Reducing the Global Burden of Cardiovascular Disease, Part 1
The Epidemiology and Risk Factors

Philip Joseph, Darryl Leong, Martin McKee, Sonia S. Anand, Jon-David Schwalm, Koon Teo, Andrew Mente, Salim Yusuf

Abstract: Current global health policy goals include a 25% reduction in premature mortality from noncommunicable diseases by 2025. In this 2-part review, we provide an overview of the current epidemiological data on cardiovascular diseases (CVD), its risk factors, and describe strategies aimed at reducing its burden. In part 1, we examine the global epidemiology of cardiac conditions that have the greatest impact on CVD mortality; the predominant risk factors; and the impact of upstream, societal health determinants (eg, environmental factors, health policy, and health systems) on CVD. Although age-standardized mortality from CVD has decreased in many regions of the world, the absolute number of deaths continues to increase, with the majority now occurring in middle- and low-income countries. It is evident that multiple factors are causally related to CVD, including traditional individual level risk factors (mainly tobacco use, lipids, and elevated blood pressure) and societal level health determinants (eg, health systems, health policies, and barriers to CVD prevention and care). Both individual and societal risk factors vary considerably between different regions of the world and economic settings. However, reliable data to estimate CVD burden are lacking in many regions of the world, which hampers the establishment of nationwide prevention and management strategies. A 25% reduction in premature CVD mortality globally is feasible but will require better implementation of evidence-based policies (particularly tobacco control) and integrated health systems strategies that improve CVD prevention and management. In addition, there is a need for better health information to monitor progress and guide health policy decisions. (Circ Res. 2017;121:677-694. DOI: 10.1161/CIRCRESAHA.117.308903.)

Key Words: blood pressure ■ cardiovascular diseases ■ epidemiology ■ risk factors ■ tobacco

The epidemiological transition in the 20th century was accompanied by a fall in deaths and disability from communicable diseases and an increase in noncommunicable diseases (NCDs). Of the NCDs, cardiovascular disease (CVD) is now the leading cause of mortality and morbidity worldwide. In 2013, the World Health Organization launched the 25×25 Global Action Plan, an ambitious road map for countries to reduce NCD-related premature mortality by 25% by 2025. The global action plan focuses on strengthening health services and public policy to prevent and manage 4 major NCDs (CVD, cancer, diabetes mellitus, and chronic respiratory diseases), which contribute most to global morbidity and mortality, and 4 main health-related behaviors: tobacco use, diet, physical activity, and alcohol. Of these 4 diseases, CVD deaths are among the most amenable to rapid change, suggesting that if the ambitious target is to be achieved, it will be necessary to reduce CVD deaths by >25%. This international commitment is now enshrined in the Sustainable Development Goals, which form the basis for measuring the progress of countries to improve health outcomes at all levels of development until 2030. However, effective action requires reliable global data on CVD, its main risk factors, and information on major barriers to effective CVD treatment and prevention if evidence-based health policy is to be designed and implemented.

The first part of this review summarizes the global epidemiology of CVD and its risk factors, noting how epidemiological data inform the 25×25 Global Action Plan, as well as the need to improve global CVD epidemiology data if we are to achieve these goals. We draw extensively on the work undertaken by the Institute of Health Metrics Global Burden of Disease (GBD) project and on the PURE study (Prospective Urban Rural Epidemiology), a prospective, multinational cohort study across >25 countries (with 190 000 participants) examining individual-, community-, and societal-level health determinants of NCDs.
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BP</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>HIC</td>
<td>high-income country</td>
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<td>IHD</td>
<td>ischemic heart disease</td>
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<td>LDL</td>
<td>low-density lipoprotein</td>
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<td>LIC</td>
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<td>myocardial infarction</td>
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<td>MIC</td>
<td>middle income country</td>
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<td>NCD</td>
<td>noncommunicable disease</td>
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<td>PAR</td>
<td>population attributable risk</td>
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<td>PURE</td>
<td>Prospective Urban Rural Epidemiology Study</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RHD</td>
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Global Estimates of CVD

The principal source of data on the global burden of CVD is the GBD project. Disease burden comprises premature deaths, expressed as years of life lost and years lived with disability. These are combined to produce disability-adjusted life years. CVD is the leading cause of deaths and disability-adjusted life years globally, and the contributions of the main causes of CVD are summarized in Table 1.8,9

The global number of deaths from CVD has increased during the past decade by 12.5%.3 CVD now accounts for approximately one third of all deaths globally. These changes are driven by population growth and aging populations, with the largest number occurring in countries of South and East Asia because of their large and growing populations.

Age-specific death rates have actually fallen by 15.6% between 2005 and 2015 (Figures 1 and 2) although recent data suggest that this rate of decline has been slowing.8–10 These declines have been greatest in high-income countries (HICs), but they are also occurring in many middle income countries (MICs) and low-income countries (LICs).5,11 The net effect of these changes is that most CVD deaths now occur in LICs and MICs. Over 95% of all CVD deaths are attributable to 6 conditions: ischemic heart disease (IHD), stroke, hypertensive heart disease, which ultimately results in heart failure, cardiomyopathy, and rheumatic heart disease (RHD), and atrial fibrillation (AF; Table 1).9,11

We now describe the epidemiology of these conditions in turn:

Ischemic Heart Disease

Ischemic heart disease is the leading component of the global CVD burden. Both the prevalence and mortality of IHD increase dramatically with age.8 During the past 25 years, both incidence and mortality (age standardized) have decreased globally, with the greatest declines observed in HICs.12,13 Despite this positive trend, the burden remains disproportionately high in Eastern Europe and Central Asia although the large increases there during the 1990s are now reversing.8,12 Age-standardized mortality also remains high in South Asia, North Africa, and the Middle East.8 Years of life lost because of IHD are highest in South Asia, reflecting both the large population and early onset of IHD.12,13

Stroke

Stroke is the second leading contributor to CVD disease burden. The prevalence of stroke increases with age, peaking in those between 74 and 79 years of age.8 Stroke-related mortality also increases with age.8 Approximately 63% of ischemic and 80% of hemorrhagic stroke now occur in LICs and MICs.14 Ischemic stroke is more common than hemorrhagic stroke although hemorrhagic stroke is associated with higher mortality and contributes more to disability.15,16 Populations in MICs and LICs suffer strokes 6 years younger, on average, than in HICs.14 Countries with the highest age-standardized prevalence of stroke currently are in Oceania, Eastern Europe, Central Asia, and South-East Asia while mortality from stroke is highest in Oceania and Sub-Saharan Africa.8,14

Heart Failure

Estimates from the GBD suggest that heart failure as a consequence of IHD, hypertensive heart disease, or cardiomyopathy/myocarditis contributes significantly to disease burden.8 Both the prevalence of these common causes of heart failure and their associated mortality increase with age.8 Population-based studies in North America and Europe estimate a prevalence of heart failure of 1% to 2%, with 80% of new cases occurring in those >65 years of age.17,18 There are few large studies in other regions of the world that can reliably inform estimates of heart failure burden, but limited data from Asia suggest that the prevalence of heart failure may be higher (ranging between 1% and 7% in different studies) although this is predominantly based on either single-center or hospital-based studies, which may not truly reflect community rates and so may not be reliable.19 Finally, despite advances in heart failure management during the past 3 decades, data from HICs suggest that 5-year survival after the diagnosis of heart failure is still only 50% to 60%, with mortality rates being substantially higher in LICs and MICs.17,20

Atrial Fibrillation

Atrial fibrillation is the sixth leading cause of CVD-related mortality and the eighth leading cause of disability among cardiovascular conditions.18 The prevalence of AF increases dramatically in older age groups as does its associated mortality.8 Unlike most other cardiovascular conditions, the age-adjusted prevalence and incidence of AF have increased (albeit modestly) during the past few decades.21 The reasons underlying this trend could reflect higher rates of detection in addition to a true increase in disease burden. The highest prevalence of AF has been reported in North America and lowest in the Asia-Pacific region.21 However, these data also may not be reliable because few large community-based studies have examined AF epidemiology outside of Western countries, and methods used to detect AF have varied.

Rheumatic Heart Disease

RHD is the fifth leading cause of CVD-related mortality and ranks sixth in disability from cardiovascular conditions;
the disease burden is concentrated in poor countries, where overcrowding, reduced access to appropriate care, and inadequate management of valvular disease coexist.\textsuperscript{8} Most HICs have reported substantial declines in the incidence of RHD during the past 100 years. Current estimates suggest that the highest prevalence of RHD now occur in countries of Oceania, South Asia, some parts of South East Asia (eg, Laos, Cambodia), Sub-Saharan Africa, the Caribbean, Central Asia, and in parts of the Middle East (eg, Yemen).\textsuperscript{22} Since 1990, the prevalence of RHD appears to have increased in these endemic regions while incident acute rheumatic fever has decreased.\textsuperscript{23} Although these divergent trends may be related to longer survival of patients with RHD, this may also be the result of more RHD cases being identified earlier with wider use of echocardiography (eg, detection bias).\textsuperscript{22}

### Extent and Quality of Global CVD Data

Most HICs and some MICs have compete vital registration systems, based on medical death certification, to record virtually all deaths and their causes.\textsuperscript{24} Although there are inherent inaccuracies and variations between countries in recording the cause of mortality on death certificates, especially among older people who experience multiple conditions (eg, vascular mortality may be overestimated by as much as 10%), it remains the best method for collecting complete mortality data at the country level.\textsuperscript{24,25} Even without complete data, reliable estimates of mortality can be derived using representative population sampling. For example, through a nationally representative survey of 2.4 million households in India, the Million Death Study (in collaboration with the Registrar General of India) has collected information on 1 million deaths to estimate cause-specific mortality. Verbal autopsy tools are useful in classifying causes of death where death certificates are not available or where most deaths occur outside the hospital.\textsuperscript{26,27}

The GBD project has now assembled a wealth of data using many sources covering much of the world while developing innovative approaches to overcome problems, such as garbage codes, and deriving estimates of disease burden where precise data are lacking. Yet, many LICs and lower-MICs continue to have limited mortality data, making estimates from Africa, Middle East, South Asia, Central Asia, and the South-East Asia less robust (Figure 3).

The challenges are even greater in relation to measures of disease incidence, prevalence, and case fatality. There are high-quality, mature cohort studies (albeit confined to specific communities) in North America (eg, Framingham) and Europe but less data are available from other regions. The most recent iteration of the GBD reported that while 74% of regions had available data that could support modeling of nonfatal stroke, only 51% had the corresponding data for IHD, 31% for heart failure, 27% for AF, and 16% for hypertensive heart disease.\textsuperscript{5,28} Finally, certain CVD conditions may be substantially underestimated (eg, AF) in MICs and LICs because access to healthcare and diagnostic tools are limited.

### Modifiable CVD Risk Factors, Their Variations, and Their Impact on CVD

Risk factors act at several levels.\textsuperscript{29} Here, we begin with the individual factors for CVD, in particular the behavioral and metabolic influences on health, such as diet, smoking, and alcohol. We then examine the upstream determinants
of health, some of which act through the individual risk factors. These include aspects of the physical and social environments, including pollution and health systems. Most cases of CVD are associated with a handful of common, modifiable risk factors. The INTERHEART case–control study examined the predominant modifiable risk factors for

Figure 1. Trends in the risk of death from 1970 to 2010 in those 0 to 69 y of age. During this period of time, the risk of death from any cause significantly declined across age groups and in all county income groups. Trends were estimated using United Nations Population Division historical life tables between 1970 and 2010. Reprinted from Norheim et al10 with permission of the publisher. Copyright ©2015, Elsevier.

Figure 2. Contribution of population growth, population aging, and age-specific cardiovascular disease (CVD)–related death to the number of CVD-related deaths from 1990 to 2015. The change in the number of CVD-related deaths occurring in a given region can be characterized as a function of population growth, population aging, and changes in the age-specific CVD mortality rate (reflecting the impact of modifiable factors). For example, in Western sub-Saharan Africa, both population growth and age-specific CVD mortality contributed to increasing the total number of CVD-related deaths, which was partially counterbalanced by fewer deaths because of population aging. The net effect resulted in a 101% increase in the number of CVD deaths from 1990 to 2013. In most regions, the absolute number of CVD deaths is increasing in most regions of the world even though age-specific CVD mortality is declining, reflecting the dominant effect of population growth and aging. Reprinted from Roth et al7 with permission of the publisher. Copyright ©2015, Massachusetts Medical Society. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
first myocardial infarction (MI) in 15,152 cases and in 14,820 age- and sex-matched controls in 52 countries. It found that 9 risk factors accounted for >90% of the population attributable risk (PAR) for MI (listed in Table 2). Dyslipidemia was the single most important risk factor for first MI. The INTERSTROKE case–control study of 13,447 cases and 13,472 age- and sex-matched controls in 32 countries also demonstrated that 91% of stroke burden is attributable to the same 9 modifiable risk factors, with the addition of cardiac causes (such as AF; Table 2). The PAR attributable to these 10 risk factors was similar for ischemic and hemorrhagic strokes, and hypertension was the predominant risk factor for both types of stroke.

In contrast, the relative contributions of major risk factors for heart failure differ considerably among world regions. IHD is the most important in North America, accounting for 61% of the PAR, with hypertension, smoking, physical inactivity, obesity, and diabetes mellitus contributing to a lower extent (ie, PARs ranging between 8% and 17%); and valvular disease only explaining 2.2% of the PAR. Conversely, data from African populations attribute most heart failure to hypertension (45% of cases) or RHD (14% of cases), with a much smaller contribution from IHD (7.7% of cases).

There are even fewer data on risk factors for AF. The Atherosclerosis Risk in Communities study from the United States found that hypertension, diabetes mellitus, smoking, obesity, and cardiac diseases collectively explained ~55% of the PAR for AF. It seems likely, in the absence of extensive data, that conditions such as valvular disease, will be more important in other parts of the world.

Given that CVD is the largest contributor to disease burden globally, it is not surprising that major risk factors for CVD also have the largest impact of overall health. Estimates from the 2015 GBD study suggest that high blood pressure (BP), smoking, high fasting plasma glucose, and high body mass index (BMI) are the largest contributors to the global disease burden (measured as disability-adjusted life years). Within these estimates, it is equally important to characterize the extent to which these risk factors are modifiable. For example, although both BP and low-density lipoprotein (LDL) concentration show continuous associations with CVD risk in observational studies, primary prevention randomized controlled trials (RCTs) of BP lowering have not shown a clear reduction in CVD when the initial BP is <140 mm Hg (ie, the nonhypertensive range). By contrast, LDL lowering reduces CVD risk in populations irrespective of the initial level, with no clear lower threshold. Therefore, the modifiable burden of CVD attributed to elevated BP may have been over-estimated, and the importance of LDL as a modifiable risk factor underestimated. These data (which are further discussed in the following section of this review) urge caution in assuming that the data from observational studies indicate causality and care in interpreting the estimates of diseases burden solely from observational studies.

Figure 3. Quality of vital registration data on which mortality estimates have been derived by the Global Burden of Disease study, 2015. Many countries have vital registration systems in place or alternative methods to reasonably estimate deaths through extensive verbal autopsy studies. However, data are lacking in several countries within Africa, South Asia, and South-East Asia, making estimates from these regions prone to greater uncertainty. VA indicates verbal autopsy. Reprinted with permission from GBD 2015 Mortality and Causes of Death Collaborators. Copyright ©2016 The Authors.
Individual Risk Factors

Smoking
Smoking even 1 cigarette a day increases the risk of MI (Figure 4) as does exposure to second-hand smoke.40,41 There is also growing evidence of adverse effects on the cardiovascular system of electronic cigarettes, now being promoted aggressively by the tobacco industry.42 Accordingly, health policy goals should be directed at eliminating use of all forms of tobacco products. Since 1980, there has been a steady decline in tobacco smoking in most countries with current estimates indicating that 31% of adult men and 6% of adult women in the world smoke tobacco products daily.43 However, patterns of tobacco consumption vary considerably between different regions and, especially, by sex and social class.

Although the prevalence of smoking has declined in many HICs, it remains high in Europe, Russia, among men in China, and in parts of South America.43 Among men in HIC, smoking is more common in lower socioeconomic groups. However, this pattern has not been consistently observed in women. High smoking rates in men have been observed in North Africa, South East Asia, South Asia, China, and the Asia-Pacific regions. Also, several countries in East Asia, South East Asia, Europe, the Middle East, and South America report both a high prevalence of smoking and high average consumption of cigarettes (eg, >20/d) among smokers. These patterns primarily reflect the balance between efforts by the tobacco industry to promote its products and the efforts of governments to prevent their use.43

Blood Pressure
Observational studies indicate a graded increase in risk of CVD with even modest increases in BP even within normal ranges (eg, systolic BPs between 120 and 140 mm Hg).44 However, BP reduction has thus far only reliably been shown to reduce CVD risk in those with established hypertension (systolic BP >140 mm Hg) in primary prevention; targeting a lower systolic BP of 120 mm Hg has only been shown to be effective in those at high cardiovascular risk (including those with established vascular disease).45 Furthermore, although some drugs that lower BP, such as angiotensin-converting enzyme inhibitors and β-blockers, reduce CVD in high-risk individuals (eg, those with vascular disease) even when their BP is not in the range considered to be hypertensive, this has not been observed in individuals who do not have vascular disease (Figure 5).45 Therefore, estimates of CVD burden attributed to elevated BP which use a lower counterfactual to define the threshold of BP at which the general population is at lowest risk for developing CVD may overestimate the modifiable disease burden from elevated BP.

Worldwide, it is estimated that 24% of adult men (≥18 years of age) and 21% of adult women have elevated BP (defined as ≥140/90 mm Hg).46 Four decades ago, population BP levels were highest in HICs, but these have steadily declined. Current estimates suggest that BP levels in these regions now are among the lowest in the world. Conversely, MICs and LICs in East Asia, South-East Asia, Oceania, and sub-Saharan Africa have experienced an increase in population BP levels.46 Current estimates suggest that population mean systolic BP levels (and the prevalence of elevated BP) are now highest in Central and Eastern Europe and sub-Saharan Africa.46 Not surprisingly, these regions also experience a high burden of stroke, which will be difficult to control without strengthening systems aimed at hypertension prevention and management.

Cholesterol
Higher atherogenic lipid burden (measured by the concentration of total cholesterol, LDL, or apolipoprotein B; or the ratio of total cholesterol/high-density lipoprotein, or apolipoprotein B/apolipoprotein A1) is associated with a graded increase in CVD events. Furthermore, reducing LDL lowers...
the risk of CVD, which is consistent across the range of pretreatment LDL levels (Figure 6). The degree of reduction in CVD is proportionate to the degree of lowering of LDL cholesterol, and it is estimated that a 1-mmol reduction in LDL cholesterol in middle-aged individuals for 5 years leads to a 20% reduction in CVD risk. In 2008, the worldwide age-standardized mean total cholesterol concentrations in men and women were estimated to be 4.64 and 4.76 mmol/L, respectively. In North America, Australia, and most of Europe, serum cholesterol levels have modestly declined (by ≈4%) during the past 40 years; and these regions continue to have the highest mean total cholesterol levels in the world. At the same time, population mean cholesterol levels have been steadily increasing in East Asia, South East Asia, and South Asia.

Diabetes Mellitus

In addition to the increased risk of IHD and stroke associated with diabetes mellitus, microvascular complications (eg, retinopathy, nephropathy, and neuropathy) can significantly impact morbidity. As a consequence, the GBD estimates that diabetes mellitus is now the sixth leading cause of disability worldwide. Mortality and morbidity from diabetes mellitus continue to increase globally, which is a consequence of both demographic changes (eg, population growth and aging) and a higher burden of risk factors for diabetes mellitus development (eg, obesity).

Since the 1980s, the worldwide age-standardized prevalence of diabetes mellitus in those ≥18 years of age has increased substantially in both men (from 4% to 9%) and women (from 5% to 8%). Diabetes mellitus prevalence has either increased or remained constant in almost every country, with the highest age-standardized prevalence of diabetes mellitus in Polynesia, Micronesia, Melanesia, the Middle East, and North Africa. Population growth means that the largest numbers of people with diabetes mellitus now reside in South and East Asia but with substantial numbers also in the Middle East. Current trends suggest that the burden of disability will continue to rise as more individuals live longer with diabetes mellitus. This highlights the importance of strengthening policies to prevent and control diabetes mellitus worldwide.

Obesity

Traditionally, underweight and undernourishment were the main diet-related health challenges, but especially in HIC, overnutrition has become the dominant problem. However, the combination of under- and overnutrition creates a double burden in many LIC and some MIC. During the past 40 years, steady increases in mean population BMI and prevalence of obesity (ie, BMI >30) have been observed in virtually all regions of the world. Some of this is because of reductions in undernutrition and some because of the transition from normal weights to overweight and obesity. In healthy nonsmokers associations of markers of obesity and diseases are U shaped, with the lowest risk of death observed with a BMI ≈22 to 25, but the exact value differs between different populations, with higher optimal values reported in those at higher risk for CVD.

Between 1975 and 2014, the global prevalence of obesity (defined as a BMI >30) has increased from 3% to 11% in men and 6% to 15% in women ≥18 years of age. Prevalence of obesity is highest in Polynesia, Micronesia, and English-speaking HICs (defined as Australia, Canada, Ireland, New Zealand, United Kingdom, and United States), exceeding 30% in these populations. In women, a high prevalence of obesity has also been observed in Southern Africa, North Africa, and the Middle East.

Physical Inactivity

Standardized measures of overall physical activity (measured using either the international- or global physical activity questionnaire) have been collected in 122 countries through the World Health Organization Global Health Observatory. Based on these data, it is estimated that one third of adults (>18 years of age) are physically inactive (defined as <30 minutes of moderate-intensity physical activity on at least 5 days each week, <20 minutes of vigorous-intensity physical
activity on at least 3 days each week, and achieving a total of <600 metabolic equivalent-min per week, based on all forms of activity). In general, women are more physically inactive compared with men. Physical inactivity is highest in the Americas and eastern Mediterranean regions. Also, in several African countries, women have disproportionately high levels of physical inactivity when compared with men. The highest prevalence of sedentary behavior (defined as sitting >4 hours a day) has also been reported in the Americas and Europe.

**Alcohol Consumption**

Low levels of regular alcohol consumption are thought to be associated with a reduction in MI risk. However, the most extensive recent review of alcohol and health, undertaken for the United Kingdom’s Chief Medical Officers, concluded that any protective effect was limited to those at significant risk, especially older people, and there were still unresolved concerns about residual confounding. Noting how the incidence of MI in the United Kingdom has been falling, and how any protective effect is achieved with consumption of ≈1 unit of alcohol per day, it counseled against recommending drinking for health reasons. It also noted other research showing how even low levels of consumption are associated with increased risk of certain cancers. Heavy consumption, in contrast, is consistently associated with an increased risk of death and acute episodes of heavy drinking, which have different effects on the cardiovascular system from moderate regular consumption, may trigger acute MI.

**Alcohol consumption is influenced by cultural and religious factors; agricultural production (eg, wine growing areas); individual characteristics, including sex, education, and income; and by price, availability, and marketing of alcoholic beverages. Per capita alcohol consumption generally increases as countries become wealthier, with the lowest consumption observed in LICs and highest in HICs.**

**Diet**

Current dietary recommendations are based from Western countries, which are concerned with the impact of

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**Figure 5. Blood pressure and cardiovascular disease risk.** Observational data from the Prospective Studies Collaboration suggest that higher systolic blood pressure is associated with an increased risk of stroke, even within ranges considered normal (eg, between 120 and 140 mm Hg; A and B). However, results of the HOPE-3 (Heart Outcomes Prevention Evaluation-3) primary prevention study showed a lack of benefit of blood pressure reduction within this normal range and a benefit only in the subgroup of participants with hypertension (C). CI indicates confidence interval; and IHD, ischemic heart disease. Reprinted from Lewington et al (A, B) and Lonn et al (C) with permission of the publishers. Copyrights ©2002 and ©2016, Elsevier and Massachusetts Medical Society, respectively.
overnutrition and do not consider that undernutrition is still a major problem for large parts of the world. The patterns of diet, cooking methods, and costs of foods vary substantially between different countries and regions of the world. Furthermore, the approach of recommending levels of intake below or above certain targets for most macro- and micronutrients do not take into account that there is likely an optimal physiological range where levels of nutrition are adequate. These considerations suggest that nutrition recommendations should target optimal health, which may vary depending on the nutritional status of each population, rather than using global cut-offs values, or taking the approach that lower is always better (which has occurred with sodium and saturated fat consumption).

**Sodium**

The optimal amount of sodium consumption that is associated with the lowest risk of CVD remains controversial. Many recommendations that advocate for low sodium consumption (eg, <2 g per day) have been based on data relating sodium consumption to BP as a surrogate marker of CVD risk and then assuming that the lower the BP, the lower the risk of CVD. However, studies directly examining the relationship between sodium intake and CVD outcomes across a broad range of consumption levels have now observed that both high (eg, >6 g sodium/d) and low sodium consumption (eg, <3 g/d) are associated with higher CVD risk with the lowest risk of CVD or death being between 3 and 5 g/d. Similarly, a meta-analysis of 25 observational studies has recently demonstrated that both low and excessive amounts of sodium consumption are associated with increased all-cause mortality when compared with moderate consumption levels. The increase in risk of death and CVD with low sodium consumption may be related to the marked activation of the renin–angiotensin–aldosterone system. Despite some recommendations urging sodium reduction to <2 g/d, there is no evidence to support that this is feasible, effective, or even safe. Several experts have recommended that large RCTs are needed to assess whether low sodium intake (ie, <3 g/d) leads to a lower risk of CVD compared with usual intake (ie, 3–5 g/d). Until the results of such trials are available, it is prudent to recommend lowering sodium intake only in individuals with intakes that are >6 g/d, especially if they also have elevated BP (Figure 7).

**Other Macronutrients**

Clinical outcome data from observational studies now provide consistent evidence that industrially produced trans fats...
and refined carbohydrates are associated with increased CVD risk.\textsuperscript{67-69} Although dietary policies recommend reduction of saturated fat consumption, a growing body of evidence from observational studies and RCTs suggests that saturated fats either do not or only modestly increase CVD risk.\textsuperscript{67,70,71} Although polyunsaturated fats seem to have a protective effect on both lipids and clinical outcomes in observational studies, there are only modest data from RCTs that replacing saturated fats with polyunsaturated fats reduces CVD events.\textsuperscript{72} There are increasing data that high consumption of refined carbohydrates may be more harmful than fats and so the widespread recommendation of replacing fats (especially saturated fats) with other foods (usually carbohydrate based foods) needs to be reconsidered. Finally, average levels of carbohydrate and fat consumption substantially vary in different regions of the world, precluding a single recommendation for each nutrient globally.

**Food Types and Dietary Patterns**

Observational studies consistently demonstrate that higher fruit and vegetable consumptions are associated with a lower CVD risk. Most of these data are from North America or Europe, with sparse data from LICs and MICs.\textsuperscript{72} Recent data from China indicate that consumption of even 1 fruit serving per day confers substantial protection from CVD-related death, but the large effect size (a 40\% relative risk reduction with consumption of just 1 serving of fruit per day) and the lack of adjustment for consumption of other nutritional factors (eg, vegetable or other food groups) or socioeconomic status suggest that the apparently large benefits of fruits on CVD in this study may be exaggerated due to confounding.\textsuperscript{73} Processed meats are associated with an increase in CVD risk while data on natural red meats have been more inconsistent, ranging from a neutral effect to a modest increase in CVD risk.\textsuperscript{74} Fish consumption is associated with lower CVD risk in some observational studies (but not in others). Protection is attributed to omega-3 and omega-6 fatty acids, but RCTs of fish oil supplementation have shown no benefit.\textsuperscript{75} Whether this is related to a truly neutral effect, or limited bioavailability of supplemental polyunsaturated fats (as compared with

![Figure 7. Sodium and cardiovascular disease (CVD) risk.](http://circres.ahajournals.org/)

**Figure 7. Sodium and cardiovascular disease (CVD) risk.** A and B, Relationship between sodium intake and cardiovascular events across 3 studies. In this analysis, low sodium intake was consistently associated with a higher risk of CVD. High sodium intake was also associated with a higher CVD risk in participants with hypertension (A), but this was not observed in those without hypertension (B). C. Theoretical framework by which nutrients could impact risk. A U shaped curve reflects that below a lower threshold, nutrient deficiency can increase the risk of disease development, and above an upper threshold, toxicity related to the nutrient can also increase risk. Dietary guideline should reflect the optimal physiological ranges of nutrient intake in their recommendations. EAR indicates estimated average requirement; RDA, recommended dietary allowance; and UL, tolerable upper intake level. CI indicates confidence interval. Reprinted from Mente et al\textsuperscript{62} (A, B), Heaney,\textsuperscript{63} and Otten et al\textsuperscript{115} (C) with permission of the publishers. Copyrights ©2016, ©2013, and ©2006, Elsevier, Oxford University Press, and The National Academies Press, respectively.
fats directly obtained from fish), is unclear. Observational data suggest that sugar-sweetened beverages are associated with greater weight gain, obesity, and may increase the risk of IHD.76,77

Shifting dietary patterns may have a greater impact on CVD risk than targeting 1 specific food source or nutrient. The Prevención con Dieta Mediterránea study randomized participants to either a low-fat diet or to 1 of 2 arms testing a Mediterranean diet (which predominantly differed by a higher consumption of fish, legumes, and supplementary nuts or extra virgin olive oil). In the 2 arms of the Mediterranean diet, there was a reduced risk of major cardiovascular events and death of ≈30%.78 Because this intervention involved both healthy food supplementation and substitution, it may have produced a greater impact on CVD risk than trials that focused on supplementing a single component to the diet, which have thus far failed to demonstrate clear benefits.90 However, it is important to consider that most observational and all randomized studies of diet have been conducted in Western populations. Given that food sources, cooking methods, and food preservation practices vary substantially across the world, it is necessary to identify which dietary patterns are protective in regions of the world outside of Europe or North America, and ideally this should be followed by well-designed large randomized trials.79

Community Determinants of CVD

Indoor and Outdoor Air Pollution

Estimates from the 2015 GBD project suggest that among environmental exposures, ambient particulate matter and household air pollution are the leading risk factors for health lost.3 Risk estimates are derived from data on multiple sources of fine particulates, including ambient particles, household air pollution, tobacco, and second-hand smoke; and additional data from studies focused on ambient particulate matter alone are essential to better inform these estimates.2 Several cohort studies, mostly from North America and Europe, have shown that long-term exposure to ambient fine particulate matter (comprised particles matter <2.5 μm in diameter and primarily derived from combustion of fossil fuels) is associated higher CVD-related mortality, with less robust data supporting associations with nonfatal CVD.80 Recent data from the United States in 60 million individuals observed a clear, graded increase between fine particulate matter levels and all cause mortality, although cause specific mortality was not examined.81 In some regions of the world, the use of biomass-based fuels (eg, wood, diesel, and kerosene) for indoor cooking or heating can result in substantial exposure to air pollutants, and available data suggest that the use of these fuels increases the risk of CVD-related mortality.82 Several regions of the world have substantially higher levels of exposure to ambient particulate matter (eg, China, South Asia, and Middle East), but few studies have examined the impact of ambient or household air pollution on CVD risk in these populations.83 In this regard, multinational studies that capture a wide range of pollution levels and sources of exposure may provide better insight into the global impact of air pollution on CVD risk.

Health Systems

Although it has been shown that economic development and urbanization are associated with a higher burden of CVD risk factors, most HICs have also developed health systems to manage CVD and its risk factors effectively and relatively equitably.84 Recent research from the GBD study has quantified the contribution of health systems to the decline in cardiovascular mortality in much of the world.85 This involved age and risk standardizing mortality data (by removing country-specific risks and adding back global risk functions). This revealed large differences in progress in reducing all causes of death amenable to healthcare while the breakdown by cause showed substantial variations in performance in 2015. Other research from the GBD study also showed that when countries with low to moderate levels of social development are compared, CVD mortality is higher in those with lower social development; whereas the opposite trend occurs across countries with moderate to high social development.1 It is possible that in countries with lower social development, the dominant determinant of CVD mortality is risk factor burden (coupled with poor healthcare); while in socially and economically developed countries, the risk associated with higher risk factors is mitigated by the protective effects of stronger health systems. PURE has demonstrated that while traditional CVD risk factors are highest in HICs, the incidence of major CVD events is lowest in these regions, suggesting that protective societal factors (eg, better health policies, access to treatment for risk factors, and CVD) are mitigating risk.86

Effective treatments for CVD and its risk factors are underused worldwide, particularly in LICs and MICs. In PURE, awareness, treatment, and control of hypertension were found to be substantially lower in MICs and LICs compared with HICs, with 46% of patients with hypertension achieving adequate control in HICs compared with only 32% controlled in LICs.87 In India, low use of proven therapies for acute MI has been documented in a large registry of acute coronary syndromes, where only 58% of patients with ST-segment–elevation MI received thrombolysis and 8% underwent percutaneous coronary intervention.88 Treatment rates were lowest among poor patients and played a larger role in explaining mortality than CVD risk factor burden. In patients with established CVD, the PURE study has also documented low rates in the use of proven medications, with 80% of patients in LICs receiving no medical treatment compared with 69% in low-middle income countries, 45% in upper middle income countries, and 11% in HICs.89

In many MICs and LICs, a key challenge will be overcoming barriers to the implementation of proven therapies.90 These barriers can be complex because multiple obstacles to the adoption of specific treatments exist. These occur at the health systems, provider, or patient levels, creating large gaps between the evidence and practice. Using hypertension as an example, it is now evident that individuals face multiple barriers to hypertension detection, treatment, and control.91 Table 3 summarizes these barriers in LICs and MICs, where rates of hypertension control are lowest, as well as strategies that may overcome these barriers.91 Similar barriers exist in the management of CVD and its other risk factors. Thus, it is necessary
to understand and address the context-specific barriers that are limiting adoption of proven treatments. Where these barriers are widespread, as in medication availability and affordability, co-ordinated global responses may be needed.93,94

**Built Environment**

Understanding the causal pathway between aspects of the built environment and CVD risk is complex, with many intervening factors. Urban neighborhoods with greater land use mix are associated with a lower prevalence of obesity. Moreover, close proximally to walkable destinations (e.g., parks, trails, and recreational facilities) is associated with greater physical activity and lower obesity rates.95 Observed features within neighborhoods associated with obesity include poor sidewalk quality, physical disorder of the neighborhood, and the presence of garbage.96 Availability of healthy food sources may also contribute, with studies showing less obesity in communities closer to grocery stores and more obesity in communities with more fast food restaurants or convenience stores.95–99 Most studies evaluating the built environment have been cross-sectional, and therefore it is difficult to ascertain the extent to which aspects of the built environment are truly causal, or whether healthier individuals choose to live in specific environments (i.e., self-selection bias).98 Also, most data on the impact of the built environment on cardiovascular health are from HICs. The health impact of many aspects of the built environment may vary with context, and to date, there is a paucity of data from MICs and LICs to inform global policy.

**Health Policies**

Impacting change at the population level will undoubtedly require active health policies that aim to shift health-related behaviors at the community or societal level. Population-level measures, tackling price, availability, and marketing, are the most effective approaches to reduce smoking rates.100 Many of these policies have been brought together in the World Health Organization Framework Convention on Tobacco Control, which is the first global public health treaty, created in response to the worldwide health problems resulting from tobacco. A combination of fiscal measures (progressive increases in cigarette taxes), marketing restrictions (banning tobacco advertisements and health warnings), and legislation (smoke-free zones) have led to halving of smoking rates in the United States since 1965 and in Brazil since 1989.101,102 These form the basis of the Framework Convention on Tobacco Control MPOWER guidelines to control tobacco use.103 However, the tobacco industry actively seeks to undermine these measures, investing heavily in lobbying and misrepresenting evidence of the effectiveness of measures, such as standardized packaging.104 Modeling studies indicate that full implementation of the Framework Convention on Tobacco Control will lead to enormous population health benefits at

**Table 3. Key Barriers to Effective Hypertension Awareness, Treatment, and Control**91,92

<table>
<thead>
<tr>
<th>Stage of Hypertension Management</th>
<th>Barrier Impacting Management</th>
<th>Strategies to Overcome Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awareness</strong></td>
<td>Health system barriers: lack of availability of clinics within close proximity, lack of trained health workers to check BP, and screen for other common conditions</td>
<td>Health system level: opportunistic screening (e.g., at HIV clinics), health centers close to rural areas, teaching community health workers to screen</td>
</tr>
<tr>
<td></td>
<td>Provider barriers: lack of education of the importance of measuring BP in patients even without CVD or when presenting with noncardiac issues</td>
<td>Provider: education on opportunistic measurement of BP, simplified screening guidelines to diagnose hypertension</td>
</tr>
<tr>
<td></td>
<td>Patient barriers: lack of knowledge of hypertension and its complications</td>
<td>Patient level: education on importance of regularly having BP checked</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Health system barriers: lack of personnel to treat hypertension, unavailability or unaffordability of antihypertensive agents, distance to clinics</td>
<td>Health system: promoting task sharing with nonphysician health workers, integration of hypertension treatment with other disease programmes (e.g., malaria, HIV), use of high-quality generic medications, bulk purchasing, insurance, or subsidization of costs, providing inexpensive fixed-dose combination therapy, ensuring continuous drug supply through efficient supply chain management</td>
</tr>
<tr>
<td></td>
<td>Provider barriers: lack of adherence to guidelines, knowledge, or time</td>
<td>Provider level: simplification of diagnosing hypertension (e.g., using 1 measurement), simplification of treatment guidelines, clinical support systems, audits</td>
</tr>
<tr>
<td></td>
<td>Patient barriers: lack of knowledge of how BP is effectively treated</td>
<td>Patient level: education on medication and lifestyle modification</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>System barriers: lack of personnel, medication unavailability, and unaffordability</td>
<td>System level: see above (treatment)</td>
</tr>
<tr>
<td></td>
<td>Provider barriers: lack of guidelines adherence, knowledge of hypertension treatment, or time</td>
<td>Provider level: initiating combination treatment for hypertension, simplification of treatment guidelines, incentives for blood pressure control</td>
</tr>
<tr>
<td></td>
<td>Patient barriers: belief that treatment is not lifelong, polypharmacy, adherence, side effects, memory</td>
<td>Patient level: education, simplified treatment regimens (e.g., fixed-dose combination therapy)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CVD, cardiovascular disease; and HIV, human immunodeficiency virus.
Table 4. Targets for the Prevention and Control of Cardiovascular Disease as Part of the Global Action Plan

<table>
<thead>
<tr>
<th>Global Action Plan Targets</th>
<th>Strength of Evidence to Support Target and Feasibility of Achieving Goal</th>
<th>Priorities for Strengthening Current Epidemiological Data to Monitor Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes mellitus, or chronic respiratory diseases</td>
<td>Strength of evidence: high</td>
<td>Developing methods to capture representative, cause-specific mortality data in countries that currently lack vital registration systems from representative populations</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: moderate. Will require successful implementation of multiple policies aimed at improving CVD risk factor control and the management of CVD globally, particularly in regions with a relatively high burden of CVD</td>
<td>Developing large, prospective epidemiological platforms to estimate the incidence, prevalence, and case fatality rates of major conditions impacting CVD mortality (eg, IHD, stroke, AF, heart failure, RHD) in regions outside of North America or Europe (eg, PURE study, Kadoorie study)</td>
</tr>
<tr>
<td>2. At least 10% relative reduction in the harmful use of alcohol, as appropriate, within the national context</td>
<td>Strength of evidence: high</td>
<td>Creating simple survey systems that can track changes in alcohol health-related behaviors over time across representative population groups within a country</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: high. Will require greater health promotion on the harmful effects of alcohol and implementation of evidence-based policies (eg, taxation), particularly in areas where prevalence of alcohol use is high (eg, Russia, Eastern Europe, parts of Western Europe)</td>
<td>Developing stronger epidemiological data on how specific community-level factors (eg, built environment, health policies) impact physical activity, particularly in MICs and LICs.</td>
</tr>
<tr>
<td>3. A 10% relative reduction in prevalence of insufficient physical activity</td>
<td>Strength of evidence: high</td>
<td>Creating simple survey systems that can track changes in health-related behaviors over time across representative population groups within a country</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: moderate. Will require greater health promotion on benefits of physical activity and the implementation of multilevel strategies that target individuals, groups (eg, school-based physical activity), and communities (eg, built environment). Regions where physical activity levels are lowest should be given high priority.</td>
<td>Developing stronger epidemiological data on how specific community-level factors (eg, built environment, health policies) impact physical activity, particularly in MICs and LICs.</td>
</tr>
<tr>
<td>4. A 30% relative reduction in mean population intake of salt/sodium</td>
<td>Strength of evidence: low</td>
<td>Developing or strengthening epidemiological platforms to include measures of sodium consumption using simple methods that provide accurate estimates for populations (eg, morning fasting urine)</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: low. Sodium reduction strategies should be focused in regions with high mean consumption levels (eg, China/East Asia) and in individuals with hypertension. Targeting moderate sodium consumption (eg, 3–5 g/d) for most other populations</td>
<td></td>
</tr>
<tr>
<td>5. A 30% relative reduction in prevalence of current tobacco use in persons aged 15+ y</td>
<td>Strength of evidence: high</td>
<td>Creating simple survey systems that can track changes in smoking-related behaviors over time in representative population groups within a country</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: high. Will be dependent on the willingness and success of countries at implementing multiple health policies aimed at tobacco control (outlined in FCTC MPOWER guidelines).</td>
<td></td>
</tr>
<tr>
<td>6. A 25% relative reduction in the prevalence of raised blood pressure or contain the prevalence of raised blood pressure, according to national circumstances</td>
<td>Strength of evidence: high</td>
<td>Creating simple, representative survey systems to track changes in hypertension prevalence over time. Should also be supplemented with physical measurements in a subset of the population to better refine estimates hypertension prevalence, awareness, treatment, and control.</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: moderate. Will require greater health promotion of hypertension knowledge (including prevention, lifestyle modification, and pharmacological treatment). Will also require local understanding of barriers that impact hypertension awareness, treatment, and control in a given region and implementation of directed policies that overcome these barriers.</td>
<td></td>
</tr>
<tr>
<td>7. Halt the rise in diabetes mellitus and obesity</td>
<td>Strength of evidence: high</td>
<td>Creating simple, representative survey systems to estimate obesity and diabetes mellitus prevalence and track changes over time (including physical measurements and fasting plasma glucose measurements). Reliable measures are also needed to track upstream determinants, such as diet and physical activity. Although population estimates of physical activity are available in many countries, diet varies enormously between regions of the world. Further data relating dietary factors to CVD risk within regions where patterns are similar are essential.</td>
</tr>
<tr>
<td></td>
<td>Feasibility of achieving goal: moderate. Will require significant improvements in health promotion as to the key lifestyle factors that prevent diabetes mellitus and obesity. Health promotion and policies to improve physical activity, prevention of diabetes mellitus and obesity should be a priority in all countries. In addition, significant changes to dietary policy will be required that increase the promotion of healthy foods, including their supply, access, and affordability.</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)

Because CVD is the predominant cause of death in most of the world, achieving the 25×25 Global Action Plan to reduce premature NCD mortality and the health targets in the Sustainable Development Goals will greatly depend on the success of strategies directly targeting CVD and its risk factors. The global action plan encompasses 9 global targets aimed at NCD and risk factor control (Table 4). Reducing the burden of CVD should be a priority for virtually all countries in the world given its major contribution to NCD mortality and morbidity. However, these strategies should be evidence-based and feasible and be able to overcome major barriers to effective CVD prevention and management. These barriers vary in different populations, and the ability to overcome them depends on resources. For example, many LICs and MICs continue to experience high burdens of diseases of poverty (undernutrition and infectious diseases) while having to tackle the emerging burdens of NCDs. This is compounded by inadequate investment in health and weak healthcare systems. These triple challenges mean that controlling CVD is much more difficult in MICs and LICs compared with HICs. In Table 3, we also summarize high-priority regions within each target based on current epidemiological data and highlight key areas where global CVD epidemiology needs to be strengthened to better inform strategies and monitor progress.

It is evident that while significant advances have been made in our understanding of global CVD epidemiology, there are large gaps in data, predominantly in MICs and LICs. In these countries, there is a need for greatly enhanced systems for surveillance of risk factors and disease and for policies that can reduce CVD at low cost in ways that are pragmatic and sustainable. The former can be accomplished with large but simple health surveys (or health observatories) that collect representative information on health behaviors, CVD risk

Table 4. Continued

<table>
<thead>
<tr>
<th>Global Action Plan Targets</th>
<th>Strength of Evidence to Support Target and Feasibility of Achieving Goal</th>
<th>Priorities for Strengthening Current Epidemiological Data to Monitor Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. At least 50% of eligible people receive drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes</td>
<td>Strength of evidence: high Feasibility of achieving goal: moderate. Will require understanding of local barriers to drug availability and affordability and implementation of policies to overcome these barriers. Priority in LICs and some MICs, where use of proven medications for both CVD treatment and control of risk factors, such as hypertension, is low</td>
<td>Simple, representative survey methods to track availability, affordability, and use of essential medications for CVD and for major modifiable risk factors</td>
</tr>
<tr>
<td>9. An 80% availability of the affordable basic technologies and essential medicines in both public and private facilities</td>
<td>Strength of evidence: high Feasibility of achieving goal: moderate. Will require a greater understanding and methods to overcome barriers in the use of essential health resources (eg, physician resources, infrastructure for management of acute MI, and stroke). Priority in LICs and MICs, where personnel and facilities for management of CVD and its risk factors are either unaffordable and unavailable to a substantial number of individuals</td>
<td>Community-based surveys that can capture the availability of health facilities to provide essential technologies for the management of CVD (eg, fibrinolysis for myocardial infarction), the use of these technologies, and barriers to their use. These essential technologies are further discussed in part 2 of this review.</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CVD, cardiovascular disease; FCTC, Framework Convention on Tobacco Control; LIC, low-income country; MI, myocardial infarction; MIC, middle income country; PURE, Prospective Urban Rural Epidemiology Study; and RHD, rheumatic heart disease.
factors, common CVD conditions incidence, CVD mortality, and access to care in each country or parts of countries. These data can in turn be used to inform locally appropriate strategies for CVD prevention and management, coupled with lessons drawn from countries that have achieved good health at low cost.11

The second part of this review will examine key, evidence-based strategies that can be used in priority areas to reduce CVD development, associated morbidity, and mortality.

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**Disclosures**

None.

**References**


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