work, published 30 years ago, established a standard of excellence that is rarely, if ever, achieved in publishing. Dr. Braunwald personally wrote half of the book and expertly edited the rest. He did the same for the next four editions, taking a 6-month sabbatical every 4 to 5 years to accomplish that. For the sixth edition, published in 2001, he invited two of us (PL, DPZ) to share the experience with him, increasing the editors by one (ROB) for the seventh edition. A new editor (DLM) joined for the eighth edition, and Dr. Braunwald no longer directly participated in the day-to-day editing of the print text, while still contributing some of the key chapters. However, he kept his finger on the pulse of the text and for that edition began *twice-weekly* electronic updates. Incorporating the most recent research, reviews, and opinions into the electronic text has continued through this ninth edition, making *Braunwald's Heart Disease* truly a living work and setting it apart from other texts. Dr. Braunwald, through his research, teaching, and mentorship, has shaped much of contemporary cardiovascular medicine, and it is with gratitude and admiration that we dedicate this edition of *his work* to him.

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PREFACE TO THE NINTH EDITION

Advances in cardiovascular science and practice continue at a breathtaking rate. As the knowledge base expands, it is important to adapt our learning systems to keep up with progress in our field. We are pleased to present the ninth edition of *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine* as the hub of an ongoing, advanced learning system designed to provide practitioners, physicians-in-training, and students at all levels with the tools needed to keep abreast of rapidly changing scientific foundations, clinical research results, and evidence-based medical practice.

In keeping with the tradition established by the previous editions of *Braunwald's Heart Disease*, the ninth edition covers the breadth of cardiovascular practice, highlighting new advances and their potential to transform the established paradigms of prevention, diagnosis, and treatment. We have thoroughly revised this edition to keep the content vibrant, stimulating, and up-to-date. Twenty-four of the 94 chapters are entirely new, including nine chapters that cover topics not addressed in earlier editions. We have added 46 new authors, all highly accomplished and recognized in their respective disciplines. All chapters carried over from the eighth edition have been thoroughly updated and extensively revised. This edition includes nearly 2500 figures, most of which are in full color, and 600 tables. We have continued to provide updated sections on current guidelines recommendations that complement each of the appropriate individual chapters.

A full accounting of these changes in the new edition cannot be addressed in the space of this Preface, but we are pleased to present a number of the highlights. The ninth edition includes two entirely new chapters—ethics in cardiovascular medicine by Paul Mueller and design and conduct of clinical trials by Elliot Antman—that supplement the initial section on the fundamentals of cardiovascular disease. Thomas Gaziano has joined J. Michael Gaziano in authoring the first chapter on the global burden of cardiovascular disease. With recognition of the increasing relevance of genetics, J.G. Seidman joins Reed Pyeritz and Christine Seidman in the updated chapter on inherited causes of cardiovascular disease, and David Tester and Michael Ackerman have contributed a new chapter on the genetics of cardiac arrhythmias.

Acknowledging the unremitting burden and societal impact of heart failure, the section on heart failure receives continued emphasis and has undergone extensive revision, including five new chapters. Barry Greenberg teams with Andrew Kahn in addressing the clinical approach to the patient with heart failure; Mihai Georghiade, Gerasimos Filippatos, and Michael Felker provide a fresh look at the evaluation and management of acute heart failure; Michael Acker and Mariell Jessup address advances in surgical treatment the failing heart; Mandeep Mehra and Bartley Griffith discuss the role of device therapy in assisted circulation; and William Abraham reviews the emerging role of devices for monitoring and managing heart failure.

The chapters that address cardiovascular imaging have kept abreast of all of the exciting advances in this field. Raymond Kwong and Allen Taylor have written excellent and comprehensive new chapters on cardiac magnetic resonance and cardiac computed tomography, respectively, with accompanying sections addressing the American College of Cardiology appropriate use criteria for the use of these advanced technologies. Updated ACC appropriate use criteria also follow the chapters on echocardiography and nuclear cardiology. In addition, the imaging section has been further enhanced by the inclusion of two new chapters focusing on the evolving applications of intravascular ultrasound, authored by Jean-Claude Tardif and Philippe L'Allier, and cardiovascular molecular imaging, provided by Peter Libby, Farouc Jaffer, and Ralph Weissleder.

In recognition of the growing importance of atrial fibrillation in cardiovascular practice, a new chapter devoted to the evaluation and treatment of this rhythm disturbance, authored by Fred Morady and Douglas Zipes, has been added to the section on cardiac arrhythmias. The other updated chapters in the heart rhythm section continue to inform our readers on the current state-of-the-art in this important aspect of heart disease.

Dariush Mozaffarian and Edzard Ernst have added expertly authored new chapters on nutrition and complementary medicine, respectively, to the section on preventive cardiology. In the atherosclerotic disease section, Marc Sabatine joins Chris Cannon in the revised discussion of the approach to the patient with chest pain, and William Boden joins David Morrow in a new chapter on stable ischemic heart disease. Deepak Bhatt teams with Jeffrey Popma in creating a new chapter on percutaneous coronary intervention, and he joins Andrew Eisenhauer and Christopher White in updating the discussion on endovascular treatment of noncoronary vascular disease. We welcome John Webb to our authorship team with his new chapter on catheter-based interventions in structural heart disease that includes discussion of the exciting novel catheter-based techniques for repair and replacement of cardiac valves. Our other new chapters include a fresh commentary on diseases of the aorta by Alan Braverman, Robert Thompson, and Luis Sanchez; diabetes and cardiovascular disease by Darren McGuire; hemostasis, thrombosis, and fibrinolysis by Jeffrey Weitz; and psychiatric and behavioral aspects of cardiovascular disease by Viola Vaccarino and Douglas Bremner. Finally, we are delighted that José Ramires, Andrei Sposito, Edécio Cunha-Neto, and Maria de Lourdes Higuchi have expanded our discussion of the global nature of cardiovascular disease by contributing an excellent chapter on the pathophysiology, evaluation, and treatment of Chagas' disease.

We are indebted to all of our authors for their considerable time, effort, and commitment to maintaining the high standards of *Braunwald's Heart Disease*. As excited as we are about bringing this edition of the text to fruition, we are even more energized regarding the expanding *Braunwald's Heart Disease* website. The electronic version of this work on the companion Expert Consult website includes greater content in terms of figures and tables than the print version can accommodate. Figures and tables can be downloaded directly from the website for electronic slide presentations. In addition, we have a growing portfolio of video and audio content that supplements the print content of many of our chapters. Dr. Braunwald personally updates the chapter content on a weekly basis, thus creating a truly unique living textbook with expanding content that includes the latest research, clinical trials, and expert opinion.

Moreover, the family of *Braunwald's Heart Disease* companion texts continues to expand, providing detailed expert content for the subspecialist across the broad spectrum of cardiovascular conditions. These include: *Clinical Lipidology*, edited by Christie Ballantyne; *Clinical Arrhythmology and Electrophysiology*, authored by Ziad Issa, John Miller, and Douglas Zipes; *Heart Failure*, edited by Douglas Mann; *Valvular Heart Disease*, by Catherine Otto and Robert Bonow; *Acute Coronary Syndromes*, by Pierre Théroux; *Preventive Cardiology*, by Roger Blumenthal, JoAnne Foody, and Nathan Wong; *Cardiovascular Nursing*, by Debra Moser and Barbara Riegel; *Mechanical Circulatory Support*, by Robert Kormos and Leslie Miller; *Hypertension*, by Henry Black and William Elliott; *Cardiovascular Therapeutics*, by Elliott Antman and Marc Sabatine; *Vascular Medicine*, by Marc Creager, Joshua

Beckman, and Joseph Loscalzo; and recent atlases on cardiovascular imaging such as *Cardiovascular Magnetic Resonance*, by Christopher Kramer and Gregory Hundley; *Cardiovascular Computed Tomography*, by Allen Taylor; and *Nuclear Cardiology*, by Ami Iskandrian and Ernest Garcia.

The ninth edition of *Braunwald's Heart Disease* does indeed represent the central hub of a burgeoning cardiovascular learning system that can be tailored to meet the needs of all individuals engaged in cardiovascular medicine, from the accomplished subspecialist practitioner to the beginning student of cardiology. *Braunwald's Heart Disease* aims to provide the necessary tools to navigate the ever-increasing flow of complex information seamlessly.

Robert O. Bonow

Douglas L. Mann

Douglas P. Zipes

Peter Libby

PREFACE—ADAPTED FROM THE FIRST EDITION

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous scourges—bubonic plague, yellow fever, and smallpox—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 causes, diagnosis, treatment, and prevention of heart disease is moving ahead rapidly.

In order to provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I chose to enlist 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.

Since the early part of the 20th 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. 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.

Eugene Braunwald
1980

PART I

FUNDAMENTALS OF CARDIOVASCULAR DISEASE

CHAPTER 1

Global Burden of Cardiovascular Disease

Thomas A. Gaziano and J. Michael Gaziano

Over the last decade, cardiovascular disease (CVD) has become the single largest cause of death worldwide. In 2004, CVD caused an estimated 17 million deaths and led to 151 million disability-adjusted life years (DALYs) lost—about 30% of all deaths and 14% of all DALYs lost that year.[1] Like many high-income countries during the last century, low- and middle-income countries are seeing an alarming increase in the rates of CVD, and this change is accelerating. In 2001, 75% of global deaths and 82% of total DALYs lost caused by coronary heart disease (CHD) occurred in low- and middle-income countries.[2]

This chapter reviews the features of the epidemiologic transition 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 and their regional variations and trends follows. The next section reviews the economic impact of CVD and the cost-effectiveness of various strategies to reduce it. The chapter ends with a discussion of the diverse challenges posed by the increasing burden of CVD for various regions of the world and potential solutions to this global problem.

Shifting Burdens

CVD now causes the most deaths in all developing regions with the exception of sub-Saharan Africa, where it leads causes of death in those older than 45 years. Between 1990 and 2001, of all deaths in low- and middle-income countries, deaths from CVD increased from 26% to 28%, a reflection of the rapid pace of the epidemiologic transition (**Fig. 1-1**). Within the six World Bank–defined low- and middle-income regions, there exist vast differences in the burden of CVD (**Fig. 1-2**), with CVD death rates as high as 58% in eastern Europe and as low as 10% in sub-Saharan Africa. These numbers compare with a CVD death rate of 38% in high-income countries.

Epidemiologic Transitions

Humans evolved under conditions of pestilence and famine and have lived with these for most of recorded history. Before 1900, infectious diseases and malnutrition constituted the most common cause of death in almost every part of the world. These conditions, along with high infant and child mortality rates, resulted in a mean life expectancy of approximately 30 years. But thanks largely to improved nutrition and public health measures, communicable diseases and malnutrition have declined and life expectancy has increased dramatically. Increased longevity and the impact of smoking, high-fat diets, and other risk factors for chronic diseases have now combined to make CVD and cancer the leading causes of death in most countries. These changes began in higher income countries, but as they gradually spread to low- and middle-income countries, CVD mortality rates have increased globally. In absolute numbers, CVD causes four to five times as many deaths in developing countries as in developed countries.

The overall increase in the global burden of CVD and the distinct patterns in the various regions result in part from the epidemiologic transition, which includes four basic stages (**Table 1-1**)[3,4]: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. 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 the low- and middle-income countries, it has also occurred more rapidly, driven largely by the transfer of low-cost agricultural technologies and public health advances.

The first stage, pestilence and famine, is characterized by the predominance of malnutrition and infectious disease and by the infrequency of CVD as a cause of death. CVD, which accounts for

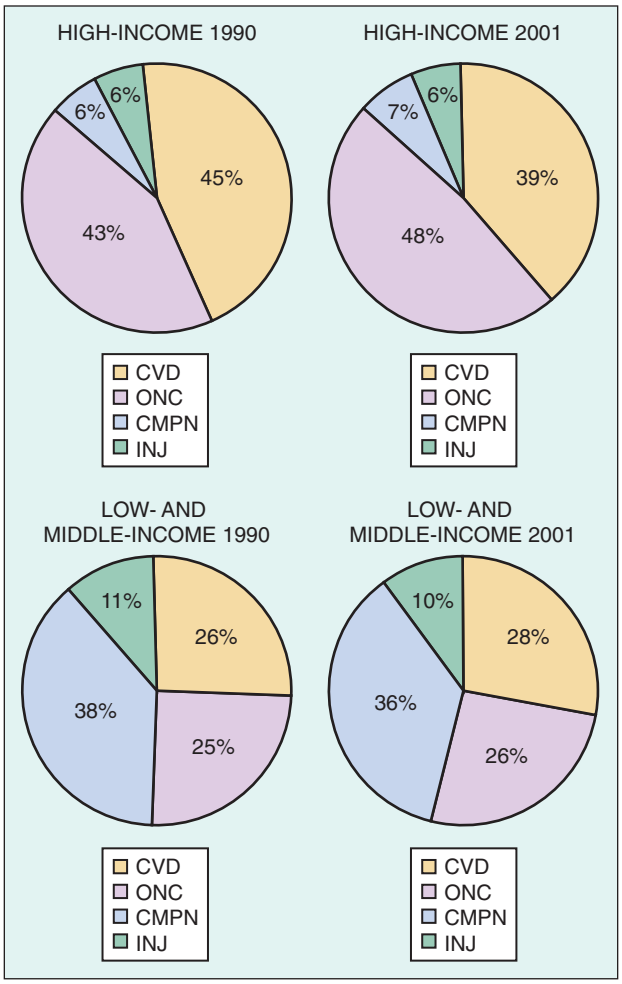

FIGURE 1-1 Changing pattern of mortality, 1990 to 2001. CMPN = communicable, maternal, perinatal, and nutritional diseases; CVD = cardiovascular disease; INJ = injury; ONC = other noncommunicable diseases. *(From Mathers CD, Lopez A, Stein D, et al: Deaths and disease burden by cause: Global burden of disease estimates for 2001 by World Bank Country Groups, 2005. Disease Control Priorities Working Paper 18 [http://www.dcp2.org/file/33/wp18.pdf].)*

less than 10% of deaths, takes the form of rheumatic heart disease and other cardiomyopathies caused by infection and malnutrition.

Per capita income and life expectancy increased during the age of receding pandemics as the emergence of public health systems, cleaner water supplies, and improved food production and distribution combined to drive down deaths from infectious disease and malnutrition. These advances, in turn, increased the productivity of the average worker, further improving the economic situation. The change most characteristic of this phase is a precipitous decline in infant and child mortality accompanied by a substantial increase in life expectancy. Rheumatic valvular disease, hypertension, and stroke cause most CVD. CHD often occurs at a lower prevalence rate compared with 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 as smoking. The increase in availability of foods with high saturated fat content coupled with decreased physical activity led 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 have remained the major causes of morbidity and mortality, with CVD accounting for 25% to 40% of all deaths. However, the age-adjusted CVD mortality rate has declined, aided by preventive strategies such as smoking cessation programs and effective blood pressure control, acute hospital management (including the use of coronary care units), and technologic advances such as invasive revascularization. Reductions in risk behaviors and factors may make even greater contributions to the decline in age-adjusted rates of death. In many cases, these result from concerted efforts by public health officials and health care communities. In other cases, secular trends play a role. For example, the widespread availability of fresh fruits and vegetables year-round in developed countries, and thus increased consumption, may have contributed to declining mean cholesterol levels before effective drug therapy was widely available. CHD, stroke, and congestive heart failure are the primary forms of CVD during this phase, with CHD remaining a significantly greater cause of death in all regions. Congestive heart failure dramatically increases as people live longer because of improved survival from myocardial infarction (MI). Japan and Portugal have been an exception to this transition, with rates of CHD never exceeding those of stroke. A further characteristic of the CVD transition in developed countries is that members of higher socioeconomic classes tend to pass through them first, whereas there is a lag for those of lower socioeconomic status.

TABLE 1-1 Four Typical Stages of the Epidemiologic Transition

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, malnutrition
Receding pandemics	Improvements in nutrition and public health leading 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 leading to emergence 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 major causes of morbidity, mortality; better treatment and prevention efforts help avoid deaths in those with disease, delay primary events; age-adjusted CVD mortality declines; CVD affecting older and older individuals	40-50	CHD, stroke, congestive heart failure

Modified from Omran AR: The epidemiologic transition: A theory of the epidemiology of population change. Milbank Q 49:509, 1971; and Olshansky SJ, Ault AB: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. Milbank Q 64:355, 1986.

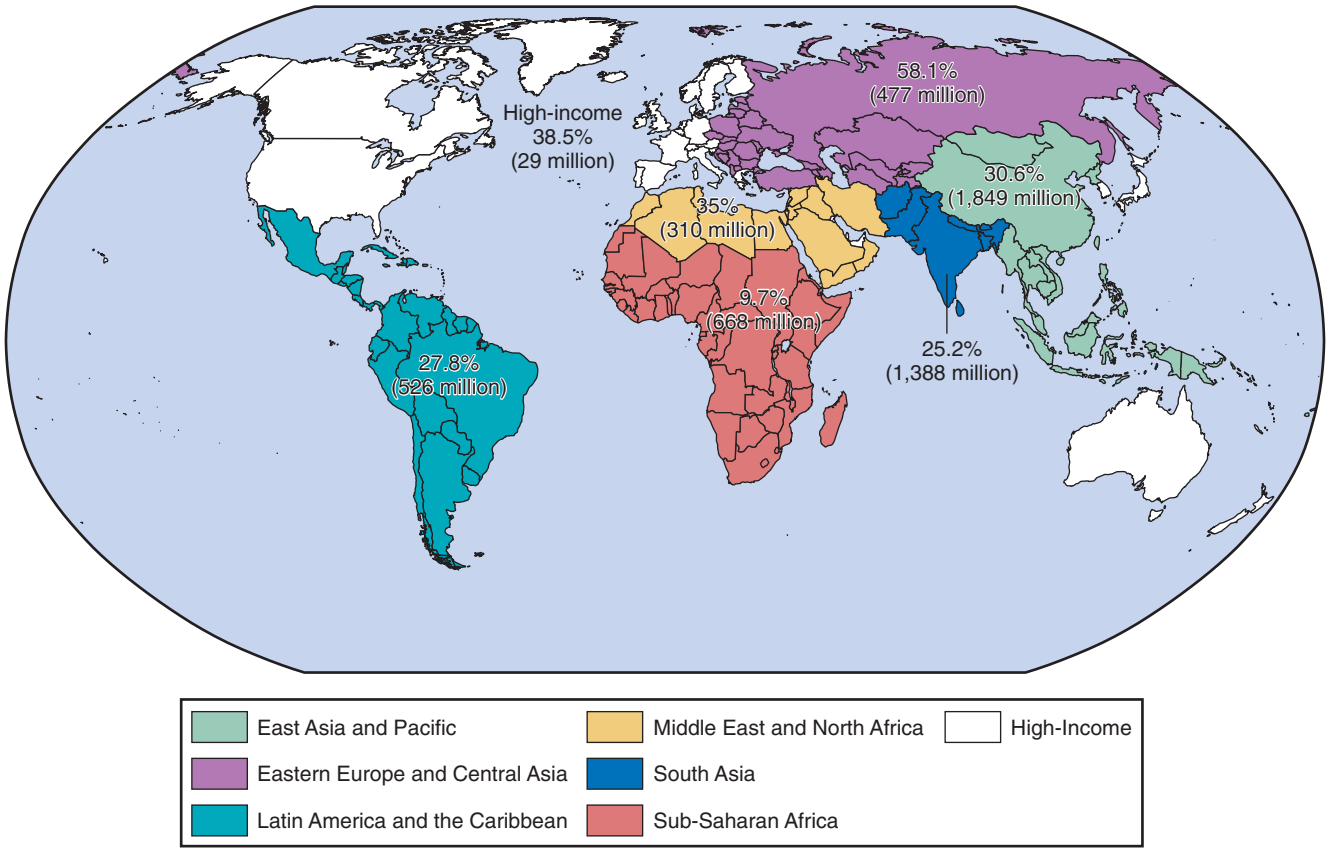

FIGURE 1-2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2001. *(Data from Mathers CD, Lopez A, Stein D, et al: Deaths and disease burden by cause: Global burden of disease estimates for 2001 by World Bank Country Groups, 2005. Disease Control Priorities Working Paper 18 [http://www.dcp2.org/file/33/wp18.pdf].)*

Is There a Fifth Phase: Age of Inactivity and Obesity?

Troubling trends in certain risk behaviors and risk factors may foreshadow a new phase of the epidemiologic transition, the age of inactivity and obesity.[5] 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. As a consequence, rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are rising, trends that are particularly evident in children.[6,7] These changes are occurring at a time when 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 developed countries, could level or even increase in the coming years. This trend pertains particularly to age-adjusted stroke death rates. Also of concern, even in the developing world, is the increase in obesity. According to a recent study, one in five Chinese is overweight or obese.[8] Other new data indicate that as many as 40% of South African women may be overweight.

Epidemiologic Transition in the United States

Like other high-income countries, the United States has proceeded through four stages of the epidemiologic transition and is perhaps entering the fifth phase. Given the large amount of economic, social, demographic, and health data available (**Table 1-2**), the United States serves as a useful reference point for other countries.

Age of Pestilence and Famine (Before 1900)

The United States, like almost all other countries and regions, first experienced pestilence and famine. About half of the Pilgrims arriving in the New World in November 1620 died of infection or malnutrition by the following spring. In addition, the infectious diseases that the immigrants brought with them from Europe had a devastating impact on Native American populations. At the end of the 1800s, the U.S. economy was still largely agrarian, with more than 60% of the population living in rural settings. By 1900, life expectancy had increased to 47.8 years for men and 50.7 years for women. Infectious diseases—primarily tuberculosis, pneumonia, and diarrheal diseases—accounted for more deaths than any other cause. CVD accounted for less than 10% of all deaths. Tobacco products were beyond the economic reach of a large segment of the population.

Age of Receding Pandemics (1900-1930)

Early in the 20th century, the pace of industrialization accelerated. The population of urban areas outnumbered that of rural areas for the first time by 1920. By 1930, 56% of the population lived in or near urban centers. The shift from a rural, agriculture-based economy to an urban, industry-based economy had a number of consequences on cardiovascular risk behaviors and factors. The railway network in place at the turn of the century could move food from the farm to the city. Because the trains were not refrigerated, however, perishable foodstuffs such as fresh fruits and vegetables could not readily be transported, whereas cereal grains and livestock could. As a result, consumption of fresh fruits and vegetables declined and consumption of meat and processed grains increased. In addition, the manufacture of factory-rolled cigarettes made them more portable and more affordable for much of the population.

TABLE 1-2 U.S. Trends During the 20th Century

PARAMETER	1900	1930	1970	2000
Population (millions)	76	123	203	281
Median income (real dollars)	NA	$15,050 (1947)	$26,333	$29,058
Age-adjusted cardiovascular disease mortality (*N*/100,000)	325	390	699	341
Age-adjusted coronary heart disease mortality (*N*/100,000)	NA	NA	448	186
Age-adjusted stroke mortality (*N*/100,000)	140	100	148	57
Urbanization (%)	39	56	74	76
Life expectancy (yr)	49.2	59.3	70.8	76.9
Smoking				
Cigarettes per capita (*N*)	54	1,185	3,969	1,977
Smokers (%)	NA	NA	37.4	23.3
Total caloric intake (kcal)	3,500	3,300	3,200	3,800
Fat intake (% of total calories)	31.6	37.3	41.2	33
Cholesterol level (mg/dL)	NA	NA	216	204
Overweight or obese (%)	NA	NA	47.7	64.5

NA = not available.

Population: U.S. Bureau of the Census: Current Population Reports, P60-203, Measuring 50 Years of Economic Change Using the March Current Population Survey. Washington, DC, U.S. Government Printing Office, 1998; and U.S. Bureau of the Census: Money Income in the United States, 2000, P60-213. Washington, DC, U.S. Government Printing Office, 2001.

Cardiovascular disease, coronary heart disease, stroke mortality: Morbidity & Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. Bethesda, Md, National Heart, Lung, and Blood Institute, 2002.

Urbanization: Measuring America: The Decennial Censuses, 1790 to 2000: U.S. Bureau of the Census, Washington, DC, U.S. Government Printing Office, 2002.

Life expectancy: Arias E: United States life tables, 2000. *In* National Vital Statistics Report, vol 51, no 3. Atlanta, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.

Smoking: Federal Trade Commission: Cigarette report for 2001 (http://www.ftc.gov/os/2003/06/ 2001cigreport.pdf).

Total caloric intake and fat intake: Nutrient content of the U.S. food supply, 1909-1994: A summary. Washington, DC, U.S. Department of Agriculture, 1998; and Kennedy ET, Bowman SA, Powell R: Dietary-fat intake in the U.S. population. J Am Coll Nutr 18:207, 1999.

Cholesterol level and obesity: National Center for Health Statistics: Health, United States, 2002. (http://www.cdc.gov/nchs/data/hus/hus02.pdf).

By 1900, a public health infrastructure had emerged; 40 states had health departments, and many larger towns had major public works efforts to improve water supply and sewage systems. Municipal use of chlorine to disinfect water was becoming widespread, and improvements in food handling such as pasteurization were introduced. The Flexner Report of 1910, which examined carefully the quality of medical education in the United States and Canada, was the first step toward organized quality improvement in health care personnel that, along with other public health changes, contributed to dramatic declines in infectious disease mortality rates throughout the century. These rates fell dramatically, from a crude death rate of approximately 800/100,000 people in 1900 to approximately 340/100,000 people in 1930. Life expectancy increased by 10 years between 1900 and 1930, to 57.8 years for men and 61.1 years for women. Age-adjusted CVD mortality rates, at approximately 390/100,000 people, were in the midst of their steady climb up from slightly more than 300/100,000 people in 1900. This increase was largely driven by rapidly rising CHD rates.

Age of Degenerative Man-Made Diseases (1930-1965)

By the middle of the 20th century, the United States was predominantly an industrial economy, with 64% of the population living in urban and suburban settings. With continued mechanization and urbanization, activity levels declined considerably. The prevalence of smoking, one of the major contributors to premature mortality and chronic disease, hit its zenith among adult men at 57% in 1955 and among women 10 years later at 34%.[9] Deaths from infectious diseases had fallen to fewer than 50/100,000 people/yr, and life expectancy was up to almost 70 years. However, almost 52% of men and 34% of women were smokers, and fat consumption (much of it saturated) represented 41% of total calories. Age-adjusted CHD mortality rates were at their peak, at approximately 225/100,000 people. Stroke rates were also high, at 75/100,000 people.

One of the most remarkable changes in the years after World War II was the growth of the health care industry. Only some of this growth was stimulated by rises in per capita gross domestic product (GDP). In the private sector, the growth of labor unions propelled a major expansion in private health care insurance. In fact, by the late 1950s, more than two thirds of the working U.S. population had some form of private insurance. The federal government also played an important role. Increases in federal funding (the Hill-Burton Act of 1948) led to the construction of more hospitals to deal with the acute manifestations of chronic illnesses. In 1966, two key federal insurance programs, Medicare and Medicaid, provided access to medical care for the medically indigent and older adults. The establishment of the National Institutes of Health, spurred largely by scientific achievements in medicine that occurred during World War II, not only promoted health-related research but also transformed medical education by providing financial support for the establishment of full-time medical school faculty.

Age of Delayed Degenerative Diseases (1965-2000)

A decline in age-adjusted CVD mortality rates began in the mid-1960s, and substantial reductions in age-adjusted rates of mortality from both stroke and CHD have followed since then (**Fig. 1-3**). These reductions have occurred in whites and blacks, men and women, and all age groups. Age-adjusted CHD mortality rates fell approximately 2%/yr, and stroke rates fell 3%/yr in the 1970s and 1980s. At the beginning of the 21st century, the nation was fully industrialized, with only 2% of the population involved in farming and a per capita GDP of approximately $37,800. **Table 1-3** provides an overview of CVD in 2005, the last year for which complete statistics are available.

Two significant advances have contributed to the decline in CVD mortality rates—new therapeutic approaches and prevention measures targeted at those with CVD and those potentially at risk for it.[10] Treatments once considered advanced, including the establishment of emergency medical systems, coronary care units, and widespread use of new diagnostic and therapeutic technologies such as echocardiography, cardiac catheterization, angioplasty, bypass surgery, and implantation of pacemakers and defibrillators, have now become the standard of care. Advances in drug development have also had a major beneficial impact on acute and chronic outcomes. Efforts to improve the acute management of MI have led to the application of lifesaving drugs such as beta-adrenergic blocking agents, percutaneous coronary intervention, thrombolytics, angiotensin-converting enzyme (ACE) inhibitors, and others (see Chaps. 49 and 55). 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 Chap. 46) and the development of highly effective cholesterol-lowering drugs such as statins have also made major contributions to primary and secondary prevention by reducing deaths from CVD (see Chaps. 47 and 49).

In concert with these advances, public health campaigns have indicated that certain behaviors increase the risk of CVD and that lifestyle modifications can reduce risk. In this regard, smoking cessation has been a model of success. In 1955, 57% of men smoked cigarettes; today, 23% of men smoke. Among women, the prevalence of smoking has fallen from a high of 34% in 1965 to 18.5% currently. Campaigns beginning in the 1970s have resulted in dramatic improvements in the

detection and treatment of hypertension. This intervention likely has had an immediate and profound effect on stroke rates and a more subtle effect on CHD rates. Similar public health messages concerning saturated fat and cholesterol largely account for the decline in overall fat consumption as a percentage of total calories, from approximately 45% in 1965 to 34% in 1995, and the decline in population mean cholesterol levels, from 220 mg/dL in the early 1960s to 203 mg/dL by 2002.[11]

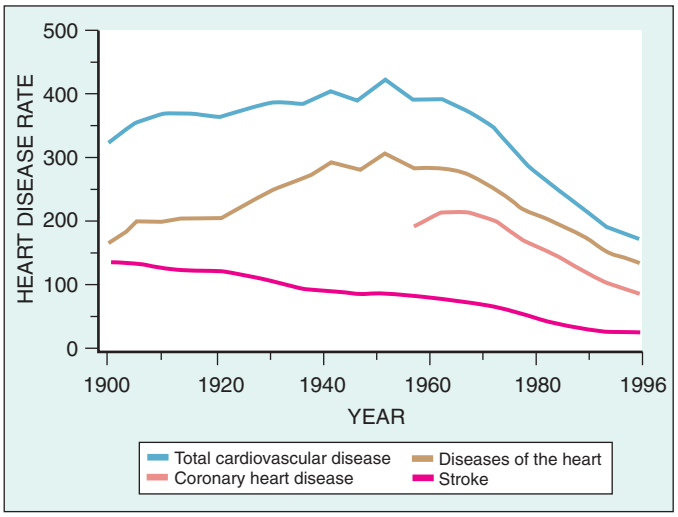

FIGURE 1-3 Increase and decline in age-adjusted heart disease rates through the epidemiological transition in the United States, 1900 to 1996. Rate is per 100,000 population, standardized to the 1940 U.S. population. Diseases are classified according to International Classification of Diseases (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975. *(From Centers for Disease Control and Prevention (CDC): Achievements in public health, 1900-1999: Decline in deaths from heart disease and stroke—United States, 1900-1999. MMWR Morbid Mortal Wkly Rep 48:649, 1999.)*

A main characteristic of the age of delayed degenerative diseases is the steadily rising age at which a first CVD event occurs or at which people die of CVD. Despite declines in age-adjusted mortality, the aging of the population will maintain CVD as the predominant cause of morbidity and mortality. Life expectancy at birth is 74.8 years for men and 80.1 years for women, and at age 65 is 16.8 years for men and 19.8 for women. CVD still causes most morbidity and mortality, but it afflicts an older population than it did in the middle of the century.

Age of Inactivity and Obesity

Overweight and obesity have increased at an alarming pace, and only a minority of the population meets minimal physical activity recommendations, favoring the development of even more diabetes and hypertension in the future. Increases in childhood obesity and physical inactivity are leading to an upsurge in diabetes and hypertension among younger individuals.[6,7] Fortunately, recent trends in the first decade of this century suggest that there may be a tapering in the increases in obesity among adults, although the rates of obesity remain alarmingly high, at almost 34%.[12] Rates of detection and treatment of hypertension have plateaued.[13] The decline in smoking rates has leveled off, with approximately 20% of adults classified as current smokers.[14] These worrisome changes in CVD risk behaviors and factors may slow the rate of decline and could even contribute to future increases in age-adjusted rates of CVD unless they are prevented. However, continued progress in the development and application of therapeutic advances appears to have offset the effects from the changes in obesity and diabetes rates. For example, cholesterol levels continue to decline. Overall, in this decade, the age-adjusted death rate has continued to decline by about 3%/yr, from 342 to 263/100,000.

Current Worldwide Variations in the Global Burden of Cardiovascular Disease

An epidemiologic transition much like the one that occurred in the United States is occurring worldwide. However, the rate of transition

TABLE 1-3 Cardiovascular Disease in the United States, 2005

TYPE	PREVALENCE (MILLIONS)	CRUDE MORTALITY (THOUSANDS)	PERCENTAGE OF TOTAL DEATHS	RATE/100,000
Cardiovascular disease	80.0	864.5	35.3	288.8
Hypertension	73.6	57.4	2.3	18.4
Ischemic heart disease	16.8	445.7	18.2	150.4
Stroke	6.5	143.6	5.9	48.4
Congestive heart failure	5.7	292.2	1.2	19.9
Rheumatic heart disease	NA	3.4	0.14	1.1
	ANNUAL EVENTS (THOUSANDS)			
Myocardial infarction	1255			
New	785			
Recurrent	470			
Stroke	795			
New	610			
Recurrent	185			
CABG	448			
PTCA	1313			
Valve surgery*	106			

*Total costs, $403.1 billion—direct, $257.6 billion; indirect, $145.5 billion.
CABG = coronary artery bypass grafting; NA = not available; PTCA = percutaneous transluminal coronary angioplasty.
Data from American Heart Association: 2009 Heart and Stroke Statistical Update. Dallas, American Heart Association, 2009; Kung H, Hoyert DL, Xu J, Murphy SL: Deaths: Final Data for 2005. National Vital Statistics Reports; vol. 56 no. 10. Hyattsville, Md, National Center for Health Statistics, 2008; and American Heart Association. Heart Disease and Stroke Statistics—2008 Update. Dallas, American Heart Association, 2008.

varies widely, leading to large discrepancies in disease burden. After a review of high-income countries that have followed a transition similar to that in the United States, other high-income regions that have followed a somewhat different course will be described. Finally, the status of the epidemiologic transition in low- and middle-income countries, where data are more limited, will be summarized.

High-Income Countries

Approximately 940 million people (15% of the world's population) live in high-income countries, including the United States, Canada, Australia, New Zealand, Japan, and the countries of the European Union. The movement of most of these countries through the epidemiologic transition, with rising levels of risk factors and CVD death rates until the 1960s, and then declines in both over the next 40 years, is similar to what has occurred in the United States. CHD is the dominant form, with rates that tend to be twofold to fivefold higher than stroke rates. There are two notable exceptions. In Portugal, stroke rates for men and women are higher than CHD rates. The same is true in Japan, where stroke causes more fatalities than CHD. In both of these countries, however, the pattern seems to be moving toward that seen in other high-income countries, with more rapid declines in stroke than in CHD rates.

In high-income countries, despite the overall increase in CVD burden, the age-adjusted death rates for CVD are declining, predominantly driven by large stroke rate reductions. This age-adjusted decline results largely from preventive interventions that allow people to avoid 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 of death from CVD continues to climb and, as a result, affects a larger population in retirement. Almost 80% of deaths in high-income countries occur in those older than 60 years, compared with 42% in low- and middle-income countries.[2] Between 1990 and 2020, CHD deaths alone are anticipated to increase by 120% for women and 137% for men in developing countries.[15] However, distinct differences remain in the severity of the burden affecting the various populations.

The rates of CVD in Western Europe tend to be similar to those in the United States. However, the absolute rates vary threefold among the countries of Western Europe, with a clear north-south gradient of higher CHD and stroke rates in the north. The highest CVD rates in the European high-income countries (two to three times higher than the median rates) are in Finland, Ireland, and Scotland. Although still high, deaths from CHD among Finnish men of working age have decreased by almost 80% over the last 30 years, from 508 deaths/100,000 in 1967 to 126/100,000 in 2003. A program called "Success in Finland" has contributed to this decline, including a more than 40% decrease in CHD death rates in men and women between 1989 and 1999. The Scottish government is also taking measures to decrease rates, including banning smoking in all enclosed places as of spring 2006. The lowest CVD rates in Europe are in the Mediterranean countries of France, Spain, and Italy, where age-adjusted CHD rates are less than 125 and 40/100,000 for men and women, respectively.[16] Although both stroke and CHD rates are higher in northern Europe, the disparity in CHD rates is much greater. For example, CHD rates for men are 222% higher in Finland than in Spain, whereas stroke rates are only 21% higher. CVD rates in Canada, New Zealand, and Australia are similar to rates in the United States. Rapid declines in CHD and stroke rates since the early 1970s have signaled that the high-income countries were in the fourth phase of the epidemiologic transition, the age of delayed degenerative diseases. In these countries, however, the rapidly increasing rate of obesity seems to indicate that many may be entering the fifth phase. CVD death rates continue to decline, at least in part because of the technical advances in treating CVD.

JAPAN. This country is unique among high-income countries. As its rates of communicable diseases fell in the early part of the 20th century, stroke rates increased dramatically; by the middle of the century, they were the highest in the world. CHD rates, however, did not rise as sharply as in other industrialized nations and have remained lower than in any other industrialized country. Overall, CVD rates have fallen 60% since the 1960s, largely because of a decrease in age-adjusted stroke rates. Japanese men and women currently have the highest life expectancies in the world—86 years for women and 79 years for men. The difference between Japan and other industrialized countries may stem in part from genetic factors, but it is more likely that a fish- and plant-based, low-fat diet and resultant low cholesterol levels have played a more important role. As is true for so many countries, dietary habits in Japan are undergoing substantial changes. Since the late 1950s, cholesterol levels have progressively increased. A study that analyzed diet and cholesterol levels in a cohort of rural Japanese men found that their carbohydrate intake decreased significantly, from 84% in 1958 to 62% in 1999, whereas protein and fat intake increased dramatically, from 11% to 18% for protein and 5% to 20% for fat.[17] Although average cholesterol levels rose from 152.5 to 194.2 mg/dL, the incidence of coronary artery disease in this population remains low. This situation could change, however, because there seems to be a long lag phase before dietary changes become manifest as CHD events.

Low- and Middle-Income Countries

The World Bank places countries in regions based on geography and income level. Low- and middle-income countries are divided into six geographic subregions—East Asia and Pacific, (Eastern) Europe and Central Asia, Latin America and the Caribbean, Middle East and North Africa, South Asia, and sub-Saharan Africa. The high-income countries, however, are not geographically distinct. For example, the Europe and Central Asia region is made up of low- and middle-income countries from eastern Europe, whereas the wealthier western European countries are part of the high-income region, as defined by the World Bank. Significant costs and infrastructure limitations prohibit most low- and middle-income countries from having completely representative demographic surveys, vital registration systems, or disease registries; therefore, the review highlights countries with large populations and reliable data.

The six regions that constitute the low- and middle-income countries have a high degree of heterogeneity with respect to the phase of the epidemiologic transition, as illustrated by the dominant disease rates in each region (**Fig. 1-4**). The two regions where stroke still exceeds CHD as a cause of CVD death are the East Asia and Pacific and sub-Saharan Africa regions (**Fig. 1-5**). The East Asia and Pacific region appears to be following more of a Japanese-style transition, with relatively high stroke rates, whereas in Africa this may reflect their position in an earlier stage of the epidemiologic transition. Hypertensive heart disease is the largest single contributor among the remaining causes of CVD morbidity and mortality, accounting for as much as 11% in Middle East and North African countries and as little as 2% in the South Asia region.

The variability in disease prevalence in the 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/or 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 rising in both countries. Third, certain additional competing pressures exist in some regions, such as war or infectious diseases (e.g., human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]) in sub-Saharan Africa.

In many low- and middle-income countries, the age-adjusted death rates for CHD are increasing. Because CHD afflicts a younger population in developing regions, an increased number of deaths affect the working-age population. For some developing countries, the severity of the epidemiologic transition has appeared to follow a reverse social gradient, with members of lower socioeconomic groups suffering the highest rates of CHD and highest levels of various risk factors.[18] 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 treatments. Consequently, CVD mortality rates decline later in those of lower socioeconomic status.

EAST ASIA AND PACIFIC

Demographic and Social Indices

The East Asia and Pacific (EAP) region is the most populated low- and middle-income region in the world, with almost 1.9 billion people. The gross national income (GNI) per capita is $1630, ranging from $2720 in Thailand to $430 in Laos.[19] In 2004, total health expenditure was 4.4% of total GDP, or $62 per capita. China is the most populated country, representing almost 70% of the region.

Life expectancy has risen quickly across the EAP region. Nowhere is this more evident than in China, which saw its life expectancy increase from 37 years in the mid-1950s to 71 years in 2000. This increase has been accompanied by a large rural to urban migration pattern, rapid urban modernization, aging of the population, decreased birth rates, major dietary changes, increased tobacco use, and a transition to work involving physical inactivity.

Burden of Disease

According to the World Health Organization (WHO) Global Burden of Disease (GBD) Project, CVD caused more than 4.4 million deaths in the EAP region in 2004, approximately 1.2 million from CHD and 2.2 million from cerebrovascular diseases.[1] The prevalence of angina and cerebrovascular diseases was 8.2 and 9.1 million people, respectively. The numbers of DALYs lost caused by CHD were 11.8 million for CHD and 24.2 million for cerebrovascular diseases. Between 1950 and 1990, the rate of CVD mortality increased threefold as a percentage of total deaths in China.

Stroke and CHD are the most prevalent forms of CVD in the EAP region. Together they account for between 60% and 77% of CVD mortality in China.[20] In contrast to North America and Europe, stroke is the leading cause of CVD in most areas of the EAP region.[21] In the country as a whole, China appears to be straddling the second and third stages of a Japanese-style epidemiologic transition. Among men aged 35 to 64 years in China, stroke death rates are 217 to 243/100,000, versus CHD death rates of 64 to 106/100,000.[20]

Even with high stroke rates, CHD is emerging as a large and growing burden in East Asia. Data from the largest death registration and classification study in China have shown that CHD accounts for 13% to 22% of overall CVD deaths and 4% to 9% of total deaths, with the higher percentages seen in urban areas. In 2004, the WHO estimated that almost 400,000 people died in China from CHD, and 652,000 cases were diagnosed.[21] The age-adjusted mortality from CHD was 80 to 128/100,000 for men and 57 to 98/100,000 for women. Higher rates were seen in urban versus rural areas (by a factor of six), higher income compared with lower income areas, and northeastern areas of China compared with southern areas.

CHD rates have grown quickly over the past two decades in China. Age-adjusted CHD mortality increased 39% in women and 41% in men aged 35 to 74 years between 1984 and 1999. Furthermore, the incidence of CHD increased by 2.7% annually in men and 1.2% annually in women. Although rates are higher, hospitalizations are somewhat low. Acute MI accounted for 4.1% of all hospital discharges in 2004 in large cities, and 2.1% of discharges in smaller cities and rural areas.[21]

The data for the burden of CHD in the Pacific Islands is much more limited. However, estimates from the WHO GBD Project suggest that Pacific Island age-standardized CHD rates exceed those in China by at least twofold to threefold; CHD age-standardized death rates range from 110/100,000 in the Federated States of Micronesia to 125/100,000 in Samoa and up to 181/100,000 in Nauru.[1]

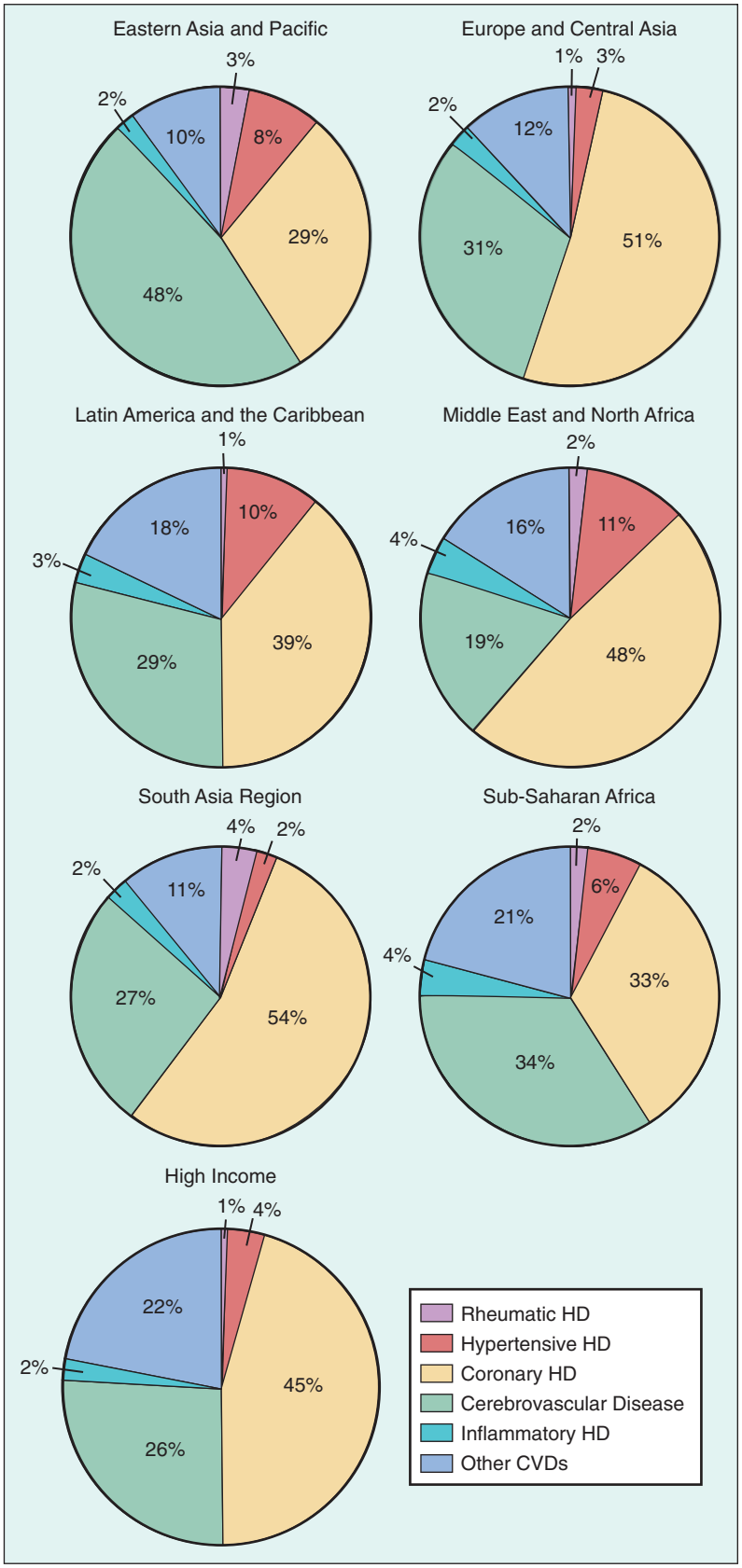

FIGURE 1-4 Cardiovascular disease deaths by specific cause by region.

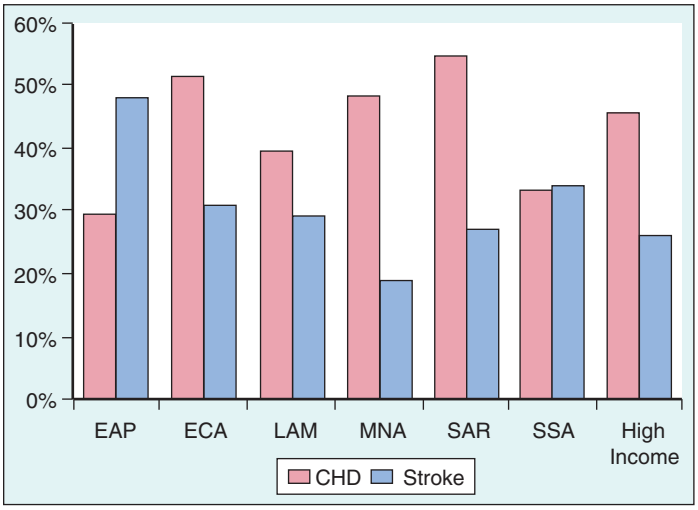

FIGURE 1-5 Comparison of percentages of cardiovascular disease mortality attributable to coronary heart disease (CHD) and stroke by developing region. EAP = East Asia and Pacific; ECA = Europe and Central Asia; LAM = Latin America and the Caribbean; MNA = Middle East and North Africa; SAR = South Asia Region; SSA = sub-Saharan Africa.

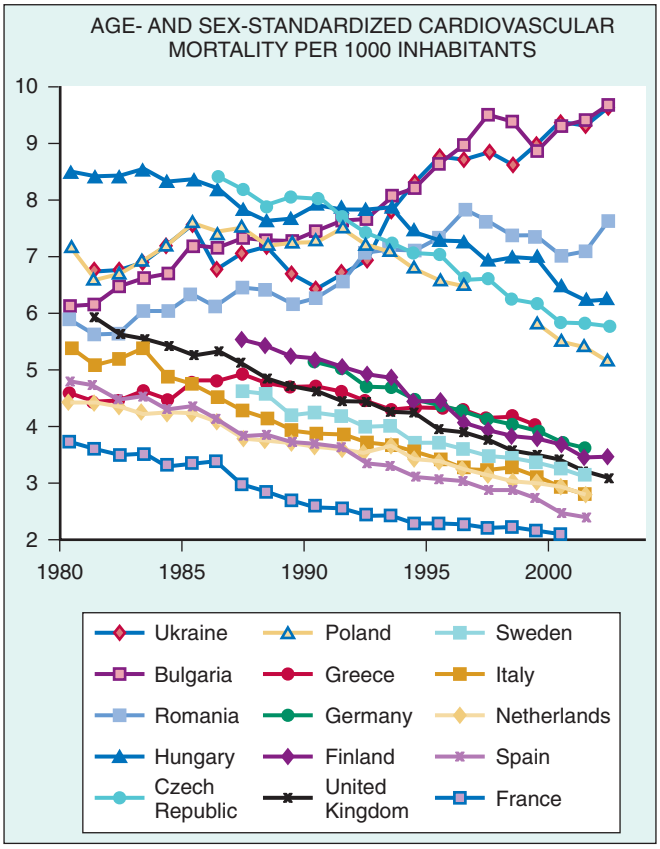

FIGURE 1-6 Trends in age- and sex-standardized cardiovascular mortality in selected European countries. *(From European Society of Cardiology: Cardiovascular Diseases in Europe: Euro Heart Survey and National Registries of Cardiovascular Diseases and Patient Management 2004 [http://www.escardio.org/guidelines-surveys/ehs/documents/ehs-cvd-report-2006.pdf.].)*

EUROPE AND CENTRAL ASIA

Demographic and Social Indices

Low- and middle-income areas in the Europe and Central Asia (ECA) region include countries east of Poland, the Czech Republic, and Croatia; the most populated is Russia, with 30% of the region's 472 million inhabitants. The average GNI for the region is $1,954; GNI ranges from $330 in Tajikistan to $11,220 in the Czech Republic. Russia has a GNI of $4,460.[19] The ECA region spends an average of 6.6% of total GDP on public and private health care, and the average health expenditure per capita is $250. Tajikistan spends the least, at $14 per capita, and Hungary spends the most, at $800 per capita. Russia spends about $245 per capita, or 6% of its GDP.[19]

Burden of Disease

According to the GBD study, the ECA has the highest regional rates of CVD mortality in the world, with approximately 60% of deaths caused by CVD. Overall rates resemble those seen in the United States in the 1960s, when CVD was at its peak. CHD is generally more common than stroke, which suggests that the countries that constitute Eastern Europe and Central Asia are largely in the third phase of the epidemiologic transition. As expected in this phase, the average age of those who develop and die of CVD is lower than that in high-income economies. CHD accounts for 1.685 million deaths annually (roughly 30% of all deaths) in the ECA, and 18.510 million DALYs are lost to CHD in this region.[2]

Although the GBD study provides a common estimate for the whole ECA region, an analysis of country-level information reveals important differences in CHD profiles among the countries in this region (**Fig. 1-6**) and compared with high-income countries from Western Europe. Since the dissolution of the Soviet Union, there has been a surprising increase in CVD rates in some of these countries, with the highest rates in Ukraine, Bulgaria, Belarus, and Russia.[22] In Russia, increased CVD rates have contributed to falling life expectancy, particularly for men, whose life expectancy has dropped from 71.6 years in 1986 to 59 years today. Percentage increases in CHD mortality between 1980 and 1992 ranged from 8.3% for men and 7.8% for women in Hungary, to 57.4% and 45.7%, respectively, in Romania.[23]

In contrast, CHD death rates have declined remarkably in ECA countries that experienced economic and market transformations in the early 1990s. In Poland, Slovenia, Hungary, the Czech Republic, and Slovakia, CHD rates declined dramatically throughout the 1990s, across both sexes, ages, and residential and educational groups.[24] In the meantime, in the former Soviet Republics (FSRs), where economic and market transformations were delayed, CHD mortality continued to increase throughout the early 1990s, and has only experienced modest declines since then.

By 2002, CHD mortality in all ECA countries was still much higher than that in Western Europe or North America; however, the highest rates were seen in the FSRs, with the Russian Federation claiming the highest rates of CHD deaths in the world.[25] Importantly, deaths caused by CHD in these countries are not restricted to older adults. The GBD study has estimated that 601,000 (35.7%) of all CHD deaths in the ECA region occur in the working-age population (ages 15 to 69 years). High rates of CHD are especially troublesome in Ukraine and other FSRs in transition, where health systems are not sufficiently financed to respond to a high demand for chronic disease treatment, and out-of-pocket health care expenditures incurred by patients' households are often catastrophic.[26]

LATIN AMERICA AND THE CARIBBEAN

Demographic and Social Indices

The Latin America and Caribbean region (LAM) comprises Central America, South America, and most island nations in the Caribbean, and has a total population of about 560 million.[27] Brazil, the region's most populous country, has a 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. Average GNI per capita in the region is approximately $5500 dollars (purchasing power parity [PPP] $9321)[28] and all the countries spend less than 10% of their GDP on health care.[29] This level of spending translates into health care expenditures that range from $28 in Haiti to $775 in Barbados per capita.

Burden of Disease

The WHO GBD study ranked CHD as the single leading cause of mortality in the region, estimating it to be responsible for 11% of all deaths in 2004. An additional 8% can be attributed to stroke. Overall, CVD causes 28% of all deaths. Data available from the Pan American Health Organization (PAHO) also indicate that circulatory diseases accounted for 29% of all deaths in the region in 2004. In contrast, TB, malaria, HIV/AIDS, and other communicable diseases account for 10% of deaths. Unlike high-income countries, where CHD dominates among circulatory diseases, CHD and CVD are equivalent contributors to mortality, at 35% and 29%, respectively, indicating relatively higher rates of untreated hypertension in this region. No regional data on morbidity from CHD are readily available, but a household survey conducted in Brazil found that about 3.6% of the population, or around 7 million people, reported having heart disease.[30] In addition, CHD accounts for about 1% of total hospitalizations in the country. In 2002, Haiti and Guyana had the highest mortality rates for stroke (176/100,000 and 175/100,000, respectively) whereas Colombia and El Salvador had the lowest (37/100,000 and 38/100,000, respectively).[31]

An assessment of the trends in mortality caused by CHD and stroke in the Americas from 1970 to 2000 has shown a decline of about 60% for each condition in both the United States and Canada.[32] The reductions in Latin America ranged from 25% to 40% among men and 20% to 50% among women. Venezuela had the highest CVD rate in 2000 (137/100,000), whereas Brazil had the highest stroke rate (86/100,000 for men and 62/100,000 for women). The lower reductions in Latin America are attributed to rapid lifestyle changes—dietary changes, increased smoking, increased obesity, and less exercise.

With some exceptions, similar regional trends likely apply to age-adjusted CHD mortality. For example, in Brazil, age-adjusted circulatory disease mortality has declined 3.9% annually, and age-adjusted CHD mortality has declined 3.6% annually.[33] The decline, seen across all age groups and both genders, was most significant in those 44 years of age and younger. In another study analyzing trends in age-adjusted CHD mortality from 1970 to 2002, Argentina, Brazil, Chile, Colombia, and Puerto Rico all experienced declines, ranging from 2% to 68%.[32]

Over the same period, however, age-adjusted CHD mortality trended upward in Mexico, Costa Rica, and Venezuela. Together, CHD (13%), cerebrovascular disease (9.7%), and hypertensive heart disease (3.2%) accounted for almost 25% of all deaths in Mexico in 2004, and 9.9% of deaths were attributed to high blood pressure.[34] One explanation is that these countries may have been in an earlier stage of development and are likely catching up with the rest of the region. For example, in Mexico, although age-adjusted CHD mortality increased from 90% to 94% over the three-decade period, the age-adjusted mortality was 82/100,000 in men and 53/100,000 in women in 2000, falling within the overall range of 21 to 136/100,000 for the region.

MIDDLE EAST AND NORTH AFRICA

Demographic and Social Indices

The 17 countries of the Middle East and North Africa (MNA) region represent 6% of the world's population (306 million people). Egypt and Iran are the two most populous countries in the region, with Egypt having 24% of total inhabitants and Iran 22%. According to the World Bank indicators from 2005, the GNI per capita for the region is $2,198 ($6,084 PPP).[19] GNI per capita for individual countries ranges from $600 ($920 PPP) in Yemen to $30,630 ($24,010 PPP) in Kuwait. Approximately 5.6% of the total GDP for the MNA region is used for public and private health care, according to World Bank data from 2004. The average health expenditure per capita is $103. Egypt spends $64 per capita, and Iran spends $158. At $34, Yemen spends the least amount on health care per capita, and the United Arab Emirates spend the most, $711.[19]

Burden of Disease

Statistics from the 2002 WHO GBD study show that about 5% of CVD deaths in low- and middle-income countries occur in the MNA region. Over 35% of all deaths in the region are attributable to CVD. CHD, the leading cause of mortality in 2001, accounted for 16.9% of total mortality and almost half of CVD mortality. Cerebrovascular disease causes 6.8% of total deaths and 19% of CVD deaths. This translates into approximately 323,000 deaths in 2001 in the region.[2]

Mortality rates for the region have declined over time, whereas life expectancy has increased from 64.05 years in 1990 to 67.35 years in 2001. The crude death rate for the region has notably decreased. The newest data show that the crude death rate was 7.55% in 1990 and 6.15% in 2001. Also in 2001, 1.235 million deaths in the MNA region were attributable to noncommunicable diseases.[2] For CVD specifically, the number of deaths reported was 671,000. However, with the increase in life expectancy, there is an expectation that CHD will increase in the region.

Individual country surveys have shown that Iran may have a higher burden than other countries, including Saudi Arabia and Jordan. A study of a random sample of 3,723 people in Iran found that 11.3% had coronary symptoms and an additional 1.4% had had an MI. The age-adjusted prevalence was therefore 12.7%.[28] Another study, done in Saudi Arabia and involving 17,232 people from the general population, found that 5.5% were diagnosed with CHD. The data also showed that the prevalence was higher—6.2% compared with 4%—in urban versus rural areas.[35] In Jordan, a study found that a total of 5.9% out of 3,083 participants were told that they had an MI.[36] A 2001 Tunisian study of 20% of the male population found age-standardized rates of MI of only 163.8 in Tunis, 161.9 in Ariana, and 170.5/100,000 in Ben Arous.[37]

SOUTH ASIA

Demographic and Social Indices

The South Asia region (SAR), one of the world's most densely populated regions, comprises about 20% of the world's population, with a total of more than 1.4 billion residents. Home to almost 75% of the region's inhabitants, India is the largest country in the region. Average GNI per capita for the region is $692 ($3142 PPP), according to World Bank Indicators in 2005. GNI per capita ranges from $270 ($1530 PPP) in Nepal to $2560 in the Maldives. India is close to the average, with a GNI per capita of $730 ($3460 PPP). Figures from 2004 indicate that all countries spend an average of 4.6% of their total GDP, or $27 per capita, on health care. The Maldives spends the most per capita, at $208, and India spends $31, or 5% of its GDP. The lowest expenditure for health care is $14 per capita in Pakistan, Nepal, and Bhutan.[19]

Burden of Disease

In 2001, based on statistics from the GBD study, more than 25% of CVD deaths in low- and middle-income countries occurred in the SAR. Similarly, CVD accounts for more than 25% of all deaths in this region. This translated into a total of 3.4 million CVD deaths in 2001; CHD was the leading cause of mortality that year. CHD was responsible for 13.6% of total mortality, or 1.8 million deaths, and more than 50% of CVD mortality. CVD accounted for 6.8% of all deaths and 27% of CVD deaths. By comparison, communicable diseases were responsible for 43% of total mortality.[2]

Over time, regional mortality rates have declined as life expectancy has increased, from 57.2 years in 1990 to 60.7 years in 2001. The crude death rate for the region has decreased significantly; in 1990, it was 11.4% but had fallen to 9.75% in 2001.[2] However, deaths from CHD in India are increasing; from 1990 to 2000, CHD deaths rose from 1.17 million to 1.59 million. It is predicted that annual deaths from CHD will be approximately 2.03 million by 2010.[38] Similarly, overall CVD burden is expected to increase as well. In the 30-year period from 1990 to 2020, a 111% increase in CVD deaths is expected.[27]

Several studies in India and Pakistan have suggested substantial morbidity caused by CHD in this region. An estimated 31.8 million people are living with CHD in India alone,[27] a 10-fold increase over 40 years ago, which translates into an overall prevalence of about 11% in urban India and an age-adjusted prevalence of 9%, based on 2001 figures. Additional evidence suggests that women are more likely than men to have CVD in India.[39] The Initiative for Cardiovascular Health's National Cardiovascular Disease Database cited a study in India that found prevalence in men was more than 6% and in women more than

10%. More recently, a CHD study in Pakistan found a prevalence of about 6% in men and 4% in women, but active ischemia was twice as high in women. The study's authors[40] suggested that one in five adults in urban areas of Pakistan has CHD and, of these, it is estimated that only 25% are aware of their disease and are seeking medical care. Despite this, a survey of hospital data in Delhi has revealed that almost 25% of all medical admissions are because of CHD. Patients who do not seek treatment die at a rate of 7% to 8%/yr.[27]

Contrary to the epidemiologic transition in developed countries, recent evidence suggests that individuals in the SAR who have a lower socioeconomic status are developing a higher burden of CHD first. One possible explanation is that a higher proportion of the poor use tobacco products.[38]

Another demographic trend is the considerable increase in urban residents, normally associated with increased rates of CHD. Currently, about 30% of all inhabitants in the region live in an urban setting, a number that is expected to reach 43% by 2021.[41] Among urban dwellers, CHD prevalence has increased from 7% in 1980 to 9.7% in 1990 to 10.5% in 2000. CHD prevalence is increasing in urban areas as well, from 2.5% in 1980 to 4% in 1990 to 4.5% in 2000.[27] More recent data from the rural region of Andhra Pradesh in South India have suggested that the prevalence may actually be even higher in many rural regions.[42] CHD death rates were higher than 15% in this study, meaning that the rural/urban protection no longer exists—or the urban rates, if more carefully measured, could be much higher.

The rise in CHD mortality contributes to the economic burden in the Indian subcontinent. Data indicate that symptoms of CHD arise a full 10 years earlier here than in Western European and Latin American countries.[43] In India, 52% of CVD deaths occur among those younger than 70 years,[41] resulting in a considerable burden from CHD on working-age citizens.[27]

SUB-SAHARAN AFRICA

Demographic and Social Indices

Sub-Saharan Africa (SSA), as defined by the World Bank, comprises 31 island and continental nations. Approximately 782 million people lived in SSA in 2006, with Nigeria being the most populous nation (145 million) and Mauritius and Cape Verde having the smallest populations (1 million). The average annual population growth rate for 2000 to 2006 (4.7%) was almost twice the rate for 1990 to 2000 (2.5%). The average GNI per capita was $830 (U.S. dollars), on a gradient of $100 per capita in Burundi to $5570 in Botswana. Overall, the SSA region also had the lowest average life expectancy, 50 years.

Average public and private health care expenditures for the region are 6.3% of the total GDP, an average of $45 per capita according to 2004 World Bank indicators. The range of health care expenditures per capita for the region 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 its total GDP.[19]

Burden of Disease

CHD was the leading cause of death in low- and middle-income countries in 2001, accounting for 11.8% (5.7 million) of all deaths, and in the SSA region, CHD accounted for 3.2% of all deaths.[2] In 2001, CVD accounted for 46% of all deaths caused by noncommunicable diseases (1,048,000) in SSA, and CHD accounted for 33% of all cardiovascular diseases (343,000). Stroke was responsible for 4.5% of the global burden of disease and 9.5% of the regional mortality in low- and middle-income countries in 2001. The burden of HIV/AIDS was 5.1% globally, with middle- and low-income countries contributing only 5.3% of mortality in the region.

Human Immunodeficiency Virus and Cardiovascular Disease

Given the large burden of disease caused by HIV/AIDS, the potential risk of CVD among those being treated with antiretroviral medications is of growing concern (see Chap. 72). HIV-positive men older than 50 years have a greater prevalence of dyslipidemia, diabetes, and peripheral artery disease (50% of cases were asymptomatic) compared with their noninfected counterparts.[44] Of note, 55% of these HIV-infected men are prior smokers, and they are also more likely to have used antihypertensive drugs, lipid-lowering agents, and antidiabetic medications. A recent study of 95 patients initiating antiretroviral drugs indicated that patients who had high baseline lipid levels showed a marked increase in lipoprotein(a).[45] Grover and colleagues[46] have conducted a randomized controlled trial comparing lipid level changes after 32 weeks of treatment with two different highly active retroviral therapy (HAART) regimens, atazanavir and nelfinavir. Levels of total cholesterol and low-density lipoprotein (LDL) increased significantly more among patients using nelfinavir (+24%, +28%) compared with those using atazanavir (+4%, +1%), increasing the 10-year risk of CHD by 50% in the former group. These data indicate that the interaction of positive HIV status, HAART therapy, and risk for CVD warrants continued attention.

Global Trends in Cardiovascular Disease

Examination of regional trends is helpful for estimating global trends in the burden of disease, particularly CVD. Because 85% of the world's population lives in low- and middle-income countries, rates in these countries largely drive global rates of CVD. Even as rates fall in high-income countries, CVD rates worldwide are accelerating because most low- and middle-income countries are entering the second and third phases of the epidemiologic transition, marked by rising CVD rates. The economic impact of chronic diseases could be dominated by CVD. Over the next decade or so, countries such as China, India, and Russia could forego between $200 and $550 billion in national income as a result of heart disease, stroke, and diabetes.[47]

In 1990, CVD accounted for 28% of the world's 50.4 million deaths and 9.7% of the 1.4 billion lost DALYs. By 2001, CVD was responsible for 29% of all deaths and 14% of the 1.5 billion lost DALYs.[44] By 2020, the world population will grow to 7.8 billion and 32% of all deaths will be caused by CVD; by 2030, when the population is expected to reach 8.2 billion, 33% of all deaths will be caused by CVD (**Table 1-4**).[22] By 2030, WHO predicts that worldwide, CVD will be responsible for 24.2 million deaths.[22] Of these, 14.9% of deaths in men and 13.1% of deaths in women will be caused by CHD, and stroke will account for 10.4% of all deaths in men and 11.8% of all deaths in women.

Risk Factors

Table 1-5 displays the population-attributable fractions (PAF) of deaths caused by CHD for leading risk factors. Elevated levels of blood pressure and cholesterol remain the leading causes of CHD; tobacco, obesity, and physical inactivity remain important contributors. Diabetes is not listed because the GBD project considers it a disease, not a risk factor. The PAFs add up to more than 100% because there is interaction among the risk factors. Unique features regarding some CHD risk factors in the developing countries are described below.

Hypertension

Elevated blood pressure is an early indicator of the epidemiologic transition. A rising mean population blood pressure is apparent as populations industrialize and move from rural to urban settings. The high rate of undetected and therefore untreated hypertension presents a major concern in developing countries; throughout Asia, this likely contributes to the high prevalence of hemorrhagic stroke.

Worldwide, approximately 62% of strokes and 49% of cases of CHD are attributable to suboptimal (>115 mm Hg systolic) blood pressure, a factor thought to account for more than 7 million deaths annually. In a recent study,[48] it was estimated that 14% of deaths and 6% of DALYs lost globally were caused by nonoptimal levels of blood pressure. Although hypertension is usually defined as a systolic blood pressure higher than 140 mm Hg, Lawes and associates[48] have found that just over 50% of the attributable CVD burden occurs in those with a systolic blood pressure less than 145 mm Hg.