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## The contributions of risk factor trends and medical care to cardiovascular mortality trends

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### Abstract

Ischaemic heart disease, stroke, and other cardiovascular diseases (CVDs) are responsible for an estimated 17.5 million annual deaths in the world. If account is taken of population aging, death rates from CVDs are estimated to be steadily decreasing in the world as a whole, and in regions with reliable trend data. The declines in high-income countries and some countries in Latin America have been ongoing for decades with no indication of slowing. In high-income countries, these positive trends have broadly coincided with, and benefited from, declines in smoking and physiological risk factors like blood pressure and serum cholesterol. Improvements in medical care, including effective primary prevention through management of physiological risk factors, better diagnosis and treatment of acute CVDs, and post-hospital care of those with prior CVDs, are also likely to have contributed to declining CVD event and death rates, especially in the past 40 years. However, the measured risk factor and treatment variables neither explain why the decline began when it did, nor much of the similarities and differences in the start time and rate of the decline across countries or between men and women. There have been sharp changes and fluctuations in CVDs in the former communist countries of Europe and the Soviet Union since the fall of communism in the early 1990s, with changes in volume and patterns of alcohol drinking, as a major cause of the rise in Russia and some other former Soviet countries. The challenge of reaching more definitive conclusions concerning the drivers of what constitutes one of the most remarkable international trends in adult mortality in the past half-century in part reflects the paucity of time trend data not only on disease incidence, risk factors, and clinical care, but also on

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### Contributions

ME developed the review concept and coordinated the review and writing of the article. All authors contributed to the review materials and writing, and discussed the contents of the article.

### Competing interest

None

other potential drivers, including infection and associated inflammatory processes throughout the lifecourse.

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## Introduction

Ischaemic heart disease (IHD) and stroke are the two most common causes of death in the world. Together they are estimated to be responsible for 14 million annual deaths in the world, a quarter of all global deaths.<sup>1</sup> Other cardiovascular diseases (CVDs) are responsible for an additional 3.5 million deaths. The absolute numbers of deaths from CVDs is increasing in the world and in most countries. What is not widely appreciated is that the rise in the number of deaths is occurring mostly in people older than 70 years of age, and is due to increased longevity and the associated population aging.<sup>2,3</sup> If account is taken of population aging, death rates from CVDs are steadily decreasing in the world as a whole, and in regions with reliable trend data (Figure 1).<sup>2-4</sup>

A natural question of scientific and public health interest is how much trends in known risk factors, individually and in combination, are responsible for trends in CVD mortality and its variations across countries. The answer will help anticipate likely trends in future CVD mortality under specific projected risk factor scenarios.<sup>3</sup> We review the major studies that have examined the role of trends in preventable risk factors as drivers of trends in CVD mortality. Our focus is not whether a factor is a cause of CVD occurrence or death, which is the subject of epidemiological studies in individual participants. Rather, we summarise and critically evaluate the evidence on whether *change* in risk factor levels in whole communities and populations is associated with *change* in mortality. Although our primary focus is on risk factors, we briefly consider the role of improved medical care for two reasons. First, as we describe below, trends in major physiological risk factors for CVDs are due to a combination of changes in behaviour and pharmacological treatment. Second, we find it incomplete, if not impossible, to attribute change to specific risk factors without any consideration of other major determinants of CVDs which have changed markedly at the same time.

The paper begins with a short review of the existing data on trends in CVD mortality and risk factors. We focus primarily on IHD and stroke when data allow, and on all CVDs when factors like changes in classification of causes of death make trends in specific diseases less reliable. We then review studies on the role of risk factors in CVD trends, organised largely by how the scientific knowledge has evolved. While socio-economic inequalities are an important feature of CVDs, and of their trends, we do not deal with them as they have been addressed elsewhere, including in a recent review by Harper et al.<sup>5-8</sup>

## Worldwide CVD mortality trends

### Rise and fall in high-income countries of Asia, Australasia, North America, and Western Europe

As early as the middle of 20<sup>th</sup> century, trends in deaths from CVDs were being discussed in the literature. Studies from Australia, Europe, and the United States (US) found that, with

the exception of some countries during World War II (WWII), CVD death rates rose in the first few decades of the 20<sup>th</sup> century.<sup>9–14</sup> Some of these early studies systematically considered whether changes in diagnostic and classification criteria or the expanding geographical coverage of death registration within countries had influenced the observed trends and concluded that, while present, these factors were unlikely to explain the rising trend. Importantly, some of these studies noted that a substantial proportion of the rise in crude death rates was due to the aging of the population, which, as stated above, continues to be overlooked even today. A rising trend was nonetheless seen in age-specific and age-standardised death rates.<sup>10–13</sup> In the US, trends were diverging among population subgroups as early as the 1940s, rising among white men, while declines were already evident at working ages for white women and blacks.<sup>15</sup> By the 1960s, CVD mortality was declining in most western high-income countries.<sup>16,17</sup> This reversal in the trend was initially missed or even dismissed by some people but was noted by more discerning reports.<sup>18,19</sup>

Data on total CVD mortality mask the fact that for most of the first half of the 20<sup>th</sup> Century, IHD and stroke had opposite trends in high-income countries like the UK and the US, with stroke (and hypertensive disease) mortality declining decades before the IHD decline began.<sup>12,16,17,20–26</sup> Of the two main types of stroke, ischaemic stroke shares many risk factors with IHD. The earlier decline of stroke as a whole might reflect that haemorrhagic stroke may have begun declining much earlier in the 20<sup>th</sup> Century, as has been recently suggested in an analysis of data from England and Wales.<sup>23</sup>

Japan, the only country in Asia with reliable long-term mortality data, seems to also have experienced rising IHD mortality (albeit from very low levels) from 1950 until the 1970s and rising stroke until the 1960s, after which death rates began to decline.<sup>27–32</sup> IHD death rates in Japan never reached the levels seen in western high-income countries. As in western countries, haemorrhagic stroke began its decline well before ischaemic stroke, at least in the 1950s.<sup>29</sup>

Following pioneering works in the 1950s and 1960s to document the rise in IHD mortality, seeking explanations for the decline in IHD mortality in western countries became a focus of research efforts from the 1970s.<sup>33–35</sup> This focus is exemplified by two major milestones in research on CVD mortality trends. First, data and perspectives on the topic came together at the 1978 Bethesda Conference on the Decline in Coronary Heart Disease Mortality (Panel 1).<sup>24</sup> Second, the MONICA (Multinational MONIToring of trends and determinants in Cardiovascular disease) Project was initiated to assess prospectively the influence of changes in major risk factors on change in IHD mortality over a period of ten years in the 1980s and early 1990s in 21 countries (Panel 2).<sup>36</sup> Decades after these pioneering investigations, we use national mortality and risk factor data to revisit these trends with the advantage of having data from much longer period of time and a larger, and more diverse, set of countries than has been previously considered (Panel 3).<sup>37</sup>

### **Continued decline in high-income countries of Asia, Australasia, North America, and Western Europe**

Figure 2 shows per cent decline in total CVD mortality for 20 western high-income countries with reliable vital statistics in each of the past six decades. The figure reveals two

important features of CVD mortality trends: first, the decline in CVD mortality had already begun in the 1950s among women in these 20 countries, especially in those under the age of 70 years. Although the decline in men became fully established in later years, in some countries, like Canada, Sweden, and Switzerland, declining trends were seen in the 1950s (Figure 3). By the 1970s, total CVD death rates were declining in most high-income countries, including in Japan (Figure 3). Greece was possibly the only western high-income country where CVDs continued to rise until the 1980s before joining the wave of declines. Second, there was substantial variation across countries in the rate of decline with the best and worst performing country in each decade about 30% apart.<sup>21,22</sup> While these points were apparent to some earlier investigators, what is so extraordinary today is that the CVD mortality decline shows no signs of slowing; in fact the proportional rate of decline in the most recent decade seems even larger than previous decades. Taken over the nearly 60 years since it began, this decline in CVD mortality is arguably one of the most notable health phenomena of the late 20<sup>th</sup> and early 21<sup>st</sup> centuries, resulting in over 70% lower death rates, relative to their peak, from this group of causes among men and over 75% lower among women in countries like Australia, Canada, Finland, France, and Switzerland. Total CVD mortality in Japan began to decline in the early 1960s, due to the decline in total stroke deaths while IHD continued to rise as stated earlier.

### Latin America

Historical mortality data with details on age and cause of death are available for fewer countries in Latin America than in the high-income world although efforts are ongoing to collate such data (see <https://www.ssc.wisc.edu/cdha/latinmortality/>). Among those with better quality data, CVD mortality has been declining at least since the 1970s in Argentina, Chile, Costa Rica, Uruguay, and Venezuela with the pace of decline only slightly slower than in high-income countries, with declines in Mexico (and Brazil which is not shown in the figure) beginning around the same time or shortly after (Figure 3).<sup>38-40</sup> More recently, CVD death rates seem to be declining in the region as a whole, again at a slower pace than in high-income countries (Figure 1).

### Former communist countries of Central and Eastern Europe

The former communist countries include those of Central and Eastern Europe such as Hungary and Poland as well as those of the former Soviet Union. While the precise nature of the political regimes varied, and some may describe them as having being socialist rather than communist, as a group they manifest trends that are quite different to those of other industrialised and high-income countries. Most importantly, declines in CVD mortality had a far later onset than in high-income countries of Asia, Australasia, North America, and Western Europe. As early as the Bethesda conference it was noted that IHD mortality was increasing in many Central and Eastern European countries, especially among men (Figure 3).<sup>21,22,41,42</sup> The increases in CVD death rates in countries such as Czech Republic, Hungary, Poland, Romania, and Slovakia continued for decades after the decline started in high-income countries, and only reversed in the mid-late 1980s and early-mid 1990s, with the decline starting earlier in women than in men. However, once the CVD decline began in these countries, the rates of decline rapidly converged with those in other high-income countries (Figure 3).<sup>43</sup> Like high-income countries of Asia, Australasia, North America, and

Western Europe, there were variations in when the declines began and its rate in these countries.

The countries of the former Soviet Union including Belarus, Moldova, Russia, Ukraine and the Baltic states of Estonia, Latvia, and Lithuania show a more complex trajectory. Unlike high-income countries, CVD mortality in these countries was on a shallow upward trend among men and stagnant among women in the last few decades of the Soviet Union. Death rates declined in both sexes after Gorbachev's anti-alcohol campaign in 1985 in some of these populations, only to rise steeply from the early 1990s coinciding with the collapse of the Soviet Union. These fluctuations, which were different from relatively gradual changes seen elsewhere, were particularly dramatic for working age men.<sup>44–46</sup> In Russia and Ukraine, CVD death rates declined between 1994 and 1998, and increased again until the mid-2000s since when they have declined.<sup>47</sup> In contrast, in Estonia and Latvia the decline was established from the early-mid 1990s. The dramatic fluctuations in CVD mortality in Russia were parallel to fluctuations in external causes of death from injuries and acute alcohol poisonings (Figure 4).<sup>48</sup> There is some suggestion that the apparent fluctuations in deaths attributed to IHD might in fact be due to misclassification of sudden cardiac deaths induced by heavy drinking (for which death rates from acute alcohol poisoning act as proxy),<sup>48</sup> rather than being classic manifestations of atherosclerotic disease such as myocardial infarction.<sup>49</sup>

## China

The absence of complete vital registration makes data on trends in China less reliable. Data from the MONICA study and from other community studies seem to indicate a decline in total stroke death rates (driven by relatively large declines in haemorrhagic stroke), similar to earlier trends in Japan, and possibly a small rise in IHD death rates.<sup>50–52</sup> In Hong Kong, where there are high-quality data, IHD seems to have plateaued and even begun declining in the 1980s, especially at younger ages.<sup>53</sup>

## Sub-Saharan Africa

There are very few data on CVD trends from low-and-middle-income countries because vital registration systems do not exist, or are incomplete and have limited information on causes of death. A notable exception is high-quality vital registration data with medical certification of causes of death in Seychelles, a middle-income country in Africa. These data show steady declines in death rates from stroke, IHD, and other CVDs.<sup>54</sup> South Africa, another country with somewhat complete vital statistics also seems to have had declining age-standardised death rates from IHD and stroke.<sup>55</sup>

## Trends in CVD mortality sex ratios

One of the striking features of the CVD mortality trends is the difference in their start time and pace for men and women. Figure 5 shows the sex ratios in CVD death rates for people aged 30–69 years, an age range commonly considered as premature death, for the same countries as in Figure 3. The figure shows that historically, premature CVD death rates in men were 1–2 times those in women in high-income countries. The ratio increased over

time, reaching 2–3 in most countries, and nearly 4 in Finland. It has plateaued or is decreasing in English-speaking and North-Western Europe.<sup>26</sup> The male-to-female ratio of premature CVD death rates is still increasing in Central and Eastern Europe, Japan, and Latin America.

## CVD risk factors

Observational studies and randomised trials have identified numerous behavioural, environmental, nutritional, physiological, and psychosocial risk factors for CVDs. Today there are hundreds of risk factors above and beyond the “classic” risks (smoking, blood pressure, serum cholesterol, and blood glucose or diabetes) considered in studies such as the Framingham Heart Study and the MONICA Project.<sup>56–58</sup> These risks span the life course and include factors such as impaired fetal and childhood growth and nutrition, adult height and lung function, psycho-social factors including social gradient and status, and numerous environmental and occupational exposures and components of diet. They also include an increasing number of physiological risk factors such as persistent low-grade inflammation (including that related to infections) and a putative role for the gut microbiome, which may in turn be affected by diet and biophysical environment.<sup>59,60</sup>

Despite the proliferation of putative risk factors, we will focus on the established risk factors for which there is extensive evidence from observational epidemiology and/or randomised trials, and for which trend data are available and reliable for an appreciable number of countries. We also look at trends in adiposity, aspects of diet, and alcohol use. Before considering trends in each of these we briefly discuss some fundamental issues concerning the conceptualisation of the link between risk factors and CVD mortality trends.

Any explanatory framework for changes over time in CVD incidence and death has to assume that the factors considered are either directly causal or are proxy markers for causal factors. Causal influences can be along a continuum from the most proximal (usually physiological) to the most distal (such as large scale social or economic changes that can set in train changes in behaviour).<sup>61,62</sup> This is represented very simply in the following:

Societal level factors » Individual behaviours and exposures » Intermediate traits » CVDs

In reviewing which factors might be responsible for trends in CVD, it is necessary to take into account this hierarchy of influences. Changes in the intermediate trait of blood pressure and serum cholesterol might be the result of a range of behavioural factors such as exercise and diet. These physiological traits should be regarded in this sense as mediators of behavioural or societal changes. However, there is a further level of complexity for several intermediate traits, which is that trends in these can be influenced by medical interventions (e.g., decline in lipids or blood pressure as a result of statin use and anti-hypertensive medications). In this regard, any role that trends in blood pressure or serum cholesterol levels may have in trends in CVD morbidity or mortality does not neatly fall into either lifestyle or treatment effects, the apparent objective of analyses that seek to apportion the more recent declines in CVD mortality into these two categories. The usual, but important caveat concerning genetic influences needs to be made. While the huge postgenome effort to

identify genetic determinants of cardiovascular traits and disease is showing some progress, it sheds little light upon the dramatic and largely simultaneous temporal trends we have described.

As discussed briefly below, the extent to which some the less-established risk factors are truly causal is controversial. Even for those risk factors that are believed to be causally related to CVDs, such as blood pressure, serum lipids, and smoking, which measure best captures the causal element is open to question. For example, total cholesterol appears to be a poorer marker of risk than LDL, HDL, or their ratio (or ratio of ApoB to ApoA1).<sup>63</sup> Finally, when considering the likely role played by 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.<sup>3</sup> For a number of risk factors a combination of observational and trial evidence suggests that risk of IHD and stroke falls relatively rapidly following reductions in risk factor levels. For example, among people who give up smoking, the risk of CVD falls to that of non-smokers within as short a time as up to five years, although other estimates suggest something closer to ten years (Figure 6).<sup>3,64</sup> This is in contrast to lung cancer and chronic obstructive pulmonary disease, where the risk for former smokers decays over a much longer time period of many decades.<sup>3,64</sup> There is also evidence that following smoking bans in public places, there were rapid falls in hospitalisation rates for acute coronary syndromes.<sup>65,66</sup> For cholesterol and blood pressure, evidence from randomised trials suggests that reductions in CVD risk occur within five years.<sup>67</sup> For alcohol, body mass index (BMI), and dietary salt there is relatively little evidence available on which to estimate the temporal responsiveness of CVDs, although effects on intermediate traits like blood pressure occur rapidly.<sup>68–72</sup> Moreover, there is scant evidence for any of these factors about the induction period – time from when increases in exposure levels result in increased risk of a CVD event.<sup>73</sup> What is known, however, is that the development of atherosclerotic plaques or the hardening of the arteries is a gradual life-long process.<sup>74,75</sup> In contrast, risk of a fatal obstruction of the coronary arteries may be reduced relatively abruptly, particularly if it affects late-stage factors in the process such as clotting and thrombus formation. Although not directly related to CVD, mortality from alcoholic liver cirrhosis well illustrates this sort of temporal asymmetry. Cirrhosis risk increases among moderate to heavy drinkers only after many years of alcohol consumption. However, at a population level, declines in alcohol consumption (typically those that are the result of governmental regulation of availability and price) can result in very abrupt reductions in liver cirrhosis mortality, as those with compromised livers have a reduced risk of experiencing a final, life-threatening binge. This complexity of risk factors is summarised in Table 1.

## Trends in CVD risk factors

Historical population-based data on CVD risk factors, especially at the national level, are less plentiful than mortality data which are collected routinely where there is vital registration. Health surveys, food and alcohol production and trade data, and sales receipts for tobacco and alcohol have all been used to reconstruct trends in behavioural and dietary risks. Reconstructing trends in physiological risk factors, including adiposity, blood pressure, cholesterol, and glycaemia and diabetes, require population-based measurement data as self-reports or measurements from groups attending clinics or hospitals are biased.



The longest-duration nationally representative health examination survey (HES) began in 1948 in Japan and has been conducted virtually every year since then.<sup>76,77</sup> Subsequently, other countries developed HES programmes, with regular or periodic surveys that allow direct measurement of more recent trends in physiological risk factors and diet in specific countries. More recently, WHO has coordinated a series of HES through its STEPwise approach to Surveillance (STEPS) programme in countries where traditionally there have been fewer data on CVD risks. In addition to studies of trends in individual countries, there are a small number of multi-country comparative studies. The MONICA Project provided a picture of change in CVD risk factors in 21 countries in the 1980s and 1990s. More recently, the Metabolic Risk Factors of Chronic Diseases Collaboration ([www.imperial.ac.uk/medicine/globalmetabolics/](http://www.imperial.ac.uk/medicine/globalmetabolics/)) has collated much of the available population-based data on major cardio-metabolic risk factors throughout the world and has used advanced statistical methods to reconstruct trends in risk factors for all countries.<sup>78–83</sup> Despite these efforts, data on trends in important CVD risk factors are more limited than on mortality in most countries, and the estimated trends to have large uncertainty.

### Smoking

There has been a great deal of attention to trends in smoking with summaries of available data presented every decade or so.<sup>84,85</sup> These studies show that there was a steady rise in smoking among men in English-speaking and Northern European high-income countries throughout much of 20<sup>th</sup> century, with the trend reversing in the 1960s; the rise, and to a lesser extent the decline in smoking, had a strong birth-cohort pattern.<sup>86–90</sup> Subsequent to the start of the smoking epidemic in English-speaking and Northern European countries, smoking rates rose among men in Central, Eastern, and Southern Europe; in Japan; in 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 Middle East.<sup>84</sup> Smoking prevalence is still relatively low among men in Africa, where smokers smoke fewer cigarettes than in other regions.

The dynamics of the smoking epidemic in women were somewhat different, with the increases and declines in women occurring decades after those in men. The rise in smoking in women began after WWII, first in English-speaking high-income countries and in Northern European countries and continued to the 1980s but did not become as prevalent as it was among men. Countries varied considerably in sex differences in smoking prevalence. For example, in Denmark and the UK women as well as men historically had relatively high prevalences of smoking, with similar sex ratios seen later in Southern Europe and some Latin American (e.g., Argentina and Chile) and Central European (e.g., Austria, Czech Republic, and Hungary) countries. In contrast, Smoking remains relatively rare among women in much of Asia and Africa, with regional prevalences less than 5%;<sup>86,91,92</sup> Elsewhere, e.g., in Russia and Ukraine where 50–60% of adult men and 15–25% of adult women smoke, there are intermediate sex ratios of smoking.<sup>86,91,92</sup>

In addition to changes in the prevalence of smoking and amount smoked by smokers, over the past 60 years there have been changes in the type of cigarettes available, including the introduction of “low-tar” and “light” cigarettes that aimed to reduce the tar and carbon

monoxide yields of cigarettes.<sup>93,94</sup> Some studies have associated these factors with differences in the risk of CVD events,<sup>95</sup> making their changes a candidate explanation for some portion of the decline in CVD mortality (and its timing). However, recent Reports of the Surgeon General concluded that changes in cigarette design, including low-yield cigarettes, had not reduced overall disease risk, and that focus should be on preventing smoking initiation and facilitating quitting among current smokers.<sup>96,97</sup>

### Alcohol use

Trends in alcohol use have been more heterogeneous than those of smoking, and highly influenced by cultural, socioeconomic, and political factors; by the larger diversity of alcohol types, scale, and ownership of production; and by alcohol policies and regulations. We will not review the full trends in alcohol use here as these have been done elsewhere,<sup>86,98–102</sup> but note a few important features. First, alcohol consumption has declined steadily in traditional wine drinking countries (mainly Southern Europe and a few countries in South America) for decades (Figure 7).<sup>86,103,104</sup> In other western countries, trends have been more variable, downwards in the presence of alcohol control policies like taxes and regulation that raise prices and restrict access, e.g., in Australia and Canada in the 1980s and 1990s, and upwards where there has been little policy intervention, e.g., Denmark, Finland, and the UK. Alcohol use is rising steadily in many countries in Asia, reflecting higher purchasing power coupled with 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 Russia and some of its neighbouring countries from the mid-1980s to the end of the 1990s.<sup>105</sup> Even what constitutes alcohol sales is complex in these countries and includes much illegal and otherwise unrecorded consumption, making it difficult to estimate total consumption levels.<sup>106–109</sup> What is clear, however, is that patterns of consumption in Russia and neighbouring countries are particularly hazardous, with high fraction of ethanol drunk as spirits and in intense drinking spells. Trends in such drinking patterns are reflected in the substantial fluctuations in mortality from acute alcohol poisonings as mentioned above.<sup>110</sup> Although some debate remains about whether light or moderate drinking is cardio-protective,<sup>111</sup> agreement is emerging that harmful patterns of alcohol use, especially heavy drinking, is associated with increased CVD risk.<sup>112</sup> Yet, much less has been written on trends in drinking patterns elsewhere (in fact, the first international conference focusing specifically on patterns was only held in the mid 1990s,<sup>113,114</sup> and systematic data collection on patterns of consumption only began afterwards).<sup>115</sup>

### Diet

The early evidence on the effects of dietary factors on CVDs was largely from observational studies in humans and animal experimental studies.<sup>34</sup> Given the strong correlations between diet and other behaviours, and among various features of diet themselves, there was and remains significant potential for confounding of effects in observational studies. However, well-designed randomised trials are increasingly common in nutritional epidemiology, have confirmed the effects of some dietary factors on CVDs and their intermediate physiological risks, including the harms associated of high salt intake on blood pressure (and in one case with additional follow-up on CVDs),<sup>116–119</sup> and the benefits of replacing saturated fats with

unsaturated fats, and of diets rich in fruits, vegetables, whole grains, low fat dairy, and nuts.<sup>120–127</sup>

Among dietary traits, trends in fats, especially animal-source and saturated fats, have received the most attention, because they have been considered an important risk factor for IHD.<sup>9</sup> Using food supply, Antar and Kahn each concluded that there had been a rise in fat content of the American diet but that the rise was too small to alone explain the rising IHD mortality in the early part of the 20<sup>th</sup> century (rather, Antar hypothesised a role for the replacement of complex carbohydrates by processed ones).<sup>128,129</sup> Similar analyses using data on food supply or dietary surveys associated reductions in saturated and animal-source fats as a driver of IHD decline in the last few decades of the 20<sup>th</sup> century in Finland, Germany, New Zealand, Poland, Sweden, the UK, and the US (with some also documenting a decline in salt intake and a rise in consumption of fruits).<sup>19,26,130–135</sup> Addressing a longer period, Stephen and colleagues fitted a quadratic relationship to all available nutrition surveys and concluded that fat intake increased in the US until the 1960s before declining; the peak in the UK was in the 1970s.<sup>136,137</sup> They associated these peaks with the timing of IHD mortality decline (but overlooked the fact that the peak for women had occurred at an entirely different time). The analysis of Japan's impressive time-series of surveys also found an increase in fats while there was a rise in IHD, but concluded that trends in fats, when converted to cholesterol using Keys' relationships, could not alone account for the observed change in IHD.<sup>27,30,76,77</sup>

Animal-source foods as well as vegetable oils seem to have increased in China for decades, as have the former in some Mediterranean countries like Greece.<sup>86,138</sup> Pooling of worldwide nutrition surveys and analysis of food availability data from the UN Food and Agricultural Organization (FAO) both found that there has been little change in the availability or intake of animal fats at the global level, balancing a decline in high-income countries and a rise in the developing world.<sup>139,140</sup>

Trans fats, which are made by hydrogenating edible oils and are harmful for CVDs, were common in many countries because of reduced storage cost. Their use seems to have decreased in high-income countries, at least partially in response to regulation,<sup>141,142</sup> and in some Central and Eastern European countries after the introduction of market economy;<sup>143,144</sup> there may have been an increase in India and parts of Middle East.<sup>140,145</sup>

High levels of salt intake are now recognised as major risk factor for CVDs, especially for stroke, largely through effects on blood pressure.<sup>72,116,146,147</sup> While 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 more regular availability of fresh foods, and it changes (mostly but not necessarily upwards) salt intake through the use of packaged and prepared foods which tend to use salt, often in high doses, for flavouring. Dietary salt in Japan, one of the countries with the best historical data, changed little from 1950s to 1970s, but declined subsequently.<sup>148,149</sup> Similar reductions are occurring in parts of China but were not seen in South Korea.<sup>150</sup> Among western countries, there have been long-term reductions in Finland, associated with lower deaths from stroke (and from stomach cancer), and more recently in

the UK as a result of specific efforts to engage the food industry in reducing salt content of their products.<sup>132,133,151–155</sup> Analyses of worldwide surveys have found high salt intake, with little change over time, in many regions,<sup>156,157</sup> but the estimated trends have likely been affected by very limited data availability.

Less has been done on trends in the consumption of fruits and vegetables, and whether they are consumed fresh, cooked, or processed into juices; at least in their fresh form, fruit and vegetable consumption is linked to lower blood pressure and CVD risk.<sup>120,158,159</sup> The limited available studies are divided between those that have reported increasing absolute intakes, at least in some high-income western and Asian countries (with a possible recent plateau)<sup>129,132,151,160–163</sup> and those that have focused on their decreasing share of total energy,<sup>160,164</sup> which is simply a reflection of the increase in intake of other foods and hence total calories. There is also some recent attention to trends in overall food and diet patterns, broadly concluding higher intake of vegetable fats (although not necessarily the healthy unsaturated fats) in low-income countries; higher availability of animal-source foods and dairy in middle-income countries and lower consumption in western high-income countries; higher use of refined carbohydrates and sugars and less of whole grains and foods with high fibre content; more fruits; and higher dietary diversity.<sup>86,139,160,165,166</sup>

### **Adiposity, glycaemia, and diabetes**

BMI and adiposity are risk factors for IHD and stroke.<sup>167</sup> The systematic pooling and analysis of data by the Metabolic Risk Factors of Chronic Diseases Collaboration showed that since 1980, age-standardized mean BMI 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.<sup>79</sup> These trends resulted in a doubling of the prevalence of obesity in the world between 1980 and 2008.<sup>83</sup>

Largely associated with rising BMI, there has been a rise in blood glucose and diabetes in the world and in most regions, with the largest rise occurring in some Pacific islands and in countries in the Middle East and North Africa and in Central America.<sup>81</sup> When compared to the increasing trend in BMI, the rise in diabetes was slower in Western Europe relative to other regions; in South Asia, it occurred faster than other regions. As we describe below, unlike diabetes, trends in blood pressure and serum cholesterol in high-income countries (and in many low- and middle-income countries with reliable data) have been opposite those of BMI, although the declines in blood pressure and serum cholesterol were smaller where BMI rose more.<sup>168</sup>

### **Blood pressure**

Between 1980 and 2008, systolic blood pressure (SBP) declined slightly globally,<sup>80</sup> with the largest declines occurring in high-income countries of Australasia, North America, and Western Europe. SBP rose in Oceania, East Africa, and South and Southeast Asia for both sexes, and in West Africa for women. The few longer term country studies also show decades of decline in blood pressure in a few high-income countries like the USA, Japan, and Finland.<sup>30,148,149,151,169,170</sup> The declining blood pressures seem to be a result of both cohort and period effects.<sup>169,171</sup> In other words, blood pressure has been lower in subsequent

birth cohorts when they reach their 3<sup>rd</sup> and 4<sup>th</sup> decade of life with the improvement persisting through their lifecourse; above and beyond this cohort effect, people have experienced lower blood pressure at every age as time has passed, regardless of when they were born. Further, the reductions happened through the full distribution of blood pressures but there were additional benefits to those with hypertension.<sup>169,172,173</sup>

Little is known about the reasons for these trends and even analyses of the rich time-series Japanese data could only explain a part of the observed trend.<sup>148,149</sup> The drivers however are likely to include lower intake of salt in some countries and higher and/or year-around use of fruits and vegetables which are a source of potassium (even in their less healthy form of juices), and the use of antihypertensive medications especially at middle and older ages. Additional reasons for cohort patterns can only be hypothesised and may include changes in early life nutrition or infection that persist through a cohort's life. Importantly, these reductions in mean blood pressure occurred despite rising adiposity in high-income countries. More recently, similar declines have been recorded in Seychelles, a middle-income country in Africa, again despite rising BMI.<sup>174</sup> As a result, while in 1980 population mean blood pressure was directly associated with mean BMI, by 2008 the association had become null for men and inverse for women.<sup>175</sup>

### Cholesterol

There has been a long history of interest in trends in serum cholesterol, due to its role as a cause of IHD,<sup>9</sup> although it shows a surprisingly weak association with stroke risk.<sup>167</sup> Researchers have used time series food data to estimate upward trends in (dietary) cholesterol in the US for the first 60 years of the 20<sup>th</sup> century and in Japan between 1949 and 1960s, although neither was sufficiently large to have alone led to the observed changes in IHD death rates<sup>27,128</sup>. Studies starting in the 1960s or 1970s using HES data have also shown rising serum cholesterol levels in Japan,<sup>170,176,177</sup> and declines in western high-income countries.<sup>19,132,151,178,179</sup> Pooling of global HES data showed that global serum total cholesterol levels have been virtually constant since 1980, as a result of a decline in Australasia, North America and Europe offset by a rise in East and Southeast Asia and Pacific, including in China, Japan, and Thailand.<sup>82</sup> The decline in Western countries began well before widespread use of lipid lowering drugs such as statins.<sup>179</sup> There was little evidence of change in total cholesterol in Latin America and Caribbean, North Africa and Middle East, South Asia, and sub-Saharan Africa, partly due to limited historical data in these regions.

### The early signals and studies on risk factors and CVD mortality trends

Once researchers noted trends in CVD mortality, they also attempted to understand the drivers of these trends, both the rise and the subsequent decline. Moriyama and colleagues, who were among the first to note the long-term trends and its differences by sex, sought to find hypotheses by asking experts about explanations for these trends.<sup>33</sup> The hypothesised explanations included changes in diet especially higher fat, energy imbalance and obesity (which they submitted as being worse in men because “the emergence in the early 1920s of the slim figure fashion” would have led to lower obesity in women), psychosocial stresses

and strains (which was believed to affect men more due to the nature of their jobs hence partially accounting for differences in trends by sex), decline in infections and related CVDs, improvements in pregnancy care, and improvements in women's economic and social status due to more job opportunities and because "by virtue of smaller families and mechanical aids, women had been liberated from prolonged, exhausting household drudgery."<sup>33</sup> The use of postmenopausal oestrogen – a topic to which attention returned nearly half a century later after the Women's Health Initiative showed an associated increase in IHD risk<sup>180</sup> – was deemed too recent and still too limited to have contributed to the trend.

Moriyama's hypothesis-generating study aside, the earliest studies of the drivers of CVD trends focused almost solely on fats, saturated fats, and cholesterol in diet, followed by studies that also considered a role for trends in blood pressure, smoking, and eventually obesity. Occasionally other factors, such as the type of carbohydrates, were considered.<sup>129</sup> Some of these studies found coinciding trends in risk factors and CVD mortality; others did not find an association or found inconsistent evidence on the role of the same risk factor between men and women (or other subgroups – for example Utah Mormons, who rarely smoked, had similar declines in CVD mortality as the general US population around when smoking began to decline).<sup>10,19,20,26,27,30,129,181–184</sup> Walker went as far as attributing the decline in coronary disease to specific policy acts including the 1964 Report of the Surgeon General on Smoking and Health and the American Heart Association statement on diet.<sup>20</sup>

Taken altogether, two features of these studies emerge: First, there was substantially more focus 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, may have led to additional possible explanations being overlooked. A more careful look at countries with long time-series of data indicates that decline in CVD mortality in at least some countries, may have begun before its classical risk factors started to decline,<sup>53,168,185,186</sup> raising the possibility that other important factors, and their combinations, may have been partly responsible for its initiation.

## The Bethesda conference and the MONICA Project

The decade-long work on the determinants of decline came together at the Bethesda Conference on the Decline in Coronary Heart Disease Mortality (Panel 1).<sup>24</sup> It also contributed to initiating the MONICA Project (Panel 2) which measured IHD risk factors (BMI, blood pressure, serum cholesterol, and smoking), incidence, treatment, case fatality, and mortality in 38 communities in 21 countries from mid-1980s to mid-1990s, aiming to quantify the contributions of risk factors, and subsequently medical care, to trends in IHD.<sup>36</sup>

IHD death rates declined in most MONICA centres, with an average cross-centre decline of 2.7% per year in men and 2.1% per year in women across centres, although they rose in most of the former communist countries of Europe and China. Change at specific centres ranged between a >7% per year decline in some Australian and Western European centres and a 4% per year rise in some of the Central and Eastern European centres.<sup>187</sup> IHD (fatal plus non-fatal) event rates fell by 2.1% per year in men and 1.4% in women; 28-day case-fatality (which broadly represents hospital-related care) fell by 0.8% and 0.6%, respectively.

Based on these results, the MONICA collaborators concluded that declining event rates contributed about twice as much as improvements in 28-day case-fatality to mortality decline; we will return to the role of medical care later in this article. The two components had heterogeneous effects across countries and in some places were working in opposite directions.

Despite its pioneering, visionary, and unique character the MONICA study is limited in how much light it can throw on the contribution of individual risk factors to changes in event rates. With only a few dozen data points and four risk factors, the estimates of effects had considerable imprecision, and there is a concern that there may have been over-fitting which might make findings not replicable.<sup>188</sup> Nevertheless after mutual adjustment, change in IHD event rate was found to be positively associated with changes in blood pressure and cholesterol, but inversely associated with change in BMI, for both men and women.<sup>189</sup> Moreover, while the association with change in smoking was direct for men, for women it was inverse in adjusted analysis. In addition to the above factors, this implausible result may be due to under-adjustment for other factors that confound the effects of smoking in women, which increased in many European countries where IHD was declining rapidly. Inverse associations of change in IHD with change in BMI may be due to similar reasons, or because the effects of rising BMI were countered by declining blood pressure and cholesterol, which are important mediators of its effects on IHD<sup>190</sup> (importantly, these two risks, and smoking, declined more steeply in overweight and obese people than in those with normal weight;<sup>191</sup> such within-population correlations of risk factors were not taken into account in the MONICA analysis and in similar subsequent studies).<sup>168</sup>

The magnitudes of associations aside, risk factor trends only explained about one half of the cross-country variation in IHD decline in men, and less than 20% in women, across the MONICA centres. While this may be partly due to measurement error in risk factors, it also implies that other important factors were acting to reduce IHD rates at the population level. The important role of these other factors 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 to empirically investigate why heart disease mortality was declining. Notable among these, Pell began to investigate incidence and shorter (24-hour and 30-day) and longer term survival from myocardial infarction among employees of Du Pont Company in 1957.<sup>192,193</sup> As the employees had regular medical examinations and their health and vital status was known, this investigation was among the few to document trends in both incidence and survival.<sup>193</sup> This analysis found that incidence had declined since 1957, when data collection began. Case-fatality began to decline in the early 1970s, which continued steadily to 1983, the last year of data.

Nonetheless, most of the activities in this area began around and after the Bethesda Conference. In addition to the MONICA Project the Bethesda Conference motivated a

number of community-based studies in the US, including the Minnesota Heart Study, the Olmsted County Study, Worcester Community Study, and the Atherosclerosis Risk in Communities (ARIC) Study. These studies collected population-based data on trends in hospitalisation for CVDs, treatment, survival of hospitalised patients, and in some cases risk factors.<sup>194–198</sup> Most of these studies used hospital records to track trends in hospital admissions and discharges with IHD (some confirmed by chart review – typically symptomatology, electrocardiogram features, and an ever-evolving set of cardiac enzymes – and sometimes with additional efforts to find cases that either did not appear in these databases or whose cause of admission or death was coded incorrectly). 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 followed individuals vs. whole communities.<sup>199,200</sup> More recently, the availability of electronic data on hospitalisation and the ability to link these data to death records has allowed monitoring trends in CVD event rates, and in- and out-of-hospital survival.<sup>201–206</sup> Bureaucratic and legal obstacles to linkage, packaged as privacy concerns, however have so far not permitted the potential of such data to be fully utilised, or are threatening them where there have been advances.

### Risk factor attribution modelling studies

Around the same time as the MONICA Project, numerous prospective cohort studies were initiated, and helped identify new risk factors for CVDs (but could not assess how their changes affect disease trends in populations) and randomised trials showed the efficacy of new treatments and led to changes in clinical guidelines (but could not examine their uptake and effectiveness in whole populations). A different group of studies used estimates of the size of aetiological effects of risk factors and treatment from these individual-level studies to attribute, using modelling, either levels or changes in CVD mortality to specific risk factors and to treatment.<sup>7,62,207–213</sup> These studies all attributed relatively large proportions of current CVD mortality or change in mortality, to risk factor levels and trends. They also found that treatment, either acute or long-term secondary prevention among people with a history of CVD, was partly responsible for the CVD mortality decline. The number of risk factors in such studies has increased over time,<sup>214,215</sup> including the effects of multiple risks.<sup>210,211,216,217</sup>

An important difference between these modelling studies and the analyses done in the MONICA Project is that the contributions of risk factors in MONICA were directly estimated as associations between the data on change in risk factors and in CVD disease or mortality across populations (which of course might introduce different sources of error compared to the modelling studies). The attribution modelling studies, on the other hand, by necessity assume that the individual-level associations apply to the populations considered, which may be different from the epidemiological cohorts that generated them (there is some effort to evaluate the evidence for such similarity or its absence in relation to region and ethnicity).<sup>167,190,218</sup> Some of these studies have accounted for the fact that the effects of different risk factors, and of risk factors and treatment, cannot be simply added,<sup>3,216,217</sup> i.e., when multiple risk factors improve and treatment improves, the reductions in some CVD deaths may be attributed to more than one factor.<sup>219,220</sup> Others did not, and constrained the contributions to add to 100% (theoretically, the sum of individual contributions, if not



considered jointly, could add 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<sup>221–223</sup> – as described earlier, such predictions are the opposite of the actual trend data, which have shown a consistent decline in CVD mortality even as BMI rose. More recently, these models have been extended to model the future impacts of continued risk factor trends or alternative scenarios.<sup>3,221–223</sup> A recent study analysed the impacts of achieving the globally-agreed targets on risk factors on future trends in “premature” (i.e. under 70 years of age) mortality from various noncommunicable diseases (NCDs) (targets were set following the 2011 UN High Level Meeting on NCDs).<sup>3</sup> The study found that, under a so-called business-as-usual trajectory, premature CVD mortality (i.e., projections based on current trends with no additional action) are expected to decline by 18% between 2010 and 2025. Achieving the globally-agreed targets on smoking, alcohol use, salt intake, obesity, and raised blood pressure and glucose will nearly double the decline, to 34%.

### Recent studies on risk factors and CVD mortality trends

More recently, some studies have returned to the empirical traditions of 1970s and 1980s, and have implicated trends in a specific risk factor in explaining those of CVDs, often making use of convenient natural experiments which had engendered a change 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 non-hydrogenated vegetable oils after the fall of communism,<sup>143,144</sup> although there was no attempt to deal with the numerous other socioeconomic, behavioural, and nutritional changes in these countries. Careful analysis of trends was instrumental in establishing the fall of alcohol consumption in the Soviet Union during Gorbachev years, and the subsequent rise in harmful and heavy drinking, as the most important determinant of decline and sharp rise in CVD mortality in Russia and some other former Soviet republics.<sup>46,224,225</sup> This role was initially challenged by epidemiologists in view of 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.<sup>226–229</sup>

Recently, researchers credited a decade of salt reduction in the UK as an important driver of the decline in blood pressure, and by extension in stroke and IHD deaths, above and beyond other factors such as medication and increased consumption of fruits and vegetables in the UK.<sup>153</sup> In a recent study from Cuba, researchers associated changes (both decline and increase) in body weight during periods of economic crisis and recovery with decline and increase in diabetes and changes in the *rate of CVD decline* (i.e., CVD continued to decline regardless of whether weight declined or increased).<sup>230</sup>

Finally, in an analysis similar to the MONICA Project in terms of included risk factors and approach, data on population blood pressure, serum total cholesterol, BMI, and smoking (measured by lung cancer to account for cumulative effects)<sup>231,232</sup> were used to examine empirically the association of changes in risk factors with those of cardiometabolic (CVDs plus diabetes) mortality;<sup>168</sup> Figure 8 shows the results of this study for CVDs alone. Similar to the MONICA Project, change in CVD mortality was positively associated with those of blood pressure and cholesterol; unlike MONICA results, there was also positive association

with change in smoking for both sexes, and in BMI for women, after adjustment for other risk factors (when CVDs and diabetes were used together, the association with change in BMI was positive for both sexes).<sup>168</sup> 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 only explained a relatively small share of cross-country variation in mortality change demonstrating the crucial role of other determinants at the population level. The above-mentioned caveats in terms of measurement error and temporal features of change also apply to these results.

## The role of medical care

When analysing trends in CVDs and eliciting their drivers, it is inevitable to wonder about the relative contributions of risk factor prevention and medical care. Modelling studies aside, the Bethesda conference, the MONICA Project, and some community studies remain among the few attempts to investigate the contributions of prevention and medical care to CVD mortality decline (noting that sometimes this was only in the form of data on incidence and case-fatality which do not map completely to the underlying questions of interest because treatment can affect risk factors like blood pressure and serum lipids, and some lifestyle changes can improve post-event survival).

The period following the Bethesda Conference coincided with a multiplication of effective (and some less effective) treatments for acute coronary syndromes and stroke, as well as management of those who survived the acute events (although in his study of Du Pont employees Pell documented better survival starting from early 1970s).<sup>193,233</sup> The enthusiasm for coronary care units appears to have been misplaced, as they improved diagnosis and in-hospital management without a corresponding change in actual deaths at the population level which were dominated by out-of-hospital deaths.<sup>19,234</sup> On the other hand, the efficacy of anti-thrombotic and reperfusion therapies – including aspirin, systemic thrombolytics, and more recently percutaneous coronary interventions – was demonstrated in randomized clinical trials in the mid-late 1980s. These interventions were subsequently taken up in clinical guidelines and practice in high-income countries (albeit at varying degrees and speeds as described below) with emphasis on reducing time to access to acute treatments.<sup>235–240</sup>

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 was accrued from randomized controlled trials for the benefits of primary prevention through pharmacological treatments (anti-hypertensive medications, statins, and low-dose aspirin). Following the first Veterans Administration Trial in the US, which reported a large reduction in cardiovascular events (mainly stroke) from anti-hypertensive medication,<sup>241</sup> placebo-controlled trials in Australia and the UK confirmed the benefits of anti-hypertensive medication for people with moderately-elevated blood pressures.<sup>242,243</sup> More recent studies, including in the elderly, and meta-analyses, have shown reductions in cardiac events as well as all cardiovascular events from blood pressure lowering medicines.<sup>244–248</sup> Since the 1970s, treatment of high blood pressure has increased steadily in high-income countries of Asia, Australasia, North America, and Western Europe, and

subsequently in upper-middle-income countries in Latin America and elsewhere.<sup>30,148,149,249–255</sup>

The epidemiologic and animal evidence on the role of cholesterol as an important CVD risk factor produced intense interest in cholesterol-lowering treatments, with the first of HMG-CoA reductase inhibitors (statins) released in 1987.<sup>179,256,257</sup> The evidence from randomised trials that the benefits of statins depend on baseline risk of CVD disease, regardless of baseline cholesterol levels, led to changes in treatment guidelines and a rapid increase in their use, especially in the US (uptake in other countries was slower due to some debates regarding the generalizability of early findings on mortality reductions, which have been settled in more recent trials).<sup>256,258–263</sup>

Inevitably, pharmacological treatment has been responsible for some of the reductions in blood pressure, especially at older ages, and for more recent reductions in cholesterol. The extent of such contributions are difficult to establish due to simultaneous and partially correlated trends in various known (as well as unknown) determinants of blood pressure and cholesterol in even the best population-based data, such as those from Japan.<sup>148</sup> Further, if treatment is based on absolute risk of disease, vs. the level of risk factor, it can have large contributions to CVD disease and mortality without much effect on mean population exposure. Preventive treatments remain relatively uncommon in low-income countries, even among people with a history of CVD events.<sup>255,264</sup>

Although it has been known for decades that hyperglycaemia and diabetes are associated with higher risk of CVDs,<sup>265</sup> the contribution of pharmacological glycaemic control to the CVD decline is less clear, both because of the paucity of evidence from population-based studies and the mixed signals from clinical trials in terms of CVD benefits (vs. on microvascular complications, like retinopathy and nephropathy, for which there is more evidence).<sup>266</sup> For example, the United Kingdom Prospective Diabetes Study (UKPDS) trial found a minor effect of glycaemic control on MI and mortality during the trial, which became significant at 10-year follow-up.<sup>267</sup> The ACCORD study, on the other hand, was stopped early because of increased all-cause and cardiovascular mortality in the intensive treatment arm.<sup>268</sup> These conflicting results likely represent a trade-off between the benefits of good glycaemic control on long-term cardiovascular outcomes, and the risks of hypoglycaemia, especially in patients with advanced diabetes or prior CVD.<sup>269–271</sup> Combined with such equivocal results in trials, rates of treatment and glycaemic control are low even in high-income countries.<sup>272</sup> Therefore, one may speculate that changes in glycaemic management have perhaps made only a modest impact on CVD mortality trends.

Given this rise in effective treatments, the MONICA Project provided an opportunity for examining the contributions of both risk factors and treatment in the same study. The role of medical care was initially presented only as changes in short-term case-fatality which measures only the role of acute care.<sup>187</sup> Subsequently, MONICA data were analysed to also examine how much changes in measured medical care and treatment, including acute and sub-acute coronary event management and secondary prevention in people with a history of IHD, had affected changes in coronary-event rates and case-fatality, and in IHD mortality (even then the contributions of changes in risk factors and medical care were reported in

separate papers, possibly to avoid over-fitting, with relatively few participating centres ( $n$ ) and a large number of explanatory variables ( $p$ ), a problem that is more tractable today than it was in the 1990s owing to methodological advances related to the analysis of 'omic data in which so-called ' $p > n$ ' problems are common).<sup>273,274</sup>

The MONICA investigators analysed the coverage of a variety of treatments that could prevent acute events and improve both short- and long-term survival (antiplatelet therapy, antihypertensive medications, and acute coronary reperfusion procedures) separately, and also aggregated them into an overall score measuring treatment intensity/quality. They then correlated changes in these measures to changes in study outcomes.<sup>273</sup> As perhaps expected, improvements in treatment intensity were strongly associated with lower case-fatality, with treatment change accounting for 51% of variation in case-fatality change across MONICA sites. Geographically, treatment improved more in Western Europe, North America, Australia, and New Zealand than MONICA centres from in Eastern Europe and China, with the improvements in the best-performing countries associated with about 25% larger decline in case-fatality than those in those with the smallest improvement – little has been done on the reasons for this variation in the uptake of effective treatment, which is seen even among high-income countries.

More surprisingly, they also found strong associations between change in treatment intensity and change in event rates, with treatment change explaining 41% of change in coronary event rates and 64% of change in overall IHD mortality rate – both larger than the corresponding numbers for the proportion explained by changes in risk factors (although as noted above the investigators made no formal comparison between the contributions of risk factors and treatment towards lower event and death rates).<sup>273</sup>

The apparent difference in contributions of treatment vs. prevention to decline in event rates in MONICA could have been affected by better measurement of treatment coverage than risk factors and by differences in how fast they act (immediate for treatment and more gradual for risk factor changes), biasing the estimated effect of the latter towards zero. However, while the correlation between treatment intensity and CVD trends in the MONICA Project could be confounded by other, as yet unmeasured, factors, the expansion of evidence-based acute care and secondary prevention measures over this period provide a fairly convincing mechanistic and temporal explanation for an important part of the decline.<sup>274</sup>

Further support for the important contribution of treatment to declines in mortality from CVDs, especially from IHD, came from the above-mentioned community studies in the US (and before that from the above-mentioned detailed study among Du Pont employees by Pell). All of these studies found declines in IHD deaths and in case-fatality of hospitalized patients, alongside striking increases in treatment intensity, between the 1980s and 1990s; in those studies that had measured both hospitalisation and out-of-hospital deaths, the share of events that were admitted to hospitals increased.<sup>194–198,275,276</sup> The Minnesota Heart Survey, which also collected data on risk factors in the same community, found significant but modest declines in cholesterol (by 3–5 mg/dl), smoking (2–3%), and blood pressure (1 mm

Hg) between 1985–87 and 1990–92. In light of these findings, the authors generally attributed the decline in mortality largely to improvements in treatment.<sup>196</sup>

The interpretation of results from some of these studies was complicated by evolving diagnosis of MI over the study period, with use of troponin-based assays increasing from 8% to 98% between 1996 and 2001 in the ARIC Study. This change led to higher estimated incidence over time and a changing composition of hospital-based cases (towards those with more minor infarctions).<sup>277–279</sup> Adjusting for changes in diagnosis reversed the estimated incidence trends (from increasing to declining), and led to lower, but nonetheless significant, estimates of the contribution of treatment.<sup>274,280</sup> At the same time, better diagnosis (and hence treatment) of milder cases who would have been missed without sensitive tests should count towards the contributions of advances in medical care towards lower CVD mortality because the milder cases, once detected and treated, have an improved prognosis.<sup>281,282</sup>

## Infectious diseases and CVD trends

Going back a century or more, prior to countries passing through the epidemiologic transition, the global profile of cardiovascular disease mortality would likely have been dominated by conditions associated with infection including rheumatic heart disease (RHD), infective endocarditis, and cardiomyopathies.<sup>283</sup> Today, although IHD and stroke are the two largest CVD causes of death globally, RHD, cardiomyopathy, myocarditis, and endocarditis account for an estimated 800,000 deaths worldwide.<sup>1</sup> Infection-related CVDs remain major contributors to CVDs in many developing countries, especially in children and young adults.<sup>1,284,285</sup> Trends in RHD, and its underlying risk factor of rheumatic fever, over the past 150 years have been characterized by four important features.<sup>286,287</sup> First, the incidence of rheumatic fever began to decline before the introduction of antibiotics in industrialized countries,<sup>288</sup> and virtually disappeared by the 1970s or 1980s.<sup>16,289–291</sup> The reasons for this early fall are unknown but are likely to be general improvements in living and housing conditions, and in nutrition and general healthcare. The decline in RHD was a likely contributor to the above-mentioned decline in total CVD mortality, even as IHD death rates were increasing. Despite the overall downward trend in high-income nations, RHD remains an important public health problem in the aboriginal communities of Australia, Canada and New Zealand.<sup>292,293</sup> Second, there was a post-antibiotic fall in rheumatic fever in countries such as Costa Rica, Cuba, Guadeloupe, and Martinique which implemented comprehensive programmes for the prevention of rheumatic fever, through both social and environmental interventions and the use of antibiotics. Third, unlike this latter group, the incidence of rheumatic fever remains high in sub-Saharan Africa and South Asia, where there are no national programmes for the prevention and treatment.<sup>294</sup> Finally, there has been a resurgence of rheumatic fever in the former Soviet Republics in Central Asia following the collapse of the Soviet Union. Kyrgyzstan, Tajikistan, Turkmenistan, Kazakhstan, and Uzbekistan have some of the highest rates of RHD in the world.<sup>295,296</sup> Less is known on trends in cardiomyopathies, which are endemic in tropical countries.<sup>297–299</sup>

More broadly, populations exposed to a chronic burden of infections, with associated profiles of inflammation, may also be at a resultant increased risk for IHD, especially in the presence of other behavioural and environmental risk factors.<sup>300</sup> It is therefore reasonable to

hypothesise that lower incidence of infections, and more treatment, may also have been partly responsible for decreasing IHD mortality as countries develop. Although there are no data on trends in inflammatory markers to evaluate this possibility, the increasing use of antibiotics and the resultant decline in the burden of infections in many countries from the late 1940s onwards, came just before the rising trends of 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 in countries and communities affected by it. Untreated HIV infection is associated not only with an overall shortening in life expectancy but also with weight loss and a fall in systolic blood pressure.<sup>301</sup> By contrast, in infected individuals there is higher incidence of inflammatory cardiovascular disorders, resulting in cardiomyopathy, tuberculous pericarditis, pulmonary hypertension, stroke, and vasculopathy. The use of some antiretroviral treatments is associated with an increase in insulin resistance, dyslipidaemia, and lipodystrophy. 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.<sup>302,303</sup>

## Conclusions

As we have reviewed, since the middle of the 20<sup>th</sup> century, there has been attention to trends in CVD deaths, and a desire to understand its drivers. We found that with the exception of the well-designed and carefully executed MONICA Project and a few other within- or cross-country studies, most analyses of the role of risk factors or treatment in CVD mortality trends relied on qualitative observations or basic quantitative tests of whether the two variables changed together, with limited attention to other explanations for the decline.

This seemingly critical assessment is however at least partly an outcome of both the changing epidemiological and clinical knowledge on CVD causes and treatments and of the changing nature of CVDs themselves. All of 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: partially correlated trends in some risk factors and opposite trends in others; changes in demography of people with CVD events with average age increasing and changes in sex composition of CVD events and deaths (issues that MONICA was less able to capture given that it did not assess people over 65 years old and that fewer of the events were in women than in men); and dramatic changes in how AMI was defined, diagnosed, and treated with increased awareness on the part of physicians and the general public about symptoms and the importance of early in-hospital treatment, increasingly sensitive biomarkers capable of detecting minor events that would not be captured by symptoms alone or the electrocardiogram, and uptake of more effective treatments both at the hospital and among survivors. As a result of the multiplicity of other changes, measured and unmeasured, over this period, and the paucity of high-quality longitudinal population-based data (many of which had been proposed at the Bethesda Conference but were not pursued), the answer to the question of what set into motion the decline in mortality, and the relative roles of treatment and prevention, is likely to remain largely correlational and somewhat speculative, rather than causal. Despite these limitations,

the vast body of research on CVD mortality trends also allows some conclusions with some confidence:

First, in high-income countries and in some middle-high-income countries in Latin America, once the CVD mortality decline began, it never stopped or even slowed down, a situation that was hard to envision in the 1970s and 1980s. Even today, there is little indication that the relative rate of decline in CVD mortality in high income countries is reducing; if anything, it is increasing proportionally in many countries. If current downwards trends continue, IHD and stroke will become uncommon causes of death under 70 years of age in high-income countries. Recent data and modelled mortality trends by WHO and others seem to indicate that currently middle-income and upper-middle-income countries have begun similar trends. This decline in turn will lead to an increase in longevity and life expectancy, because CVDs are a major cause of mortality worldwide.<sup>213</sup>

Second, trends since the 1970s have almost certainly benefited from a mixture of continued declines in key behavioural risk factors such as smoking; in physiological risk factors such as blood pressure and serum cholesterol, part of which is likely to be due to changes in diet (e.g., lower intake of salt and saturated fats, and year-around availability of fruits and vegetables), and due to widespread use of effective pharmacological treatments for hypertension and dyslipidaemia; and in improvements in acute care including time before reaching hospital, better diagnosis, and acute care. Blood pressure seems to have been declining for an even longer time in high-income countries, a phenomenon whose drivers are not known but which may have been responsible for the much earlier start of the decline in stroke mortality compared to IHD. While the contributions of both risk factors and treatments to the decline in CVDs is likely real, none of the measured drivers explains the similarities and differences across countries or between men and women in *when the decline began*.<sup>184</sup> This leaves room for hypotheses related to other phenomena – related to subtle changes in diet or health systems, to reductions in infections and resulting inflammatory response, and to improved fetal and childhood nutrition and health – as possible determinants of the decline.

Third, the nearly universal increase in adiposity does not seem so far to have attenuated the long-term declining trend of CVD mortality in high income countries since the 1960s. It may be that the rate of decline in these countries might have been even steeper if the obesity epidemic had not occurred, but to date the correlation and the magnitude of such an effect seems modest (see Figure 8).<sup>168,189</sup> This contrast with the relatively important effect of obesity in individual-level epidemiological studies may have been partly due to more aggressive management of physiological risks that mediate the effects of adiposity among overweight and obese people,<sup>190</sup> leading to a “decoupling” of BMI from blood pressure and lipids (but not diabetes) both across populations and in individuals.<sup>175,191</sup> Nevertheless in low-income countries, where maternal and child under-nutrition are still widespread and where the thinly stretched healthcare system may be unable to screen and treat physiological risk factors,<sup>304</sup> rising rates of obesity might result in increased population risk of CVDs beyond the relatively modest impacts in high-income countries; reliable mortality trend data to better envision this possibility are however not available.

Finally, whatever the explanations for a century of rise and fall in CVD mortality in the high-income world, former communist countries in Central and Eastern Europe, defy their universal generalisation. The extraordinary patterns of change in these countries appear to be closely synchronised with massive political and social changes following the collapse of communism starting in the early 1990s. Although an important role for hazardous alcohol drinking has been identified, especially in Russia, there remains an uncertainty about the precise mechanisms involved.

Going forward, it is reasonable to advocate more systematic population-based data to better understand 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 may help further accelerate the decline in high-income countries and extend it to other regions where they remain the leading cause of mortality (and, paradoxically, their absolute mortality and morbidity burden is set to rise due to population aging). The availability of electronic population-based data on hospitalisation and mortality, and the ability to link across them, as well as regular health and nutrition surveys mean that such data can be obtained with relatively modest additional investments to bring together existing data sources and complement them with additional ones. These data have national coverage, and also allow time trends and subnational variations and inequalities to be studied.<sup>5,8,305</sup> Such data exist in most high-income and some middle-income countries but their use requires overcoming the increasing bureaucratic and legal obstacles to using and linking across administrative data on health risks and outcomes. In lower income countries in Africa and Asia, the first step may be to assess trends in CVD mortality and subsequently incidence without the current overreliance on models. This in turn requires strengthening vital registration and disease and risk factor surveillance systems in these settings.

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

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Key points

Death rates from ischaemic heart disease (IHD), stroke and other cardiovascular diseases (CVDs) have declined for decades in high-income countries and in many countries in Latin America. There is no indication that the decline is slowing.

These trends have likely benefited from declines in some key behavioural risk factors including smoking and physiological risk factors such as blood pressure and serum cholesterol.

The nearly universal increase in adiposity does not so far seem to have modified the long-term declining trend of CVD mortality in high income countries. However, the rate of decline might have been slightly steeper if the obesity epidemic had not occurred.

Improvements in medical care, including effective treatment of physiological risk factors, better diagnosis and treatment of acute CVDs, and post-hospital care of those with prior CVDs, have also contributed to declining CVD event and death rates.

Measured risk factor and treatment variables, while important, neither explain why the decline began when it did, nor much of the similarities and differences in the start time and rate of the decline across countries or between men and women.

Trends in CVDs in the former communist countries of Europe and the Soviet Union, whether declining or increasing, appear to be closely synchronised with massive political and social changes following the collapse of communism in the early 1990s, with hazardous alcohol use as an important behavioural mediator.

### **Panel 1: The Bethesda Conference on the Decline in Coronary Heart Disease Mortality**

The Bethesda Conference on the Decline in Coronary Heart Disease Mortality was organised by the National Heart, Lung, and Blood Institute (NHLBI) and held in October 1978, a decade after the decline in IHD had begun. The meeting aimed “(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.”<sup>24</sup> The meeting systematically considered a large number of potential explanations from artefact, to the classic risk factors of smoking, cholesterol, and blood pressure, to new risk factors such as ambient air pollution and physical activity,<sup>306,307</sup> to pre-hospital and in-hospital treatment and survival. The papers and discussion from the Bethesda Conference were exhaustive and comprehensive, involving some of the best epidemiologists, statisticians, and clinical scientists of the day. However, their conclusion 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”.<sup>24</sup>

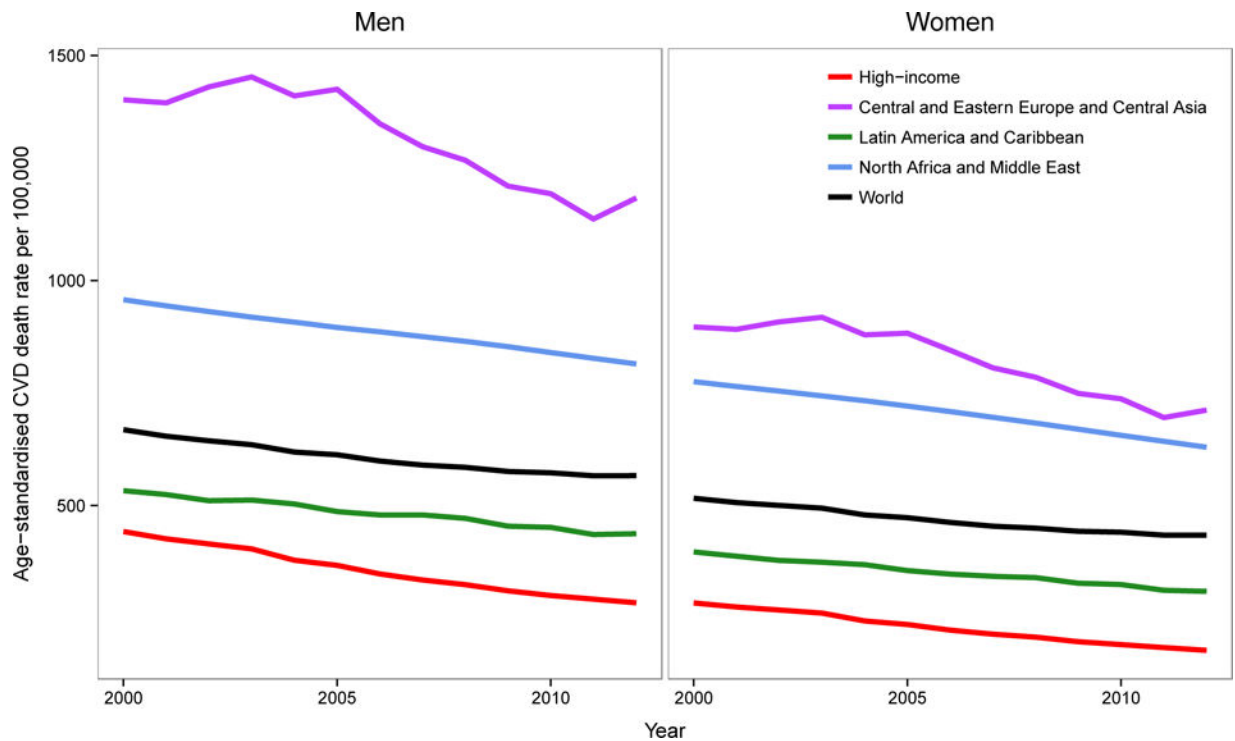
Three key areas for research were identified: (1) improve data collection systems on morbidity and mortality for IHD; (2) evaluate contributions, and future potential, of preventive and therapeutic “patient management”; and (3) continue to undertake basic clinical and non-clinical research into pathogenesis, risk factors, and clinical management of IHD.<sup>24</sup> The Bethesda Conference was an important catalyst for the initiation of the MONICA Project and a number of US community-based studies discussed later in this review. Nonetheless, population-based data on outcomes and on risk factor and treatment determinants remained weaker than recommended at the Conference.

### Panel 2: The MONICA Project

Partly motivated by the discussions and recommendations of the Bethesda Conference, the World Health Organization (WHO) coordinated the initiation of the MONICA (Multinational MONItoring of trends and determinants in CARDiovascular disease) Project in 1979.<sup>36,308</sup> The MONICA Project aimed to assess prospectively the influence of changes in major CVD risk factors including serum cholesterol, blood pressure, cigarette smoking, and later on body-mass index, plus in 28-day case-fatality, on change in IHD mortality. Change in treatment was subsequently analysed as one of the variables 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.<sup>36,308</sup> Data for the main study were collected between mid-1980s and mid-1990s although many MONICA centres have continued to collect data and monitor trends. The focus was on premature mortality, at that time defined as death before 65 years of age. The key defining feature of the MONICA protocol was the use of identical or very similar protocols in all centres including standardised case definitions for incident IHD. The criteria remained in use for population-based surveillance years after the study ended.<sup>309</sup>

### **Panel 3: Analysing and reporting trends in cardiovascular disease (CVD) mortality**

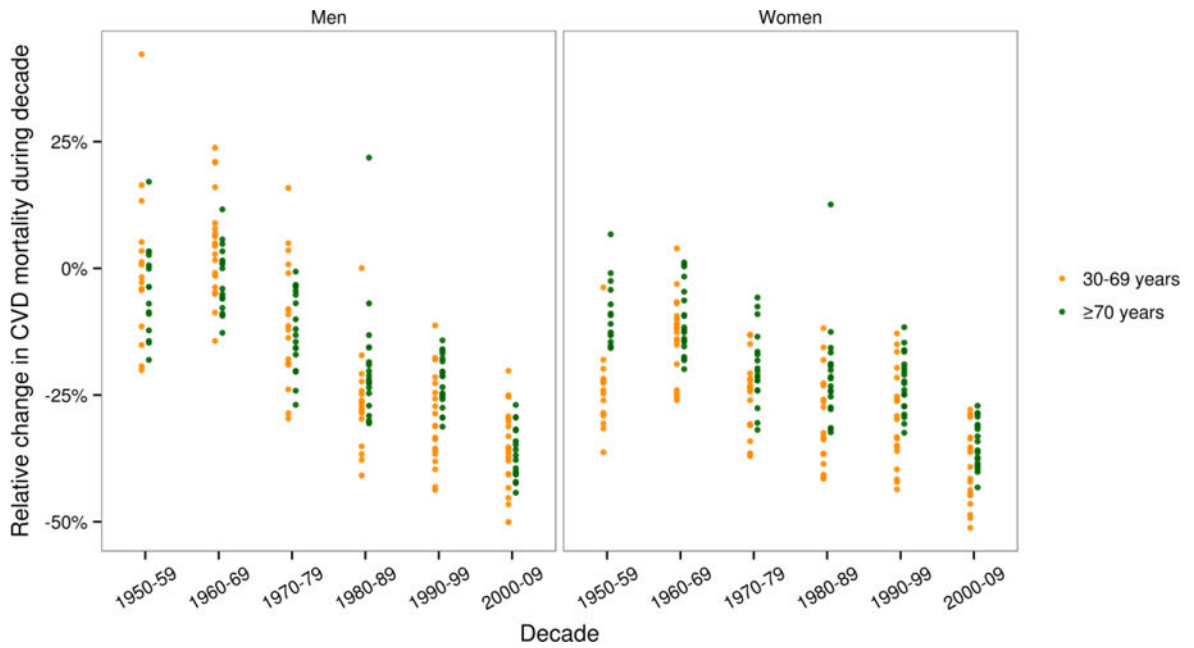
The early works on CVD trends, like those of Moriyama and colleagues,<sup>11,12</sup> pointed out and attempted to address a series challenge of analysing and reporting trends in cause-specific mortality at the population level that continue to persist today.<sup>26,213,310,311</sup> These issues include the differences over time in relation to the 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 certain areas, often urban centres or a subset of provinces, before incorporating other parts of the country. Whether immigrants and/or emigrants are covered differs across countries and changes over time. Limitations in the civil registration and statistical systems lead to incomplete death registration, with completeness changing over time. And combinations of changes in the International Classification of Disease (ICD) system, and clinical culture and training, lead to both inappropriate assignment of cause of death and inconsistently and incomparability in how this is done over space and time. The methods used for dealing with these issues, by the World Health Organization (WHO) and researchers, have become increasingly more complex and sophisticated over time.<sup>285,310,312,313</sup> Nonetheless, fundamentally they involve a combination of clinical and epidemiological judgements and assumptions plus analytical methods that formalise these judgements and assumptions. The trends in Figures 1–3 are based on data and work at the WHO, and are described in various WHO publications.<sup>213,310,314</sup> In brief, the countries shown in Figures 2 and 3 have complete or near-complete registration of deaths with medical certification of causes of death. WHO uses demographic methods to test and, if needed, adjust for completeness of death registration, and redistributes ill-defined and improbable causes of death (e.g., deaths assigned to senility and to signs and symptoms such as pain) based on patterns in countries with high-quality cause of death assignment.



**Figure 1.**

Trends in age-standardised death rates from cardiovascular diseases for adults aged 30 years and older, by region and sex between 2000 and 2012. Death rates are age-standardized to the WHO standard population. Source: World Health Organization (WHO) Global Health Estimates.<sup>1</sup>

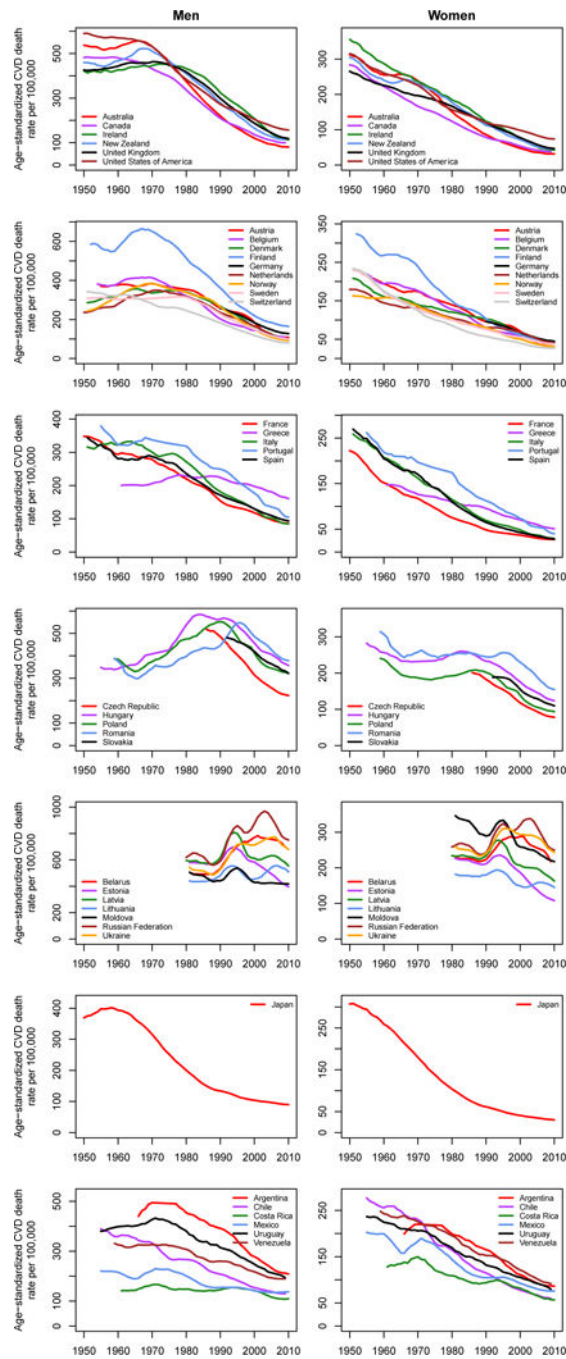
Note: WHO estimates mortality trends using on available data from vital statistics, from sample registration of deaths, and from representative verbal autopsy surveys.<sup>310</sup> These data are used together with demographic and epidemiological models, to reconstruct trends.<sup>310</sup> Trends are not shown for sub-Saharan Africa and for East, South, and Southeast Asia and the Pacific (with the exception of Japan, Singapore, and South Korea which are included in the high-income group) because mortality data from these regions are very limited, especially for estimating time trends. As described in the text, studies from selected countries and communities in these regions show a modest decline in total CVD mortality and in mortality from stroke and hypertensive disease.

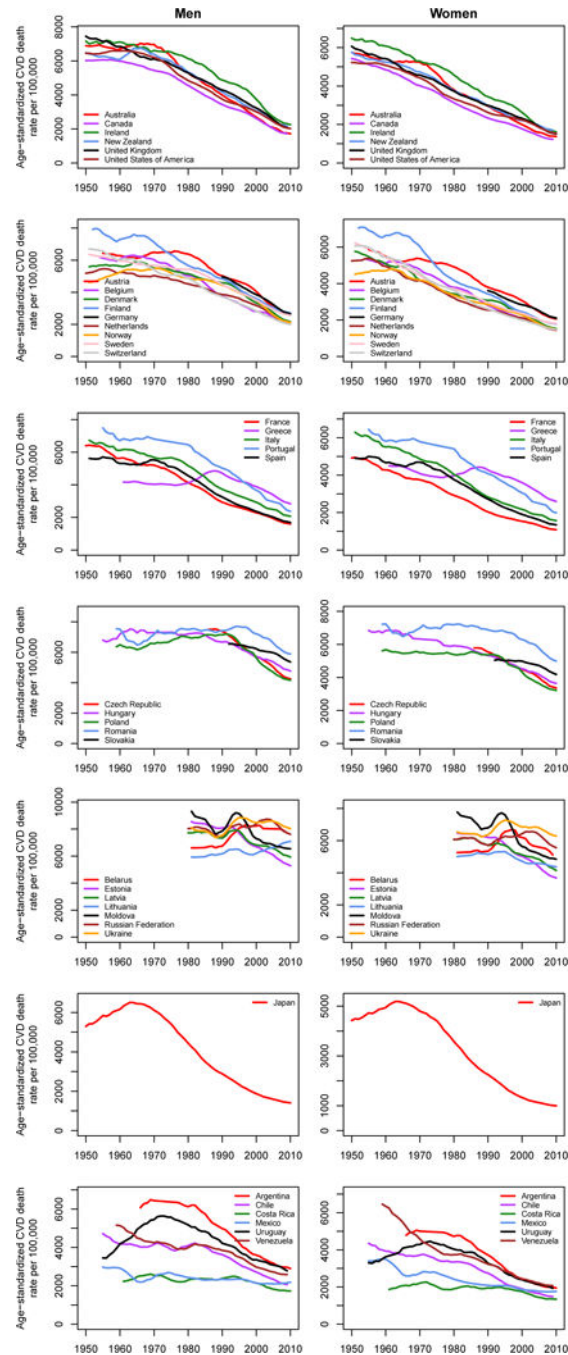


**Figure 2.**

Relative (per cent) decline in death rates from cardiovascular diseases by decade, sex, and age group in 20 western high-income countries. Within each age group, death rates were age-standardised using the WHO standard population. The countries are English-speaking high-income countries (Australia, Canada, Ireland, New Zealand, UK, and USA) and countries in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, and Switzerland). Germany was excluded because its boundaries changed during the period of display. We also have not shown data for smaller countries like Cyprus, Iceland, Luxemburg, and Malta.







**Figure 3.**

Trends in death rates from cardiovascular diseases for adults (A) aged 30–69 years and (B) 70 years and older. Within each age group, death rates are age-standardized to the WHO standard population. Trends are smoothed using a 5-year moving average. See Figure S1 for results for 30 years and older combined.

Countries in this figure were selected based on recent work by Mathers *et al.* on trends in life expectancy and cause-specific mortality in ageing populations.<sup>213</sup> Of the countries analysed by Mathers *et al.*,<sup>213</sup> we have shown trends for Japan, English-speaking high-income

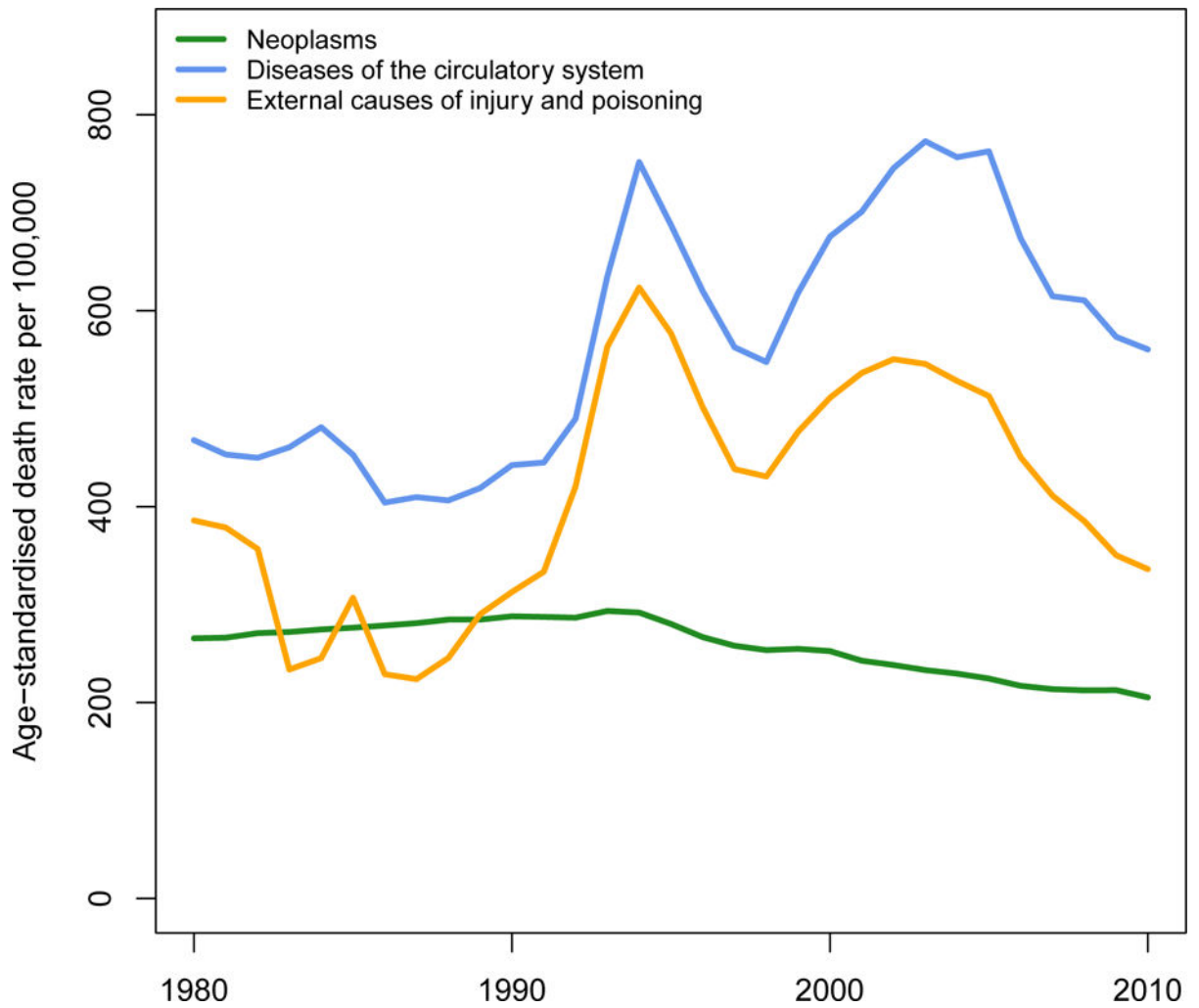
countries, and countries in Western Europe (excluding the above-mentioned smaller countries and Germany), in Central and Eastern Europe, and in Latin America.

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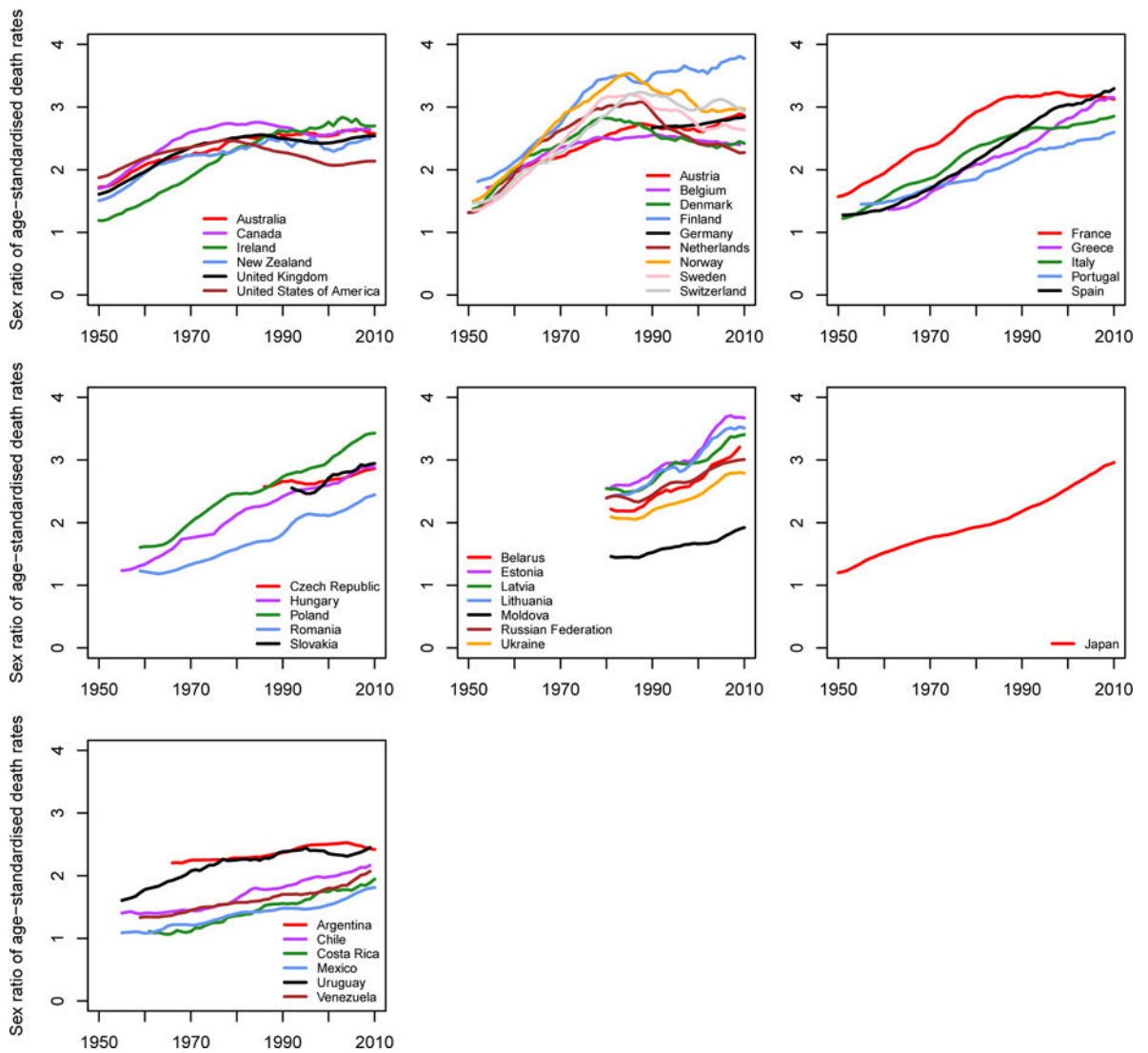
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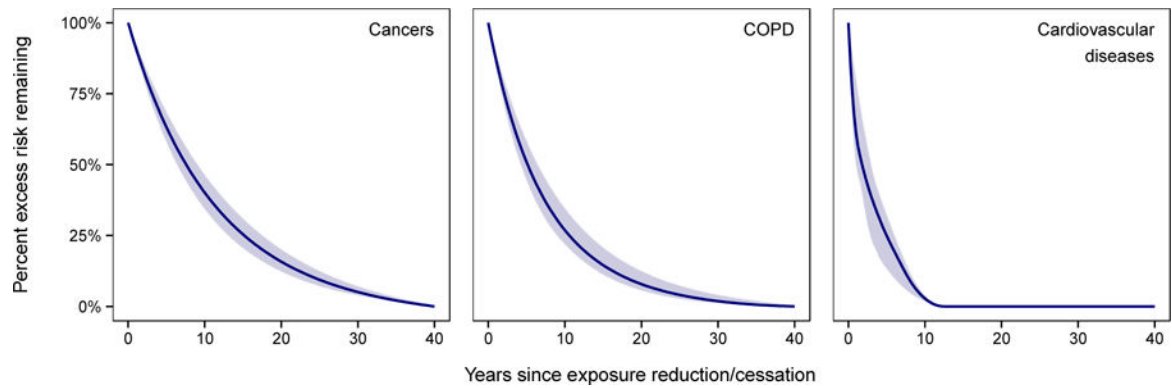
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**Figure 4.** Trends in death rates from cardiovascular diseases, compared with external causes and cancers, in adults aged 25–64 years of age in Russia.



**Figure 5.** Trends in male-to-female ratio of cardiovascular disease death rates for people aged 30–69 years in selected countries with reliable mortality data. Within this age group, death rates are age-standardized to the WHO standard population. Trends are smoothed using a 5-year moving average.

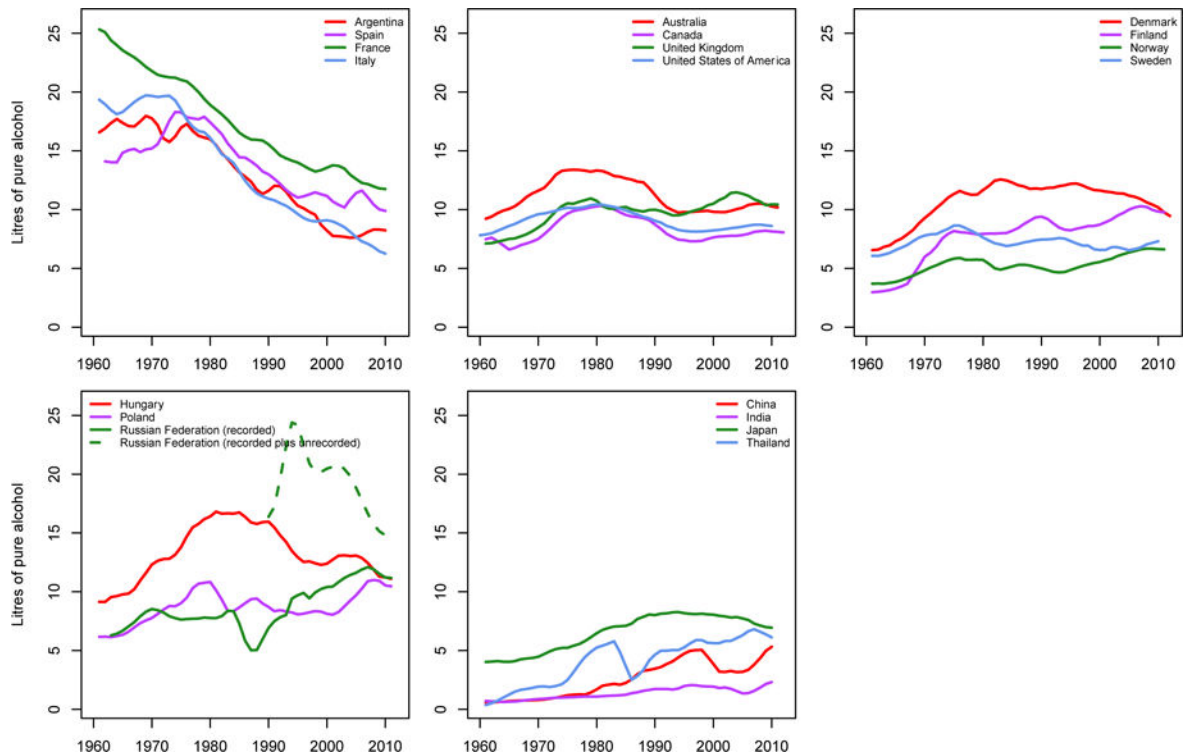


**Figure 6.**

Proportion (percentage) of excess relative risk (relative risk minus one) of cardiovascular diseases remaining over time since smoking cessation, compared to cancers and chronic obstructive pulmonary disease (COPD). The shaded area shows the uncertainty of the fitted curve. Source: Kontis et al.<sup>3</sup>

In summary, data on changes in disease-specific mortality RRs after cessation were from a re-analysis of American Cancer Society Cancer Prevention Study II (CPS-II) data.<sup>64</sup> A convex constrained b-spline (fitted using the library “cobs” in statistical software R) was fitted to the raw RR data (which can be seen in Figure 2 of Oza and colleagues<sup>64</sup>) to obtain a smooth continuous relationship of RR over time since smoking cessation. The proportion

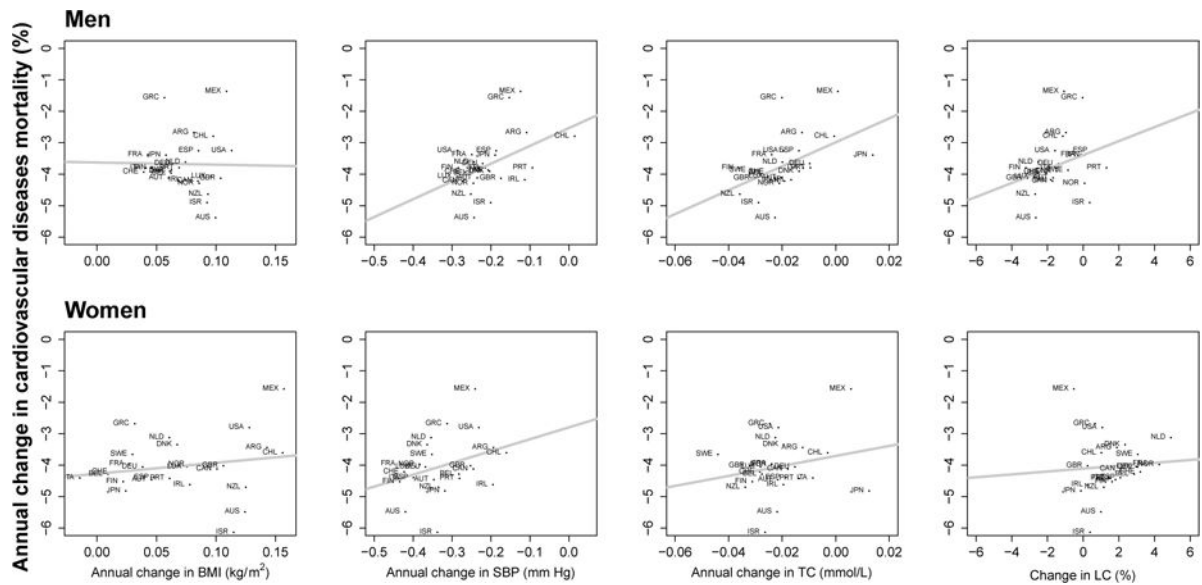
(percentage) of excess relative risk over time since cessation as  $\frac{RR_t - 1}{RR_0 - 1}$ , where  $RR_t$  is the RR  $t$  years after quitting smoking and  $RR_0$  is the RR of smokers.



**Figure 7.**

Trends in recorded per-capita alcohol consumption by adults aged 15 years and older in selected countries. Data were smoothed using a 3-year moving average. Data on recorded consumption are from the WHO Global Information System on Alcohol and Health (<http://apps.who.int/gho/data/node.main.GISAH>).

Note: In addition to recorded consumption, there is unrecorded consumption in some countries. For example, adult per capita unrecorded consumption is estimated to be less than 0.5 litres per year in Japan and France, and 1 to 2 litres per year in China, Sweden, the United Kingdom, and the United States.<sup>102</sup> The unexpected drop followed by rise in Chinese trends may be due to change in the source of data on alcohol consumption from industry reports to government reports around 2000.



**Figure 8.**

The cross-country associations between change in risk factors and change in cardiovascular death rates between 1980 and 2008 in 26 industrialised countries. Each point shows one country. All variables were age-standardized. The lines show the fitted linear associations. Source: Di Cesare et al.<sup>168</sup>

Note: Lung cancer (LC) death rate was used to measure cumulative population exposure to smoking using because data on lung cancer mortality trends are more widely available and more reliable than on smoking prevalence and intensity.<sup>231,232</sup>

ARG: Argentina; AUS: Australia; AUT: Austria; BEL: Belgium; CAN: Canada; CHE: Switzerland; CHL: Chile; DEU: Germany; DNK: Denmark; ESP: Spain; FIN: Finland; FRA: France; GBR: United Kingdom; GRC: Greece; IRL: Ireland; ISR: Israel; ITA: Italy; JPN: Japan; LUX: Luxembourg; MEX: Mexico; NLD: Netherlands; NOR: Norway; NZL: New Zealand; PRT: Portugal; SWE: Sweden; USA: United States of America



**Table 1**

Characteristics of important cardiovascular risk factors which may be partly responsible for trends in CVD mortality.

<b>Risk factor</b>	<b>Type</b>	<b>Temporal responsiveness</b>
Smoking	Behavioural	Observational evidence that following cessation risk begins to fall immediately and reaches that of non-smokers within 5–10 years. <sup>3,64</sup>
Alcohol	Behavioural	Little good observational evidence, <sup>68</sup> with the exception of Russia and other former communist countries which suggests abrupt changes in CVD mortality. The changes might be due to sudden cardiac deaths misclassified to IHD.
Adiposity	Intermediate trait; mediators include blood pressure, lipids, inflammation, and glycaemia and diabetes	Limited evidence that weight management (accompanied by broader lifestyle change) reduces the risk of diabetes within a few years in people with impaired glucose tolerance, <sup>315</sup> but no good evidence on temporal responsiveness for CVDs. <sup>316</sup>
Blood pressure	Intermediate trait with direct effect	Evidence primarily from randomised trials that decline in blood pressure results in fall in IHD and stroke risk to start immediately.
Serum cholesterol	Intermediate trait with direct effect	Evidence from randomised trials that decline in serum cholesterol results in fall in IHD risk to start immediately with risk reversibility largely complete in 5 years. <sup>67</sup>
Glycaemia and diabetes	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 had short duration. <sup>266</sup>
Diet and nutrition	Behavioural; potential mediators include BMI, blood pressure, lipids, inflammation, and oxidation	Some evidence from randomised trials that changes in salt or the type of fats/oils can result in changes in mediators or CVD risk, with declines starting immediately. Less is known about how long before the full benefits are achieved because of the limited duration of the trials.