2 Global Burden of Cardiovascular Disease

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SHIFTING BURDEN

Between 1990 and 2017, deaths from cardiovascular disease (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 reflects a rise in LMICs and a decline in high-income countries (HICs) (Fig. 2.1). CVD now causes most deaths in all low- and middle-income regions, with the exception of sub-Saharan Africa, where it is the second leading cause of death overall, and the leading cause in those 50 years and older. In absolute numbers, five times as many CVD deaths occurred in the low- and middle-income regions combined than in the High-Income region in 2017 (14.8 million to 3 million). Within the six World Bank–defined low- and middle-income regions, the CVD burden differs vastly (Fig. 2.2), with CVD deaths accounting for as much as 43.7% of all deaths in Europe and Central Asia and as little as 12.3% in sub-Saharan Africa. Cardiovascular disease accounts for 31.8% of deaths 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 2.1): 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 stage 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 stage 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 increased during the stage of Receding Pandemics as the emergence of public health systems, cleaner water supplies, and improved food production and distribution combined to reduce deaths from infectious disease and malnutrition. Improvements in medical education and 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 as smoking. For example, in the United States, deaths from infectious diseases decreased to less 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, contribute 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 stage 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.[4,5]

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 37 and 38). Advances in both heart failure and diabetes management have led to new angiotensin-receptor neprilysin inhibitors, SGLT2 inhibitors, and GLP-1 agonists which reduce cardiovascular

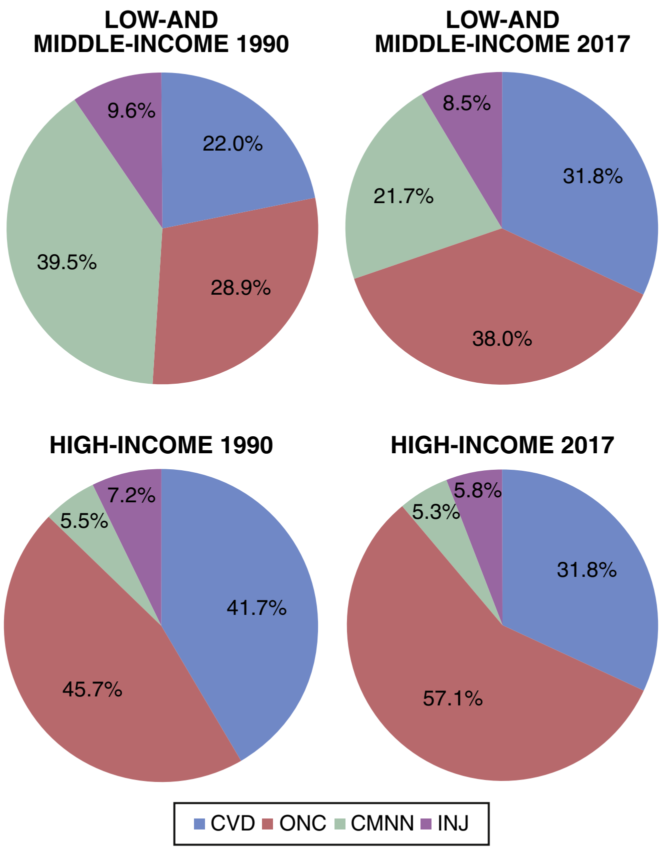

FIGURE 2.1 Changing pattern of mortality, 1990 to 2017. *CMNN*, communicable, maternal, neonatal, and nutritional diseases; *CVD*, cardiovascular disease; *INJ*, injury; *ONC*, other noncommunicable diseases. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

events. 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 26) 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-related deaths (see Chapter 27).

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 2018, 15.6% of men smoked. The prevalence of smoking among U.S. women has fallen from 34% in 1965 to 13.7% in 2018.[6] Campaigns from 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 191 mg/dL by 2016,[7] with a simultaneous decrease in the prevalence of elevated low-density lipoprotein (LDL) cholesterol.

Stage 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 stage of Inactivity and Obesity (see Chapters 30 and 31).[8] 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, the rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are rising, a particularly evident trend in children.[9] 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

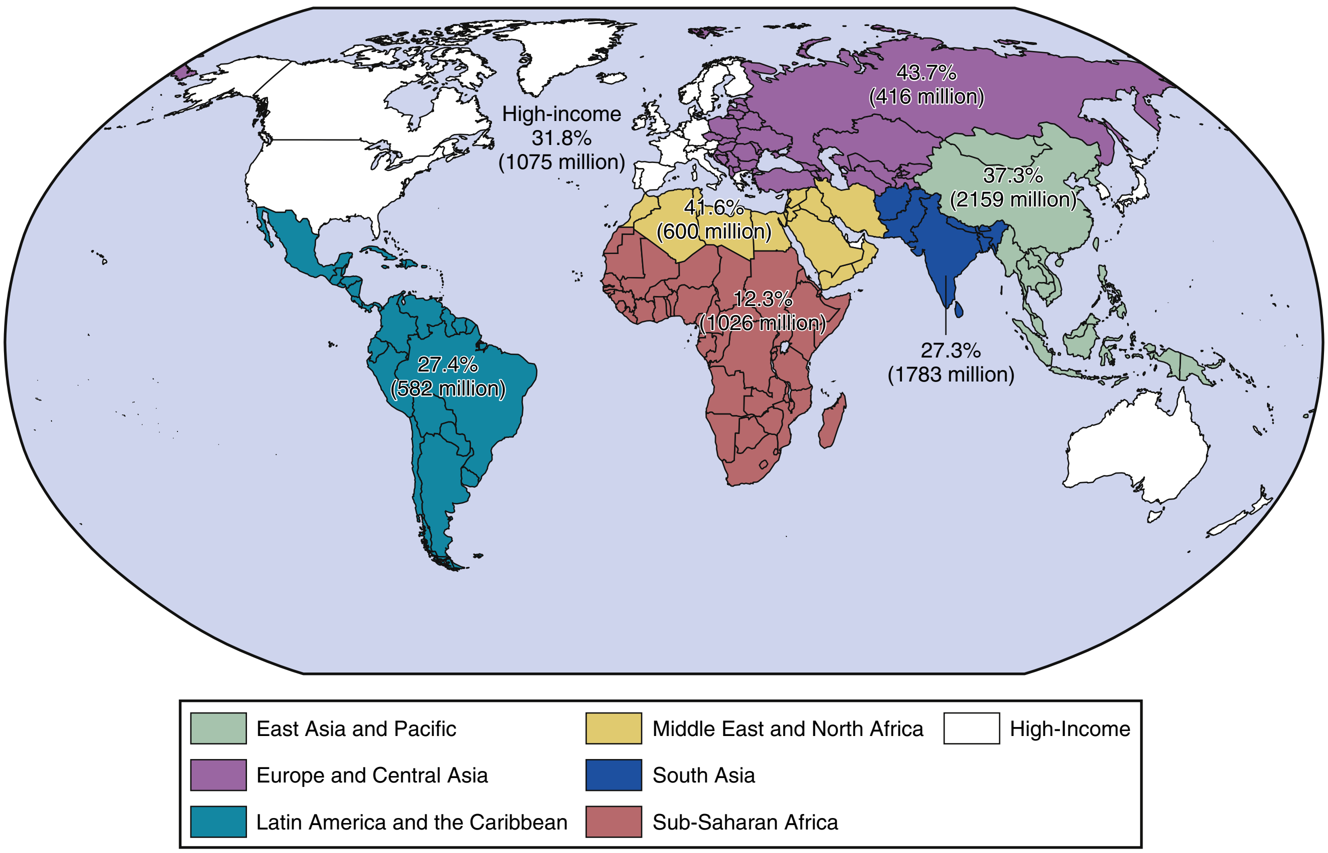

FIGURE 2.2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2017. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017; and World 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 2.1 Five Typical Stages of Epidemiologic Transition in Cardiovascular Disease 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	

CHD, Coronary heart disease; *CVD,* Cardiovascular 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 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.[10]

Fortunately, recent trends in the first decade of the present century suggest a tapering in the increase in obesity rates among adults, although the rates remain alarmingly high at almost 42.4%.[11] 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.[12]

Different Patterns of Epidemiologic Transition

The HICs have followed different patterns of the CVD transition, which differ in both the peak of death rate from CHD and the time of transition. Three patterns emerge that rely on data from countries with an established death certification system. Countries in Latin America appear to follow the three different patterns as well (Fig. 2.3).[13] 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. In Latin America, Argentina has followed this pattern with a rapid decline from 1985 to 2016 with a CHD-related death rate of 70 per 100,000 at the end of the time period. A second pattern showed a peak in the same period in CHD-related deaths of 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 decline in rate. In central European countries (Austria, Belgium, and Germany), the decline was slower compared to northern European countries (Finland, Sweden, Denmark, and Norway), but had lower peaks of 300 to 350 per 100,000 in the 1960s and 1970s. Colombia appears to follow this pattern with relatively flat to declining levels at 150 deaths per 100,000, with a small decline from 2010 to 2015. 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). Mexico appears to follow this pattern with rates nearly doubling from 80 to 160 per 100,000 from 1985 to 2015. Whether other LMICs will follow a "classic" pattern of significant increases then rapid declines in rates (as happened in North America, Australia, and northwestern European HICs), a more gradual rise and fall (as in 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 of 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 manifest at early stages. 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 2017. Although extensive, data from GBD 2017 have limitations. The availability and reliability of data on the cause of death, especially in LMICs without standardized protocols, are uncertain.

Globally, CVD-related deaths increased by 49% between 1990 and 2017. The increase in overall CVD-related deaths results from both increases in CHD and stroke-related deaths. CHD was the leading cause of death in 2017, accounting for 16% of all deaths worldwide. The second-ranking cause of death was stroke, at 11%. An estimated 15.1 million people died from CHD and stroke, which together accounted for more than a quarter of all deaths worldwide in 2017.[1]

Although still substantial, deaths from communicable, neonatal, and maternal diseases are decreasing worldwide,[1] with a 32.5% decrease between 1990 and 2017. Deaths from noncommunicable diseases increased by 53% in the same period. In 2017, CHD accounted for the largest portion of global years of life lost (YLLs) and the second highest of DALYs. Stroke was the third-ranking contributor to both 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-related deaths, the age-adjusted death rates decreased by 30.4% in the same period, from 335 to 233 per 100,000 population, suggesting significant delays in the age of occurrence and/or improvements in case-fatality rates. Unfortunately, not all countries 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

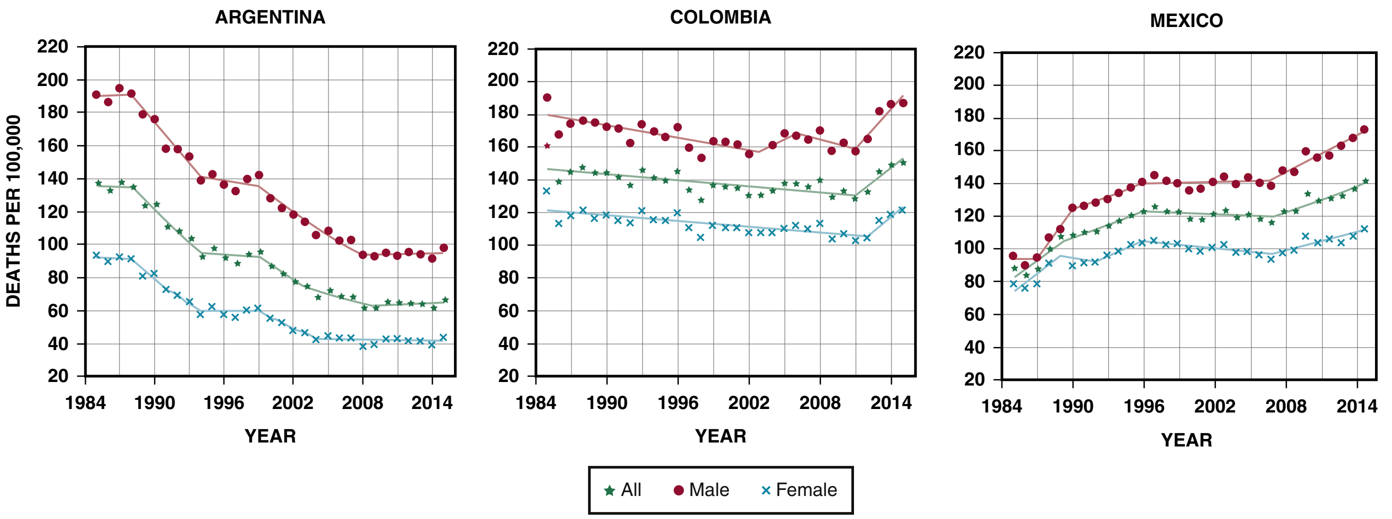

FIGURE 2.3 Trends in age-standardized mortality rates per 100,000 by sex for coronary heart disease. Argentina, Colombia, and Mexico. 1985–2015. Star: all; circle: male; cross: female. (From Arroyo-Quiroz C, Barrientos-Gutierrez T, O'Flaherty M, et al. Coronary heart disease mortality is decreasing in Argentina, and Colombia, but keeps increasing in Mexico: a time trend study. *BMC Public Health.* 2020;20(1):162. http://creativecommons.org/licenses/by/4.0/.)

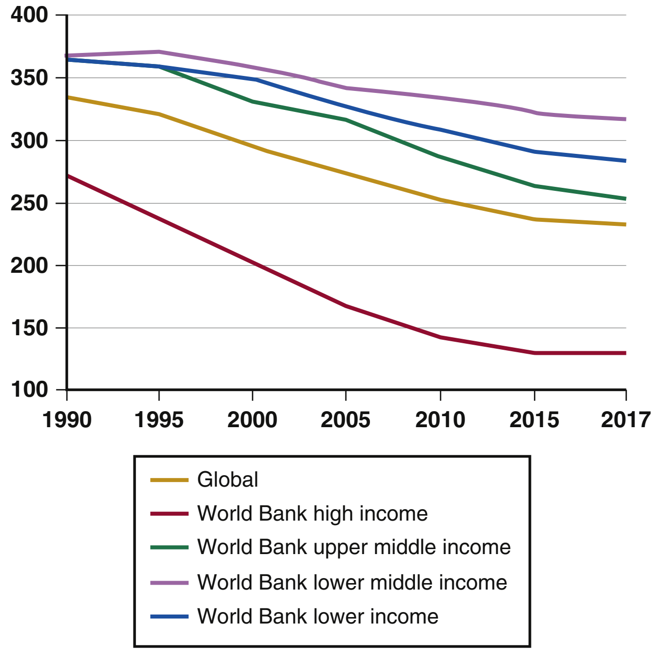

FIGURE 2.4 Cardiovascular disease death rates per 100,000 population from 1990 to 2017, by World Bank income categories. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

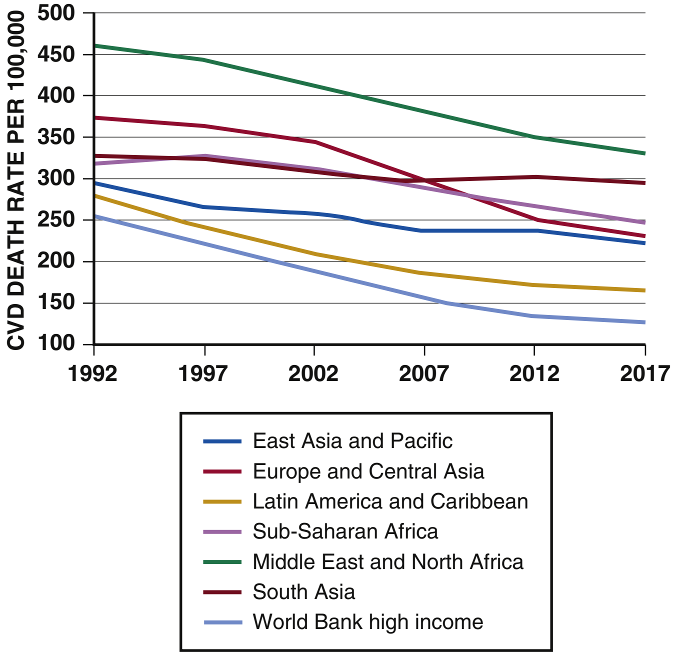

FIGURE 2.5 Cardiovascular disease death rates per 100,000 population from 1990 to 2017 in low- and middle-income countries by region, compared to World Bank high-income countries. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

modeling mortality rates in areas where established death certification–based vital registration systems do not cover the entire country. Even as age-adjusted rates have been falling globally, the pattern is different when assessed by income (Fig. 2.4) or by region (Fig. 2.5).

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, further divided by sub-regions: the High-Income, East Asia and Oceania, Central and Eastern Europe and Central Asia, Latin America and Caribbean, Middle East and North Africa, and sub-Saharan Africa regions. All these regions had declines in age-adjusted CVD mortality rates from 1990 to 2017. South Asia had only a slight decrease in its age-adjusted CVD mortality rates.

Much of the variation is related to income, which is one proxy for the stages of the epidemiologic transition. Looking at age-adjusted CVD-related death rates by World Bank, the high-income regions had different trends over the last two and a half decades. In the low-income region, the death rate has decreased from 364 to 285 per 100,000 between 1990 and 2017. The Lower Middle-Income region saw a small increase (368 to 371 per 100,000) between 1990 and 1995, followed by a fall to 317 per 100,000 in 2017. The upper middle-income region saw a 30% decline, from 365 to 254 per 100,000 between 1990 and 2017. The high-income region had a 53% decline, from 272 to 128 CVD deaths per 100,000.

The LMICs have a high degree of heterogeneity with respect to the phase of the epidemiologic transition. First, LMIC sub-regions differ by age-adjusted CVD death rates (Fig. 2.6). Next, low- and middle-income sub-regions are unique, as illustrated by the different CVD disease rates by cause in each region (Fig. 2.7). Lastly, in the East Asia and Oceania region, stroke still exceeds CHD as a cause of CVD-related death.

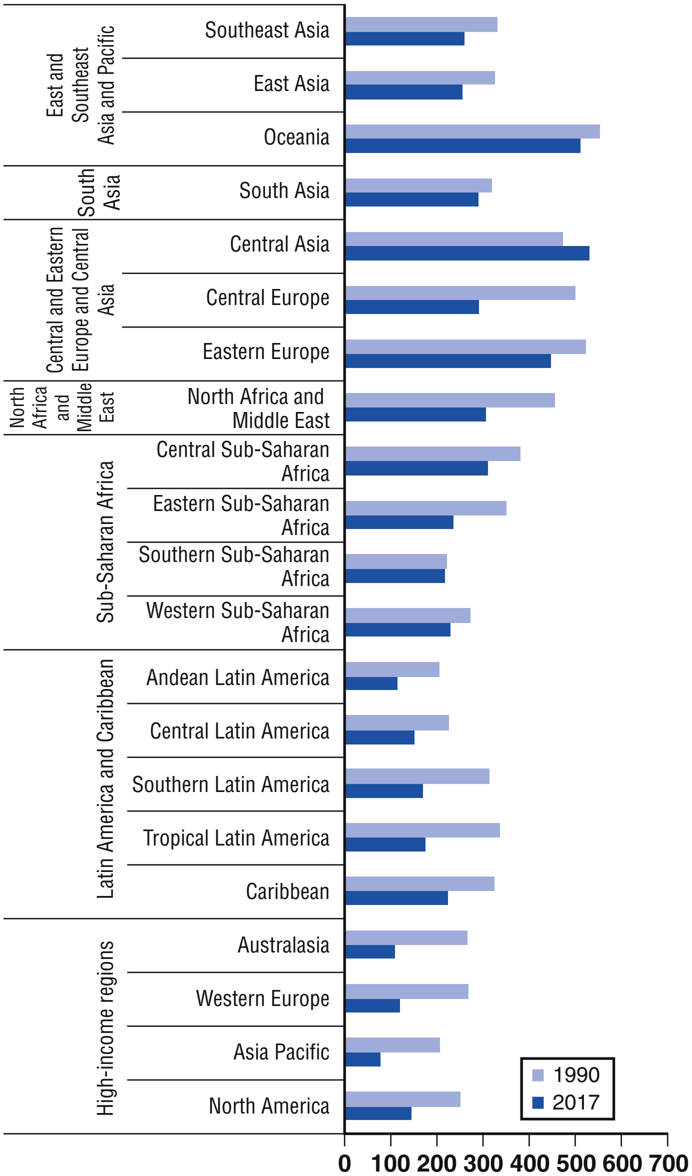

FIGURE 2.6 Age-adjusted death rates per 100,000 population for cardiovascular disease, 1990 and 2017. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

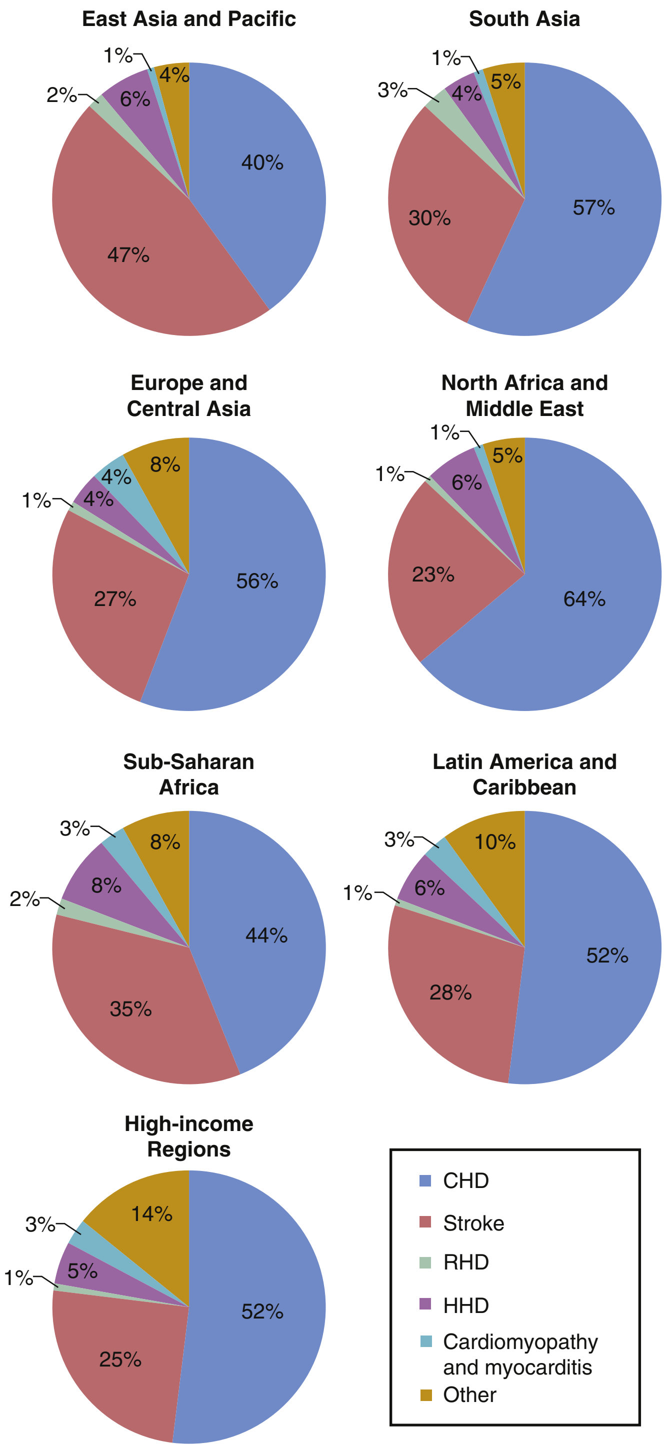

FIGURE 2.7 Cardiovascular disease death by specific cause and region. *CHD*, Coronary heart disease; *HHD*, hypertensive heart disease; *RHD*, rheumatic heart disease. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

Hypertensive heart disease is the largest single contributor among remaining causes of CVD morbidity and mortality, and sub-Saharan Africa remains the region with the largest contribution from this cause.

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 2017, CVD accounted for almost 32% of all deaths in high-income regions, and more than half of these deaths were due to CHD (see Fig. 2.7). 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, is similar to what occurred in the United States. CHD is the dominant form, with death rates per 100,000 twice as high as stroke rates. In Portugal however, stroke rates for women exceed 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 the disease, treatments to prevent death during an acute manifestation of the disease (particularly stroke or MI), and interventions that prolong survival once CVD manifests. Thus the average age at death from CVD continues to increase, and as a result, CVD affects a larger retired population.

Of the five sub-regions, Western Europe, with an overall CVD mortality rate of 313 per 100,000 in 2017, and Southern Latin America, with an age-standardized rate of 172 per 100,000, had the highest mortality rates, whereas Australasia and Southern Latin America tied for the lowest overall (222/100,000) rate, and high-income Asia Pacific had the lowest age-adjusted rate (80/100,000). As mentioned, high-income regions have higher mortality rates for CHD than for stroke. Japan is unique among HICs; as its communicable disease rates fell in the early 20th century, its stroke rates increased drastically. 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 dropped to 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: 87.3 years for women and 81.3 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.[14] 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- and middle-income region in the world, with 2.2 billion people; approximately 56% of the region is urban. The gross national income (GNI) per capita is $7601, ranging from $12,060 and $10,590 in Nauru and Malaysia to $1310 in Myanmar. In 2017, total health expenditure was 4.9% of total gross domestic product (GDP), or $344 per capita.[15] The region is divided into three distinct sub-regions: Southeast Asia, East Asia, and Oceania. China is by far the most populated country, representing 65% of the region. Life expectancy has risen quickly across the EAP region in past decades, up to an average of 75 years. In China the increase has been dramatic: from 37 years in the mid-1950s to 77 years in 2018.[15] 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 6.3 million deaths in the EAP region in 2017, accounting for 37% of all deaths in the region. Almost half of these deaths resulted from stroke, whereas 40% were caused by CHD (see Fig. 2.7). CVD death rates differ significantly between sub-regions, most notably in Southeast Asia. Age-adjusted CVD mortality rates were highest in Oceania, at 517 per 100,000 in 2017, even though the overall mortality for CVD was 253 per 100,000, suggesting that many premature deaths from CVD occurred in Oceania.

Stroke and CHD are the lead causes of death in all three sub-regions. Whereas stroke and CHD rates increased in both East Asia and Southeast Asia between 1990 and 2017, stroke rates decreased slightly in Oceania, from 87 to 83 per 100,000. China is straddling the second and third stages of a Japanese-like epidemiologic transition. Men in China age 50 to 69 have stroke death rates of 232 per 100,000, versus CHD death rates of 168 per 100,000.[1]

Central and Eastern Europe and Central Asia

Demographic and Social Indices

Of the three sub-regions that constitute this region (Central Asia, Central Europe, and Eastern Europe), Eastern Europe is the most populated. Russia alone accounts for 35% of the region's 416 million inhabitants. Sixty-seven percent of the population in the region is urban, with an average life expectancy of 73.7 years. The average GNI per capita for the region ranges from $1010 in Tajikistan to $24,500 in Slovenia. Russia has a GNI of $10,230. On average, the region spends 5.2% of its total GDP on public and private health care. Health expenditure per capita ranges from $58 per capita in Tajikistan to $1920 in Slovenia. Russia spends about $586 per capita, or 5.3% of its GDP.[15]

Burden of Disease

The highest rates of CVD mortality, both overall and age-adjusted, have occurred in this region for the entire span of the GBD project. Overall CVD mortality rates are 747 per 100,000 in Eastern Europe, 569 per 100,000 in Central Europe, and 359 per 100,000 in Central Asia. Overall rates are similar to 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 those in HICs. In 2017, CVD accounted for 54% of all deaths in the region, 56% of which resulted from CHD and 27% from stroke.

A country-level analysis reveals important differences in CHD profiles within the Central and Eastern Europe and Central Asia region (see Fig. 2.3). Since the dissolution of the Soviet Union, CVD rates have increased surprisingly in some of these countries, with overall rates of 956, 769, and 684 per 100,000 in Ukraine, Belarus, and Russia, respectively. 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 years, for example, result from CVD. For people age 60 to 64 years, CVD accounts for almost half of all deaths, and 60% of CVD-related deaths are caused by CHD.[1]

Latin America and the Caribbean

Demographic and Social Indices

The Latin America and Caribbean (LAM) region comprises Andean Latin America, Central Latin America, Tropical Latin America, and the Caribbean. The region has a total population of 582 million, 80% of which is urban.[15] Brazil, the region's most populous country, represents about one third of the population (36%), with Colombia, Mexico, Peru, and Venezuela making up another 41%. The Caribbean nations account for 8% of the population in the region. Life expectancy in the LAM region is approximately 75 years but varies greatly. In 2018, for example, Haiti and Chile had life expectancies of 64 years and 80 years, respectively. Average GNI per capita in the region is about $8696 (purchasing power parity [PPP] of $15,944). The region spends an average of 8.0% of its GDP on health care. This level of spending translates into health care expenditures that range from $62 per capita in Haiti to $1772 per capita in The Bahamas.[15]

Burden of Disease

The LAM region bears a substantial CVD burden. In 2017, CVD caused 27% of all deaths in the region. As in HICs, CHD dominates among circulatory diseases (see Fig. 2.7). Mortality rates vary significantly by sub-region. The Caribbean has the highest age-standardized mortality rates for CHD and stroke: 115 deaths per 100,000 and 69 per 100,000, respectively. Andean Latin America had the lowest: 61 and 34 deaths per 100,000, respectively. As with other global trends, overall mortality for the region increased slightly between 1990 and 2017, but age-adjusted mortality declined significantly. Between 1990 and 2017, age-adjusted CVD death rates nearly halved in Tropical Latin America while decreases of 44%, 33%, and 31% occurred in Andean Latin America, Central Latin America, and the Caribbean, respectively. Together, CHD (15%), stroke (5.9%), and hypertensive heart disease (1.6%) accounted for almost one quarter of all deaths in Central Latin America in 2017. Age-adjusted overall CVD, CHD, and stroke mortality rates decreased in this sub-region between 1990 and 2017, but to a lesser extent than for global changes. 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 Middle East

Demographic and Social Indices

The 21 countries of the North Africa and Middle East region represent approximately 8% of the world's population (600 million people). Egypt and Iran are the two most populous countries in the region, with Egypt representing 16% of total inhabitants and Iran 14%. Approximately 65% of the population is urban, with an average life expectancy of 74 years. The average GNI per capita for the region is $7693, ranging from $1460 in Yemen to $61,150 in Qatar. Approximately 5.7% of the GDP, or approximately $459 per capita, is expended for health in the region. The per capita health expenditure ranges from $72 in Yemen to $1649 in Qatar.[15]

Burden of Disease

Thirty-nine percent of all deaths in the North Africa and Middle East region result from CVD: 26% from CHD and 10% from stroke. In 2017, the region had lower overall CVD mortality rates than global averages yet higher than global age-standardized rates. In 2017 the overall death rates per 100,000 for CHD, stroke, and overall CVD were 118, 45, and 187, respectively. The mortality rates for CHD, stroke, and overall CVD declined marginally in the region since 1990, when the rates were 130, 51, and 202 deaths per 100,000 population, respectively. However, age-adjusted mortality rates for CVD declined by 33% across the region. In 2017, CVD accounted for 26 million DALYs lost, or 16% of all DALYs lost, in the region. The DALYs lost were split differently between CHD and stroke, at 15.9 million and 6.6 million, respectively.[1]

South Asia

Demographic and Social Indices

The South Asia region (SAR), one of the world's most densely populated regions, accounts for about 23% of the world's population, with almost 1.8 billion residents. India, home to 77% of the region's inhabitants, is the largest country in the region.[16] Only 34% of the region is urban, and life expectancy is approximately 69 years. Average GNI per capita for the region is $1923, ranging from $970 in Nepal to $2970 in Bhutan. India's GNI per capita of $2020 sits near the regional average. Countries in the SAR spend an average of 3.5% of their total GDP, or $64 per capita, on health care. Bhutan spends the most per capita at $97, and India spends $70, or 3.5% of its GDP. The lowest expenditures for health care are $36 per capita in Bangladesh and $45 in Pakistan.[15]

Burden of Disease

CVD accounts for 27% of all deaths in the SAR. CHD was the lead cause of mortality in 2017, accounting for 15.5% of total reported fatalities, or 1.9 million deaths, and more than half of CVD mortality. Stroke accounted for 8.2% of all deaths and 30% of CVD deaths. The region lost almost 83.5 million DALYs from CVD in 2017, accounting for 13.5% of the total. CHD contributes 55% of the DALYs lost because of CVD, nearly twice as high as for stroke. Overall mortality rates for CVD are increasing in the region, while age-adjusted rates are slowly decreasing.[1]

CVD represents 27% 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 CVD onsets at least a decade earlier in the Indian population than in comparison with those of European ancestry.[17,18]

Sub-Saharan Africa

Demographic and Social Indices

The GBD study divides sub-Saharan Africa into four sub-regions: Central, Eastern, Southern, and Western sub-Saharan Africa. Approximately one billion people live in these four regions, with Nigeria being the most populous (206 million) and Cape Verde being the least populous (545,000). Only 40% of the population in the region is urban. The average GNI per capita is $1519, ranging from $280 in Burundi to $7750 in Botswana. Overall, the region also has the lowest average life expectancy—61 years.[15] Average public and private health care expenditures for the region are 5.2% 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 $19 in the Democratic Republic of the Congo to $499 in South Africa. Nigeria spends $74 per capita, or 3.8% of the total GDP.[15]

Burden of Disease

Communicable, neonatal, and maternal disorders still dominate causes of death in sub-Saharan Africa. HIV/AIDS and neonatal disorders are the leading causes of death, accounting for almost 19% of deaths in the region, while CHD and stroke account for 9.2%.[1] In Western sub-Saharan Africa, CVD accounts for 10.3% of all deaths. The highest portion of CVD-related deaths occurred in Southern sub-Saharan Africa, where 15.9% of all deaths were caused by CVD. Overall CVD mortality rates in the region are lower than global averages and are decreasing, while global rates have held steady. The exception is Southern sub-Saharan Africa, where rates increased from 109 to 135 per 100,000 between 1990 and 2017. Communicable, neonatal, and maternal disorders still dominate causes of death in sub-Saharan Africa.

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 25 to 31). 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 below.

Tobacco

By many accounts, tobacco use is the most preventable cause of death in the world. More than 1.4 billion people use tobacco worldwide, with 5.8 trillion cigarettes smoked globally in 2014.[19,20] Around 80% of the world's tobacco smokers live 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. 2.8). Although historically greatest in HICs, tobacco consumption has shifted dramatically to LMICs in recent decades; some of the highest-known tobacco use now occurs in the EAP region. Kiribati has the highest known prevalence of age-adjusted tobacco use in the world, 52.0%: 68.6% in men and 35.5% in women. For men, Indonesia, Myanmar, and Timor-Leste, all of the EAP region had similarly high tobacco use prevalence rates in 2018 (70.5%, 70.2%, and 65.8%, respectively). For women, the highest known prevalence rates in 2018 were in Serbia, Chile, and Lebanon (40.0%, 49.2%, and 49.4%, respectively).

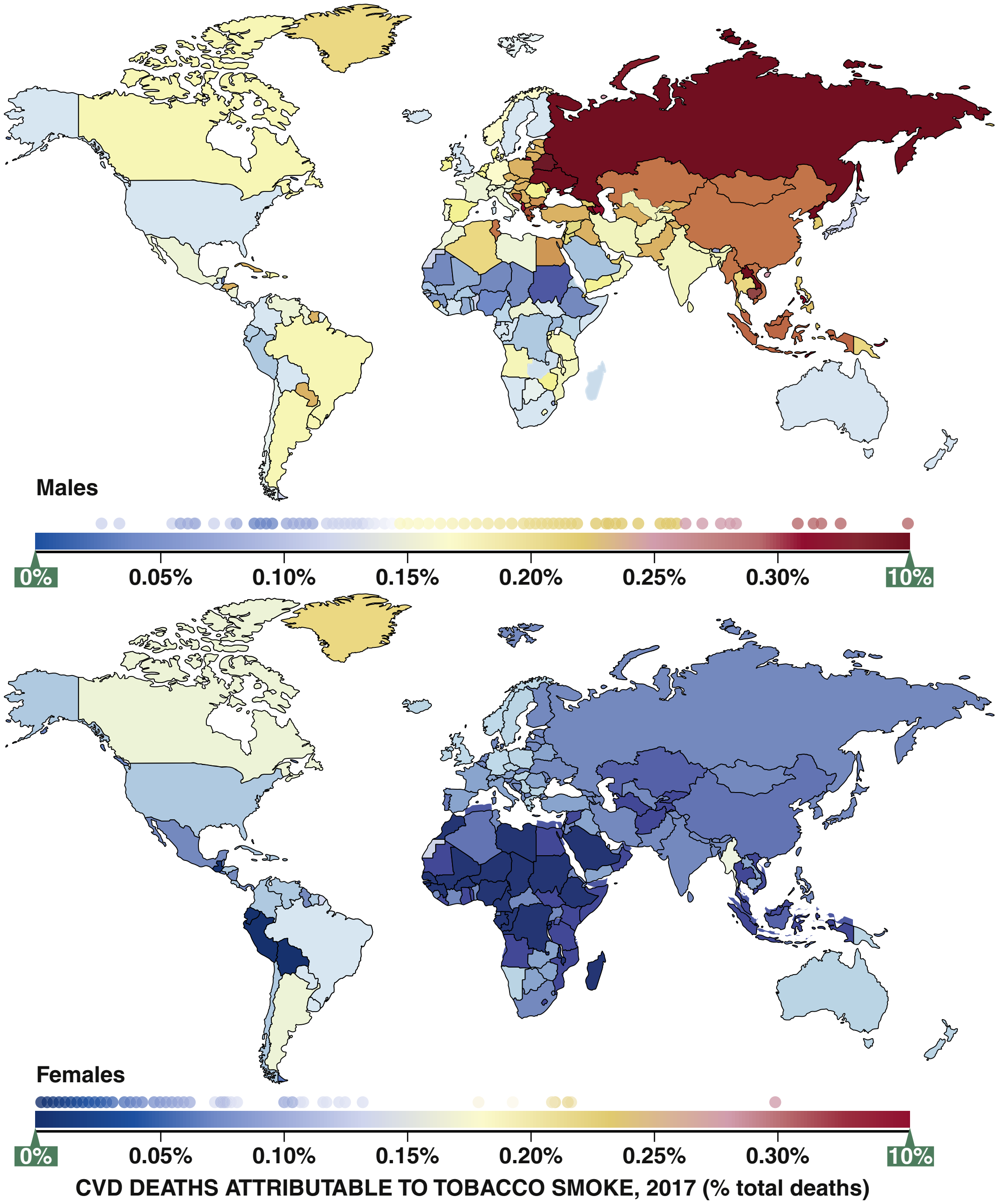

FIGURE 2.8 Cardiovascular disease mortality attributable to tobacco smoke in 2017, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

China is the largest consumer of tobacco in the world, with an estimated 270 million daily smokers in 2015 (40.6% prevalence in men). Daily smoking prevalence in China increased slightly from 21.4% in 1980 to 22.0% in 2015. Several countries in Central and Eastern Europe also have alarmingly high prevalence rates, including Russia (approximately 41.8% in men and 11.5% in women), Ukraine (43.7% prevalence in men), and Albania (29.1% 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 8% and 1% prevalence in men and women, respectively.

Women also have a high and increasing smoking prevalence in several countries, including Kiribati (22.7%), Austria (21.1%), and Greece (25.8%). In general, however, considerably more men than women smoke. Where they do occur, variations by sex can be substantial. In China, for example, tobacco use prevalence is 47.7% in men but only 1.8% in women. Indonesia has similarly diverging trends: prevalence in men is 70.5% and only 5.3% 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 4% 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 (see Chapter 28). 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 2017, approximately 575,000 non-smokers died of CVD as a consequence of exposure to secondhand smoke.[1] The risk assessment analysis of 195 countries for the GBD Study 2017 found that the largest portion of secondhand smoke–related deaths in 2017 resulted from ischemic heart disease.[21] Smoking bans have both immediate and long-term effects in reducing admissions for acute coronary syndrome (ACS).[22]

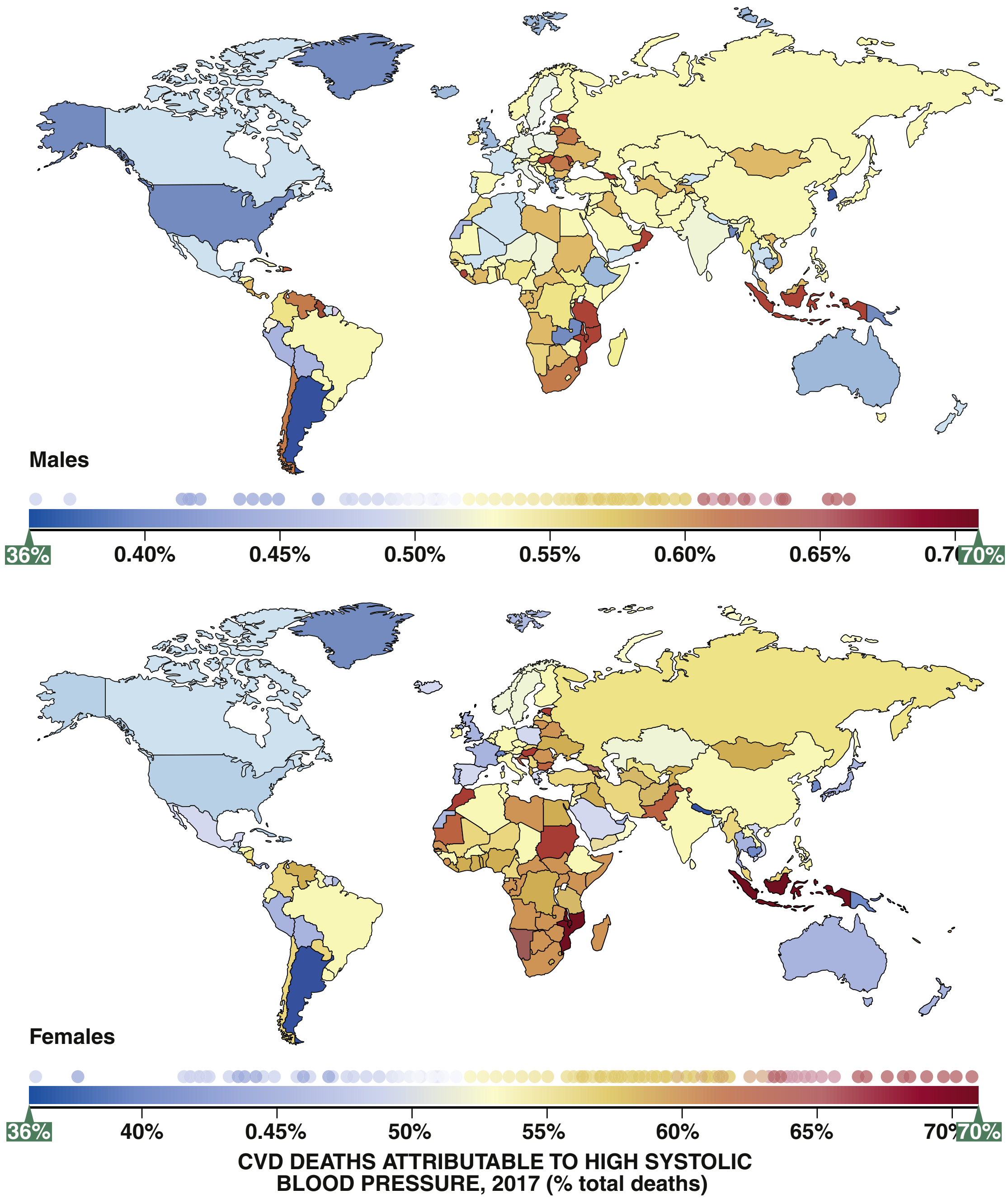

FIGURE 2.9 Cardiovascular disease mortality attributable to high systolic blood pressure in 2017, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

Hypertension

Elevated BP is an early indicator of an epidemiologic transition. Rising mean population BP occurs as populations industrialize and move from rural to urban settings. Worldwide, 55% of stroke-related deaths and 55% of ischemic heart disease-related deaths are attributable to sub-optimal (>115 mm Hg) systolic BP (SBP) control, accounting for 8.25 million deaths in 2017. The GBD project estimates that 19% of deaths and 9% of DALYs lost globally result from non-optimal levels of BP.[1] 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 SBP 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. 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 (SBP ≥140 mm Hg) has increased; in 1990, 442 million had uncontrolled hypertension, and by 2015, the number increased to 874 million.[23] The trend results largely from population growth and aging. Globally, mean SBP 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 SBP 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 2017 varied by sex (Fig. 2.9).

The highest mean SBP in 2015 occurred in East and West African countries, where both men and women had SBP levels that were significantly higher than global averages (men: 129.4; women: 126.2). In

Mozambique and in São Tomé and Príncipe, for example, mean SBP in women was 134.9 and 137.1 mm Hg, respectively. In men, mean SBP was as high as 138.6 mm Hg in Mozambique and 130.9 mm Hg in Niger. Men in Eastern Europe had mean SBP levels comparable to those in East and West Africa. Mean SBP was lowest in high-income regions such as Australasia (124.0 mm Hg in Australian women) and North America (122.8 mm Hg in U.S. men).

The most significant decreases occurred in the high-income Asia Pacific region, where mean SBP decreased by 2.5 mm Hg on average per decade between 1975 and 2015 in men and 3.2 mm Hg on average per decade in women. The decrease in men ranged from 0.2 to 2.5 mm Hg per decade. The decrease in mean SBP in women ranged from 1.1 mm Hg per decade in Central Asia, North Africa and the Middle East to 3.2 mm Hg per decade in High-Income Asia Pacific.

Mean SBP increased in several regions. In South Asia, SBP increased by 1.2 mm Hg on average per decade in men and 1.3 mm Hg on average per decade in women. South and East Asia saw similar increases: 1.1 mm Hg on average per decade in men and 0.8 mm Hg on average per decade in women. In Sub-Saharan Africa, mean SBP increased by 0.5 mm Hg on average per decade in men and 0.9 mm Hg on average per decade in women.

Notable sex differences occurred in Oceania and Central and Eastern Europe. In Oceania, mean SBP in women increased by 2.5 mm Hg on average per decade, the largest increase in any female cohort in the world. In men in this region, however, mean SBP increased by only 1.4 mm Hg on average per decade despite being the largest increase of all male cohorts. Data from Central and Eastern Europe show diverging trends in men and women: although mean SBP in men decreased by 0.2 mm Hg on average per decade, it decreased in women by 1.8 mm Hg.

Lipids (see Chapter 27)

Worldwide, high cholesterol causes about 42% of ischemic heart disease deaths and 9% of stroke deaths, accounting for 4.3 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 total 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. Eventually there is a decline, as seen in the last set of trend data produced by the GBD through 2009.

There has not been a systematic estimate of global trends in total cholesterol levels since 2011. More recent data also suggest that following only total cholesterol levels may be misleading. In an analysis of 438 populations from 21 Western and Asian countries totaling 82 million participants, several different patterns emerged in the lipid parameters from 1980 to 2015.[24] In Asia, for Japan and South Korea, the rise in total cholesterol was primarily due to an increase in HDL cholesterol whereas in China the risk was due primarily to non-HDL cholesterol. For most Western countries there was a decline in total cholesterol, which included the net effect of both a rise in HDL cholesterol and an even greater reduction in non-HDL, with the greatest changes occurring in New Zealand and Switzerland. Overall the total-to-HDL cholesterol ratio declined in Japan, Korea, and most Western countries.

Diabetes (see Chapter 31)

Diabetes prevalence has increased rapidly worldwide in the past 30 years. As a result, death rates of CVD attributable to diabetes have increased for many LMICs, particularly in East Asia, South Asia, and Eastern Europe and Central Asia (Fig. 2.10). According to the GBD study, an estimated 476 million people worldwide have diabetes.[25] 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 451 million adults had diabetes in 2017.[26] Almost 50% of these cases were undiagnosed. By 2045 the number of people with diabetes is expected to increase to 693 million.[26]

Almost 80% of people with diabetes live in LMICs. The highest regional age-standardized prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 8.2% of the population has diabetes. However, the top ten countries with the highest age-standardized prevalences (ranging from 14.2% to 23.5%) are all within the Southeast Asia, East Asia, and Oceania regions.[1]

Asian countries face a relatively larger burden of diabetes compared to 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: 67.8 million and 89.5 million, respectively.[1]

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 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 (see Chapter 30)

In 2015, an estimated 603.4 million adults and 107.7 million children were obese.[27] Global obesity prevalence was 12.0% among adults (5.0% among children) and is increasing throughout the world and particularly in LMICs, which have steeper trajectories than in HICs. Explanations for this rapid rise include changes in dietary patterns, physical activity, and urbanization. Rapid changes in the global food system have increased the availability and consumption of inexpensive, ultra-processed food and beverages rich in refined carbohydrates, fat, sugar, and salt in LMICs.[28] 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. The poor are relatively more susceptible to obesity as a developing country's GNP approaches the middle-income range. 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 by obesity than men; the proportion of the world's adult women who are either overweight or obese rose from 29.8% to 38.0% between 1980 and 2013, while an increase from 28.8%

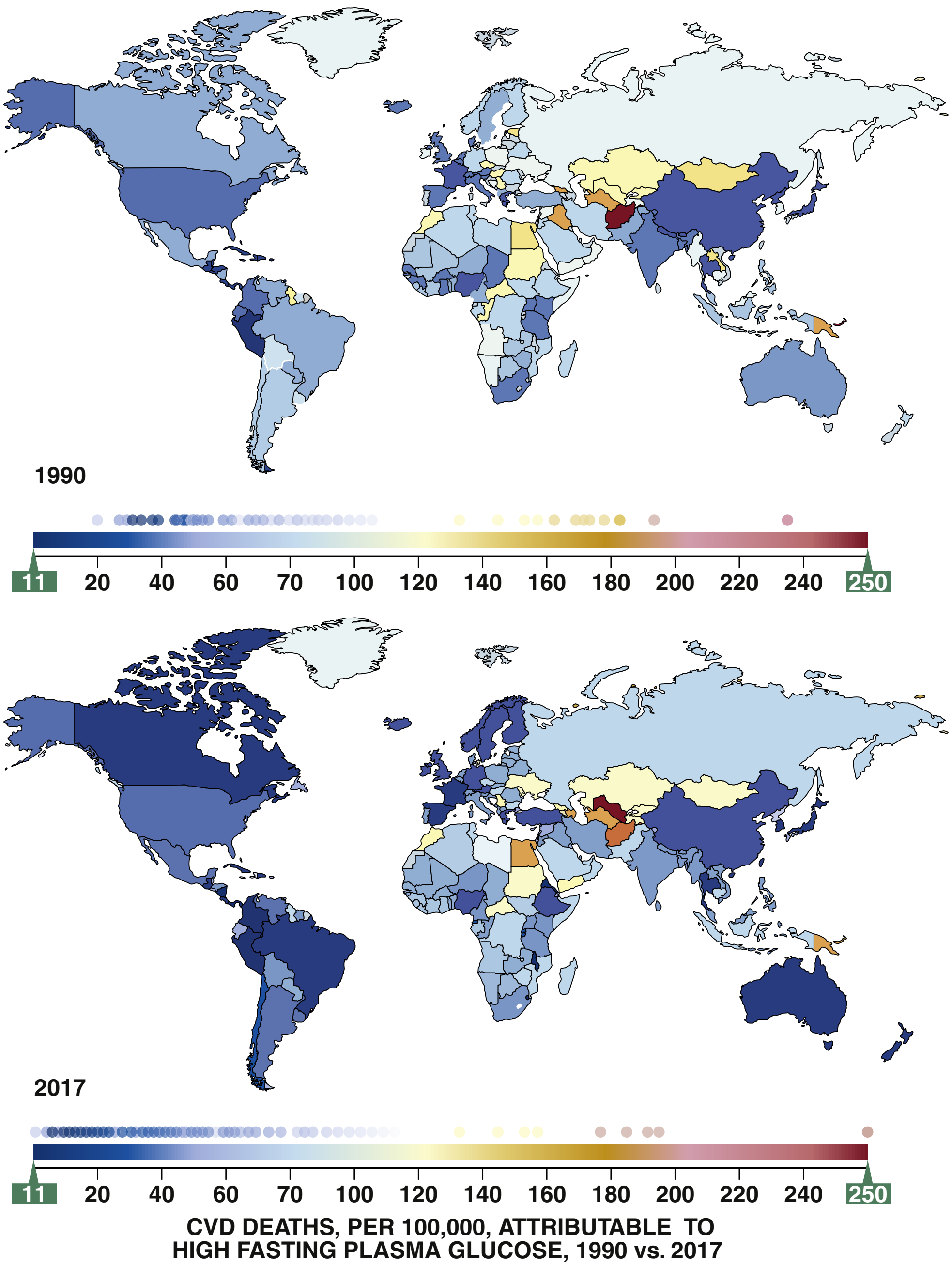

FIGURE 2.10 Cardiovascular disease mortality attributable to high fasting plasma glucose, deaths per 100,000, 1990 versus 2017. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

to 36.9% was observed for men. Adolescents are at particular risk: 18% of children and adolescents aged 5 to 19 were overweight or obese in 2016, up from 4% in 1975. The number of overweight children is increasing in countries as diverse as China, Brazil, India, Mexico, and Nigeria. The World Health Organization (WHO) estimates that in 2019, 38.2 million children younger than 5 years were overweight. In 1975 worldwide obesity prevalence was 3.2% in men and 6.4% in women. By 2014, prevalence had increased to 10.8% in men and 14.9% in women.[29]

Globally, BMI rose in both men and women. Between 1975 and 2014, global age-standardized mean BMI rose from 22.1 to 24.4 kg/m^2 in females and 21.7 to 24.2 kg/m^2 in males.[29]

BMI varies 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-related 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. 2.11). In 2016 the age-standardized mean BMI in the United States was 29.0 kg/m^2 in men and 29.1 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 20.1 kg/m^2, and women in Bangladesh have a mean BMI of 22.1 kg/m^2.

The largest increase in BMI occurred in Oceania. Between 1980 and 2008, mean BMI rose by 1.3 kg/m^2 per decade in men and 1.8 kg/m^2 per decade in women. Of the islands in the Oceania region, Nauru had the largest BMI increase of more than 2 kg/m^2. BMI trends were similar in the North American high-income region (1.1 kg/m^2 per decade in men and 1.2 kg/m^2 per decade in women). In Latin America and the Caribbean, mean BMI for women increased from 0.6 to 1.4 kg/m^2 per decade. By contrast, mean BMI decreased in Central African men by 0.2 kg/m^2 per decade and remained unchanged in South Asian men. In women, mean BMI remained static, with changes less than 0.2 kg/m^2 per decade in Central Asia, Central Europe, and Eastern Europe.

Although regional trends generally showed concordance between sexes, some exceptions occurred. There was no change in mean BMI in South Asian men, but mean BMI in women increased at a rate close to the global average, 0.4 kg/m^2 per decade. The most significant discrepancy in sex trends occurred in Central Africa. BMI in men in Central Africa decreased by 0.2 kg/m^2 per decade, the only significant decrease in any male population in the world. In women in Central Africa, however, mean BMI increased by 0.7 kg/m^2 per decade, a rate greater than the world average.

Diet (see Chapter 29)

As humans have evolved, selective pressures have favored the ability to conserve and store fat as a defense against famine. This adaptive mechanism has become unfavorable in light of the larger portion sizes, processed foods, and sugary drinks that many people now regularly consume. Between 1970 and 2010, the average daily per capita caloric intake in the United States increased from 2076 to 3766 calories.[30] As per capita income increases, so does consumption of fats and simple carbohydrates, whereas intake of plant-based foods decreases. A key element of this dietary change is an increased intake of saturated animal fats and inexpensive hydrogenated vegetable fats, which contain atherogenic *trans* fatty acids. New evidence suggests that high intake of *trans* fats may also lead to abdominal obesity, another risk factor for CVD.

China provides a good example of such a "nutritional transition"—rapid shifts in diet linked to socioeconomic changes. The China Nationwide Health Survey found that between 1982 and 2002, calories from fat increased from 25% to 35% in urban areas and from 14% to 28% in rural areas, as calories from carbohydrates fell from 70% to 47%. Recently in 1980, the average BMI for Chinese adults was about 20 kg/m^2, and less than 1% had a BMI of 30 kg/m^2 or greater. From 1992 to

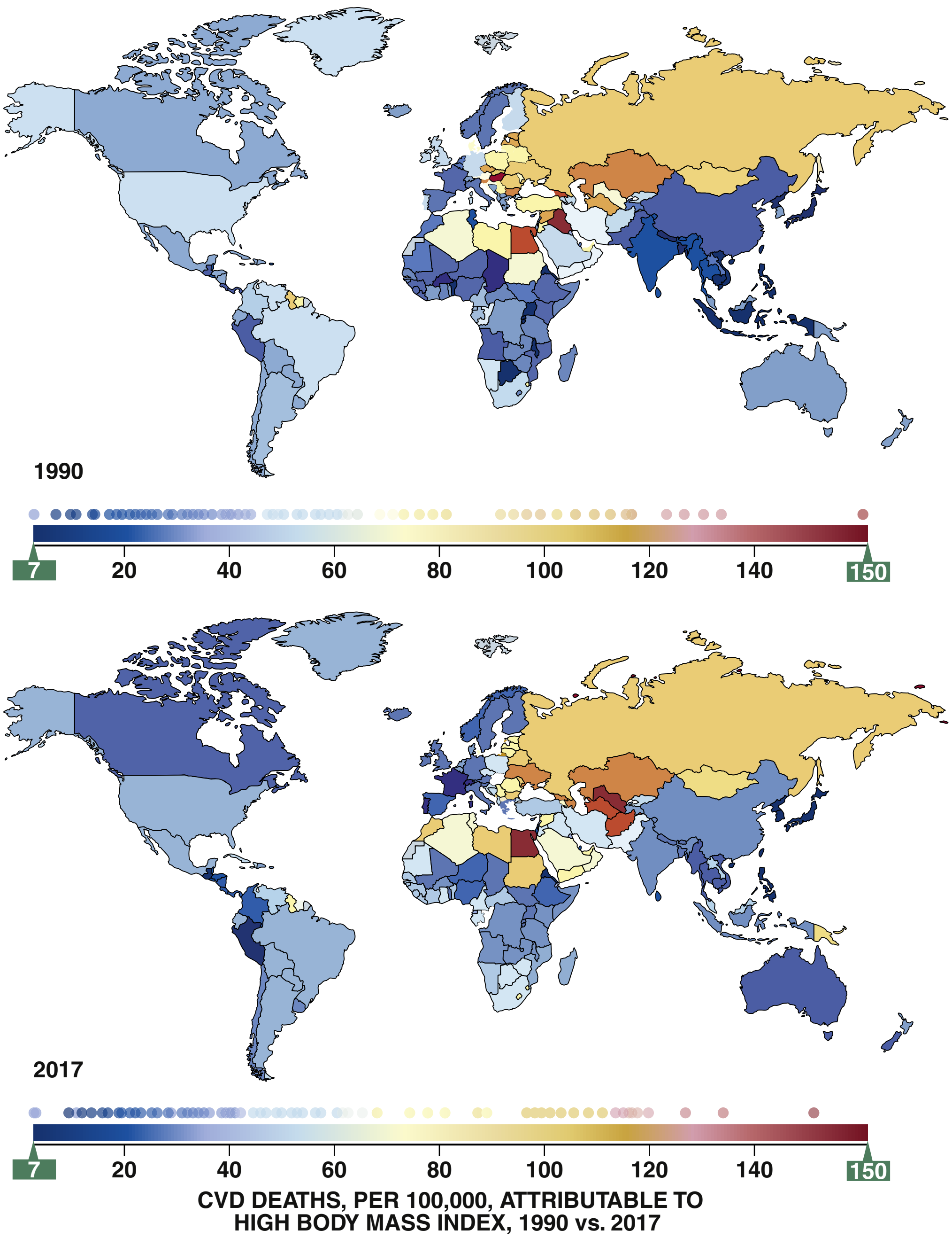

FIGURE 2.11 Cardiovascular disease mortality attributable to high body-mass index, deaths per 100,000, 1990 versus 2017. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

2002, the number of overweight adults increased by 41%, and the number of obese adults increased by 97%.

China and other countries in transition have the opportunity to spare their populations from the high levels of *trans* fats that North Americans and Europeans have consumed over the past 50 years by avoiding government policies that can contribute to the CVD burden. An estimated 919 CVD-related deaths per million adults could be averted each year in the United States by eating the recommended amounts of fruits, vegetables, nuts/seeds, whole grains, polyunsaturated fats, omega-3 oils, and eliminating sugar-sweetened beverages, processed meats, and excess sodium.[31] Another facet of the nutritional transition for countries adopting a Western diet is the introduction of high-sugar beverages associated with weight gain and increased risk for type 2 diabetes. A meta-analysis suggests up to a 16% relative risk increase in CHD per unit of sugar-sweetened beverages consumed daily.[32] Improvements in consumption could save the United States $50 billion a year in CVD-related health costs.[31]

Physical Inactivity (see Chapters 30 and 32)

Physical inactivity is responsible for 1.3 million global deaths annually. The global age-standardized prevalence of physical inactivity has remained steady between 2001 and 2016 (28.5% to 27.5%). In HICs the widespread prevalence of physical inactivity produces a high population-attributable risk of cardiovascular consequences. Physical inactivity is also increasing in low- and middle-income regions of the world, witnessing a shift from physically demanding, agriculture-based work to largely sedentary, service industry-based and office-based work. A switch to mechanized transportation accompanies this work shift.

Current WHO recommendations call for moderate-intensity exercise for at least 150 minutes, or 75 minutes of vigorous exercise per week. In the United States, approximately one-quarter of the adult population does not participate in any leisure-time physical activity, and only 24.3% of adults reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet federal guidelines. Physical inactivity levels vary by region and by sex. The lowest levels of physical inactivity in 2016 were in men from Oceania (12.3%), East and Southeast Asia (17.6%), and sub-Saharan Africa (17.9%), while the highest levels were in women in high-income Western (42.3%), South Asia (43.0%), and Latin America and the Caribbean (43.7%). A study of adults in China using data from randomized national surveys from 2000 to 2014 found that despite increased participation in leisure-time physical activity, there were in also increases in overweight or obesity.[33]

Aging Populations (see Chapter 90)

Between 1990 to 1995 and 2015 to 2020, global life expectancy at birth increased by 7.7 years and is projected to increase by an additional 4.5 years between 2015 to 2020 and 2045 to 2050.[34] This increase is associated with a decline in overall infant mortality and fertility rates. Although older adults will constitute a greater percentage of the population in HICs, more than 53.3 million Americans were older than 65 years in 2019 and is projected to increase to 84.8 million by 2050. Low- and middle-income regions will see the population over 65 more than double from 2019 to 2050.

The time of transition to an older population is sharply shorter in LMICs. For example, whereas it took the United States and Canada more than 65 years to double their over-65 population, LMICs will do so every 25 years for the next 50 years. Such acute changes in the population structure leave less time to expand an already overburdened health infrastructure to address the chronic diseases of older adults, which prominently include cardiovascular conditions.

Genetic

A great deal of effort has recently been invested in understanding how genes impact cardiovascular health in populations. These have focused on germline genetic variants that are related to specific cardiovascular diseases as well as those that are associated with cardiovascular risk factors. In either case, every year the number of associated variants has increased meaningfully, to the point that hundreds or even thousands of variants are associated with these conditions, each explaining a small amount of the population variability in disease and risk factors. Collections of variants have been combined in polygenomic risk scores, but these too explain only a small amount of the variability of the disease in the population. More data will be available in the coming years about these associations, mechanisms that explain these associations, relationships of variants that are specific to certain tissues such as the heart or the brain, and the interactions between genetic and lifestyle factors that cause the disease. Currently, most of the data are among those with European ancestry; however, large-scale efforts are underway to understand the relationships between genes and diseases and their risk factors around the world. The early data suggest nontrivial differences among various world populations.

Fetal Influences

Adverse influences such as undernutrition during fetal life (fetal "programming") and early postnatal life appear to affect the prevalence of adult CVD and contribute to its risk factors. Barker,[35] in his "developmental origins of adult disease" hypothesis, suggested that adverse influences early in development, particularly during intrauterine life, could result in permanent changes in the physiology and metabolism of the pancreas, kidney, muscle, and vascular endothelium, resulting in adult insulin resistance, metabolic syndrome, hypertension, and CHD. Recent evidence indicates that the first thousand days of life, comprising intra-uterine life (270 days) and the first 2 years of postnatal life, is a sensitive or "critical" period of development, and any stimulus or insult during this period appears to have lasting or lifelong significance for adult-onset CVD.[36] Extensive data support these associations.[37] More recent studies tried to evaluate the role of multiple micronutrient supplementation as well, but a recent meta-analysis concluded that there is no added benefit in improving later life outcomes like childhood survival, growth, body composition, BP, respiratory or cognitive outcomes.[38] The mechanisms of increased risk appear to be both biologic (alterations in fetal tissues and postnatal epigenetic modifications) and social (cognitive impairment, low productivity, and higher prevalence of cardiovascular risk factors among those with lower birth weight and early-life adverse influences), and childhood obesity and sedentary habits aggravate this risk. Thus the prevention of adverse fetal exposures and subsequent long-term consequences require a holistic approach. An understanding of prenatal risk factors and their early childhood modifiers will provide an opportunity for interventions before the development of risk factors. Remedies include improved maternal nutrition during pregnancy and lactation, emphasis on breastfeeding through early infancy, and ensuring adequate balanced nutrition to infants. Focus on the adolescent group has shown added benefit of building maternal reserve prior to pregnancy to ensure optimal birth outcomes. On the basis of current understanding, policymakers and health care professionals should design and develop preventive strategies that effectively influence these very early determinants of CVD development.[37]

Environmental Exposures (see Chapter 3)

Environmental pollution, especially both indoor and outdoor air pollution, has emerged as a major cause of death and disease burden (see Chapter 52).[39] Exposure to particulate-matter (PM) air pollution,[40,41] heavy metals (e.g., cadmium, arsenic, lead, mercury),[42] and polyaromatic hydrocarbons[43] is associated with increased risk of mortality and morbidity from CVD. The GBD comparative risk assessment of 2017 has shown that more than 23% of all DALYs from ischemic heart disease and about 28.9% of DALYs from ischemic strokes result from environmental risk factors,[21] approximately the same as those attributable to tobacco smoke. Of these exposures, air pollution (household and ambient) is the most prominent risk factor, contributing to approximately 7 million premature deaths annually, with a majority occurring in LMICs such as India and China.

In many developing countries, populations experience a continuum of exposure to ambient air pollution (from vehicles, industry, etc.) and household air pollution (from cooking, heating, and lighting), resulting in significant contributions to the health burden, as in India, where it is the second most important risk factor for poor health. More than half of all deaths associated with air pollution exposure are through cardiovascular and cerebrovascular pathways, involving ischemic heart disease, heart failure, stroke, and hypertension.[44,45] Three pathways, listed below in order of the strength of the evidence base, may contribute to the mechanisms that link PM exposure to CVD and cerebrovascular disease:

1. Particle transport into the lungs provoking inflammatory responses and promoting systemic oxidative stress. This leads to increased risk of thrombosis, endothelial dysfunction, atherosclerosis progression, and dyslipidemia.
2. Particle transport into the lungs promoting autonomous nervous system imbalances. This leads to pathologic alterations in hypertension, endothelial dysfunction, vasoconstriction, and atherosclerosis.
3. Absorption of particles through the lungs into the bloodstream causing tissue-level interactions. This results in platelet aggregation, vasoconstriction, and endothelial dysfunction.

The epidemiologic evidence base suggests that exposure to arsenic, cadmium, and lead follows the common physiologic pathways observed with air pollution.[46] In addition, the mechanistic evidence from animal and human studies indicates that arsenic exposure is associated with carotid intima media thickness, a marker for atherosclerosis, with links to diabetes is also observed.[47]

Regardless of the primary route and the pathophysiology involved, short- or long-term exposure to various environmental pollutants is associated with an increased risk of ischemic heart disease, stroke, heart failure, and preclinical conditions such as endothelial dysfunction, thrombosis, atherosclerosis, and hypertension. Although epidemiologic evidence has been well documented for single pollutants, the synergistic impacts are understudied. From a physician's perspective, informing patients on how to avoid exposure and protect themselves should be part of primary prevention.

ECONOMIC BURDEN

Despite some overlap, at least three approaches can measure the economic burden associated with CHD. The first source of financial burden reflects the costs incurred in the health care system itself and reported in "cost-of-illness" studies. As an example, it is estimated that CVD health care costs related to poor nutrition are over $50 billion per year in the United States.[31] In these studies, the cost of CHD includes the costs of hospitalizations for angina and MI, as well as heart failure attributable to CHD. The cost of specific treatments or procedures related to CVD (e.g., thrombolytics, catheterization, PCI) and the cost associated with outpatient management and secondary prevention (e.g., office visits, pharmaceutical costs) are also included. In addition, nursing home, rehabilitation (inpatient and outpatient), and home nursing costs require consideration.

The second economic assessment is derived from microeconomic studies that assess the household impact of catastrophic health events such as MI. These studies look at out-of-pocket expenses incurred by the individual patient or family that might have other, downstream economic impacts, such as loss of savings or sale of property to cover medical costs. Many LMICs lack an extensive insurance scheme, and health care costs are almost entirely borne by individuals; over 800 million people experience financial catastrophe each year because of medical expenditures when defined by 10% of household expenditures devoted to health care expenses.[48,49] Furthermore, the limited data do not confirm the causality between chronic disease and individual or household poverty. However, expenditures for CHD or its addictive risk factors (e.g., tobacco) could lead to substantial and even impoverishing costs.

The third method of determining financial burden from CHD is based on a macroeconomic analysis. These assessments examine lost worker productivity, or the economic growth lost as a result of adults with CHD or their caregivers being partially or completely out of the workforce because of illness. The data for the impact of chronic diseases on labor supply and productivity are more robust. An additional cost usually not accounted for is the intangible loss of welfare associated with pain, disability, or suffering by the affected person. These indirect costs are often addressed by "willingness-to-pay" analyses, asking generally how much would an individual pay to avert suffering or dying prematurely from CHD. The gains are not merely improved work performance, but also enjoying activities beyond productivity. U.S. studies suggest that as much as 1% to 3% of GDP is attributable to the cost of care for CVD, with almost half of that related to CHD.[50] In China, annual direct costs of CVD are estimated at more than US$40 billion, or about 4% of GNI. In South Africa, 2% to 3% of GNI is devoted to the direct treatment of CVD, which equates to about 25% of South African health care expenditures. The indirect costs are estimated at more than double that of the direct costs. Although few cost-of-illness studies for CHD have been performed in other regions, such studies have reported on the financial burdens attributed to risk factors for CHD. For example, the direct costs caused by diabetes in the Latin American and Caribbean countries were estimated at US$10 billion. Indirect costs were estimated at more than $50 billion in 2000. The limited studies available suggest that obesity-related diseases account for 2% to 8% of all health care expenditures in HICs. In India and China, the costs for obesity are about 1.1% and 2.1% of GDP, respectively.

The costs attributable to non-optimal BP levels as mediated through stroke and MI were evaluated for all regions of the world. Globally, the healthcare costs of elevated BP represent approximately 10% of all global health care expenditures. These costs were recently confirmed in a study that showed elevated BP accounted for over $20 billion in Canada, which is 10.2% of its healthcare costs.[51] Regional variations do exist, with hypertension being responsible for up to 25% of health care costs in the Eastern Europe region (Fig. 2.12).

The high proportion of CVD burden that occurs earlier among adults of working age augments its macroeconomic impact in LMICs. Under current projections, in LMICs such as South Africa, CVD will strike 40% of adults between ages 35 and 64, compared with 10% in the United States. India and China will have death rates in the same age group that are two and three times that for most HICs. In view of the large populations in these two rapidly growing economies, this trend could have profound economic effects over the next 25 years, as workers in their prime succumb to CVD.

COST-EFFECTIVE SOLUTIONS

The large reductions in age-adjusted CVD mortality rates that have occurred in HICs result from three complementary types of interventions. One strategy targets those with acute or established CVD. A second entails risk assessment and targeting persons at high risk because of multiple risk factors for intervention before their first CVD event. The third strategy uses mass education or policy interventions directed at the entire population to reduce the overall level of risk factors. This section reviews various cost-effective interventions (see Chapter 45). Much work remains undone in LMICs to determine the best strategies given limited resources, but if implemented, these interventions could help significantly in reducing the burden. Table 2.2 lists the cost-effectiveness ratios for many high-yield interventions that could be or have been adopted in low- and middle-income regions. In 2017 the WHO published recommendations for preventing non-communicable diseases including CVD. The WHO document further divides the recommendations into 'Best buys' (interventions with cost-effectiveness analysis results less than or equal to $1000 per DALY averted in LMICs) and effective interventions (CEA >$1000/DALY averted).[52]

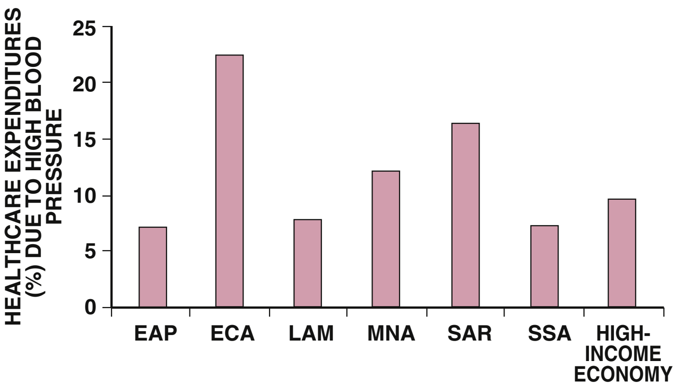

FIGURE 2.12 Percentage of health care expenditures attributed to high blood pressure. *EAP*, East Asia and Pacific; *ECA*, Europe and Central Asia; *LAM*, Latin America and the Caribbean; *MNA*, Middle East and North Africa; *SAR*, South Asia region; *SSA*, sub-Saharan Africa.

Established Cardiovascular Disease Management

People at highest risk are those having an MI or stroke; as many as half die before they ever receive medical attention. For those who do reach a hospital, many cost-effective strategies exist.[4] Four incremental strategies were evaluated for the treatment of MI and compared with a strategy of "no treatment" as a control for the six World Bank low- and middle-income regions. The four strategies compared were (1) aspirin; (2) aspirin and atenolol (beta blocker); (3) aspirin, atenolol, and streptokinase; and (4) aspirin, atenolol, and tissue plasminogen activator (t-PA). The incremental cost per quality-adjusted life-year (QALY) gained for the aspirin and beta-blocker interventions was less than $25 for all six regions. Costs per QALY gained for streptokinase were between $630 and $730 across the regions. Incremental cost-effectiveness ratios for t-PA were about $16,000/QALY gained, compared with streptokinase. Minor variations occurred between regions as a result of small differences in follow-up care based on regional costs. In some LMICs treatment with PCIs where catheterization labs are already established is now considered cost-effective.

Secondary prevention strategies have equal cost-effectiveness in LMICs. A combination of aspirin, an ACE inhibitor, a beta blocker, and a statin for secondary prevention can lead to acceptable cost-effectiveness ratios in all low- and middle-income regions. Use of currently available generic agents, even in the absence of the "polypill," could be highly cost-effective, on the order of $300 to $400 per person per QALY gained. Secondary prevention of rheumatic fever and rheumatic heart disease with prophylactic penicillin is now also recommended by the WHO. Although cost-effectiveness analyses for some therapies in most LMICs have not been conducted, the WHO recommends treatment of heart failure with beta-blockers and angiotensin-converting-enzyme inhibitors; cardiac rehabilitation post MI; and anticoagulation for medium- and high-risk non-valvular atrial fibrillation and for mitral stenosis with atrial fibrillation.

Risk Assessment

Primary prevention is paramount for the large number of people who have high risk for acquiring CVD. The WHO recommends through its 'Best buys' program drug therapy for diabetes mellitus and control of hypertension using an absolute risk approach.[52] In view of limited resources, finding low-cost prevention strategies is a top priority. Using prediction rules or risk scores to identify persons at higher risk to target specific behavioral or drug interventions is a well-established primary prevention strategy and has proved to be cost-effective.[53,54] Most such scoring systems include age, sex, hypertension, smoking status, diabetes mellitus, and lipid values; some also include family history. Other markers of risk, such as C-reactive protein, have been used that improve reclassification and discrimination. Coronary artery calcium scoring may add the most in terms of changes in C-statistic (discrimination) or

TABLE 2.2 Cost-Effectiveness for a Selection of Coronary Heart Disease Interventions in Developing Regions

INTERVENTION	COST-EFFECTIVENESS RATIO ($US/DALY)*
Drug Treatments	
Acute Myocardial Infarction	
ASA, BB (global)	11–22
ASA, BB, SK (global)	634–734
ASA, BB, t-PA (global)	15,860–18,893
Prehospital thrombolysis (Brazil)	457/LY
Secondary Treatment (CHD)	
Multidrug regimen (ASA, BB, ACEI, statin) (global)	1686–2026
Coronary artery bypass graft (global)	24,040–72,345
Primary Prevention	
Cholesterol lowering (Brazil)	441/LY
Hypertension using absolute risk approach of those with 10-year CVD risk >20% and glycemic control for those with diabetes mellitus	<100
Multidrug regimen (AR > 20%–25%) (global)	771–1195
Policy Interventions	
Tobacco	
Price increase of 33%	2–85
Nonpolicy Interventions	
(standardized packing or graphic warnings, bans on advertising and sponsorship, reduced secondhand exposure to indoor workplaces and public sites, and mass media campaigns)	33–100
Salt Reduction‡	
2–8 mm Hg reduction (via reformulation of food products to contain less sodium and setting target levels for gram of food items, mass media, and front of package labeling)	Cost-saving: 250
Fat-Related Interventions§	
Reduced saturated-fat intake	Cost-saving: 2900
Trans fat replacement: 7% reduction in CHD	50–1500
Devices	
Cardioverter-defibrillators: primary prevention (Brazil)	50,345 (US$PPP/QALY)
Physical Activity	
Community wide public education and awareness campaign and environmental programs aimed at behavioral change	<$100)

*Across six World Bank regions; *DALY,* disability-adjusted life-year; *PPP,* purchasing power parity; *QALY,* quality-adjusted life-year.
‡Range includes different estimates of cost of interventions, as well as blood pressure reduction (<$0.50 to $1.00).
§Range includes estimates of cost of interventions (<$0.50 to $6.00).
ASA, Acetylsalicylic acid (aspirin); *BB,* beta blocker; *CHD,* coronary heart disease; *SK,* streptokinase; *ACEI,* angiotensin-converting enzyme inhibitor; *t-PA,* tissue plasminogen activator; *AR,* absolute risk.
Data from Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation*. 2005;112:3547; Gaziano TA, Galea G, Reddy KS. Chronic diseases 2—scaling up interventions for chronic disease prevention: the evidence. *Lancet*. 2007;370:1939; and World Health Organization. *Tackling NCDs: "Best Buys" and Other Recommended Interventions for the Prevention and Control of Noncommunicable Diseases*. Geneva: World Health Organization; 2017.

the net reclassification improvement (NRI) in intermediate-risk populations, and is found to be cost-effective at least in high-income settings (see Chapter 25).[55]

More attention is now focused on developing risk scores that would be easier to use in resource-poor countries, without loss of predictive discrimination. A study based on the U.S. National Health and Nutrition Examination Survey (NHANES) follow-up cohort demonstrated that a non–laboratory-based risk tool that uses information obtained in a single encounter (age, systolic BP, BMI, diabetes status, and smoking status) can predict CVD outcomes as effectively as one that requires laboratory testing, with C-statistics of 0.79 for men and 0.83 for women that were no different from those obtained using the Framingham-based risk tool, and has been shown to correlate with other scores in other countries.[56] In LMICs with limited testing facilities, a prediction rule that requires a laboratory test may be too expensive for widespread screening, or the cost may preclude its use altogether. In response to this concern, WHO recently released risk-prediction charts for the different regions of the world, with and without cholesterol data.[57] Furthermore, community health workers can use the simple risk scores effectively, decreasing the cost of screening significantly.[58,59] The ankle-brachial index (ABI) also appears to add to risk discrimination and improve the NRI as an alternative noninvasive tool. The American Heart Association and the American College of Cardiology have recommended the use of ABI among high risk individuals while the US Preventative Services Task Force has written that there is limited information with regards to use in determining treatments in the general asymptomatic population.[60]

Policy and Community Interventions

Education and public policy interventions that have reduced smoking rates, lowered mean BP levels, and improved lipid profiles contribute to reduction in CHD rates.[4] Education and policy efforts directed at tobacco consumption have contributed substantially to the reductions in CVD. These included recommendations for reducing tobacco use, harmful effects of excessive alcohol, improved diets, and increases in physical activity.[52]

Tobacco Use

Tobacco control can be conceptualized in terms of strategies that reduce the supply of or the demand for tobacco. Most public health and clinical strategies to date focus on reducing demand through economic disincentives (taxes), health promotion (media and packaging efforts), restricted access (to advertising and tobacco), or clinical assistance for cessation. The WHO effort to catalyze the creation of a global treaty against tobacco use was a key milestone. In May 2003 the WHO World Health Assembly unanimously adopted the WHO Framework Convention in Tobacco Control (FCTC), the first global tobacco treaty. The FCTC had been ratified by 168 countries as of 2016, making it one of the most widely embraced treaties in the United Nations. The FCTC has spurred efforts for tobacco control across the globe by providing both rich and poor nations with a common framework of evidence-based legislation and implementation strategies known to reduce tobacco use.

Five "Best buys" for tobacco control include (1) increased excise taxes on tobacco, (2) standardized large graphic warnings on tobacco packaging, (3) enforce bans on advertising and promotion, (4) reduce exposure to secondhand smoke in work and public settings, and (5) implement mass media campaigns about harms of tobacco.[52]

Critically important for patients who have had a coronary event, smoking cessation saves lives at a greater rate than any individual medical treatment. Quitting smoking in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 trial was associated with a 40% relative risk reduction for MI. Further studies suggest that varenicline leads to increased smoking cessation rates,[61] although it is unclear whether it is better than traditional NRTs.[62]

Salt, Dietary, and Lipid Reductions

The analyses on salt reduction achieved as a result of mass interventions are also quite favorable. Four WHO "Best buys" are: (1) reduce salt intake through the reformulation of food products with target levels, (2) increase options of lower sodium food options in institutions, (3) mass media campaigns for behavioral change, and (4) front of package labeling of sodium content.[52]

Elimination of trans-fat through legislation is also proven cost-effective and recommended by eh the WHO. Four other dietary recommendations that are either cost-saving or cost-effective include (1) financial incentives to those purchasing food through government food provision programs,[63] (2) taxation of sugar sweetened beverages,[64] (3) incentives to purchase healthy food items administered through government health insurance schemes,[65] and (4) menu calorie labeling regulations.[66] Simple measures such as changing prescription length for medications such as statins[67] or training community health workers to do screening for CVD can be cost-effective.[58,68]

SUMMARY AND CONCLUSION

Cardiovascular disease remains a significant global problem. The swift pace of economic and social transformation in a postindustrial world with rapid globalization presents a greater challenge for low- and middle-income economies than for high-income economies. Although CVD age-adjusted rates have declined in HICs and some of the LMICs, the number of CVD survivors continues to increase because of aging populations and improvements in case-fatality rates for acute events. From a worldwide perspective, the rate of change in the global burden of CVD is accelerating, reflecting the changes in the low- and middle-income economies, which represent 85% of the world's population. This preventable epidemic will have substantial consequences on many levels: individual mortality and morbidity, family suffering, and staggering economic costs, both the direct costs of diagnosis and treatment and the indirect costs of lost productivity.

Different regions of the world face different stages of the epidemic. In HICs, managing an ever-older population with chronic manifestations of CVD such as heart failure will strain health care budgets. Currently, the Eastern European countries and members of the former Soviet Union face enormous burdens, with more than half of all deaths attributed to CVD. Meanwhile, countries in sub-Saharan Africa are just beginning to see increases in these chronic illnesses while still grappling with HIV/AIDS. No single global solution to the rising burden of CVD exists, in view of the vast differences in social, cultural, and economic circumstances. HICs must minimize disparities, reverse unfavorable trends in CVD risk factors and behaviors, and deal with the increasing prevalence of CVD in an aging population. The most complex challenges face LMICs, with increasing access to low-cost tobacco products and ready access to less-than-favorable dietary options. Preventing the poverty-inducing effects of catastrophic CVD events will require efforts to improve access to low-cost prevention strategies at both the societal and the individual levels and must include improved financing for at least catastrophic health coverage.

A reduction in the disease burden would similarly require both policy and personal changes. In the long term, allocation of resources to lower-cost strategies will likely prove more cost-effective than dedicating resources to high-cost management of CVD. From a societal perspective, efforts to strengthen tobacco-control strategies, improve dietary choices, and increase physical activity will be paramount. At the individual level, risk assessment strategies and treatment modalities require simplification. Furthermore, alternative deployments of allied health workers such as community health workers will need evaluation, in view of the limited human resources in most LMICs. HICs must share with leading and emerging middle-income countries the burden of research and development into every aspect of prevention and treatment. Through further expansion of the knowledge base, particularly regarding the economic consequences of various treatment and prevention strategies, the efficient transfer of low-cost preventive and therapeutic strategies may alter the natural course of epidemiologic transitions in every part of the world, thereby reducing the excess global burden of preventable CVD.

REFERENCES

Epidemiology Transitions

1. *The Global Burden of Disease Study 2017 (GBD 2017)*. Institute for Health Metrics and Evaluation (IHME), University of Washington; 2017. Accessed January 2020. http://ghdx.healthdata.org/gbd-results-tool.
2. Olshansky SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Mem Fund Q*. 1986;64(3):355–391.
3. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. *Milbank Mem Fund Q*. 1971;49(4):509–538.
4. Dugani S, Gaziano TA. 25 by 25: achieving global reduction in cardiovascular mortality. *Current Cardiol Rep*. 2016;18(1):10.
5. Gaziano T, Suhrcke M, Brouwer E, et al. Costs and cost-effectiveness of interventions and policies to prevent and treat cardiovascular and respiratory diseases. In: D. Prabhakaran SA, T. Gaziano, J. Mbanya, Y. Wu, R. Nugent, ed. *Disease Control Priorities (third edition): Volume 5, Cardiovascular, Respiratory, and Related Disorders*. Washington, DC: World Bank; 2017.
6. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults — United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:1013–1019.
7. National Center for Health Statistics Health, *United States*, 2018. Hyattsville, MD: Centers for Disease Control and Prevention;2019.
8. Gaziano JM. Fifth phase of the epidemiologic transition: the age of obesity and inactivity. *J Am Med Assoc*. 2010;303(3):275–276.

Variations in Global Burden

9. National Center for Health Statistics (NCHS). *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: NCHS; 2015. 2016.
10. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)*. 2014;384(9945):766–781.
11. Hales C, Carroll M, Fryar C, Ogden C. *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. NCHS Data Brief, No 360*. Hyattsville, MD: National Center for Health Statistics; 2020.
12. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart association. *Circulation*. 2016;133(4):e38–e360.
13. Arroyo-Quiroz C, Barrientos-Gutierrez T, O'Flaherty M, et al. Coronary heart disease mortality is decreasing in Argentina, and Colombia, but keeps increasing in Mexico: a time trend study. *BMC Publ Health*. 2020;20(1):162.
14. Sekikawa A, Miyamoto Y, Miura K, et al. Continuous decline in mortality from coronary heart disease in Japan despite a continuous and marked rise in total cholesterol: Japanese experience after the Seven Countries Study. *Int J Epidemiol*. 2015;44(5):1614–1624.
15. World Development Indicators. *The World Bank*; 2018. http://data.worldbank.org. Accessed January, 2020.
16. GBD 2017 Population and Fertility Collaborators. Population and fertility by age and sex for 195 countries and territories, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1995–2051.
17. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: current epidemiology and future directions. *Circulation*. 2016;133(16):1605–1620.

Risk Factors

18. India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Glob Health*. 2018;6(12):e1339–e1351.
19. *WHO Report on the Global Tobacco Epidemic*. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
20. Eriksen MP, Mackay J, Schluger N, et al. *The Tobacco Atlas*. 5th ed. Atlanta, Georgia: The American Cancer Society; 2015.
21. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392(10159):1923–1994.
22. Frazer K, Callinan JE, McHugh J, et al. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev*. 2016;2(2):Cd005992.
23. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *J Am Med Assoc*. 2017;317(2):165–182.
24. Collaboration NRF. National trends in total cholesterol obscure heterogeneous changes in HDL and non-HDL cholesterol and total-to-HDL cholesterol ratio: a pooled analysis of 458 population-based studies in Asian and Western countries. *J Epidemiol*. 2019;49(1):173–192.
25. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392(10159):1789–1858.
26. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Practice*. 2018;138:271–281.
27. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.
28. Popkin BM, Corvalan C, Grummer-Strawn LM. Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet*. 2020;395(10217):65–74.
29. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)*. 2016;387(10026):1377–1396.
30. Food and Agriculture Organization of the United Nations. *New Food Balances*; 2020. http://www.fao.org/faostat/en/#data/FBS/visualize. Accessed June 14, 2020.
31. Jardim TV, Mozaffarian D, Abrahams-Gessel S, et al. Cardiometabolic disease costs associated with suboptimal diet in the United States: a cost analysis based on a microsimulation model. *PLoS Med*. 2019;16(12).
32. Huang C, Huang J, Tian Y, et al. Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. *Atherosclerosis*. 2014;234(1):11–16.
33. Tian Y, Jiang C, Wang M, et al. BMI, leisure-time physical activity, and physical fitness in adults in China: results from a series of national surveys, 2000–14. *Lancet Diabetes Endocrinol*. 2016;4(6):487–497.
34. United Nations Department of Economic and Social Affairs Population Division. *World Population Ageing 2019*. ST/ESA/SER.A/444; 2020.
35. Barker DJ. Fetal origins of coronary heart disease. *BMJ*. 1995;311(6998):171–174.
36. Martorell R. Improved nutrition in the first 1000 days and adult human capital and health. *Am J Hum Biol*. 2017;29(2). https://doi.org/10.1002/ajhb.22952.
37. Alderman H, Behrman JR, Glewwe P, et al. Evidence of impact of interventions on growth and development during early and middle childhood. In: Bundy DAP, Silva ND, Horton S, Jamison DT, Patton GC, eds. *Child and Adolescent Health and Development*. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017.
38. Devakumar D, Fall CHD, Sachdev HS, et al. Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. *BMC Med*. 2016;14:90.
39. Landrigan PJ, Sly JL, Ruchirawat M, et al. Health consequences of environmental exposures: changing global patterns of exposure and disease. *Ann Glob Health*. 2016;82(1):10–19.
40. Romieu I, Gouveia N, Cifuentes LA, et al. Multicity study of air pollution and mortality in Latin America (the ESCALA study). *Res Rep*. 2012;(171):5–86.

41. Liu Z, Wang F, Li W, et al. Does utilizing WHO's interim targets further reduce the risk - meta-analysis on ambient particulate matter pollution and mortality of cardiovascular diseases? *Environmental pollution (Barking, Essex: 1987)*. 2018;242(Pt B):1299–1307.
42. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2015;12(11):627–642.
43. Alshaarawy O, Elbaz HA, Andrew ME. The association of urinary polycyclic aromatic hydrocarbon biomarkers and cardiovascular disease in the US population. *Environ Int*. 2016;89–90:174–178.
44. Stafoggia M, Cesaroni G, Peters A, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect*. 2014;122(9):919–925.
45. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(17):2054–2070.
46. Burroughs Peña MS, Rollins A. Environmental exposures and cardiovascular disease: a challenge for health and development in low- and middle-income countries. *Cardiol Clin*. 2017;35(1):71–86.
47. Liu S, Guo X, Wu B, et al. Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice. *Sci Rep*. 2014;4:6894.

Economic Burden

48. Cylus J, Thomson S, Evetovits T. Catastrophic health spending in Europe: equity and policy implications of different calculation methods. *Bull World Health Organ*. 2018;96(9):599–609.
49. Wagstaff A, Flores G, Hsu J, et al. Progress on catastrophic health spending in 133 countries: a retrospective observational study. *The Lancet Global Health*. 2018;6(2):e169–e179.
50. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29–e322.
51. Weaver CG, Clement FM, Campbell NRC, et al. Healthcare costs attributable to hypertension: Canadian population-based cohort study. *Hypertension*. 2015;66(3):502–508.
52. World Health Organization. *Tackling NCDs: 'best Buys' and Other Recommended Interventions for the Prevention and Control of Noncommunicable Diseases*. Geneva: World Health Organization; 2017.
53. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. *J Am Med Assoc*. 2015;314(2):142–150.
54. Pandya A, Weinstein MC, Salomon JA, et al. Who needs laboratories and who needs statins?: comparative and cost-effectiveness analyses of non-laboratory-based, laboratory-based, and staged primary cardiovascular disease screening guidelines. *Circ Cardiovascr Qual Outcomes*. 2014;7(1):25–32.
55. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72(4):434–447.
56. Gaziano TA, Abrahams-Gessel S, Alam S, et al. Comparison of nonblood-based and blood-based total CV risk scores in global populations. *Glob Heart*. 2016;11(1) March:37–46.
57. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health*. 2019;7(10):e1332–e1345.

Cost-Effective Solutions

58. Gaziano TA, Abrahams-Gessel S, Denman CA, et al. An assessment of community health workers' ability to screen for cardiovascular disease risk with a simple, non-invasive risk assessment instrument in Bangladesh, Guatemala, Mexico, and South Africa: an observational study. *Lancet Glob Health*. 2015;3(9):e556–563.
59. Abrahams-Gessel S, Denman CA, Montano CM, et al. Training and supervision of community health workers conducting population-based, noninvasive screening for CVD in LMIC: implications for scaling up. *Glob Heart*. 2015;10(1):39–44.
60. UPST F. Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle-brachial index: US preventive services Task Force recommendation statement. *J Am Med Assoc*. 2018;320(2):177–183.
61. Ebbert JO, Hughes JR, West RJ. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *J Am Med Assoc*. 2015;313.
62. Baker TB, Piper ME, Stein JH, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *J Am Med Assoc*. 2016;315(4):371–379.
63. Mozaffarian D, Liu J, Sy S, et al. Cost-effectiveness of financial incentives and disincentives for improving food purchases and health through the US Supplemental Nutrition Assistance Program (SNAP): a microsimulation study. *PLoS Medicine*. 2018;15(10):e1002661.
64. Wilde P, Huang Y, Sy S, et al. Cost-effectiveness of a US national sugar-sweetened beverage tax with a multistakeholder approach: who pays and who benefits. *Am J Public Health*. 2018:e1–e9.
65. Lee Y, Mozaffarian D, Sy S, et al. Cost-effectiveness of financial incentives for improving diet and health through Medicare and Medicaid: a microsimulation study. *PLoS Med*. 2019;16(3):e1002761.
66. Liu J, Mozaffarian D, Lee Y, et al. Cost-effectiveness of the U.S. Federal restaurant menu calorie labeling law for improving diet and health: a microsimulation modeling study (P22-014-19). *Current Developments in Nutrition*. 2019;3(nzz042.P22-014-19).
67. Gaziano T, Cho S, Sy S, et al. Increasing prescription length could cut cardiovascular disease burden and produce savings in South Africa. *Health Aff*. 2015;34(9):1578–1585.
68. Gaziano T, Abrahams-Gessel S, Surka S, et al. Cardiovascular disease screening by community health workers can be cost-effective in low-resource countries. *Health affairs (Project Hope)*. 2015;34(9):1538–1545.