Contributions of risk factors and medical care to cardiovascular mortality trends

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Abstract | Ischaemic heart disease, stroke, and other cardiovascular diseases (CVDs) lead to 17.5 million deaths worldwide per year. Taking into account population ageing, CVD death rates are decreasing steadily both in regions with reliable trend data and globally. The declines in high-income countries and some Latin American countries have been ongoing for decades without slowing. These positive trends have broadly coincided with, and benefited from, declines in smoking and physiological risk factors, such as blood pressure and serum cholesterol levels. These declines have also coincided with, and benefited from, improvements in medical care, including primary prevention, diagnosis, and treatment of acute CVDs, as well as post-hospital care, especially in the past 40 years. These variables, however, explain neither why the decline began when it did, nor the similarities and differences in the start time and rate of the decline between countries and sexes. In Russia and some other former Soviet countries, changes in volume and patterns of alcohol consumption have caused sharp rises in CVD mortality since the early 1990s. An important challenge in reaching firm conclusions about the drivers of these remarkable international trends is the paucity of time-trend data on CVD incidence, risk factors throughout the life-course, and clinical care.

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Introduction

Ischaemic heart disease (IHD) and stroke are the two most common causes of death worldwide. Together they are estimated to cause 14 million deaths annually, which comprises one-quarter of all global deaths.[1] Other cardiovascular diseases (CVDs) cause an additional 3.5 million deaths. The absolute numbers of deaths from CVDs is increasing both worldwide and in most individual countries, although this rise is caused mostly by the ageing population.[2,3] When ageing is taken into account, CVD mortality has been steadily decreasing, both in regions with reliable trend data and in the world as a whole (Figure 1).[2–4]

A natural question of scientific and public health interest is to what extent trends in known risk factors, individually and in combination, contribute to trends in CVD mortality and its variations between countries. In this Review, we summarize the major studies in which trends in preventable risk factors as drivers of trends in CVD mortality have been examined in whole communities and populations. To begin, we review data on trends in CVD mortality and risk factors, focusing primarily on IHD and stroke when possible, or on all CVDs when factors such as changes in classification of causes of death make examining trends in individual CVDs difficult. We then review studies on risk-factor contributions, organized largely by how scientific knowledge has evolved. We also briefly consider the role of improved medical care for two reasons: trends in major physiological risk factors for CVDs are due to a combination of changes in behaviour and pharmacological treatment; and attribution of change to specific risk factors is incomplete, if not impossible, without any consideration of other major changing determinants of CVDs. We do not discuss socioeconomic inequalities as they have been addressed elsewhere.[5–8]

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Worldwide CVD mortality trends

High-income countries

For the purposes of this Review, we use the term 'high-income countries' to mean those in Australasia, North America, and western Europe—referred to as 'western high-income countries'—as well as high-income Asian countries such as Japan, Singapore, and South Korea. As early as the mid-20th century, trends in CVD deaths in western high-income countries were being discussed. Studies from Australia, Europe, and the USA showed that, with the exception of some countries during World War II, CVD death rates rose early in the 20th century.[9–14] Some of these early studies systematically considered whether changes in diagnostic and classification criteria or the expanding geographical coverage of death registration had influenced trends, but concluded that these factors were unlikely explanations. Importantly, investigators in some of these studies noted that a substantial proportion of the rise in crude death rates was caused by ageing of the population. Nevertheless, a rising trend was seen in age-specific and age-standardized death rates.[10–13] In the USA, trends had begun diverging between population subgroups as early as the 1940s; for instance, increases were occurring among white men whereas declines were observed among white women and black people.[15] By the 1960s, CVD

Key points

- Death rates from ischaemic heart disease (IHD), stroke, and other cardiovascular diseases (CVDs) are decreasing in high-income and many Latin American countries, and this trend shows no signs of slowing
- Declines in some behavioural risk factors, including smoking, and physiological risk factors, such as blood pressure and serum cholesterol, are likely to have helped to reduce CVDs
- By contrast, the nearly universal increase in adiposity seems not to have modified the long-term declining trend in CVD mortality, although it might have had some slowing effect
- Improved medical care, including effective treatment of physiological risk factors, diagnosis, treatment of acute CVDs, and post-hospital care, has also contributed to declining CVD events and mortality
- Measured risk factor and treatment variables, while important, explain neither why the decline began when it did nor many of the similarities and differences between countries or between men and women
- Substantial fluctuations in CVDs, and in alcohol intake, in former communist countries of Europe have followed times of massive political and social changes since the early 1990s

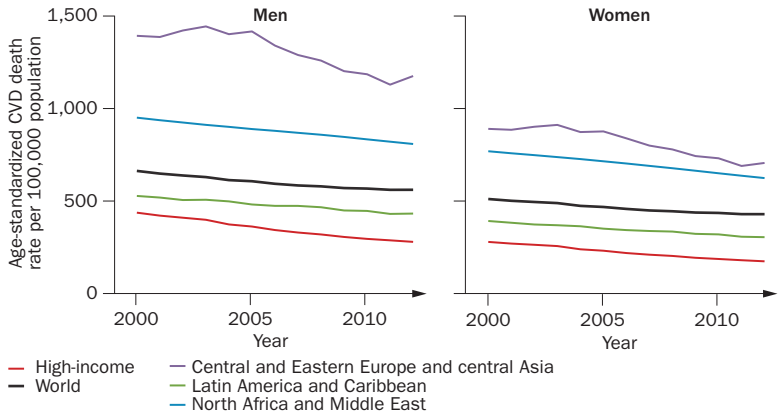


Figure 1 | Trends in age-standardized CVD death rates in adults aged ≥30 years, by geographical region and sex, from 2000 to 2012. Mortality was age-standardized on the basis of the WHO standard population. The source of the data is the WHO Global Health Estimates,[1] in which mortality levels and trends are estimated from vital statistics, sample registration of deaths, representative verbal autopsy surveys, and using demographic and epidemiological models.[312] Trends are not shown for sub-Saharan Africa or for east, south, and southeast Asia and the Pacific (except Japan, Singapore, and South Korea, which are included in the high-income group), because mortality data from these regions, especially time trends, are very limited. Abbreviation: CVD, cardiovascular disease.

mortality was declining in most western high-income countries,[16,17] but this reversal in trend was noted in only a few discerning reports.[18,19] Of note, IHD and stroke had opposite trends in high-income countries such as the UK and USA in much of the first half of the 20th century, with stroke (and hypertensive disease) mortality declining decades before IHD mortality.[12,16,17,20–26] Ischaemic stroke shares many risk factors with IHD. Therefore, the earlier decline in total stroke mortality is likely to attributable to reductions in haemorrhagic stroke.[23]

Japan, which is the only country in Asia with reliable long-term mortality data, seems to have experienced rising IHD mortality (albeit from very low levels) from 1950 until the 1970s, and rising stroke until the 1960s, before declines in these two conditions began.[27–32] Again haemorrhagic stroke mortality declined before that for ischaemic stroke, at least since the 1950s.[29] IHD mortality in Japan never reached the levels seen in western high-income countries.

After pioneering work to document the rise and early declines in IHD mortality, seeking explanations for the decline in IHD mortality in high-income countries became a focus of research efforts in the 1970s.[33–35] The data and perspectives were discussed together at the 1978 Bethesda Conference on the Decline in Coronary Heart Disease Mortality (Box 1).[24] Additionally, the MONICA Project[36] was initiated to assess prospectively the influence of changes in major risk factors on variation in IHD mortality in the 1980s and early 1990s in 21 countries (Box 2). In this Review, we return to the topics addressed in these two pioneering studies, with the advantage of having data from a much longer period of time, and from a larger and more diverse set of countries than has been previously assessed (Box 3).[37]

From today's vantage point, two important features are seen in CVD mortality trends in western high-income countries (Figure 2). First, the decline in CVD mortality among women had already begun in the 1950s, especially among those aged <70 years. The decline had begun even in men in a few countries, such as Canada, Sweden, and Switzerland in the 1950s (Figures 3 and 4). By the 1970s, total CVD death rates were declining in most high-income countries, including in Japan (Figures 3 and 4). Greece was possibly the only western high-income country in which CVDs might have continued to rise until the 1980s. Second, the rate of decline varied substantially between countries, with the best-performing and worst-performing countries per decade generally being about 30% apart.[21,22] The extraordinary feature of the decline in CVD mortality is that it shows no signs of slowing; indeed, the proportional rate of decline in 2000–2009 seems even greater than that in previous decades. Therefore, the decline in CVD mortality over the past 6 decades is arguably one of the most notable health phenomena of the late 20th and early 21st centuries, resulting in a >70% reduction in CVD death rates among men and >75% among women in countries such as Australia, Canada, Finland, France, and Switzerland. Total CVD mortality in Japan began to decline in the early 1960s, owing to the decline in total stroke deaths, whereas IHD continued to rise.

Latin America

Historical mortality data with details of age and causes of death are unavailable for many Latin American countries, although efforts to improve collection and collation are being made.[38] Overall, CVD mortality seems to be declining in the region as a whole (Figure 1), and has been declining since at least the 1970s in Argentina, Chile, Costa Rica, Uruguay, and Venezuela at a pace only slightly slower than that in high-income countries (Figures 3 and 4).[39–41]

Central and Eastern Europe

Former communist countries in central and Eastern Europe include those such as Hungary, Poland, and countries of the former Soviet Union. Although the precise

Box 1 | The Bethesda Conference, 1978

The Bethesda Conference on the Decline in Coronary Heart Disease Mortality was organized by the National Heart, Lung, and Blood Institute in 1978, a decade after the decline in IHD, already >20%, had begun. The aims were "(1) to consider whether the greater than 20% decline in coronary heart disease mortality since 1968 is real, (2) to discuss possible causes, and (3) to recommend further studies to elucidate the causes".[24] A large number of potential explanations were systematically considered, including artefact, the classic risk factors (smoking, cholesterol, and blood pressure), and novel risk factors (such as ambient air pollution and lack of physical activity).[315,316] Prehospital and in-hospital treatment was also considered. The discussions and resulting papers were comprehensive and involved some of the best epidemiologists, statisticians, and clinical scientists of the day. The conclusion, however, was stark: "Although there was general agreement that the decline in coronary heart disease is real, the probable cause or causes could not be precisely identified".[24] Three main areas for research were proposed: improve data collection systems on morbidity and mortality for IHD; evaluate contributions and future potential of preventive and therapeutic management of patients; and continue to undertake basic clinical and nonclinical research into pathogenesis, risk factors, and clinical management of IHD.[24] The Bethesda Conference was an important catalyst for the initiation of the MONICA Project and several US community-based studies. Nonetheless, population-based data on outcomes and on determinants of risk factors and treatment remain weak.

Abbreviation: IHD, ischaemic heart disease.

Box 2 | The MONICA Project

Partly motivated by the discussions and recommendations of the 1978 Bethesda Conference, the WHO coordinated the initiation of the MONICA Project in 1979.[36,317] This project aimed to assess prospectively the influence of changes in major risk factors for cardiovascular disease—including serum cholesterol, blood pressure, and cigarette smoking, and later BMI—and in 28-day case-fatality on change in IHD mortality. Change in treatment was subsequently analysed as a variable of interest. IHD risk factors, incidence, case fatality, and mortality were measured in 38 communities in 21 countries, mainly in Europe but also in Australasia, China, and North America.[36,317] Data for the main study were collected from the mid-1980s to the mid-1990s, although many MONICA centres have continued to collect data and monitor trends. The focus was on premature mortality, which at that time was defined as death in people aged <65 years. The main defining feature of the MONICA Project was the use of identical or very similar protocols in all centres, including standardized case definitions for incident IHD. The criteria remained in use for population-based surveillance for years after the study ended.[318]

Abbreviation: IHD, ischaemic heart disease.

nature of the political regimes varied, these countries as a group have trends that differ notably from those of high-income countries. As early as the Bethesda Conference, IHD mortality was noted to be increasing in many central and Eastern European countries, especially among men (Figures 3 and 4).[21,22,42,43] The increases in CVD death reversed only in the mid-late 1980s and early-mid 1990s, with the decline starting earlier in women than in men. After decline began in these countries, however, the rates rapidly converged with those in high-income countries, with some variation between nations (Figures 3 and 4).[44]

The countries of the former Soviet Union, including Belarus, Estonia, Latvia, Lithuania, Moldova, Russia, and Ukraine, show more complex trajectories. Unlike high-income countries, CVD mortality in these countries was on a shallow upward trend in men and stagnant in women in the last few decades of the Soviet Union. After Gorbachev's anti-alcohol campaign in 1985, CVD mortality declined in some of these populations, only to rise again steeply from the early 1990s after the collapse of the Soviet Union, particularly among working-age men.[45–47] This fluctuation differed from the more gradual changes seen elsewhere. In Russia and Ukraine, CVD mortality declined between 1994 and 1998, increased again until the mid-2000s, and has since begun to decline once more.[48] By contrast, in Estonia and Latvia, the decline began in, and has continued since, the early-to-mid-1990s. The marked fluctuations in CVD mortality in Russia paralleled fluctuations in deaths from external causes and acute alcohol poisoning (Figure 5).[49] Apparent fluctuations in deaths attributed to IHD are suggested to be caused by misclassification of sudden cardiac deaths induced by heavy drinking (for which death rates from acute alcohol poisoning act as a proxy),[49] rather than classic manifestations of atherosclerotic disease.[50]

China

The absence of complete vital registration data in China makes analysis of trends unreliable. Data from the MONICA Project and other community studies seem to indicate a decline in total stroke mortality (driven by substantial declines in haemorrhagic stroke), similar to earlier trends in Japan, and possibly a small rise in IHD death rates.[51–53] In Hong Kong, where there are high-quality data, IHD seemed to have plateaued and even begun to decline in the 1980s, especially in those aged <70 years.[54]

Sub-Saharan Africa

Few data on CVD trends are available from low-income and middle-income countries because vital registration systems are nonexistent or incomplete. Exceptions are Seychelles, a middle-income country with high-quality cause-of-death data, where stroke, IHD, and other CVD mortality are declining steadily,[55] and South Africa, where age-standardized IHD and stroke death rates are declining.[56]

Trends in CVD mortality sex ratios

The timings and especially the pace of CVD mortality trends differ between men and women. The male-to-female ratio of CVD mortality among people aged 30–69 years shows that, historically, premature CVD mortality was up to twofold higher in men than in women in high-income countries (Figure 6). Over time, this ratio has increased to twofold to threefold in most countries, and to nearly fourfold in Finland. The ratio has reached a plateau or has decreased in English-speaking high-income countries and northwest Europe,[26] whereas the ratio continues to increase in central and Eastern Europe, Japan, and Latin America.

CVD risk factors

Observational studies and randomized trials have identified numerous putative behavioural, environmental, nutritional, physiological, and psychosocial risk factors for CVDs beyond the classic risks,[57–59] such as impaired fetal and childhood growth and nutrition, short adult height, impaired lung function, numerous environmental

Box 3 | Analysis and reporting of cardiovascular mortality trends

The early work on cardiovascular disease trends, such as that of Moriyama and colleagues,[11,12] attempted to address a series of challenges related to the analysis and reporting of trends in cause-specific mortality at the population level that persist today.[26,216,312,319] These problems include the changes over time in geographical areas or even social and ethnic groups covered by death registration, completeness of death registration among the covered population, and assignment of medical cause of death. In many countries, death registration begins in particular areas, often urban centres or a subset of provinces, before incorporating other parts of the country. Whether immigrants and/or emigrants are covered differs between countries and changes over time. Limitations in civil registration and statistical systems have led to incomplete death registration, with completeness changing over time. Combinations of changes to the International Classification of Disease system and clinical culture and training, have led to inconsistent or inappropriate assignment of cause of death. The methods used for dealing with these issues by the WHO and researchers have become increasingly complex,[288,312,320,321] but fundamentally involve a combination of clinical and epidemiological judgements and assumptions plus analytical methods that formalize these judgements and assumptions. The trends in Figures 1–4 are based on data and work at the WHO, and are described in various WHO publications.[216,312,322] In brief, high-income countries generally have complete or near-complete registration of deaths, with robust medical certification. The WHO uses demographic methods to test and, if needed, adjust for completeness of death registration, and redistributes ill-defined and improbable causes of death (for example, deaths assigned to senility and to signs and symptoms such as pain) on the basis of clinical and epidemiological knowledge about their potential underlying causes.

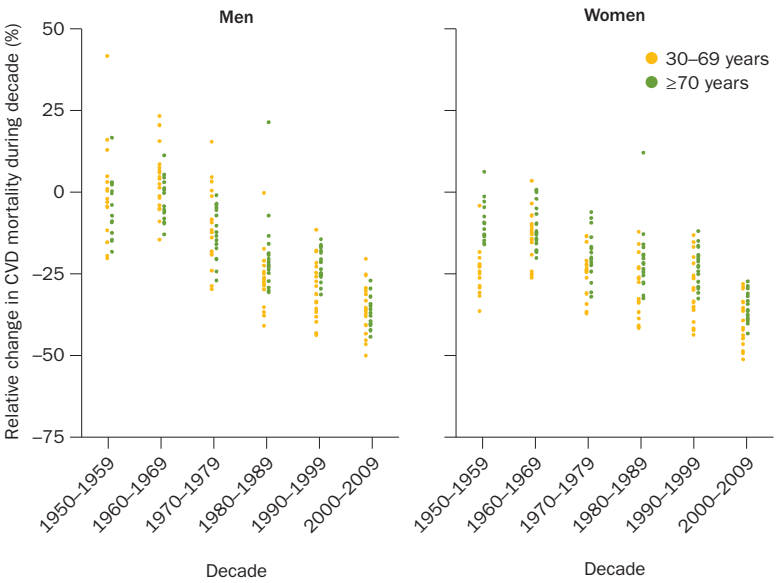


Figure 2 | Relative change in CVD death rates by decade, sex, and age group in 20 western high-income countries. Death rates were age-standardized within age groups on the basis of the WHO standard population. Countries are: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, UK, and USA. Data for smaller countries were excluded, as were those for Germany because its boundaries changed during the period of study. Abbreviation: CVD, cardiovascular disease.

and occupational pollutants, various components of diet, social position and economic status, and physiological risk factors such as persistent low-grade inflammation and the gut microbiome.[60,61] The extent to which some of the less-established risk factors are truly causal is controversial. Even for some established factors—such as blood pressure, serum lipids, and smoking—which measure best captures the causal element is open to question. For example, total-cholesterol level seems to be a poorer marker of risk than LDL-cholesterol level, HDL-cholesterol level, or their ratio, or even the ratio of apolipoprotein B to apolipoprotein A1.[62] In this Review, however, we focus on the established risk factors (smoking, blood glucose and diabetes mellitus, raised blood pressure, and serum cholesterol) for which trend data are more robust than for other risk factors. We also look at adiposity, aspects of diet, and alcohol intake.

Conceptualization of risk-factor trends

Any explanatory framework for changes over time in CVD incidence and death has to assume that the factors considered are direct causes or proxy markers for causal factors. Causal influences can be viewed as being on a continuum;[63,64] for example, from societal-level factors (the most distal factors), to individual behaviours and exposures, to intermediate physiological traits (the most proximal factors). Thus, changes in physiological traits, such as blood pressure or serum cholesterol concentrations, might be the result of behavioural factors, such as exercise and diet, which might themselves be mediators of societal influences or changes. However, an additional layer of complexity arises from the influence of medical interventions. For example, because the decline in lipids or blood pressure are partly a result of statins and antihypertensive medications, the role of these physiological traits in CVD morbidity and mortality trends cannot neatly be divided into lifestyle or treatment effects, which has previously been attempted. Finally, the usual, but important, caveat concerning genetic influences needs to be made. Although huge efforts have been made to identify genetic determinants of cardiovascular traits and disease since the mapping of the human genome—and some progress has been made—little light has so far been shed on changes and trends in CVDs.

Finally, when considering the likely role of different risk factors as determinants of CVD trends, there is the question of the time of changes in disease rates with respect to changes in risk factors (Table 1).[3] For example, risks of IHD and stroke fall within 10 years after smoking cessation to that of nonsmokers (Figure 7).[3,65] By contrast, the risks of lung cancer and chronic obstructive pulmonary disease decline over decades in former smokers before approaching that of individuals who have never smoked.[3,65] Evidence also suggests a rapid influence of smoking bans in public places on hospitalization rates for acute coronary syndromes.[66,67] For cholesterol and blood pressure, evidence from randomized trials suggests that most of the reductions in CVD risk occur within 5 years.[68] For alcohol, BMI, and dietary salt, little evidence is available on which to base temporal relations with CVD risk, although effects on intermediate traits, such as blood pressure, are rapid.[69–73] Moreover, few data are available on the time from increased exposure to increased CVD risk for any factor,[74] although the development of atherosclerotic plaques or hardening of the arteries is gradual and can be initiated in young adulthood.[75,76] By contrast, risk of a fatal obstruction of the coronary arteries might be reduced

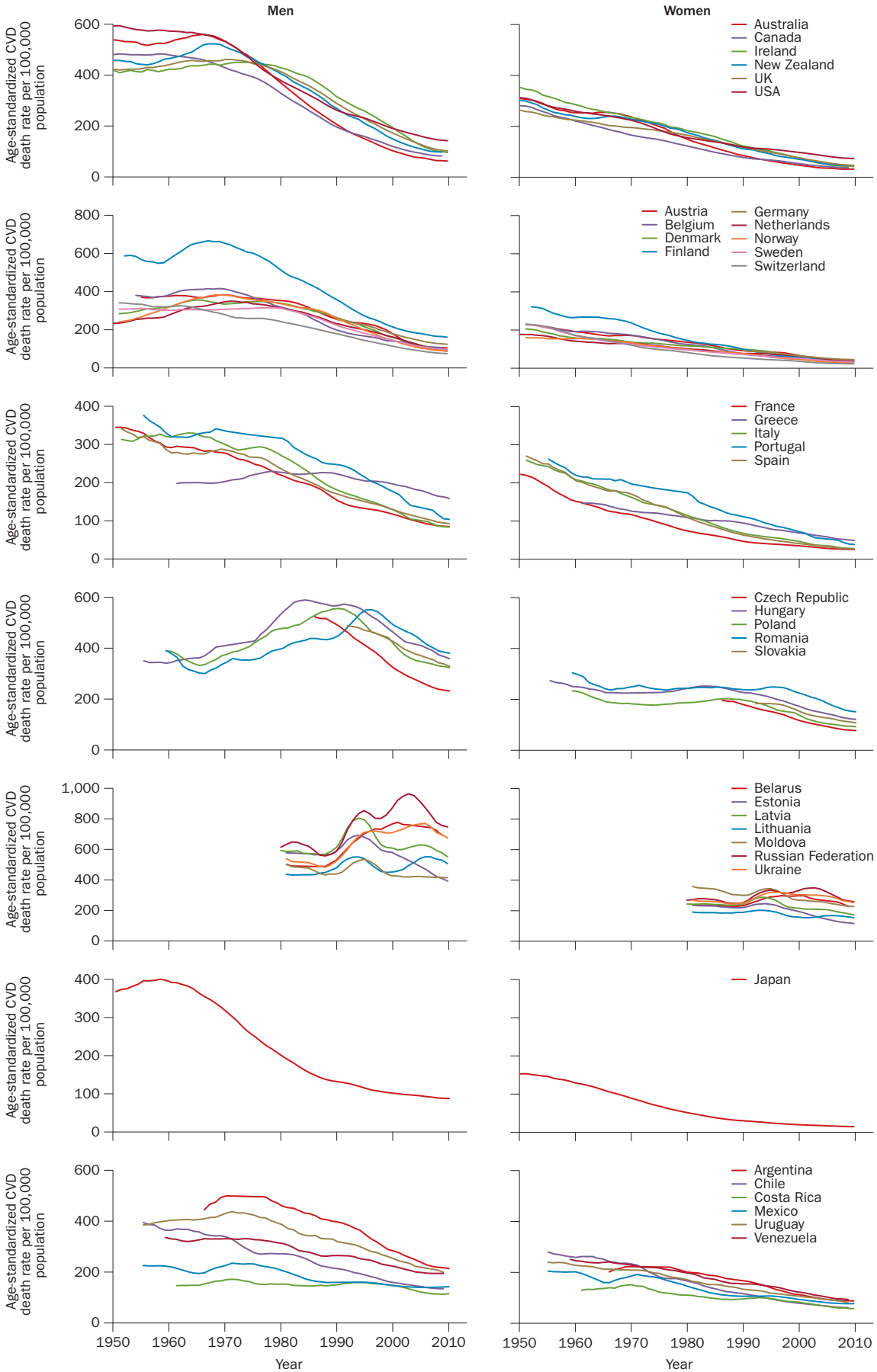


Figure 3 | Trends in CVD death rates in high-income countries for adults aged 30–69 years, by sex. Death rates were age-standardized within age groups on the basis of the WHO standard population. Trends are smoothed by use of a 5-year moving average. Data for smaller countries were excluded. See Supplementary Figure 1 for results for all ages combined. Abbreviation: CVD, cardiovascular disease.

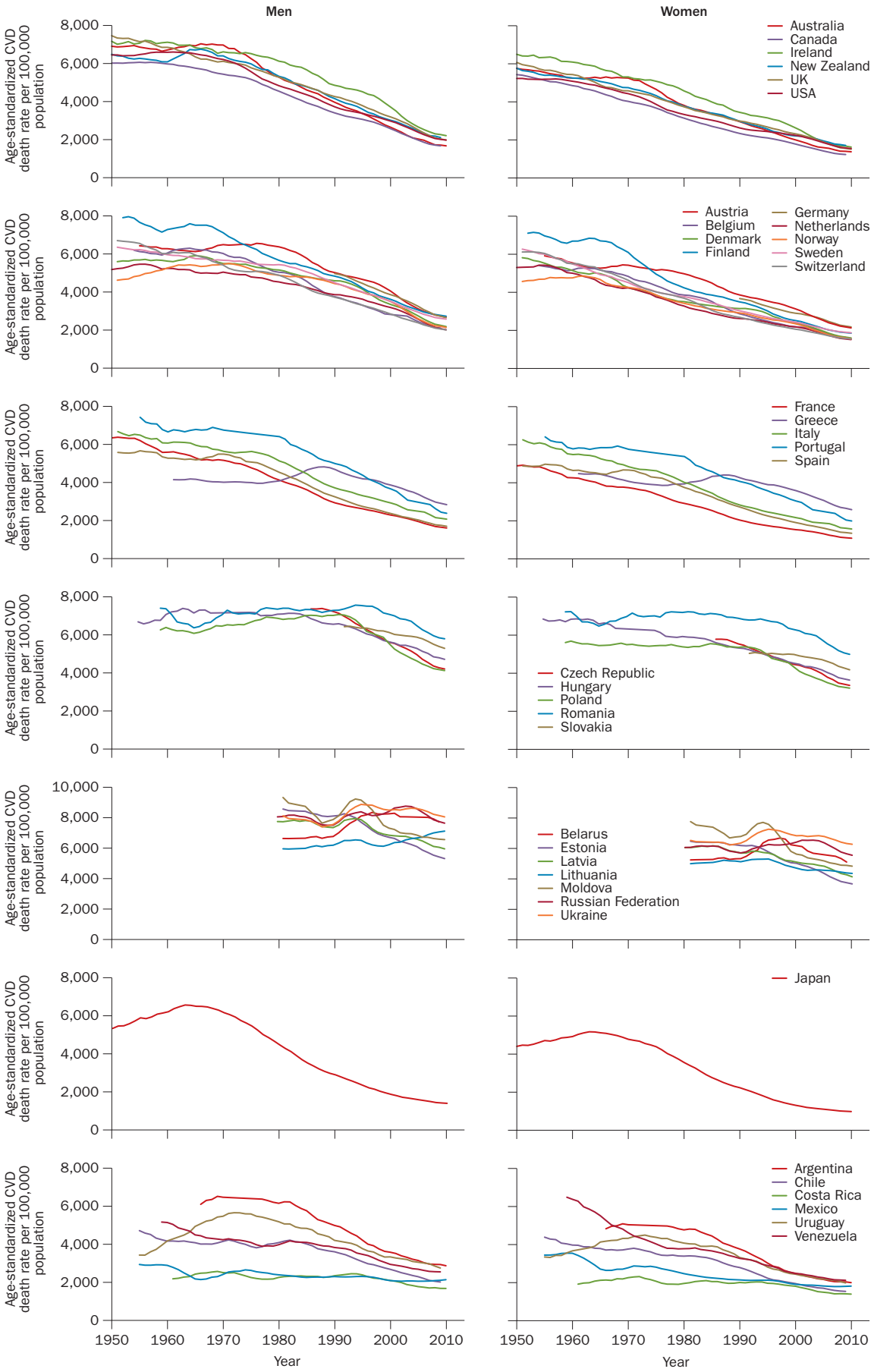


Figure 4 | Trends in CVD death rates in high-income countries for adults aged ≥70 years, by sex. Death rates were age-standardized within age groups on the basis of the WHO standard population. Trends are smoothed by use of a 5-year moving average. Data for smaller countries were excluded. See Supplementary Figure 1 for results for all ages combined. Abbreviation: CVD, cardiovascular disease.

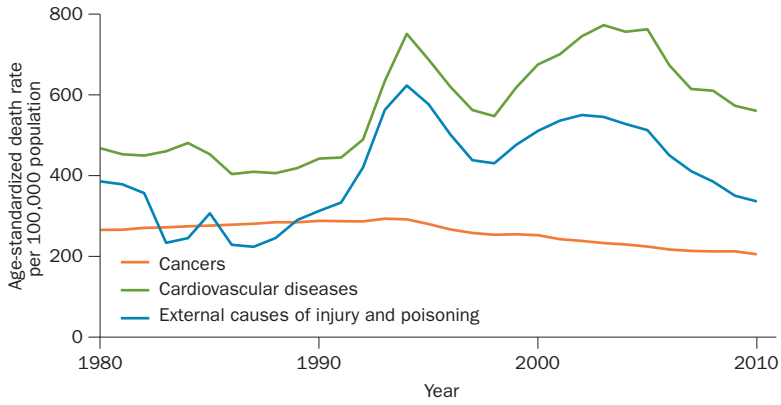


Figure 5 | Trends in death rates from cancers, cardiovascular diseases, and external causes in adults aged 25–64 years in Russia. The trends show the correlated changes in external causes and cardiovascular diseases, but not cancers, which indicates that trends in the first two causes of death are likely to have had a common determinant.

fairly quickly, particularly if a risk factor affects late-stage factors, such as clotting and thrombus formation.

Trends in CVD risk factors

Historical population-based data on CVD risk factors, especially at the national level, are less plentiful than mortality data. Health surveys, food and alcohol production and trade data, and sales receipts for tobacco and alcohol have been used to reconstruct trends in behavioural and dietary risks. Population-based measurement data are required to assess trends in physiological risk factors, because self-reported, clinic-based, and hospital-based measurements are subject to bias. The longest-duration nationally representative health examination survey began in 1948 in Japan, and has been conducted virtually every year since.[77,78] Other countries now have similar health examination programmes with periodic surveys that allow direct measurement of trends in physiological risk factors and diet. The WHO has coordinated a series of health examination surveys through its STEPwise approach to Surveillance (STEPS) programme in countries in which data on CVD risks have not traditionally been available.[79] A small number of comparative studies, such as the MONICA Project,[36] have assessed data from multiple countries. The Metabolic Risk Factors of Chronic Diseases Collaboration[80] has pooled much of the available population-based data on major cardiometabolic risk factors throughout the world and has used advanced statistical methods to reconstruct trends in risk factors for all countries.[81–86] Despite these efforts, data on trends in important CVD risk factors remain limited in most countries, and the estimated trends are uncertain.

Smoking

Summaries of smoking data have been collated periodically,[87–89] and show that the prevalence of smoking rose among men in English-speaking and northern European high-income countries throughout much of the 20th century, but began to reverse in the 1960s, according to a strong birth-cohort pattern.[90–94] Later increases in prevalence were seen among men in central, Eastern, and southern Europe, Japan, some countries in Latin America (although not to the same levels as European and English-speaking countries), and eventually in other countries in Asia and the Middle East.[87] In Africa, smoking prevalence remains low.

The dynamics of smoking prevalence in women were somewhat different from those in men, with increases and declines occurring decades later. A notable rise was seen after World War II, first in English-speaking and northern European high-income countries, which continued into the 1980s. Although prevalence in women never reached the peak levels observed in men, smoking prevalence in the two sexes varied considerably between countries. For example, prevalence in Denmark and the UK has historically been high in women and men; the proportions of women and men smoking have also been similar in southern Europe and some Latin American countries (for example, Argentina and Chile) and central European countries (for example, Austria, Czech Republic, and Hungary). By contrast, smoking is fairly rare among women in much of Asia and Africa (<5%).[90,95,96] Elsewhere, such as in Russia and Ukraine, around 50–60% of adult men smoke, compared with 15–25% of adult women, leading to intermediate sex ratios of smoking.[90,95,96]

As well as prevalence, the amount smoked and types of cigarettes available (such as low-tar and light cigarettes intended to reduce tar and carbon monoxide yield) have changed over the past 60 years.[97,98] Some studies have associated these changes with altered CVD risk.[99] However, the systematic Reports of the US Surgeon General have concluded that the use of low-tar and light cigarettes has not influenced overall disease risk, and indicated that focus should be on preventing smoking initiation and facilitating quitting.[100,101]

Alcohol use

Trends in alcohol use are more heterogeneous than those of smoking, and are highly influenced by cultural, socioeconomic, and political factors; by the large diversity of alcohol types, scale, and ownership of production; and by alcohol policies and regulations. Trends in alcohol use have been reviewed elsewhere,[90,102–106] but here we note a few important features. First, alcohol consumption has declined steadily for decades in traditional wine-drinking countries (mainly those in southern Europe and a few countries in South America; Figure 8).[90,107,108] In other western high-income countries, downwards trends have been seen in the presence of alcohol control policies, such as taxes and regulation that raise prices and restrict access, for instance in Australia and Canada in the 1980s and 1990s, and upwards trends where there has been little policy intervention, such as in Denmark, Finland, and the UK. Alcohol use is rising steadily in many countries in Asia, reflecting increases in purchasing power, low taxes, and very little regulation.

One of the most notable worldwide trends in alcohol use, with major consequences for CVDs, has been massive fluctuations in consumption in Russia and some of its neighbouring countries from the mid-1980s to the end of the 1990s. These trends are difficult to estimate owing

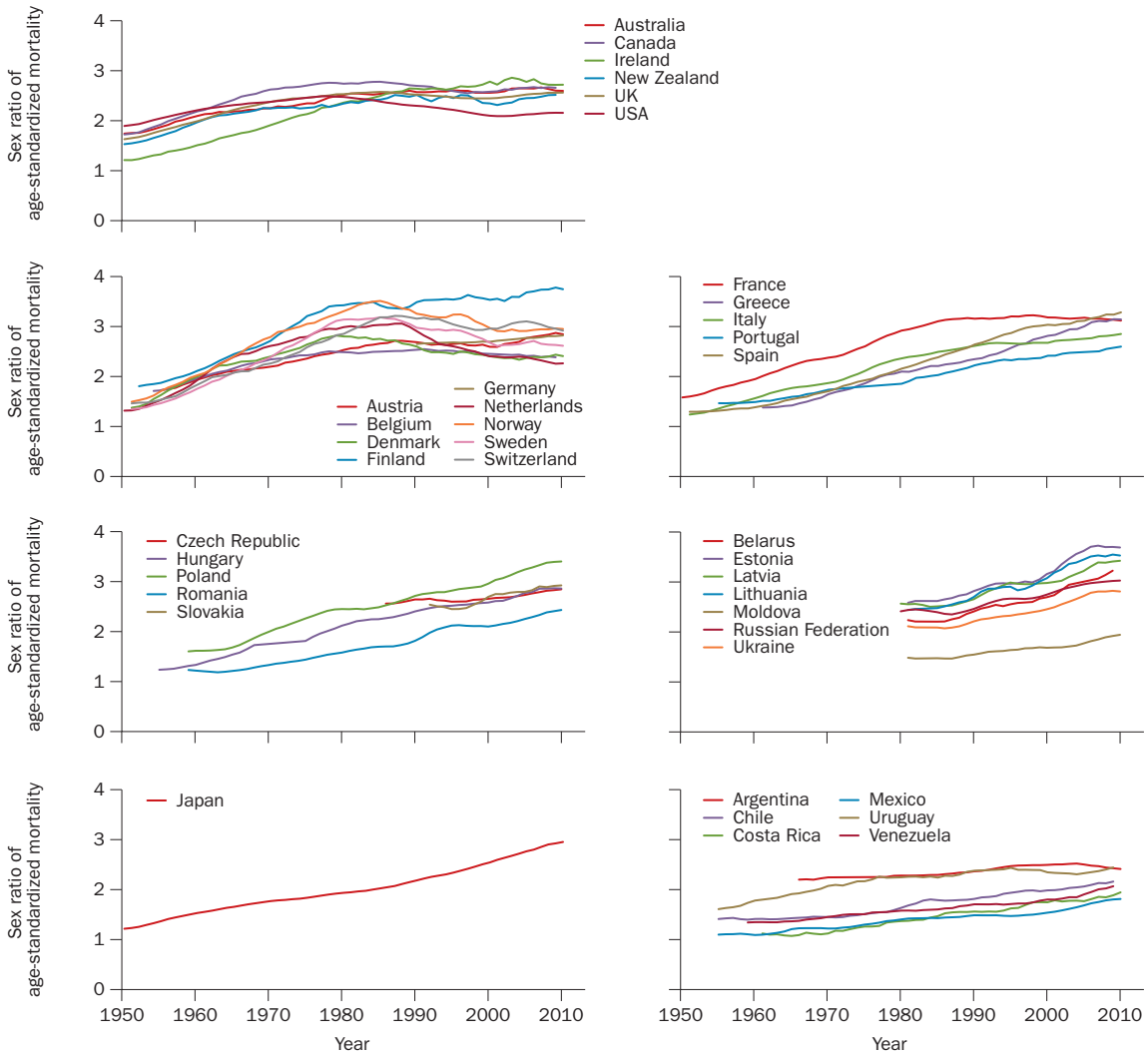


Figure 6 | Trends in the male-to-female ratio of cardiovascular death rates for adults aged 30–69 years in countries with reliable mortality data. Death rates were age-standardized on the basis of the WHO standard population. Trends are smoothed by use of a 5-year moving average.

to complexity of alcohol sales and use in these countries, such as high illegal and otherwise unrecorded consumption.[109–112] Nevertheless, hazardous drinking patterns, with a high proportion of ethanol being drunk as spirits in intense drinking spells, are clearly indicated, and are seen in trends in deaths caused by acute alcohol poisoning.[113]

Although some debate remains about whether light or moderate drinking is cardioprotective,[114] agreement is emerging that harmful patterns of alcohol use, especially heavy drinking, is associated with increased CVD risk.[115] Little information, however, is available for many countries on trends and drinking patterns. The first international conference focusing specifically on alcohol consumption patterns was held only in the mid-1990s,[116,117] and systematic collection of data began afterwards.[118]

Diet

The early evidence on the effects of dietary factors on CVDs was largely from observational studies in humans and animal experimental studies.[34] However, given the strong correlations between the various features of diet, and between diet and other behaviours, confounding of effects is likely in observational studies. Well-designed randomized and epidemiological trials of nutrition are increasingly being conducted, and have confirmed the effects of some dietary factors on CVDs and their intermediate physiological risks, such as high salt intake on blood pressure (and, in one case with additional follow-up, on CVDs),[119–122] as well as the benefits of replacing saturated with unsaturated fats, and of diets rich in fruits, vegetables, whole grains, and low-fat dairy.[123–130]

Trends in fat consumption, especially animal-derived and saturated fats, have received the most attention, because they have been regarded as an important IHD risk factor.[9] Using food-supply data, Kahn[131] and Antar[132] found that, despite a rise in the overall fat content of the US diet, this change alone was too small to explain increased IHD mortality in the early 20th century. Antar hypothesized a role for the replacement of complex with processed carbohydrates.[132] Similar analyses based on food supply

Table 1 | Cardiovascular risk factors that might underlie cardiovascular mortality trends

Risk factor	Type	Temporal responsiveness
Smoking	Behavioural	Observational evidence shows that risk begins to fall immediately after cessation and reaches that of nonsmokers within 10 years[3,65]
Alcohol	Behavioural	Little good observational evidence,[69] with the exception of Russia and other former communist countries, where abrupt changes in CVD mortality occurred after changes in alcohol use; however, these changes might have been caused by additional sudden cardiac deaths misclassified to IHD
Adiposity	Intermediate trait; mediators include blood pressure, lipids, inflammation, and glycaemia and diabetes mellitus	Limited evidence that weight management (accompanied by broader lifestyle changes) reduces the risk of diabetes within a few years in people with impaired glucose tolerance,[313] but no good evidence on temporal responsiveness for CVDs[314]
Blood pressure	Intermediate trait with direct effect	Evidence—primarily from randomized trials—suggests that, as a result of declining blood pressure, IHD and stroke risk begin to fall immediately, and continue to do so for >5 years
Serum cholesterol	Intermediate trait with direct effect	Evidence from randomized trials demonstrates that, as a result of declining serum cholesterol levels, IHD risk begins to fall immediately, with near-complete reversibility in 5 years[68]
Glycaemia and diabetes mellitus	Intermediate trait with direct effect	Little evidence on temporal responsiveness of CVDs to glycaemic control or rise, because most trials have focused on intensity of glucose lowering, and have been of short duration[269]
Diet and nutrition	Behavioural; potential mediators include BMI, blood pressure, lipids, inflammation, and oxidation	Some evidence from randomized trials that changes in salt or the type of fats or oils can result in changes in mediators or CVD risk, with declines starting immediately, but less is known about how long before the full benefits are achieved because of the short duration of trials

Abbreviations: CVD, cardiovascular disease; IHD, ischaemic heart disease.

data or dietary surveys associated reductions in saturated and animal-derived fats with decline in IHD in the late 20th century in Finland, Germany, New Zealand, Poland, Sweden, the UK, and the USA, alone or in combination with a decline in salt intake and a rise in consumption of fruits.[19,26,133–138] Stephen and colleagues fitted a quadratic relationship to nutrition survey data and showed increased fat intake in the USA until the 1960s before declining; the peak in the UK was in the 1970s.[139,140] They associated these peaks with when the IHD mortality began to decline, but overlooked that the decline in IHD mortality began at different times in men and women and, therefore, could not be explained by the same factor. Japan has detailed surveys that indicate increases in fat consumption as IHD rose, but trends in fats, when converted to cholesterol levels using Keys' relationships, could not entirely account for the observed change in IHD.[27,30,77,78]

Consumption of animal-derived foods and vegetable oils seems to have increased in China for decades, as has consumption of the former in some Mediterranean countries, such as Greece.[90,141] Pooling of worldwide nutrition surveys and analysis of food availability data from the UN Food and Agricultural Organization showed little change in the availability or intake of animal fats at the global level, owing to a balance of decline in high-income countries and rise in other countries.[142,143] Use of trans fats, which are made by hydrogenating edible oils and are associated with high CVD risk, was common in many countries because of low storage costs. Use seems to have decreased in high-income countries, partly owing to regulation,[144,145] and in some central and Eastern European countries after the introduction of market economies.[146,147] Consumption in India and parts of the Middle East might have increased.[143,148]

High salt intake is a well-recognized major risk factor for CVDs, especially stroke, largely through effects on blood pressure.[73,119,149,150] Although partly related to cultural and geographical factors, economic development also influences salt intake in two opposite ways: it reduces the need to use salt for preserving food through enhanced access to refrigeration and year-round availability of fresh foods, and it tends to increase salt intake through the use of packaged and pre-prepared foods that often contain high doses of salt for flavouring. Dietary intake of salt in Japan changed little from the 1950s to 1970s, then declined.[151,152] Similar reductions are occurring in parts of China, but not in South Korea.[153] Among western high-income countries, long-term reductions have been seen in Finland, leading to reduced stroke (and stomach cancer) mortality, and reductions have subsequently been seen in the UK.[135,136,154–158] Analyses of worldwide surveys suggest high salt intake with little change over time in many regions,[159,160] but the estimated trends are likely to have been affected by very limited data availability.

Less research has been done into trends in the consumption of fruits and vegetables and whether they are consumed fresh, cooked, or as juice. Consumption of fresh fruit and vegetables is linked to lower blood pressure and reduced CVD risk.[123,161,162] The available studies suggest an increase in absolute intake (now at a possible plateau) in at least some high-income countries.[132,135,154,163–166] Studies based on share of total energy suggest a decrease,[163,167] but this finding simply reflects the increase in intake of other foods and, therefore, total calories. Since around 2000, a few studies have been performed to examine trends in overall food and diet patterns and have found a broad increase in intake of vegetable fats, although not necessarily unsaturated vegetable fats, in low-income

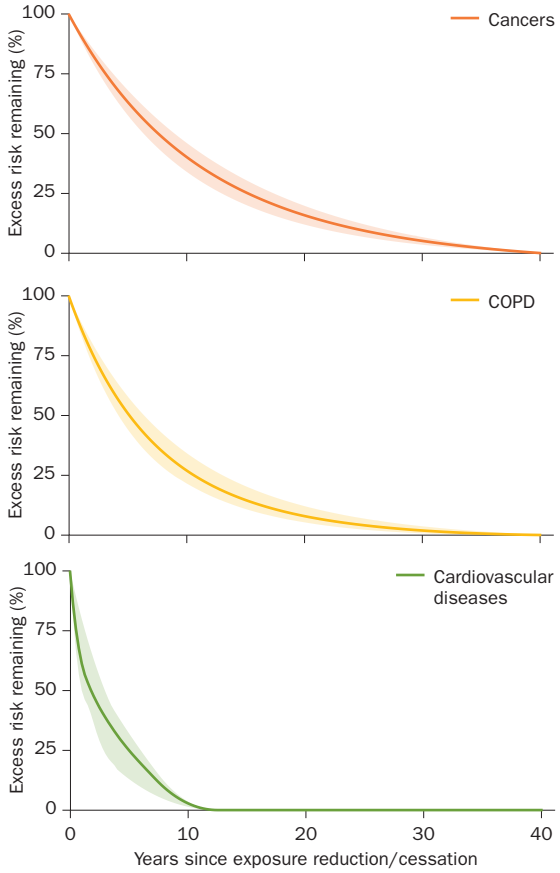


Figure 7 | Percentage of excess relative risk of cancers, COPD, and cardiovascular diseases remaining over time after exposure to a risk factor has stopped or been reduced. Excess relative risk is relative risk −1. The shaded areas show uncertainty of the fitted curve. Abbreviation: COPD, chronic obstructive pulmonary disease. Reprinted from *The Lancet* **384** (9941), Kontis, V. *et al.* Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. 427–437 © (2014), with permission from Elsevier.

countries; higher availability of animal-derived foods and dairy in middle-income countries, but consumption is low in western high-income countries; higher use of refined carbohydrates and sugars and less use of whole grains and foods with high fibre content; more fruits; and higher dietary diversity.[90,142,163,168,169]

Adiposity, glycaemia, and diabetes

BMI and adiposity are risk factors for IHD and stroke.[170] The systematic pooling and analysis of data by the Metabolic Risk Factors of Chronic Diseases Collaboration showed that, since 1980, age-standardized mean BMI has increased among men in every region except central Africa and south Asia, and among women in every region except central and Eastern Europe and possibly Japan and South Korea.[82] These increases have resulted in a doubling of the prevalence of obesity worldwide between 1980 and 2008.[86] Additionally, prevalence of raised blood glucose and diabetes has increased globally and in most regions, particularly in the Pacific islands, Middle East, north Africa, and Central America.[84] In the context of a trend of increasing BMI, the rise in diabetes was slower in western Europe and faster in south Asia than in other regions.

Blood pressure

Trends in blood pressure and serum cholesterol in high-income countries (and in many low-income and middle-income countries with reliable data) have been opposite to that of BMI, although declines in blood pressure and serum cholesterol were smaller where BMI rose more.[171] Between 1980 and 2008, systolic blood pressure declined slightly globally,[83] with the largest declines occurring in high-income countries. In Oceania, east Africa, and south and southeast Asia, systolic blood pressure rose in both sexes, as it did in women in west Africa. The few longer-term national studies also show decades of decline in blood pressure in a few high-income countries, such as Finland, Japan, and the USA.[30,151,152,154,172,173] The decline in blood pressure seems to be the result of birth cohort and period effects,[172,174] meaning that in each subsequent birth cohort, blood pressure is lower than that in the previous cohort throughout the life-course. In addition to this cohort effect, people have experienced lower blood pressure at every age as time has passed, regardless of when they were born. Furthermore, reductions have been seen across the blood-pressure distribution as a whole, with additional benefits to people with hypertension.[172,175,176]

Little is known about the reasons for trends in blood pressure, even from analysis of robust data, such as in Japan.[151,152] However, drivers probably include reduced salt, increased and/or year-around consumption of fruits and vegetables that are sources of potassium, and the use of antihypertensive medications in middle-aged and older people. Additional reasons for cohort patterns might include lifelong effects of changes in early-life nutrition or infection, but these are so far hypothetical. Importantly, these reductions in mean blood pressure occurred despite rising adiposity in high-income countries—and more recently also in Seychelles, a middle-income country.[177] As a result, although population mean blood pressure in 1980 was directly associated with mean BMI, by 2008 the association had become null for men and inverse for women.[178]

Cholesterol

Trends in serum cholesterol have been of interest for a long time because of the causal association with IHD,[9] although the association with stroke risk is surprisingly weak.[170] With use of time series food data, upward trends were identified in mean (dietary) cholesterol concentrations in the USA for the first 6 decades of the 20th century, and in Japan from 1949 to the 1960s, although neither was sufficiently large to explain the increased IHD mortality entirely.[27,131] Since the 1960s, studies that have used health examination survey data have shown rising serum cholesterol levels in Japan,[173,179,180] and declines in western countries.[19,135,154,181,182] Pooled data from health examination surveys suggest virtually no change in the global mean since 1980, driven by declines in Australasia,

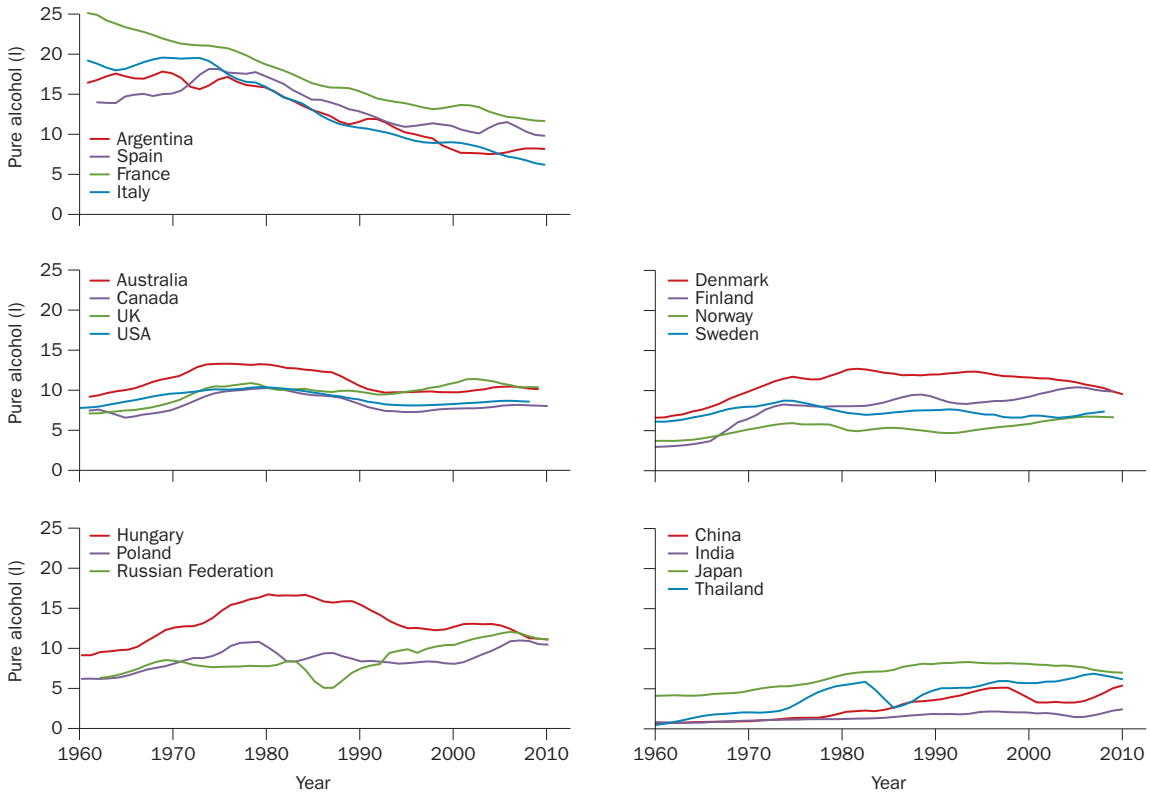


Figure 8 | Trends in recorded per-capita alcohol consumption among adults aged ≥15 years. Data are from the WHO Global Information System on Alcohol and Health,[317] and were smoothed by use of a 3-year moving average. In addition to recorded consumption, an unrecorded consumption exists in some countries, estimated as <0.5 l per person per year in Japan and France; 1–2 l per person per year in China, Sweden, UK, and USA; and as high as 4 l per person per year in Russia.[106] Unrecorded alcohol consumption in Russia has changed over time, with trends being very difficult to estimate owing to data limitations.[111,112] The unexpected drop followed by rise in Chinese trends might be due to changes in data sources.

Europe, and North America, and offset by increases in east and southeast Asia, including in China, Japan, and Thailand.[85] The decreases in western countries began long before widespread use of lipid-lowering drugs.[182] Total cholesterol concentrations seem to have changed little in other regions, but historical data are limited.

Studies of risk-factor and CVD trends

Early studies

After researchers noted the rising and declining trends in CVD mortality, they also attempted to understand the drivers of these trends. Moriyama and colleagues, who were among the first to note the long-term trends and differences between the sexes, approached experts for possible explanations, with the hypotheses including a number of factors.[33] Changes in diet, especially increases in dietary fat, energy imbalance, and obesity were proposed, and were assumed to be worse in men because "the emergence in the early 1920s of the slim figure fashion"[33] would have led to less obesity in women. Psychosocial stresses and strains were suggested to affect men more than women owing to the nature of their jobs. Decline in infections and related CVDs, improvements in pregnancy care, and improvements in women's economic and social statuses owing to increasing job opportunities and because "by virtue of smaller families and mechanical aids, women had been liberated from prolonged, exhausting household drudgery".[33] The use of postmenopausal oestrogen—a topic to which attention returned nearly half a century later, after the Women's Health Initiative showed an association with increased risk of IHD[183]—was deemed too recent and still too limited to have contributed to the trend.

Moriyama and colleagues' hypothesis-generating study aside, the earliest studies of the drivers of CVD trends focused almost solely on dietary fats, saturated fats, and cholesterol. These studies were followed by ones on the role of trends in blood pressure, smoking, and, eventually, obesity. Occasionally, other factors were considered, such as types of carbohydrate.[132] Some of these studies showed trends in risk factors that paralleled those in CVD mortality; others showed no association or reported inconsistent results in men and women or other subgroups (for example, Utah Mormons, who rarely smoked, showed a decline in CVD mortality similar to that in the general US population when smoking began to decline).[10,19,20,26,27,30,132,184–187] Some studies cited highly specific associations. For instance, Walker attributed the decline in coronary disease to specific policies, such as the 1964 Report of the Surgeon General on Smoking and Health and the AHA statement on diet.[20]

Taken together, two main features of these trend studies emerge: first, substantially more focus was placed on IHD

than on stroke or other CVDs, which were also declining; second, the epidemiological studies (and strong beliefs) about the importance of specific risk factors, especially dietary fats, potentially led to additional possible explanations being overlooked. Further assessments suggest that decline in CVD mortality—in at least some countries—began before the decline in classic risk factors,[54,171,188,189] which raises the possibility of other important factors and combinations of factors being involved.

Bethesda Conference and MONICA Project

A decade of work on the determinants of decline came together at the Bethesda Conference on the Decline in Coronary Heart Disease Mortality in 1978 (Box 1)[24] and contributed to initiating the MONICA Project (Box 2)[36] to measure IHD risk factors (BMI, blood pressure, serum cholesterol, and smoking), incidence, treatment, case fatality, and mortality in 38 communities in 21 countries from the mid-1980s to the mid-1990s, and to quantify the contributions of these factors to IHD trends.

IHD death rates declined in most MONICA sites, by an average of 2.7% per year in men and 2.1% per year in women, although they rose in most former communist European countries and China.[190] The degree of change ranged from >7% per year decline in Australia and some western European countries to 4% per year increase in some central and Eastern European countries.[190] Total (fatal plus nonfatal) IHD event rates fell by 2.1% per year in men and 1.4% in women, and 28-day case-fatality (a proxy for acute post-event treatment) fell by 0.8% and 0.6%, respectively. On the basis of these results, the MONICA collaborators concluded that, generally, declining event rates contributed about twice as much to the decline in mortality as improvements in 28-day case fatality. The two components had heterogeneous effects across countries, and in some places worked in opposite directions.

Despite the pioneering character of the MONICA Project, how much light it can shed on the contribution of individual risk factors to changes in event rates is limited. Having only a few dozen data points for the effects of four risk factors might have led to considerable imprecision and overfitting.[191] Nevertheless, adjusted analysis supported a positive association between changes in blood pressure and cholesterol and changes in IHD event rates, but an inverse association between change in BMI and IHD, in men and women.[192] A direct association with change in smoking was found for men, but an inverse association for women. This implausible result might be affected by underadjustment for other factors that confound the effects of smoking in women, which increased in many European countries where IHD was declining rapidly. Inverse associations between change in IHD and change in BMI might be due to similar reasons, or because the effects of rising BMI were countered by declining blood pressure and cholesterol levels, which are important mediators of its effects on IHD.[193] Importantly, these two risk factors and smoking declined more steeply in overweight and obese people than in those of normal weight.[194] Such within-population correlations of risk factors were not taken into account in MONICA or subsequent similar studies.[171]

The magnitudes of associations aside, risk-factor trends explained only about one-half of the variation in IHD decline in men across study centres in MONICA, and <20% in women.[192] Although measurement error is a possibility, this finding implies that other important factors are likely to have been acting to reduce IHD rates at the population level. Such a role is also apparent from the negative intercept of the association between IHD change and risk-factor changes, with the implication that, even if the risk factors considered had not changed, IHD would have declined in the MONICA study populations.

Other community-based studies

Even before the Bethesda Conference, some researchers had begun empirical investigations into declining IHD mortality. In 1957, Pell and colleagues[195,196] began to investigate incidence and short-term (24 h and 30 day) and long-term survival from myocardial infarction among employees of the Du Pont Company.[195,196] Employees had regular medical health examinations, and information was available about the timing and cause of their death. Incidence of CVDs declined from the onset of the study. Case fatality began to decline in the early 1970s—a trend that continued until the end of the study in 1983.

Most community-based studies, however, began around or after the Bethesda Conference. These included a number of studies in the USA, such as the Minnesota Heart Study, the Olmsted County Study, the Worcester Community Study, and the Atherosclerosis Risk in Communities (ARIC) study. Investigators in these studies collected population-based data on trends in hospitalization for CVDs, treatment, survival of hospitalized patients, and, in some cases, risk factors.[197–201] In most of these studies, hospital records were used to track trends in hospital admissions and discharges for IHD; in some studies these data were confirmed by chart review—typically symptomatology, electrocardiogram features, and an ever-evolving set of cardiac enzymes. Some groups of investigators also employed additional efforts to find patients who either did not appear in hospital records or whose cause of admission to hospital or death was coded incorrectly. Investigators in the Minnesota Heart Study and ARIC also used vital statistics to monitor out-of-hospital IHD deaths. The British Regional Heart Study had similar aims, but researchers followed up individuals rather than analysing trends in whole communities, which was done in MONICA and other community studies.[202,203] The availability of electronic data, which enables the linking of hospital information to death records, allows trends in CVD event rates as well as in-hospital and out-of-hospital survival to be monitored.[204–209] However, bureaucratic and legal obstacles, presented as confidentiality concerns, are hindering full use of such data.

Modelling risk-factor contributions

After the Bethesda Conference, prospective cohort studies helped to identify new risk factors for CVDs, but could not be used to assess how changes affected disease trends in populations. Randomized trials showed the efficacy of new treatments and guided clinical practice, but could not be used to assess uptake in the general population. Estimated

effects of risk factors and treatment from these individual-level studies were used to assign, with the use of models, the levels and changes in CVD mortality to specific risk factors and treatment.[64,210–216] The number of risk factors in such studies has increased over time,[217,218] and the effects of multiple risks have been considered.[213,214,219,220]

An important difference between the modelling studies and the analyses in the MONICA Project is that the contributions of risk factors in MONICA were directly estimated as associations between changes in risk factors and in CVDs across populations. By contrast, attribution modelling studies, by necessity, assume that the individual-level associations apply to the populations considered, which might be different from the epidemiological cohorts that generated the data, although some efforts are made to evaluate the evidence for similarity or its absence in relation to region and ethnicity.[170,193,221] In some of these studies, investigators have accounted for the fact that the effects of different risk factors, or of risk factors and treatments, cannot simply be added,[3,219,220] meaning that when multiple risk factors improve and treatment improves, the reductions in some CVD deaths might be attributable to more than one factor.[222,223] Other studies, however, have constrained the contributions to add up to 100% (theoretically, the sum of individual contributions, if not considered jointly, could add up to more than 100%). By their nature, such additive models predict a rise in CVDs when risk factors rise, as has been predicted for adiposity,[224–226] which proves to be the opposite of the actual trend data (for example, a consistent decline in CVD mortality with rising BMI).

Models have been extended to include the future effects of continued risk-factor trends or alternative scenarios.[3,224–226] For example, investigators in one study modelled the effects of achieving the globally agreed risk-factor targets on future trends in premature mortality (aged <70 years) from various noncommunicable diseases, and found that, with a continuation of the current trends, premature CVD mortality was expected to decline by 18% between 2010 and 2025.[3] If the globally agreed targets on smoking, alcohol use, salt intake, obesity, and raised blood pressure and glucose were also met, the decline would nearly double to 34%.[3]

Return to empirical traditions

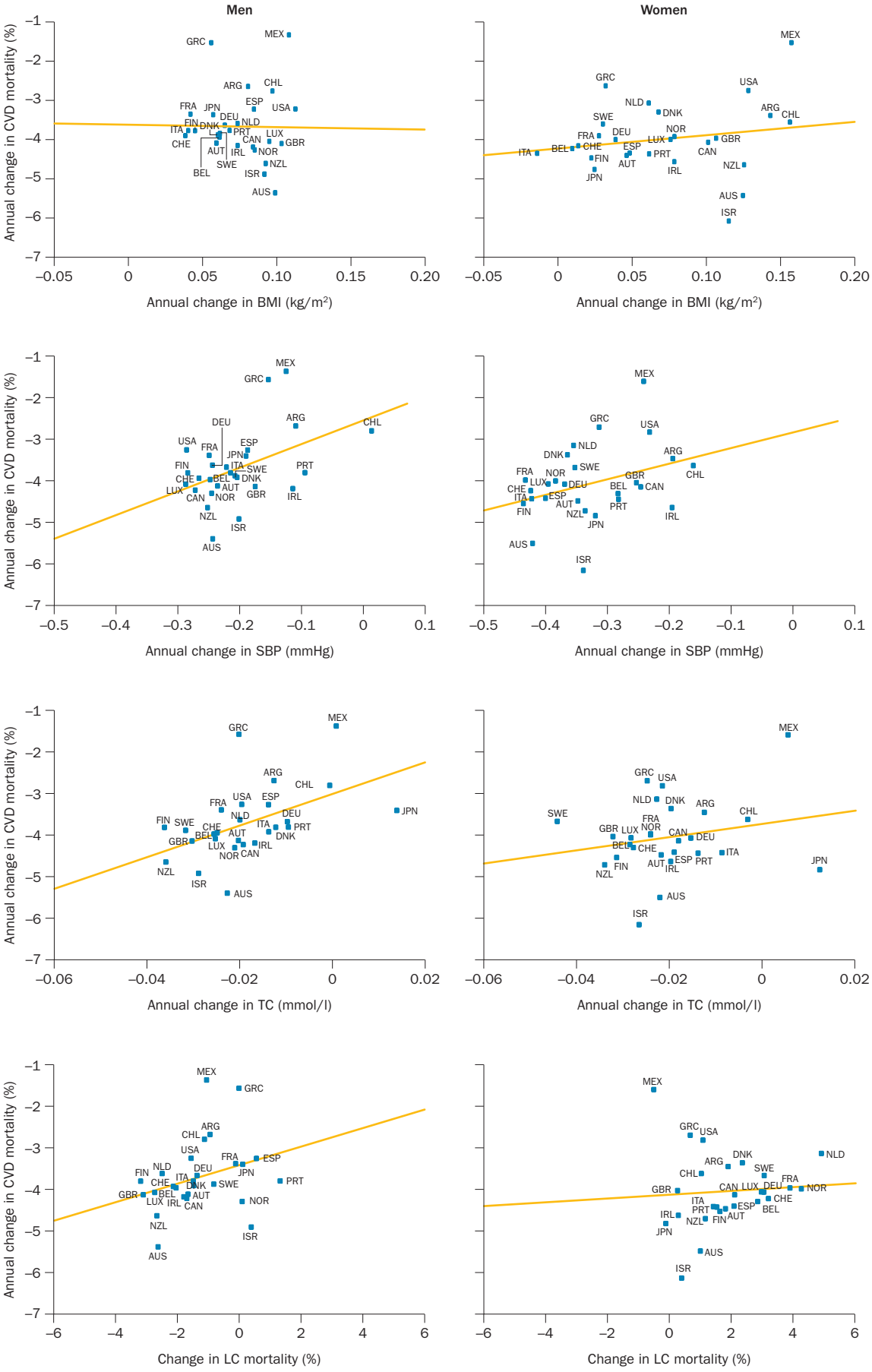
Some studies have returned to the empirical traditions of the 1970s and 1980s, and have implicated trends in specific risk factors in explaining CVD trends, often by making use of convenient natural experiments that had engendered changes in risk factors in some populations, but not others. The decline in CVDs in some countries in Eastern Europe was attributed to transition from hydrogenated fats to nonhydrogenated vegetable oils after the fall of communism,[146,147] but no attempt was made to deal with the simultaneous and numerous socioeconomic, behavioural, and nutritional changes in these countries. Careful analysis of trends was instrumental in establishing that the decrease in alcohol consumption in the Soviet Union during the Gorbachev years and the subsequent rise in harmful and heavy drinking were the most important determinants in the decline and sharp rise in CVD mortality in Russia and some other former Soviet countries.[47,227,228] This contribution was initially challenged by epidemiologists given the apparent CVD benefits of moderate drinking in western Europe, until individual-level case–control and cohort studies confirmed the massive hazardous effects in Russia.[229–232]

Researchers credited a decade of salt reduction in the UK as being an important driver of the decline in blood pressure and, by extension, in stroke and IHD deaths. This attribution was judged to be above and beyond that for other factors, such as medication and increased consumption of fruits and vegetables.[156] In Cuba, researchers associated decline and increase in body weight during periods of economic crisis and recovery, respectively, with decline and increase in diabetes, and changes in the rate of CVD decline.[233]

Finally, in an analysis similar to the MONICA Project in terms of approach and risk factors included, changes in blood pressure, serum total cholesterol, BMI, and smoking (measured by lung cancer to account for cumulative effects)[234,235] were empirically associated with changes in mortality from CVD plus diabetes.[171] When CVD was considered alone (Figure 9), change in CVD mortality was positively associated with changes in blood pressure and cholesterol (as in the MONICA Project).[171] However, unlike in the MONICA Project, a positive association was also found with change in smoking (both sexes) and BMI (in women) after adjustment for other risk factors; when CVDs and diabetes were assessed together, the association with change in BMI became positive for both sexes.[171] The magnitudes of the associations were consistent with those found in prospective cohorts of individual participants. Importantly, and as in the MONICA Project, change in risk factors explained only a fairly small share of variation in mortality change across countries, which demonstrates the crucial role of other determinants at the population level. The previously mentioned caveats of measurement error and temporal features of change also apply.

Role of medical care

When analysing trends in CVD and their drivers, one cannot avoid the issue of relative contributions of risk factors and medical care. In the period after the Bethesda Conference, the number of effective treatments for acute coronary syndromes and stroke increased notably, and management of surviving patients improved (although improved survival might have started even from the early 1970s).[196,236] Some actions, especially the introduction of coronary care units, improved diagnosis and in-hospital management without a corresponding change in the number of deaths at the population level, which was dominated by out-of-hospital deaths.[19,237] By contrast, after the efficacy of antithrombotic and reperfusion therapies—including aspirin, systemic thrombolytics, and subsequently percutaneous coronary intervention—was demonstrated in randomized clinical trials in the mid- to late 1980s, these therapies were integrated into clinical practice in high-income countries (albeit at varying degrees and speeds as described below) with emphasis on reducing time to access to acute treatments.[238–243]



◀ **Figure 9** | Cross-country associations between changes in risk factors and CVD death rates, between 1980 and 2008. All variables are for individuals aged 25–79 years and were age-standardized. The lines show the fitted linear associations. LC mortality was used as a proxy for cumulative population exposure to smoking, because data are more widely available and more reliable than those on smoking prevalence and intensity.[234,235] Abbreviations: ARG, Argentina; AUS, Australia; AUT, Austria; BEL, Belgium; CAN, Canada; CHE, Switzerland; CHL, Chile; CVD, cardiovascular disease; DEU, Germany; DNK, Denmark; ESP, Spain; FIN, Finland; FRA, France; GBR, United Kingdom; GRC, Greece; IRL, Ireland; ISR, Israel; ITA, Italy; JPN, Japan; LC, lung cancer; LUX, Luxembourg; MEX, Mexico; NLD, Netherlands; NOR, Norway; NZL, New Zealand; PRT, Portugal; SBP, systolic blood pressure; SWE, Sweden; TC, total cholesterol; USA, United States of America. Reprinted from Di Cesare, M. *et al.* The contributions of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries. *Int. J. Epidemiol.* **42** (3), 838–848 © (2013), by permission of Oxford University Press and the International Epidemiological Association.

In high-income countries, following approximately the same time course as advances in hospital care and post-hospital secondary prevention for acute cardiovascular events, evidence accumulated from randomized, controlled trials for the benefits of primary prevention using pharmacological treatments (antihypertensive medications, statins, and low-dose aspirin). The first Veterans Administration Trial in the USA reported a large reduction in cardiovascular events (mainly stroke) with the use of antihypertensive medication,[244] which was confirmed in placebo-controlled trials in Australia and the UK in individuals with moderately-elevated blood pressure.[245,246] Studies in elderly individuals as well as meta-analyses have also shown reductions in cardiovascular events with the use of medicines to lower blood pressure.[247–251] Treatment of high blood pressure has increased steadily since the 1970s in high-income countries, and later in upper-to-middle-income countries in Latin America and elsewhere.[30,151,152,252–258]

The epidemiological and animal evidence on the role of cholesterol as an important CVD risk factor produced intense interest in cholesterol-lowering treatments, leading to the introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in the late 1980s.[182,259,260] Randomized trials showed that the benefits of statins depend on baseline risk of CVDs, regardless of baseline cholesterol levels, which led to changes in treatment guidelines and a rapid increase in statin use, especially in the USA.[259,261–266]

Even with the best population-based data, such as those from Japan, the extent of reductions in blood pressure and cholesterol levels through pharmacological preventive therapy is difficult to establish because of the existence of simultaneous and partially correlated trends in various known and unknown other determinants of changes in these factors.[151] Furthermore, if treatment is based on absolute risk of disease rather than on the level of the risk factor, it can contribute substantially to decreases in CVD prevalence and mortality without much effect on mean population exposure. Preventive therapy remains fairly uncommon in low-income countries, even among people with a history of CVD events and, therefore, is likely to have done little to change risk-factor levels.[258,267]

Although hyperglycaemia and diabetes are well-established important risk factors for CVDs,[268] the contribution of pharmacological glycaemic control to CVD decline is unclear because of a lack of evidence from population-based studies and inconsistent findings in clinical trials.[269] For example, in the UKPDS trial,[270] glycaemic control had only minor effects on rate of myocardial infarction and on mortality during the trial, but these outcomes became significant at the 10-year follow-up. Conversely, the ACCORD study[271] was stopped early because of increased all-cause and CVD mortality with intensive treatment. These conflicting results probably indicate a trade-off between the benefits of good glycaemic control on long-term cardiovascular outcomes, and the risks of acute hypoglycaemia, especially in patients with advanced diabetes or previous CVDs.[272–274] Given these results, and the low rates of treatment and glycaemic control, even in high-income countries,[275] changes in glycaemic management are unlikely to have had a substantial effect on global trends in CVD mortality.

Given this rise in effective treatments, the MONICA Project provided an opportunity to examine the contributions of risk factors and treatments in the same study. The role of medical care was initially presented only as changes in short-term case fatality, which indicates the role of acute care only.[190] Subsequent analysis was performed into the extent to which changes in measured medical care and treatment—including acute and subacute coronary event management and secondary prevention in individuals with a history of IHD—had affected changes in coronary event rates, case fatality, and IHD mortality. Various preventive therapies and treatments for acute events were analysed separately and aggregated into an overall score of intensity or quality. Geographically, treatment uptake improved more in Australia, New Zealand, North America, and western Europe than in China and Eastern Europe (with the improvements in the best-performing countries associated with about a 25% larger decline in case-fatality than in countries with the smallest improvements), although the reasons for this variation, which is seen even between high-income countries, have not been fully explored. Investigators then correlated changes in these measures with changes in study outcomes.[276,277] As perhaps expected, improvements in treatment intensity were strongly associated with reduced case fatality, with treatment change accounting for 51% of variation in case-fatality change across MONICA sites.

More surprisingly, the MONICA Project[276] also showed strong associations between change in treatment intensity and change in event rates, contributing 41% of change in coronary event rates and 64% of change in overall IHD mortality. These values are both larger than the corresponding contributions of changes in risk factors (although no formal comparison was made between the contributions of risk factors and treatment towards lower event rates and mortality).[276] The apparent difference in contributions of treatment and prevention to the decline in event rates reported in MONICA could have been affected by better measurement of treatment coverage than of risk factors and by differences in time to effects of treatment (immediate) and risk prevention (gradual), which could have biased the estimated effect for prevention towards zero. Although

correlations with other, unmeasured, factors could provide another explanation for these results, the expansion of evidence-based acute care and secondary prevention measures over this period provide a fairly convincing mechanistic and temporal partial explanation for decline.[277]

Further support for the important contribution of treatment to declines in mortality from CVDs, especially IHD, came from community studies in the USA, as early as the study of Du Pont employees by Pell.[195,196] In all these studies, declines were shown in IHD mortality and case fatality among hospitalized patients, alongside striking increases in treatment intensity, including medications (such as aspirin, heparin, antihypertensives, and thrombolytics) and procedures (CABG surgery, angioplasty, and stenting), in the 1980s and 1990s. In studies that had data on both hospitalization and out-of-hospital deaths, the share of events that involved hospital admission increased.[197–201,278,279] Investigators in the Minnesota Heart Survey[199] found small, but significant, decreases in cholesterol levels (by 0.07–0.13 mmol/l), smoking (2–3%), and blood pressure (1 mmHg) between 1985–1987 and 1990–1992. The researchers, therefore, generally attributed the decline in mortality to improvements in treatment.

Interpretation of the results from treatment studies has been complicated by the changes in diagnostic assessments of myocardial infarction over the study period. For example, use of troponin-based assays increased from 8% to 98% between 1996 and 2001 in the ARIC study, which led to higher estimated incidence over time and a change in composition of hospital-based cases (more patients with minor infarction were admitted later in the study).[280–282] Adjustment for changes in diagnosis reversed the trend from increasing to declining incidence, and led to lower, although still significant, estimates of the contribution of treatment.[277,283] Improved diagnosis (and, therefore, treatment) owing to increasingly sensitive tests should be included in the contribution of medical care to the decline in CVD mortality, because patients with milder disease have an improved prognosis after they are detected and treated.[284,285]

Infectious diseases

Around a century or more ago, the global profile of CVD mortality was probably dominated by conditions associated with infection, including rheumatic heart disease, infective endocarditis, and cardiomyopathies.[286] Although greatly reduced, infection-related CVDs still account for around 800,000 deaths per year worldwide,[1] and remain major contributors to CVDs in many developing countries.[1,287,288] Trends in rheumatic heart disease, and its underlying risk factor of rheumatic fever, have been characterized by four important features.[289,290] First, the incidence of rheumatic fever began to decline before the introduction of antibiotics in developed countries,[291] possibly because of general improvements in living and housing conditions, nutrition, and general health care, and had virtually disappeared by the 1970s or 1980s.[16,292–294] The decline in rheumatic heart disease was probably a factor in the previously mentioned overall decrease in CVD mortality, despite increasing IHD mortality. Although an overall downward trend is apparent in high-income countries, rheumatic heart disease remains an important public-health problem in the aboriginal communities of Australia, Canada, and New Zealand.[295,296] Second, after the introduction of comprehensive prevention programmes involving environmental interventions and antibiotic therapy, the prevalence of rheumatic fever fell in countries such as Costa Rica, Cuba, Guadeloupe, and Martinique.[297–299] Third, the incidence of rheumatic fever remains high in sub-Saharan Africa and south Asia, where no national prevention or treatment programmes exist.[300] Finally, the incidence of rheumatic fever increased in the former Soviet republics in central Asia after the collapse of the Soviet Union. Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan have some of the highest rates of rheumatic heart disease in the world.[301,302] By comparison with rheumatic disease, less is known about trends in cardiomyopathies, which are endemic in tropical countries.[303–305]

More broadly, populations exposed to a chronic burden of infections, which are associated with inflammation, might be at increased risk of IHD, especially in the presence of other behavioural and environmental risk factors.[306] Reduced incidence of infections and improved treatment as countries develop could, therefore, be partly responsible for decreasing IHD mortality. No data on trends in inflammatory markers are available to evaluate this possibility, but the increasing use of antibiotics and resulting decline in the burden of infections in many countries from the late 1940s onwards came just before the rising trend in IHD slowed and then reversed.

An area of increasing importance is the potential role of the HIV/AIDS epidemic, and its treatment, on the future course of CVDs. Untreated HIV infection is associated with shortened life expectancy, weight loss, and a fall in systolic blood pressure,[307] but also increased incidence of inflammatory cardiovascular disorders resulting in cardiomyopathy, tuberculous pericarditis, pulmonary hypertension, stroke, and maculopathy. The use of some antiretroviral treatments is associated with increased insulin resistance, dyslipidaemia, and lipodystrophy.[302,303] These atherogenic complications of antiretroviral therapy will be of increasing relevance as more people receive long-term antiretroviral treatment and reach middle and older ages.[308,309]

Conclusions

Since the middle of the 20th century, trends in CVD mortality, and subsequently the causes of these trends, have been explored. We found that, with the exception of the MONICA Project and a few other intracountry or intercountry studies, most analyses of the role of risk factors or treatment trends have relied on qualitative observations or basic quantitative tests of whether these variables and CVD mortality changed together, with limited attention to other explanations for decline.

Our seemingly critical assessment of these earlier studies is, of course, from the vantage point of the substantial advances in epidemiological and clinical knowledge about CVD causes and treatments, most of which occurred as the early studies were taking place. As importantly, all the

major empirical studies on determinants of CVD mortality decline collected data over a period in which many aspects of CVD aetiology and survival were changing rapidly in high-income countries. First, many risk factors were changing simultaneously, with some having partially correlated trends and others opposite trends. Second, the demography of people with CVD events was changing, with increasing average age and changes in the sex composition of those experiencing CVD events and deaths (issues that the MONICA Project was not designed to capture fully, given that individuals aged >65 years were not assessed, and that fewer of the events were in women than in men). Third, dramatic changes occurred in how acute myocardial infarction was defined, diagnosed, and treated, with increased awareness from physicians and the general public about symptoms and the importance of early in-hospital treatment, increasingly sensitive biomarkers that could be used to detect minor events that would not be captured by symptoms alone or use of electrocardiography, and uptake of more-effective treatments both in hospital and among survivors. The sheer number of measured and unmeasured changes, and the paucity of high-quality longitudinal population-based data (many of which had been proposed at the Bethesda Conference, but were not pursued), mean that our understanding of what initiated the decline in mortality, and the relative roles of treatment and prevention, is likely to remain largely correlational and somewhat speculative.

Despite these limitations, some conclusions can be made with confidence. First, the decline in CVD mortality in high-income countries and in Latin America has not slowed—a situation that was hard to envision in the 1970s and 1980s. If current downwards trends continue, IHD and stroke will become uncommon causes of death in people aged <70 years in high-income countries. Data and modelled mortality trends from the WHO and others seem to indicate that middle-income and upper-middle-income countries have begun similar trends. This decline will, in turn, lead to an increase in longevity and life expectancy, because CVDs are a major cause of mortality worldwide.[216]

Second, trends since the 1970s have almost certainly benefitted from declines in important behavioural risk factors (such as smoking), physiological risk factors (such as blood pressure and serum cholesterol levels, part of which is likely to be caused by changes in diet—reduced intake of salt and saturated fats, and year-around availability of fruits and vegetables), effective pharmacological treatments for hypertension and dyslipidaemia, and improved medical care (including time taken to reach hospital, improved diagnosis, and effective care). Blood pressure seems to have been declining since before the 1970s in high-income countries, a phenomenon whose drivers are not known, but which might have produced the much earlier start to the decline in stroke mortality compared with that of IHD mortality. The contributions of both risk factors and treatments to the decline in CVDs are likely to be real effects, but none of the measured drivers explains the similarities and differences across countries or between men and women in when the decline began or in the rate of decline. Other phenomena related to subtle changes in diet or health care, reductions in infections and resulting inflammatory response, and improved fetal and childhood nutrition and health are some of the possible determinants of the decline.

Third, the nearly universal increase in adiposity does not seem so far to have attenuated the declining trend of CVD mortality in high-income countries at the population level. The rate of decline in these countries might have been even steeper if the obesity epidemic had not occurred, but to date the magnitude of such an effect seems to be modest.[171,192] Aggressive management of physiological risk factors that mediate the effects of adiposity[193] among overweight and obese people might have led to a decoupling of BMI from blood pressure and lipids (but not diabetes).[178,194] In low-income countries, where the thinly stretched health-care systems might not have the capacity to screen and treat physiological risk factors,[310] rising rates of obesity might result in increased population risk of CVDs.

Finally, whatever the explanations for a century of rise and fall in CVD mortality in western high-income countries, they cannot readily be generalized to the former communist countries of central and Eastern Europe and the former Soviet Union. The CVD mortality trends in these countries seem to be closely correlated with political and social changes after the collapse of communism starting in the early 1990s, with an important role for hazardous alcohol drinking as a mediator of these social forces.

In the future, one might advocate the collection of more systematic population-based data to improve our understanding of why the decades-long decline in CVDs continues in high-income countries, and to document its early and subsequent stages in middle-income countries. Such knowledge might help to accelerate the decline in high-income countries, and extend it to other regions in which CVDs remain a leading cause of mortality. The availability of electronic population-based data on hospitalization and mortality, and the capacity to link between them, as well as regular health and nutrition surveys, mean that such data can be obtained with little additional investment. These data will allow analysis of national time trends and subnational variations.[5,8,311] Bureaucratic and legal obstacles to such use might, however, need to be overcome. In lower-income countries, the first step might be to assess trends in CVD mortality (and subsequently incidence) without the current over-reliance on models, through strengthening vital registration and disease and risk-factor surveillance systems.

Although a fully comprehensive and convincing account of the precise drivers of the declines in CVD that we have described for many countries remains elusive, these declines are enormous and are making important contributions to improvements in life expectancy in most regions. For some countries and populations, therefore, the continued impressive pace of decline in CVDs—whatever the drivers—should be a reason to give more attention to other health conditions that are either not declining as fast or are rising, such as cancers, diabetes, and neuropsychiatric conditions.

1. WHO. *Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000–2012* (WHO, 2014).
2. Moran, A. E. *et al.* Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation* **129**, 1483–1492 (2014).
3. Kontis, V. *et al.* Contribution of six risk factors to achieving the 25x25 non-communicable disease mortality reduction target: a modelling study. *Lancet* **384**, 427–437 (2014).
4. Feigin, V. L. *et al.* Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* **383**, 245–254 (2014).
5. Asaria, P. *et al.* Trends and inequalities in cardiovascular disease mortality across 7932 English electoral wards, 1982–2006: Bayesian spatial analysis. *Int. J. Epidemiol.* **41**, 1737–1749 (2012).
6. Di Cesare, M. *et al.* Inequalities in non-communicable diseases and effective responses. *Lancet* **381**, 585–597 (2013).
7. Harper, S., Lynch, J. & Smith, G. D. Social determinants and the decline of cardiovascular diseases: understanding the links. *Annu. Rev. Public Health* **32**, 39–69 (2011).
8. Danaei, G. *et al.* The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med.* **7**, e1000248 (2010).
9. Keys, A. Coronary heart disease—the global picture. *Atherosclerosis* **22**, 149–192 (1975).
10. Strom, A. & Jensen, R. A. Mortality from circulatory diseases in Norway 1940–1945. *Lancet* **1**, 126–129 (1951).
11. Morris, J. N. Recent history of coronary disease. *Lancet* **1**, 69–73 (1951).
12. Woolsey, T. D. & Moriyama, I. M. Statistical studies of heart diseases; important factors in heart disease mortality trends. *Public Health Rep.* **63**, 1247–1273 (1948).
13. Moriyama, I. M. & Gover, M. Heart diseases and allied causes of death in relation to age changes in the population. *Public Health Rep.* **63**, 537–545 (1948).
14. Stallones, R. A. The rise and fall of ischemic heart disease. *Sci. Am.* **243**, 53–59 (1980).
15. Moriyama, I. M. & Woolsey, T. D. Statistical studies of heart disease. IX. Race and sex differences in the trend of mortality from the major cardiovascular-renal diseases. *Public Health Rep.* **66**, 355–368 (1951).
16. Klebba, A. J., Maurer, J. D. & Glass, E. J. Mortality trends for leading causes of death: United States, 1950–1969. *Vital Health Stat.* **20**, 1–79 (1974).
17. Borhani, N. O. & Hechter, H. H. Recent changes in CVR disease mortality in California. *Public Health Rep.* **79**, 147–160 (1964).
18. Walker, W. J. Coronary mortality: what is going on? *JAMA* **227**, 1045–1046 (1974).
19. Stern, M. P. The recent decline in ischemic heart disease mortality. *Ann. Intern. Med.* **91**, 630–640 (1979).
20. Walker, W. J. Changing United States life-style and declining vascular mortality: cause or coincidence? *N. Engl. J. Med.* **297**, 163–165 (1977).
21. Uemura, K. & Pisa, Z. Recent trends in cardiovascular disease mortality in 27 industrialized countries. *World Health Stat. Q.* **38**, 142–162 (1985).
22. Uemura, K. & Pisa, Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat. Q.* **41**, 155–178 (1988).
23. Lawlor, D. A., Smith, G. D., Leon, D. A., Sterne, J. A. & Ebrahim, S. Secular trends in mortality by stroke subtype in the 20th century: a retrospective analysis. *Lancet* **360**, 1818–1823 (2002).
24. Havlik, R. J. & Feinleib, M. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*. *October 24–25, 1978*. (National Heart, Lung, and Blood Institute, US Department of Health, Education, and Welfare, 1979).
25. Stallones, R. A. Epidemiology of cerebrovascular disease. A review. *J. Chronic Dis.* **18**, 859–872 (1965).
26. Charlton, J., Murphy, M., Khaw, K. T., Ebrahim, S. & Davey Smith, G. in *The Health of Adult Britain 1841–1994*, Vol. 2 (eds Charlton, J. & Murphy, M.) 60–81 (Stationary Office, 1997).
27. Wen, C. P. & Gershoff, S. N. Changes in serum cholesterol and coronary heart disease mortality associated with changes in the postwar Japanese diet. *Am. J. Clin. Nutr.* **26**, 616–619 (1973).
28. Kodama, K. Stroke trends in Japan. *Ann. Epidemiol.* **3**, 524–528 (1993).
29. Ueshima, H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J. Atheroscler. Thromb.* **14**, 278–286 (2007).
30. Ueshima, H., Tatara, K. & Asakura, S. Declining mortality from ischemic heart disease and changes in coronary risk factors in Japan, 1956–1980. *Am. J. Epidemiol.* **125**, 62–72 (1987).
31. Sarti, C., Rastenyte, D., Cepaitis, Z. & Tuomilehto, J. International trends in mortality from stroke, 1968 to 1994. *Stroke* **31**, 1588–1601 (2000).
32. Liu, L., Ikeda, K. & Yamori, Y. Changes in stroke mortality rates for 1950 to 1997: a great slowdown of decline trend in Japan. *Stroke* **32**, 1745–1749 (2001).
33. Moriyama, I. M., Woolsey, T. D. & Stamler, J. Observations on possible factors responsible for the sex and race trends in cardiovascular-renal mortality in the United States. *J. Chronic Dis.* **7**, 401–412 (1958).
34. Stamler, J. *Lectures on Preventive Cardiology* (Grune & Stratton, 1967).
35. Katz, L. N., Stamler, J. & Pick, R. *Nutrition and Arteriosclerosis* (Lea & Febiger, 1958).
36. WHO MONICA Project Principal Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J. Clin. Epidemiol.* **41**, 105–114 (1988).
37. Levi, F., Lucchini, F., Negri, E. & La Vecchia, C. Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart* **88**, 119–124 (2002).
38. Latin American Mortality Database. *Latin American Mortality Database* [online], https://www.ssc.wisc.edu/cdha/latinmortality/ (2015).
39. Curioni, C., Cunha, C. B., Veras, R. P. & Andre, C. The decline in mortality from circulatory diseases in Brazil. *Rev. Panam Salud Publica* **25**, 9–15 (2009).
40. Andre, C., Curioni, C. C., Braga da Cunha, C. & Veras, R. Progressive decline in stroke mortality in Brazil from 1980 to 1982, 1990 to 1992, and 2000 to 2002. *Stroke* **37**, 2784–2789 (2006).
41. Rodriguez, T. *et al.* Trends in mortality from coronary heart and cerebrovascular diseases in the Americas: 1970–2000. *Heart* **92**, 453–460 (2006).
42. Epstein, F. H. & Pisa, Z. in *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. October 24–25, 1978*. NIH Publication No. 79–1610 (eds Havlik, R. J. & Feinleib, M.) 58–90 (National Heart, Lung, and Blood Institute, US Department of Health, Education, and Welfare, 1979).
43. Mesle, F., Shkolnikov, V. & Vallin, J. Mortality by cause in the USSR in 1970–1987: the reconstruction of time series. *Eur. J. Popul.* **8**, 281–308 (1992).
44. Kesteloot, H., Sans, S. & Kromhout, D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. *Eur. Heart J.* **27**, 107–113 (2006).
45. Shkolnikov, V., Mesle, F. & Vallin, J. Health crisis in Russia. II. Changes in causes of death: a comparison with France and England and Wales (1970 to 1993). *Popul.* **8**, 155–189 (1996).
46. Shkolnikov, V., Mesle, F. & Vallin, J. Health crisis in Russia. I. Recent trends in life expectancy and causes of death from 1970 to 1993. *Popul.* **8**, 123–154 (1996).
47. Leon, D. A. *et al.* Huge variation in Russian mortality rates 1984–1994: artefact, alcohol, or what? *Lancet* **350**, 383–388 (1997).
48. Grigoriev, P. *et al.* The recent mortality decline in Russia: beginning of the cardiovascular revolution? *Popul. Develop. Rev.* **40**, 107–129 (2014).
49. Razvodovsky, Y. E. Alcohol consumption and ischemic heart disease mortality in Russia. *Adicciones* **24**, 23–29 (2012).
50. Leon, D. A., Shkolnikov, V. M., McKee, M., Kiryanov, N. & Andreev, E. Alcohol increases circulatory disease mortality in Russia: acute and chronic effects or misattribution of cause? *Int. J. Epidemiol.* **39**, 1279–1290 (2010).
51. Truelsen, T. *et al.* Trends in stroke and coronary heart disease in the WHO MONICA Project. *Stroke* **34**, 1346–1352 (2003).
52. Jiang, B. *et al.* Incidence and trends of stroke and its subtypes in China: results from three large cities. *Stroke* **37**, 63–68 (2006).
53. Jiang, G. *et al.* Coronary heart disease mortality in China: age, gender, and urban-rural gaps during epidemiological transition. *Rev. Panam. Salud Publica* **31**, 317–324 (2012).
54. Yu, T. S., Wong, S. L., Lloyd, O. L. & Wong, T. W. Ischaemic heart disease: trends in mortality in Hong Kong, 1970–1989. *J. Epidemiol. Community Health* **49**, 16–21 (1995).
55. Stringhini, S. *et al.* Declining stroke and myocardial infarction mortality between 1989 and 2010 in a country of the African Region. *Stroke* **43**, 2283–2288 (2012).
56. Mayosi, B. M. *et al.* Health in South Africa: changes and challenges since 2009. *Lancet* **380**, 2029–2043 (2012).
57. Dawber, T. R., Kannel, W. B., Revotskie, N. & Kagan, A. The epidemiology of coronary heart disease—the Framingham enquiry. *Proc. R. Soc. Med.* **55**, 265–271 (1962).
58. Doyle, J. T., Dawber, T. R., Kannel, W. B., Heslin, A. S. & Kahn, H. A. Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. *N. Engl. J. Med.* **26**, 796–801 (1962).
59. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N. & Stokes, J., 3rd. Factors of risk in the development of coronary heart disease —six year follow-up experience. The Framingham Study. *Ann. Intern. Med.* **55**, 33–50 (1961).
60. Howitt, M. R. & Garrett, W. S. A complex microworld in the gut: gut microbiota and cardiovascular disease connectivity. *Nat. Med.* **18**, 1188–1189 (2012).
61. Tremaroli, V. & Backhed, F. Functional interactions between the gut microbiota and host metabolism. *Nature* **489**, 242–249 (2012).
62. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* **302**, 1993–2000 (2009).

63. Murray, C. J., Ezzati, M., Lopez, A. D., Rodgers, A. & Vander Hoorn, S. Comparative quantification of health risks conceptual framework and methodological issues. *Popul. Health Metr.* **1**, 1 (2003).
64. Ezzati, M., Lopez, A. D., Rodgers, A. & Murray, C. J. L. *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. 2248 (WHO, 2004).
65. Oza, S., Thun, M. J., Henley, S. J., Lopez, A. D. & Ezzati, M. How many deaths are attributable to smoking in the United States? Comparison of methods for estimating smoking-attributable mortality when smoking prevalence changes. *Prev. Med.* **52**, 428–433 (2011).
66. Pell, J. P. *et al.* Smoke-free legislation and hospitalizations for acute coronary syndrome. *N. Engl. J. Med.* **359**, 482–491 (2008).
67. Bartecchi, C. *et al.* Reduction in the incidence of acute myocardial infarction associated with a citywide smoking ordinance. *Circulation* **114**, 1490–1496 (2006).
68. Law, M. R., Wald, N. J. & Thompson, S. G. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* **308**, 367–372 (1994).
69. Holmes, J., Meier, P. S., Booth, A., Guo, Y. & Brennan, A. The temporal relationship between per capita alcohol consumption and harm: a systematic review of time lag specifications in aggregate time series analyses. *Drug Alcohol Depend.* **123**, 7–14 (2012).
70. Law, M. R., Frost, C. D. & Wald, N. J. By how much does dietary salt reduction lower blood pressure? III—Analysis of data from trials of salt reduction. *BMJ* **302**, 819–824 (1991).
71. Xin, X. *et al.* Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* **38**, 1112–1117 (2001).
72. Whelton, P. K. *et al.* Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* **279**, 839–846 (1998).
73. Aburto, N. J. *et al.* Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* **346**, f1326 (2013).
74. Rose, G. Incubation period of coronary heart disease. *Br. Med. J. (Clin. Res. Ed.)* **284**, 1600–1601 (1982).
75. McNamara, J. J., Molot, M. A., Stremple, J. F. & Cutting, R. T. Coronary artery disease in combat casualties in Vietnam. *JAMA* **216**, 1185–1187 (1971).
76. Enos, W. F., Holmes, R. H. & Beyer, J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. *J. Am. Med. Assoc.* **152**, 1090–1093 (1953).
77. Katanoda, K. & Matsumura, Y. National Nutrition Survey in Japan—its methodological transition and current findings. *J. Nutr. Sci. Vitaminol.* **48**, 423–432 (2002).
78. Yoshiike, N., Matsumura, Y., Iwaya, M., Sugiyama, M. & Yamaguchi, M. National Nutrition Survey in Japan. *J. Epidemiol.* **6** (Suppl.), S189–S200 (1996).
79. WHO. Chronic disease and health promotion. *STEPwise approach to surveillance (STEPS)* [online], http://www.who.int/chp/steps/en/ (2015).
80. Metabolic Risk Factors of Chronic Diseases Collaboration. *Global Burden of Metabolic Risk Factors of Chronic Diseases* [online], www.imperial.ac.uk/medicine/globalmetabolics/ (2015).
81. Finucane, M. M., Paciorek, C. J., Danaei, G. & Ezzati, M. Bayesian estimation of population-level trends in measures of health status. *Stat. Sci.* **29**, 18–25 (2014).
82. Finucane, M. M. *et al.* National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* **377**, 557–567 (2011).
83. Danaei, G. *et al.* National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet* **377**, 568–577 (2011).
84. Danaei, G. *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* **378**, 31–40 (2011).
85. Farzadfar, F. *et al.* National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet* **377**, 578–586 (2011).
86. Stevens, G. A. *et al.* National, regional, and global trends in adult overweight and obesity prevalences. *Popul. Health Metr.* **10**, 22 (2012).
87. WHO. *Tobacco or Health: A Global Status Report* (WHO, 1997).
88. Shafey, O., Dolwick, S. & Guindon, G. *Tobacco Control Country Profiles*. (American Cancer Society, 2003).
89. Bilano, V. *et al.* Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet* **385**, 966–976 (2015).
90. Ezzati, M. & Riboli, E. Behavioral and dietary risk factors for noncommunicable diseases. *N. Engl. J. Med.* **369**, 954–964 (2013).
91. Burns, D. M. *et al*. in *Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control. Smoking and Tobacco Control Monograph No. 8* (eds Burns, D. M., Garfinkel, L. & Samet, J. M.) 13–112 (National Cancer Institute, 1997).
92. Kluger, R. *Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris* (Vintage Books, 1997).
93. Brandt, A. M. *The Cigarette Century: the Rise, Fall, and Deadly Persistence of the Product That Defined America* (Basic Books, 2007).
94. Wald, N. & Nicolaides-Bouman, A. *UK smoking statistics* (Oxford University Press, 1991).
95. WHO. *Global status report on noncommunicable diseases 2010* (WHO, 2011).
96. WHO. *Global Status Report on Noncommunicable Diseases 2014: Attaining the Nine Global Noncommunicable Diseases Targets; a Shared Responsibility* (WHO, 2014).
97. Wald, N., Doll, R. & Copeland, G. Trends in tar, nicotine, and carbon monoxide yields of UK cigarettes manufactured since 1934. *Br. Med. J. (Clin. Res. Ed.)* **282**, 763–765 (1981).
98. Jarvis, M. J. Trends in sales weighted tar, nicotine, and carbon monoxide yields of UK cigarettes. *Thorax* **56**, 960–963 (2001).
99. Parish, S. *et al.* Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. *BMJ* **311**, 471–477 (1995).
100. US Department of Health and Human Services. *A Report of the Surgeon General: How Tobacco Smoke Causes Disease: the Biology and Behavioral Basis for Smoking-Attributable Disease, 2010*. Report No. DHHS Publication No (CDC) 89-8411 (USDHHS, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010).
101. US Department of Health and Human Services. *A Report of the Surgeon General: the Health Consequences of Smoking—50 years of progress*. Report No. DHHS Publication No (CDC) 89-8411, (USDHHS, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014).
102. Simpura, J. Mediterranean mysteries: mechanisms of declining alcohol consumption. *Addiction* **93**, 1301–1304 (1998).
103. Simpura, J. Trends in alcohol consumption and drinking patterns: sociological and economic explanations and alcohol policies. *Nordic Studies on Alcohol and Drugs* **18** (Suppl.), S3–S13 (2001).
104. Mäkelä, K. *et al*. *Alcohol, society, and the state: 1. A comparative history of alcohol control* (Addiction Research Foundation, 1981).
105. Rehm, J. *et al*. in *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors* (eds Ezzati, M., Lopez, A. D., Rodgers, A. & Murray, C. J. L.) 959–1108 (WHO, 2004).
106. WHO. *Global status report on alcohol and health 2014* (WHO, 2014).
107. Allamani, A. & Prina, F. Why the decrease in consumption of alcoholic beverages in Italy between the 1970s and the 2000s? Shedding light on an Italian mystery. *Contemp. Drug Probl.* **34**, 187–198 (2007).
108. Cipriani, F. & Prina, F. The research outcome: summary and conclusions on the reduction in wine consumption in Italy. *Contemp. Drug Probl.* **34**, 361–378 (2007).
109. Shield, K. D. *et al.* Global alcohol exposure estimates by country, territory and region for 2005—a contribution to the Comparative Risk Assessment for the 2010 Global Burden of Disease Study. *Addiction* **108**, 912–922 (2013).
110. Poznyak, V. *et al.* The world health organization's global monitoring system on alcohol and health. *Alcohol Res.* **35**, 244–249 (2013).
111. Rehm, J. *et al.* A systematic review of the epidemiology of unrecorded alcohol consumption and the chemical composition of unrecorded alcohol. *Addiction* **109**, 880–893 (2014).
112. Rehm, J., Kanteres, F. & Lachenmeier, D. W. Unrecorded consumption, quality of alcohol and health consequences. *Drug Alcohol Rev.* **29**, 426–436 (2010).
113. Stickley, A. *et al.* Alcohol poisoning in Russia and the countries in the European part of the former Soviet Union, 1970 2002. *Eur. J. Public Health* **17**, 444–449 (2007).
114. Bergmann, M. M. *et al.* The association of pattern of lifetime alcohol use and cause of death in the European prospective investigation into cancer and nutrition (EPIC) study. *Int. J. Epidemiol.* **42**, 1772–1790 (2013).
115. Rehm, J. *et al.* The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction* **105**, 817–843 (2010).
116. Rehm, J. *et al.* On the emerging paradigm of drinking patterns and their social and health consequences. *Addiction* **91**, 1615–1621 (1996).
117. Roerecke, M. & Rehm, J. Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *Am. J. Epidemiol.* **171**, 633–644 (2010).

118. Makela, P. *et al.* Episodic heavy drinking in four Nordic countries: a comparative survey. *Addiction* **96**, 1575–1588 (2001).
119. He, F. J., Li, J. & Macgregor, G. A. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database of Systematic Reviews* Issue 4. Art. No.: CD004937. http://dx.doi.org/10.1002/14651858.CD004937.pub2.
120. Mozaffarian, D. *et al.* Global sodium consumption and death from cardiovascular causes. *N. Engl. J. Med.* **371**, 624–634 (2014).
121. Cook, N. R. *et al.* Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch. Intern. Med.* **169**, 32–40 (2009).
122. Cook, N. R. *et al.* Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* **334**, 885–888 (2007).
123. Sacks, F. M. & Campos, H. Dietary therapy in hypertension. *N. Engl. J. Med.* **362**, 2102–2112 (2010).
124. Mozaffarian, D., Appel, L. J. & Van Horn, L. Components of a cardioprotective diet: new insights. *Circulation* **123**, 2870–2891 (2011).
125. Mozaffarian, D., Micha, R. & Wallace, S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* **7**, e1000252 (2010).
126. Howard, B. V. *et al.* Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* **295**, 655–666 (2006).
127. Chowdhury, R. *et al.* Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann. Intern. Med.* **160**, 398–406 (2014).
128. Nordmann, A. J. *et al.* Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch. Intern. Med.* **166**, 285–293 (2006).
129. Estruch, R. *et al.* Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann. Intern. Med.* **145**, 1–11 (2006).
130. Estruch, R. *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* **368**, 1279–1290 (2013).
131. Kahn, H. A. Change in serum cholesterol associated with changes in the United States civilian diet, 1909–1965. *Am. J. Clin. Nutr.* **23**, 879–882 (1970).
132. Antar, M. A., Ohlson, M. A. & Hodges, R. E. Changes in retail market food supplies in the United States in the last seventy years in relation to the incidence of coronary heart disease, with special reference to dietary carbohydrates and essential fatty acids. *Am. J. Clin. Nutr.* **14**, 169–178 (1964).
133. Jackson, R. & Beaglehole, R. Trends in dietary fat and cigarette smoking and the decline in coronary heart disease in New Zealand. *Int. J. Epidemiol.* **16**, 377–382 (1987).
134. Winkler, G., Doring, A. & Keil, U. Trends in dietary sources of nutrients among middle-aged men in southern Germany. Results of the MONICA Project Augsburg: dietary surveys 1984/1985 and 1994/1995. MONItoring trends and determinants in CArdiovascular disease. *Appetite* **34**, 37–45 (2000).
135. Pietinen, P., Vartiainen, E., Seppanen, R., Aro, A. & Puska, P. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Prev. Med.* **25**, 243–250 (1996).
136. Laatikainen, T. *et al.* Sodium in the Finnish diet: 20-year trends in urinary sodium excretion among the adult population. *Eur. J. Clin. Nutr.* **60**, 965–970 (2006).
137. Krachler, B., Eliasson, M. C., Johansson, I., Hallmans, G. & Lindahl, B. Trends in food intakes in Swedish adults 1986–1999: findings from the Northern Sweden MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Study. *Public Health Nutr.* **8**, 628–635 (2005).
138. Waskiewicz, A., Piotrowski, W., Sygnowska, E., Rywik, S. & Jasinski, B. Did favourable trends in food consumption observed in the 1984–2001 period contribute to the decrease in cardiovascular mortality?—Pol.-MONICA Warsaw Project. *Kardiol. Pol.* **64**, 16–23 (2006).
139. Stephen, A. M. & Sieber, G. M. Trends in individual fat consumption in the UK 1900–1985. *Br. J. Nutr.* **71**, 775–788 (1994).
140. Stephen, A. M. & Wald, N. J. Trends in individual consumption of dietary fat in the United States, 1920–1984. *Am. J. Clin. Nutr.* **52**, 457–469 (1990).
141. Du, S. F., Wang, H. J., Zhang, B., Zhai, F. Y. & Popkin, B. M. China in the period of transition from scarcity and extensive undernutrition to emerging nutrition-related non-communicable diseases, 1949–1992. *Obes. Rev.* **15** (Suppl. 1), 8–15 (2014).
142. Wolmarans, P. Background paper on global trends in food production, intake and composition. *Ann. Nutr. Metab.* **55**, 244–272 (2009).
143. Micha, R. *et al.* Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ* **348**, g2272 (2014).
144. Leth, T., Jensen, H. G., Mikkelsen, A. A. & Bysted, A. The effect of the regulation on trans fatty acid content in Danish food. *Atheroscler. Suppl.* **7**, 53–56 (2006).
145. Angell, S. Y. *et al.* Cholesterol control beyond the clinic: New York City's trans fat restriction. *Ann. Intern. Med.* **151**, 129–134 (2009).
146. Zatonski, W., Campos, H. & Willett, W. Rapid declines in coronary heart disease mortality in Eastern Europe are associated with increased consumption of oils rich in alpha-linolenic acid. *Eur. J. Epidemiol.* **23**, 3–10 (2008).
147. Zatonski, W. A. & Willett, W. Changes in dietary fat and declining coronary heart disease in Poland: population based study. *BMJ* **331**, 187–188 (2005).
148. Butt, M. S. & Sultan, M. T. Levels of trans fats in diets consumed in developing economies. *J. AOAC Int.* **92**, 1277–1283 (2009).
149. Institute of Medicine. *Sodium intake in populations: assessment of evidence* (National Academies Press, 2013).
150. Cobb, L. K. *et al.* Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation* **129**, 1173–1186 (2014).
151. Ikeda, N., Gakidou, E., Hasegawa, T. & Murray, C. J. Understanding the decline of mean systolic blood pressure in Japan: an analysis of pooled data from the National Nutrition Survey, 1986–2002. *Bull. World Health Organ.* **86**, 978–988 (2008).
152. Ueshima, H., Tatara, K., Asakura, S. & Okamoto, M. Declining trends in blood pressure level and the prevalence of hypertension, and changes in related factors in Japan, 1956–1980. *J. Chronic Dis.* **40**, 137–147 (1987).
153. Du, S. *et al.* Understanding the patterns and trends of sodium intake, potassium intake, and sodium to potassium ratio and their effect on hypertension in China. *Am. J. Clin. Nutr.* **99**, 334–343 (2014).
154. Vartiainen, E. *et al.* Thirty-five-year trends in cardiovascular risk factors in Finland. *Int. J. Epidemiol.* **39**, 504–518 (2010).
155. He, F. J. & MacGregor, G. A. Reducing population salt intake worldwide: from evidence to implementation. *Prog. Cardiovasc. Dis.* **52**, 363–382 (2010).
156. He, F. J., Pombo-Rodrigues, S. & Macgregor, G. A. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. *BMJ Open* **4**, e004549 (2014).
157. He, F. J., Brinsden, H. C. & MacGregor, G. A. Salt reduction in the United Kingdom: a successful experiment in public health. *J. Hum. Hypertens.* **28**, 345–352 (2014).
158. Tuomilehto, J., Geboers, J., Joossens, J. V., Salonen, J. T. & Tanskanen, A. Trends in stomach cancer and stroke in Finland. Comparison to northwest Europe and USA. *Stroke* **15**, 823–828 (1984).
159. Powles, J. *et al.* Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* **3**, e003733 (2013).
160. Brown, I. J., Tzoulaki, I., Candeias, V. & Elliott, P. Salt intakes around the world: implications for public health. *Int. J. Epidemiol.* **38**, 791–813 (2009).
161. Sacks, F. M. & Kass, E. H. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am. J. Clin. Nutr.* **48**, 795–800 (1988).
162. He, F. J., Nowson, C. A., Lucas, M. & MacGregor, G. A. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *J. Hum. Hypertens.* **21**, 717–728 (2007).
163. Drewnowski, A. & Popkin, B. M. The nutrition transition: new trends in the global diet. *Nutr. Rev.* **55**, 31–43 (1997).
164. Pan, W. H. *et al.* Diet and health trends in Taiwan: comparison of two nutrition and health surveys from 1993–1996 and 2005–2008. *Asia Pac. J. Clin. Nutr.* **20**, 238–250 (2011).
165. Blanck, H. M., Gillespie, C., Kimmons, J. E., Seymour, J. D. & Serdula, M. K. Trends in fruit and vegetable consumption among, U. S. men and women, 1994–2005. *Prev. Chronic Dis.* **5**, A35 (2008).
166. Welsh, S. O. & Marston, R. M. Review of trends in food use in the United States, 1909 to 1980. *J. Am. Diet. Assoc.* **81**, 120–128 (1982).
167. Cavadini, C., Siega-Riz, A. M. & Popkin, B. M. US adolescent food intake trends from 1965 to 1996. *West. J. Med.* **173**, 378–383 (2000).
168. Wang, D. D. *et al.* Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern. Med.* **174**, 1587–1595 (2014).
169. Lee, S. *et al.* Trends in diet quality for coronary heart disease prevention between 1980–1982 and 2000–2002: The Minnesota Heart Survey. *J. Am. Diet. Assoc.* **107**, 213–222 (2007).
170. Singh, G. M. *et al.* The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS ONE* **8**, e65174 (2013).
171. Di Cesare, M. *et al.* The contributions of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries. *Int. J. Epidemiol.* **42**, 838–848 (2013).
172. Goff, D. C., Howard, G., Russell, G. B. & Labarthe, D. R. Birth cohort evidence of population influences on blood pressure in the United States, 1887–1994. *Ann. Epidemiol.* **11**, 271–279 (2001).

173. Sakata, K. & Labarthe, D. R. Changes in cardiovascular disease risk factors in three Japanese national surveys 1971–1990. *J. Epidemiol.* **6**, 93–107 (1996).
174. McCarron, P., Smith, G. D. & Okasha, M. Secular changes in blood pressure in childhood, adolescence and young adulthood: systematic review of trends from 1948 to 1998. *J. Hum. Hypertens.* **16**, 677–689 (2002).
175. Tunstall-Pedoe, H., Connaghan, J., Woodward, M., Tolonen, H. & Kuulasmaa, K. Pattern of declining blood pressure across replicate population surveys of the WHO MONICA project, mid-1980s to mid-1990s, and the role of medication. *BMJ* **332**, 629–635 (2006).
176. Hardoon, S. L. *et al.* Assessing the impact of medication use on trends in major coronary risk factors in older British men: a cohort study. *Eur. J. Cardiovasc. Prev. Rehabil.* **17**, 502–508 (2010).
177. Bovet, P. *et al.* Divergent fifteen-year trends in traditional and cardiometabolic risk factors of cardiovascular diseases in the Seychelles. *Cardiovasc. Diabetol.* **8**, 34 (2009).
178. Danaei, G. *et al.* The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. *Circulation* **127**, 1493–1502 (2013).
179. Okayama, A. *et al.* Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan 1980–1989. *Int. J. Epidemiol.* **22**, 1038–1047 (1993).
180. Okayama, A. *et al.* Different trends in serum cholesterol levels among rural and urban populations aged 40–59 in Japan from 1960 to 1990. *J. Clin. Epidemiol.* **48**, 329–337 (1995).
181. Sjol, A., Grunnet, K. & Schroll, M. Secular trends in serum cholesterol, high density lipoproteins and triglycerides 1964–1987. *Int. J. Epidemiol.* **20**, 105–113 (1991).
182. Capewell, S. & Ford, E. S. Why have total cholesterol levels declined in most developed countries? *BMC Public Health* **11**, 641 (2011).
183. Manson, J. E. *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N. Engl. J Med.* **349**, 523–534 (2003).
184. Sigfusson, N. *et al.* Decline in ischaemic heart disease in Iceland and change in risk factor levels. *BMJ* **302**, 1371–1375 (1991).
185. Dwyer, T. & Hetzel, B. S. A comparison of trends of coronary heart disease mortality in Australia, USA and England and Wales with reference to three major risk factors-hypertension, cigarette smoking and diet. *Int. J. Epidemiol.* **9**, 65–71 (1980).
186. Williams, R. R., Lyon, J. L., Brockert, J. E. & Maness, T. in *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. October 24–25, 1978*. NIH Publication No. 79–1610 (eds Havlik, R. J. & Feinleib, M.) 48–57 (National Heart, Lung, and Blood Institute, US Department of Health, Education, and Welfare, 1979).
187. [No authors listed] Why the American decline in coronary heart-disease? *Lancet* **1**, 183–184 (1980).
188. Nicolosi, A., Casati, S., Taioli, E. & Polli, E. Death from cardiovascular disease in Italy, 1972–1981: decline in mortality rates and possible causes. *Int. J. Epidemiol.* **17**, 766–772 (1988).
189. Menotti, A. & Scanga, M. Trends in coronary risk factors in Italy. Responsible Investigators of the RF2, OB43 and MICOL Research Groups. *Int. J. Epidemiol.* **21**, 883–892 (1992).
190. Tunstall-Pedoe, H. *et al.* Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* **353**, 1547–1557 (1999).
191. Babyak, M. A. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom. Med.* **66**, 411–421 (2004).
192. Kuulasmaa, K. *et al.* Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. *Lancet* **355**, 675–687 (2000).
193. Lu, Y. *et al.* Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* **383**, 970–983 (2014).
194. Gregg, E. W. *et al.* Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA* **293**, 1868–1874 (2005).
195. Pell, S. & D'Alonzo, G. A. Immediate mortality and five-year survival of employed men with a first myocardial infarction. *N. Engl. J Med.* **270**, 915–922 (1964).
196. Pell, S. & Fayerweather, W. E. Trends in the incidence of myocardial infarction and in associated mortality and morbidity in a large employed population, 1957–1983. *N. Engl. J Med.* **312**, 1005–1011 (1985).
197. Rosamond, W. D. *et al.* Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N. Engl. J Med.* **339**, 861–867 (1998).
198. McGovern, P. G. *et al.* Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. *Circulation* **104**, 19–24 (2001).
199. McGovern, P. G. *et al.* Recent trends in acute coronary heart disease—mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *N. Engl. J Med.* **334**, 884–890 (1996).
200. Roger, V. L. *et al.* Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann. Intern. Med.* **136**, 341–348 (2002).
201. Goldberg, R. J., Yarzebski, J., Lessard, D. & Gore, J. M. A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. *J. Am. Coll. Cardiol* **33**, 1533–1539 (1999).
202. Morris, R. W. *et al.* Geographic variation in incidence of coronary heart disease in Britain: the contribution of established risk factors. *Heart* **86**, 277–283 (2001).
203. Hardoon, S. L., Whincup, P. H., Petersen, I., Capewell, S. & Morris, R. W. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. *J. Epidemiol. Community Health* **65**, 770–774 (2011).
204. Capewell, S. *et al.* Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland, 1990–2000: population-based cohort study. *Heart* **92**, 1563–1570 (2006).
205. Grey, C. *et al.* Twenty-eight day and one-year case fatality after hospitalisation with an acute coronary syndrome: a nationwide data linkage study. *Aust. N. Z. J. Public Health* **38**, 216–220 (2014).
206. Hammar, N. *et al.* A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. *Int. J. Epidemiol.* **30** (Suppl. 1), S30–S34 (2001).
207. Krumholz, H. M., Normand, S.-L. T. & Wang, Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke: 1999–2011. *Circulation* **130**, 966–975 (2014).
208. Schmidt, M., Bonde, J., Lash, T. L., Bøtker, H. E. & Sørensen, H. T. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* **356**, 1–12 (2012).
209. Smolina, K., Wright, F. L., Rayner, M. & Goldacre, M. J. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ* **344**, d8059 (2012).
210. Ezzati, M., Lopez, A. D., Rodgers, A., Vander Hoorn, S. & Murray, C. J. Selected major risk factors and global and regional burden of disease. *Lancet* **360**, 1347–1360 (2002).
211. Hunink, M. G. *et al.* The recent decline in mortality from coronary heart disease, 1980–1990. The effect of secular trends in risk factors and treatment. *JAMA* **277**, 535–542 (1997).
212. Goldman, L. *et al.* The effect of risk factor reductions between 1981 and 1990 on coronary heart disease incidence, prevalence, mortality and cost. *J. Am. Coll. Cardiol.* **38**, 1012–1017 (2001).
213. Unal, B., Critchley, J. A. & Capewell, S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981–2000: comparing contributions from primary prevention and secondary prevention. *BMJ* **331**, 614 (2005).
214. Unal, B., Capewell, S. & Critchley, J. A. Coronary heart disease policy models: a systematic review. *BMC Public Health* **6**, 213 (2006).
215. Goldman, L. & Cook, E. F. The decline in ischemic heart disease mortality rates. An analysis of the comparative effects of medical interventions and changes in lifestyle. *Ann. Intern. Med.* **101**, 825–836 (1984).
216. Mathers, C. D., Stevens, G. A., Boerma, T., White, R. A. & Tobias, M. I. Causes of international increases in older age life expectancy. *Lancet* **385**, 540–548 (2014).
217. Lim, S. S. *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2224–2260 (2012).
218. Danaei, G. *et al.* The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med.* **6**, e1000058 (2009).
219. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol.* **2**, 634–647 (2014).
220. Ezzati, M. *et al.* Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet* **362**, 271–280 (2003).
221. Woodward, M. *et al.* A comparison of the associations between risk factors and cardiovascular disease in Asia and Australasia. *Eur. J. Cardiovasc. Prev. Rehabil.* **12**, 484–491 (2005).
222. Walter, S. D. Prevention of multifactorial disease. *Am. J. Epidemiol.* **112**, 409–416 (1980).
223. Yerushalmy, J. & Palmer, C. E. On the methodology of investigations of etiologic factors in chronic diseases. *J. Chronic Dis.* **108**, 27–40 (1959).

224. Thorolfsdottir, R. B. *et al.* Population assessment of future trajectories in coronary heart disease mortality. *PLoS ONE* **9**, e85800 (2014).
225. Wang, Y. C., McPherson, K., Marsh, T., Gortmaker, S. L. & Brown, M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* **378**, 815–825 (2011).
226. Webber, L. *et al.* The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. *BMJ Open* **4**, e004787 (2014).
227. Leon, D. A., Shkolnikov, V. M. & McKee, M. Alcohol and Russian mortality: a continuing crisis. *Addiction* **104**, 1630–1636 (2009).
228. McKee, M., Shkolnikov, V. & Leon, D. A. Alcohol is implicated in the fluctuations in cardiovascular disease in Russia since the 1980s. *Ann. Epidemiol.* **11**, 1–6 (2001).
229. Leon, D. A. *et al.* Hazardous alcohol drinking and premature mortality in Russia: a population based case-control study. *Lancet* **369**, 2001–2009 (2007).
230. Tomkins, S. *et al.* Identifying the determinants of premature mortality in Russia: overcoming a methodological challenge. *BMC Public Health* **7**, 343 (2007).
231. Zaridze, D. *et al.* Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. *Lancet* **373**, 2201–2214 (2009).
232. Zaridze, D. *et al.* Alcohol and mortality in Russia: prospective observational study of 151,000 adults. *Lancet* **383**, 1465–1473 (2014).
233. Franco, M. *et al.* Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980–2010: repeated cross sectional surveys and ecological comparison of secular trends. *BMJ* **346**, f1515 (2013).
234. Peto, R., Lopez, A. D., Boreham, J., Thun, M. & Heath, C. Jr. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* **339**, 1268–1278 (1992).
235. Preston, S. H., Glei, D. A. & Wilmoth, J. R. A new method for estimating smoking-attributable mortality in high-income countries. *Int. J. Epidemiol.* **39**, 430–438 (2010).
236. Beaglehole, R. Medical management and the decline in mortality from coronary heart disease. *Br. Med. J. (Clin. Res. Ed.)* **292**, 33–35 (1986).
237. Rose, G. The contribution of intensive coronary care. *Br. J. Prev. Soc. Med.* **29**, 147–150 (1975).
238. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* **1**, 397–402 (1986).
239. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* **2**, 349–360 (1988).
240. Gunnar, R. M. *et al.* Guidelines for the early management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients with Acute Myocardial Infarction). *J. Am. Coll. Cardiol* **16**, 249–292 (1990).
241. Rogers, W. J. *et al.* Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J. Am. Coll. Cardiol.* **36**, 2056–2063 (2000).
242. Nabel, E. G. & Braunwald, E. A tale of coronary artery disease and myocardial infarction. *N. Engl. J. Med.* **366**, 54–63 (2012).
243. Kumbhani, D. J. *et al.* Temporal trends for secondary prevention measures among patients hospitalized with coronary artery disease. *Am. J. Med.* **128**, 426.e1–426.e9 (2014).
244. [No authors listed] Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* **202**, 1028–1034 (1967).
245. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br. Med. J. (Clin. Res. Ed.)* **291**, 97–104 (1985).
246. [No authors listed] The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet* **1**, 1261–1267 (1980).
247. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* **265**, 3255–3264 (1991).
248. Beckett, N. S. *et al.* Treatment of hypertension in patients 80 years of age or older. *N. Engl. J. Med.* **358**, 1887–1898 (2008).
249. Law, M. R., Morris, J. K. & Wald, N. J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* **338**, b1665 (2009).
250. Stott, D. J. in *Handbook of Hypertension, Vol. 20, Epidemiology of Hypertension* (ed. Bulpitt, C. J.) (Elsevier, 2000).
251. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* **362**, 1527–1535 (2003).
252. Egan, B. M., Zhao, Y. & Axon, R. N. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* **303**, 2043–2050 (2010).
253. Hajjar, I. & Kotchen, T. A. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* **290**, 199–206 (2003).
254. Chobanian, A. V. *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **42**, 1206–1252 (2003).
255. Andersen, U. O. & Jensen, G. B. Trends and determinant factors for population blood pressure with 25 years of follow-up: results from the Copenhagen City Heart Study. *Eur. J. Cardiovasc. Prev. Rehabil.* **17**, 655–659, (2010).
256. Andersen, U. O. & Jensen, G. B. Trends and determinant factors in hypertension control in a population study with 25 years of follow-up. *J. Hypertens.* **28**, 1091–1096 (2010).
257. Fasce, E. *et al.* Trends in prevalence, awareness, treatment and control of hypertension in urban communities in Chile. *J. Hypertens.* **25**, 1807–1811 (2007).
258. Chow, C. K. *et al.* Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* **310**, 959–968 (2013).
259. Tobert, J. A. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat. Rev. Drug Discov.* **2**, 517–526 (2003).
260. Ford, E. S., Li, C., Pearson, W. S., Zhao, G. & Mokdad, A. H. Trends in hypercholesterolemia, treatment and control among United States adults. *Int. J. Cardiol.* **140**, 226–235 (2010).
261. Wald, N. J. & Law, M. R. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* **326**, 1419 (2003).
262. Cholesterol Treatment Trialists (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581–590 (2012).
263. National Cholesterol Education Program (NCEPT) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* **106**, 3143–3421 (2002).
264. Carleton, R. A. *et al.* Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction. A statement from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. *Circulation* **83**, 2154–2232 (1991).
265. Roth, G. A. *et al.* High total serum cholesterol, medication coverage and therapeutic control: an analysis of national health examination survey data from eight countries. *Bull. World Health Organ.* **89**, 92–101 (2011).
266. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* **366**, 1267–1278 (2010).
267. Yusuf, S. *et al.* Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* **378**, 1231–1243 (2011).
268. Pell, S. & D'Alonzo, C. A. Factors associated with long-term survival of diabetics. *JAMA* **214**, 1833–1840 (1970).
269. Holman, R. R., Sourij, H. & Califf, R. M. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet* **383**, 2008–2017 (2014).
270. Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R. & Neil, H. A. 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.* **359**, 1577–1589, (2008).
271. Riddle, M. C. *et al.* Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* **33**, 983–990 (2010).
272. Skyler, J. S. *et al.* Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* **119**, 351–357 (2009).
273. Ismail-Beigi, F. *et al.* Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann. Intern. Med.* **154**, 554–559 (2011).
274. Cefalu, W. T. Glycemic targets and cardiovascular disease. *N.Engl. J. Med.* **358**, 2633–2635 (2008).
275. Ali, M. K. *et al.* Achievement of goals in U.S. diabetes care, 1999–2010. *N. Engl. J. Med.* **368**, 1613–1624 (2013).
276. Tunstall-Pedoe, H. *et al.* Estimation of contribution of changes in coronary care to improving survival,

event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet* **355**, 688–700 (2000).
277. Tunstall-Pedoe, H. in *Coronary Heart Disease Epidemiology: From Aetiology to Public Health* (eds Marmot, M. & Elliott, P.) 850–864 (Oxford University Press, 2005).
278. Arciero, T. J. *et al.* Temporal trends in the incidence of coronary disease. *Am. J. Med.* **117**, 228–233 (2004).
279. Levy, D. & Thom, T. J. Death rates from coronary disease—progress and a puzzling paradox. *N. Engl. J. Med.* **339**, 915–917 (1998).
280. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur. Heart J.* **21**, 1502–1513 (2000).
281. Tunstall-Pedoe, H. Comment on the ESC/ACC redefinition of myocardial infarction by a consensus dissenter. *Eur. Heart J.* **22**, 613–616 (2001).
282. Myerson, M. *et al.* Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* **119**, 503–514 (2009).
283. Rosamond, W. D. *et al.* Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. *Circulation* **125**, 1848–1857 (2012).
284. Hamm, C. W. *et al.* The prognostic value of serum troponin T in unstable angina. *N. Engl. J. Med.* **327**, 146–150 (1992).
285. Mills, N. L. *et al.* Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA* **305**, 1210–1216 (2011).
286. Yusuf, S., Reddy, S., Ounpuu, S. & Anand, S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* **104**, 2746–2753 (2001).
287. Khatibzadeh, S., Farzadfar, F., Oliver, J., Ezzati, M. & Moran, A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int. J. Cardiol.* **168**, 1186–1194 (2013).
288. Lozano, R. *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2095–2128 (2012).
289. Mayosi, B. M. in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 10th edn (eds Mann, D. L., Zipes, D. P., Libby, P. & Bonow, R. O.) (Elsevier Saunders, 2015).
290. Kaplan, E. L. T. Duckett Jones Memorial Lecture. Global assessment of rheumatic fever and rheumatic heart disease at the close of the century. Influences and dynamics of populations and pathogens: a failure to realize prevention? *Circulation* **88**, 1964–1972 (1993).
291. Moriyama, I. M., Baum, W. S., Haenszel, W. M. & Mattison, B. F. Inquiry into diagnostic evidence supporting medical certifications of death. *Am. J. Public Health Nations Health* **48**, 1376–1387 (1958).
292. Tibazarwa, K. B., Volmink, J. A. & Mayosi, B. M. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. *Heart* **94**, 1534–1540 (2008).
293. Seckeler, M. D. & Hoke, T. R. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin. Epidemiol.* **3**, 67–84 (2011).
294. Gordis, L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones memorial lecture. *Circulation* **72**, 1155–1162 (1985).
295. Madden, S. & Kelly, L. Update on acute rheumatic fever: it still exists in remote communities. *Can. Fam. Physician* **55**, 475–478 (2009).
296. White, H. *et al.* Rheumatic heart disease in indigenous populations. *Heart Lung Circ.* **19**, 273–281 (2010).
297. Arguedas, A. & Mohs, E. Prevention of rheumatic fever in Costa Rica. *J. Pediatr.* **121**, 569–572 (1992).
298. Nordet, P., Lopez, R., Duenas, A. & Sarmiento, L. Prevention and control of rheumatic fever and rheumatic heart disease: the Cuban experience (1986–1996–2002). *Cardiovasc. J. Afr.* **19**, 135–140 (2008).
299. Bach, J. F. *et al.* 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. *Lancet* **347**, 644–648 (1996).
300. Karthikeyan, G. & Mayosi, B. M. Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa? *Circulation* **120**, 709–713 (2009).
301. Omurzakova, N. A. *et al.* Rheumatologic services in Central Asian countries: current state of development of rheumatology in Central Asia. *Int. J. Rheum. Dis.* **12**, 288–292 (2009).
302. Omurzakova, N. A. *et al.* High incidence of rheumatic fever and rheumatic heart disease in the republics of Central Asia. *Int. J. Rheum. Dis.* **12**, 79–83 (2009).
303. Alfieri, O., Mayosi, B. M., Park, S. J., Sarrafzadegan, N. & Virmani, R. Exploring unknowns in cardiology. *Nat. Rev. Cardiol.* **11**, 664–670 (2014).
304. Mocumbi, A. O. & Falase, A. O. Recent advances in the epidemiology, diagnosis and treatment of endomyocardial fibrosis in Africa. *Heart* **99**, 1481–1487 (2013).
305. Sliwa, K. & Mayosi, B. M. Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa. *Heart* **99**, 1317–1322 (2013).
306. Roivainen, M. *et al.* Infections, inflammation, and the risk of coronary heart disease. *Circulation* **101**, 252–257 (2000).
307. Barnighausen, T. *et al.* Hiding in the shadows of the HIV epidemic: obesity and hypertension in a rural population with very high HIV prevalence in South Africa. *J. Hum. Hypertens.* **22**, 236–239 (2008).
308. Ntsekhe, M. & Mayosi, B. M. Cardiac manifestations of HIV infection: an African perspective. *Nat. Clin. Pract. Cardiovasc. Med.* **6**, 120–127 (2009).
309. Zanni, M. V., Schouten, J., Grinspoon, S. K. & Reiss, P. Risk of coronary heart disease in patients with HIV infection. *Nat. Rev. Cardiol.* **11**, 728–741 (2014).
310. Farzadfar, F. *et al.* Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: a nationally representative observational study. *Lancet* **379**, 47–54 (2012).
311. Bennett, J. E. *et al*. The future of life expectancy and life expectancy inequalities in England and Wales: Bayesian spatiotemporal forecasting. *Lancet* http://dx.doi.org/10.1016/S0140-6736(15)60296-3.
312. WHO. *WHO methods and data sources for global causes of death, 2000–2012* [online], http://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2012.pdf (2014).
313. Knowler, W. C. *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
314. Look Ahead Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.* **369**, 145–154 (2013).
315. Paffenbarger, R. S. J. in *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. October 24–25, 1978.* NIH Publication No. 79–1610 (eds Havlik, R. J. & Feinleib, M.) 298–311 (National Heart, Lung, and Blood Institute, US Department of Health, Education, and Welfare, 1979).
316. Kuller, L. H., Laporte, R. E. & Weinberg, G. B. in *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. October 24–25, 1978.* NIH Publication No. 79–1610 (eds Havlik, R. J. & Feinleib, M.) 312–339 (National Heart, Lung, and Blood Institute, US Department of Health, Education, and Welfare, 1979).
317. Luepker, R. V. WHO MONICA project: what have we learned and where to go from here? *Public Health Rev.* **33**, 373–396 (2012).
318. Tunstall-Pedoe, H. *et al.* Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* **90**, 583–612 (1994).
319. Griffiths, C., Brock, A. & Rooney, C. The impact of introducing ICD-10 on trends in mortality from circulatory diseases in England and Wales. *Health Stat. Q.* **22**, 14–20 (2004).
320. Murray, C. J., Kulkarni, S. C. & Ezzati, M. Understanding the coronary heart disease versus total cardiovascular mortality paradox: a method to enhance the comparability of cardiovascular death statistics in the United States. *Circulation* **113**, 2071–2081 (2006).
321. Stevens, G. A., King, G. & Shibuya, K. Deaths from heart failure: using coarsened exact matching to correct cause-of-death statistics. *Popul. Health Metr.* **8**, 6 (2010).
322. WHO. *The Global Burden of Disease: 2004 Update* (WHO, 2008).

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