Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps

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Abstract

Information on exposure to, and health effects of, cardiovascular disease (CVD) risk factors is needed to develop effective strategies to prevent CVD events and deaths. Here, we provide an overview of the data and evidence on worldwide exposures to CVD risk factors and the associated health effects. Global comparative risk assessment (CRA) studies have estimated that hundreds of thousands or millions of CVD deaths are attributable to established CVD risk factors (high blood pressure and serum cholesterol, smoking, and high blood glucose), high body mass index (BMI), harmful alcohol use, some dietary and environmental exposures, and physical inactivity. The established risk factors plus BMI are collectively responsible for about 9.7 million annual CVD deaths, with high blood pressure accounting for more CVD deaths than any other risk factor. Age-standardized CVD death rates attributable to established risk factors plus high BMI are lowest in high-income countries, followed by Latin America and the Caribbean; they are highest in the region of central and eastern Europe and central Asia. However, estimates of the health effects of CVD risk factors are highly uncertain because there are insufficient population-based data on exposure to most CVD risk factors and because the magnitudes of their effects on CVDs in observational studies are likely to be biased. We identify directions for research and surveillance to better estimate the effects of CVD risk factors, and policy options for reducing CVD burden by modifying preventable risk factors.

Introduction

Ischemic heart disease (IHD), stroke, and other cardiovascular diseases (CVDs) are responsible for an estimated 17.5 million deaths worldwide per year, although the estimates of their burden vary across studies due to differences in data sources and methods.[1, 2] Further, as data and methods evolve, estimates are revised and refined, even for prior years.

In high-income Asian and western countries, where reliable historical data on mortality and cause of death are available, age-standardized CVD death rates have steadily decreased for decades, with no sign of slowing down.[3] Similar trends are happening in Latin America and some other middle-income countries with more recent reliable data.[3] As a result of these trends, age-standardized CVD death rates are now higher in low- and middle-income countries than in high-income nations.[4] Nonetheless, in high-income countries, population growth and ageing may increase the absolute burden of CVDs or lead to slower decline in their absolute burden than would be anticipated from the trends in age-standardized death rates.[5] There is, therefore, an imperative throughout the world to prevent CVD events and deaths by reducing exposure to their preventable risk factors.

As an important step towards reducing the worldwide burden of CVDs and other Non-Communicable Diseases (NCDs), the United Nations held a High-Level Meeting on the Prevention and Control of NCDs. Subsequently, countries agreed to reduce premature mortality from the four main NCDs (CVDs, chronic respiratory diseases, cancers, and diabetes) by 25% relative to its 2010 level by 2025 (known as the 25×25 target).[5] Countries also agreed on targets for selected NCD risk factors, all of which are associated with CVDs: tobacco use, harmful alcohol use, excessive salt intake, obesity, raised blood pressure, raised blood glucose and diabetes, and physical inactivity.[5] Therefore, there is unprecedented

interest in having better information on exposure to, and health effects of, CVD risk factors throughout the world.

To respond to this interest, researchers have attempted to quantify the worldwide effects of preventable risk factors on CVDs and other conditions for at least two decades. One of the first such studies estimated deaths from CVDs and other diseases due to smoking in so-called developed countries (Australia and New Zealand, Europe, Japan, and north America).[6] Around the same time, the Global Burden of Disease 1990 Study quantified the health effects of ten risk factors,[7] including some CVD risk factors like smoking and hypertension, although its results were not disaggregated by disease. The Comparative Risk Assessment (CRA) Study enhanced consistency and comparability in the methods used for analyzing various risks.[8] The results of the CRA study also formed the core material for the *World Health Report 2002: Reducing Risks, Promoting Healthy Life*. The CRA Study included 26 risk factors, about one third of which were associated with CVDs.[8, 9] The CRA Study showed that CVD risk factors such as elevated blood pressure and smoking were among leading causes of mortality and morbidity in the world, with a large share of their health burden borne by low- and middle-income countries.[8-10] The study also quantified the combined (joint) burden of multiple risk factors, accounting for the overlaps among their effects. The joint effect analysis showed that nearly 80% of deaths from IHD and nearly 70% of deaths from stroke in the world were attributable to a small number of physiological and behavioral risk factors including high blood pressure, high serum cholesterol, smoking, high body mass index (BMI), alcohol use, low intake of fruits and vegetables, and physical inactivity.[11]

A number of studies in the past decade have updated the CRA Study analyses or have extended the analysis to national and subnational levels.[12-18] The list of CVD risk factors in

these global and national analyses has expanded to more than sixty, and includes additional physiological (e.g., raised blood glucose), dietary, behavioral, and environmental risks.

Here, we use the global analyses of CVD risk factors to provide an overview of current data on their exposures and the associated health effects throughout the world (we do not cover temporal trends in CVD risk factors or their within-country social inequalities, because these topics have been addressed in other recent reviews).[3, 4, 19] With rapid expansion of clinical and epidemiological studies about the etiology and predictors of CVDs, there is an evolving list of putative CVD risk factors, with evidence of causality ranging from very strong to inconclusive and non-compelling.[20, 21] Therefore, we first present a simple framework that can guide the selection of risk factors for global or national analyses. We then present the current evidence on exposure to, and health effects of, different clusters of risk factors, including established risk factors (smoking, raised blood pressure, diabetes, and raised serum cholesterol) and excess weight and adiposity; alcohol use; diet; physical inactivity; environmental risks; and other putative (emerging) risk factors which are the subject of extensive research. Based on limitations and uncertainties in the current data, we suggest future directions for research and surveillance. We also discuss the implications of current knowledge for global CVD prevention.

A framework for selecting CVD risk factors for global analyses

A first step in quantifying the national and global effects of risk factors on CVDs is the selection of relevant risk factors. The inclusion of a factor implies that it is a cause of CVDs or a strong proxy marker for causal factors. To illustrate the types of factors that may be included, **Figure 1** provides a simple representation of CVD risk factors, both those that are more distant from clinical outcomes (e.g., the social environment) and those more proximate

to these outcomes (e.g., high blood pressure). The physiological factors, which mediate the effects of more distal ones, may be modified either through changes in their behavioral and environmental determinants or through medicines used for primary and secondary prevention. Other factors in **Figure 1** – which may be both genetic and non-genetic, e.g. prenatal and early life nutrition and environment – affect susceptibility and predisposition to CVDs. Prenatal and early life nutrition may affect current and future CVD burden, and be a also modifier of the CVD burden attributable to other exposures, but to date there has been little attempt to quantify its role at the population level.

Many of the factors depicted in Figure 1 have been associated with CVDs in observational studies. However, confounding and residual confounding could lead to apparent associations with CVDs that might not represent genuine causal effects or can bias the magnitudes of associations, a problem that is exacerbated by selective reporting and publication bias.[22-25] For this reason, we state throughout the paper when the associations between risk factors and CVDs in observational studies are also supported by randomized trials and/or Mendelian randomization studies. Mendelian randomization takes advantage of lifelong differences in risk factor levels due to genetic variants and is hence not confounded by lifestyle factors.[26-28] As a result, Mendelian randomization studies can shed light on the causality of associations and rule out confounding due to unmeasured factors or reverse causation. For example, Mendelian randomization analysis has helped confirm the role of height, a trait that is difficult to study in a randomized trial, as a CVD risk factor.[29] It has also helped rule out a causal role for C-reactive protein as a CVD risk factor.[30, 31] However, Mendelian randomization is affected by several other limitations including the assumption of a simple model of causality without genetic pleiotropy (i.e., when one gene influences disease risk

through multiple pathways). Further, it only provides indirect information on the magnitude of causal effects which is needed for robust quantification of the CVD burden of risk factors.

The diversity of risk factors for CVDs, and the fact that the effects of upstream factors are partially mediated through those more proximate to clinical outcomes, also means that the CVD burden attributable to individual factors cannot be added.[11] Rather, the combined CVD burden of multiple factors is often smaller than the sum of individual ones;[11, 32] its calculation requires quantitative information on their interactions,[33] and on the extent of mediation.[34] As described earlier, the original CRA Study calculated the individual and combined effects of high blood pressure, high serum cholesterol, smoking, high BMI, alcohol use, low intake of fruits and vegetables, and physical inactivity.[11] The results showed that nearly 80% of deaths from IHD and nearly 70% of deaths from stroke in the world were attributable to the combined effects of these risk factors whereas the sum of their individual effects were 226% for IHD and 165% for stroke. We present the combined effects of established risk factors and high BMI below, using more recent epidemiological evidence.[14, 34]

Established risk factors and adiposity

Causal effects of established risk factors

Smoking, raised blood pressure, raised serum cholesterol, and diabetes were established as risk factors in the development of CVDs by the Framingham Study and other early prospective studies in the USA and Europe (**Figure 2**).[35-39] These observational studies motivated randomized trials of primary and secondary CVD prevention by lowering blood pressure and lipids, starting in the late 1960s (**Figure 2**). Randomized trials confirmed the causal roles of both blood pressure and serum cholesterol as risk factors for IHD and stroke, although the association of serum cholesterol with stroke has been found to be weaker than

that of blood pressure.[40-43] After accounting for regression dilution bias due to imprecision of exposure measurement in observational data, effect sizes from prospective cohorts are consistent with those from trials for these two risk factors.[44, 45]

Although there is limited trial data for smoking, its association with CVDs in observational studies has been robust in repeated re-analyses and after adjustments for other factors.[46, 47] Further, it is now established that secondhand smoke is a risk factor for CVDs. Exposure to secondhand smoke is common in many parts of the world, and has been included in recent global analyses.[13]

The evidence on the CVD effects of diabetes and raised glucose has been more mixed. Despite strong associations between diabetes or high glucose levels and CVDs in observational studies, glucose lowering, especially through drug treatment, has not consistently resulted in the anticipated reductions in CVD events.[48] The inconsistency between observational and trial data may be because of a number of reasons.[49-51] First, most trials compared more vs. less intensive glucose lowering and did not have a true placebo group. Second, most diabetes treatment trials had short follow-up, and these conflicting results may indicate a trade-off between the benefits of long-term good glycemic control for CVD outcomes, and the risks of acute hypoglycemia, especially in patients with advanced diabetes or prior CVD history. Third, glucose lowering treatments tested in trials might have been partially ineffective or they may have resulted in unexpected, and harmful, pleiotropic effects on other CVD risk factors. Finally, diabetes may affect CVD risk through deleterious disease pathways other than high glucose levels that are not targeted by current glucose lowering medications. Nonetheless, the inconsistency between observational and clinical trial

evidence suggests that the magnitude of the association between high glucose and CVD is less reliable than those of blood pressure and lipids.

Causal effects of adiposity

Studies on adiposity as a risk factor for CVDs began in the 1950s.[52, 53] Different studies have used different measures of adiposity including relative weight, skinfold, BMI, and more recently waist circumference and waist-to-hip ratio.[54, 55] A systematic review of epidemiological studies that had used BMI as well as waist circumference and/or waist-to-hip ratio found that taken together, these studies do not show that any of the measures of adiposity had "superior discriminatory capability" in terms of risk of adverse cardiometabolic outcomes; any observed difference was "too small to be of any clinical relevance".[56] Therefore, we focus on BMI in this review because there are substantially more population-based data on BMI than other measures of adiposity in different countries.[57, 58]

There is consistent evidence from observational studies that high BMI is associated with increased risk of CVDs, but the limited trial evidence to date has been primarily negative.[59] Weight management and weight loss, sometimes together with other dietary and lifestyle changes, have resulted in lower levels of blood pressure and lipids, and delayed incidence of diabetes, which are all established CVD risk factors.[59-62] Also, observational data have shown that bariatric surgery is associated with favorable cardiovascular risk factor changes and lower incidence of cardiovascular events.[63, 64] Further, Mendelian randomization studies support a causal link of high BMI with CVD risk.[65-67] Nonetheless, like elevated glucose, the effect sizes used for global analyses are based on weaker evidence than those for raised blood pressure, serum cholesterol, and smoking.

Global epidemiology of established risk factors and BMI

After the initial cohort studies, multi-country studies examined established CVD risk factors and high BMI in more diverse populations – e.g., the Seven Countries Study, and more recently the case-control Interheart and Interstroke studies and the Prospective Urban Rural Epidemiology (PURE) cohort study. Further, the MONICA Project investigated whether *changes* in these risk factors are associated with changes in IHD incidence and mortality at the population level.[3, 68, 69]

Prospective cohorts were established in East Asia soon after those in western countries. In other regions, such as Africa, CVD risk factors were first studied in cross-sectional studies,[70] while prospective cohorts largely began in the 1970s.[71] There is now an abundance of prospective cohorts studying CVD risk factors in most regions, although many of these cohorts are small.

More recently, researchers have pooled cohorts and trials in western and Asian populations.[34, 40, 72, 73] There are no cohort pooling studies in Latin America and Africa. The large sample sizes in these pooling studies has allowed quantifying the associations of established risk factors with CVDs not only by age group and sex, but also by ethnicity and/or region. The regional cohort pooling studies have shown that the relative risks for the effects of established risk factors on CVDs are similar between Asian and western populations (**Table 1**).[34, 40, 74] For smoking, variations in duration and intensity across the world lead to different magnitudes of association with CVDs. For this reason, analyses of CVDs attributable to smoking have had to find proxies that account for factors like smoking duration and intensity.[6, 10, 75]

Global and regional exposures

How established CVD risk factors and high BMI vary across countries is complex and their levels are only partly associated with countries' income and urbanization.[76] BMI levels are highest in middle-income countries including in the Pacific island nations, Middle East and north Africa, parts of Latin America and Caribbean, and, for women, southern Africa (**Figure 3**); BMI is still relatively low in central and east Africa, and south Asia.[57, 58, 80] Regional mean BMIs in 2014 for men ranged from 21·4 kg/m² in central Africa and south Asia to 29·2 kg/m² (95% credible interval 28·6–29·8) in Polynesia and Micronesia; for women the range was from 21·8 kg/m² (21·4–22·3) in south Asia to 32·2 kg/m² (31·5–32·8) in Polynesia and Micronesia.[81] Among high-income countries, BMI is higher in native English-speaking countries than those in Asia and continental Europe. Diabetes prevalence is also highest in most of the same regions with high mean BMI.[79, 82] For example, age-standardized diabetes prevalence in 2014 was higher than 20% in adult men and women in Polynesia and Micronesia, and around 15% in Melanesia and in the Middle East and north Africa.[79] Diabetes prevalence is higher than expected based on BMI in south Asia, and lower than expected based on BMI in northwestern Europe.[79, 82]

Blood pressure is currently highest in sub-Saharan Africa, central and eastern Europe, and central Asia; it is generally lower in high income countries where it has been declining for decades.[78] Total cholesterol is the only risk factor which follows a clear western risk model; it is high (although decreasing) in Europe, Australasia, and north America, and it is rising (from low levels) in east Asian countries such as Japan, China, and Thailand.[77] Smoking, whose prevalence depends on both social norms and tobacco control policies, is highest among men in many parts of Asia and central and eastern Europe.[83, 84] Among women, it is higher in

Europe than in other regions, with male and female smoking prevalences having become virtually the same in some European countries.

Global and regional CVD effects

The established risk factors and high BMI are collectively responsible for an estimated 9.7 million annual CVD deaths in the world, after accounting for multi-causality and for mediation of the effects of high BMI by blood pressure, total cholesterol, and glucose (**Figure 4**).[14, 34] 3.9 million of these deaths are between 30 and 70 years of age, and hence are considered premature, and the remaining above 70 years of age. The majority of the risk-factor-attributable CVD deaths result from elevated blood pressure, followed by smoking for men and by high BMI for women who, as noted above, smoke less than men in most regions. The largest number of deaths attributable to the established risk factors and high BMI, especially those attributable to high blood pressure, occurred in east Asia followed by the region of central and eastern Europe and central Asia. In high-income countries, 24% of deaths attributable to these five risks occur below 70 years of age, and the other 76% in people aged 70 years and older. The shares are 43% and 57%, respectively, in low- and middle-income countries. A higher proportion of deaths attributable to established risk factors are premature in low- and middle-income countries than in high-income countries for two reasons. First, a larger share of the population is younger than 70 years of age in the former group (96%) than in the latter (89%). Second, high-income countries have been successful in shifting CVD and high BMI to older ages, compared to low- and middle-income countries (a similar shift has been recorded for morbidity, a phenomenon known as compression of morbidity).[85]

Age-standardized CVD death rates attributable to the established risk factors plus high BMI were lowest in high-income countries, followed by Latin America and the Caribbean; they were highest in central and eastern Europe and central Asia, about four times that of high-income countries (**Figure 5**). The CVD death rates attributable to established risk factors and high BMI are lowest in high-income countries because they experience the lowest levels of CVD mortality in the world,[3, 4] and the levels of most CVD risk factors are low compared with low- and middle-income countries.[14] In contrast, CVD death rates in central and eastern Europe and central Asia are highest in the world, and the levels of established risk factors and high BMI are also high in these regions, together leading to a large absolute CVD burden attributable to risk factor exposures.

Alcohol use

Causal effects of alcohol use

Many observational studies have reported that compared with non-drinkers, light to moderate drinking is associated with a reduced risk of some CVDs and diabetes, although some debate remains about whether light or moderate drinking is truly cardioprotective.[86-89] Mendelian randomization, using genetic variants involved in alcohol metabolism as proxies for lifelong differences in alcohol consumption, also supports a causal association between all levels of alcohol intake and IHD and stroke.[90] Heavy drinking, especially when done in binge drinking episodes, is associated with increased risk of IHD, stroke and atrial fibrillation.[87, 89, 91-93]

Global and regional exposures and CVD effects

Per-capita alcohol consumption among adults ranges from close to zero in Pakistan and some countries in the Middle East and north Africa to > 15 liters of pure alcohol per adult per year in Belarus, Moldova, and Russia, largely from spirits.[94] The prevalence of heavy episodic

drinking is > 30% among men and women combined (and ~50% among men) in some parts of Europe; it is >20% in some countries in sub-Saharan Africa and in Latin America and Caribbean.[94]

Due to variations in both amount of alcohol consumed and patterns of consumption, the burden of alcohol use varies a great deal around the world; among different medical causes of death, the variation is largest for CVDs (as well as injuries).[13, 94] In particular, the rise in harmful alcohol use in Russia and some other former soviet republics due to extensive post-soviet social and political changes has led to a massive burden of CVDs attributable to alcohol in eastern Europe. Of the nearly 1 million CVD deaths attributable to alcohol use in the world, one half occur in central and eastern Europe and central Asia.[13] The CVD burden of alcohol use in this region arises from the combination of having the world's highest level of per-capita consumption and high prevalence of heavy episodic drinking.[94]

Diet

Causal effects of dietary risks

The number of dietary factors included in global risk factor analyses in relation to CVD outcomes has increased from one (inadequate intake of fruits and vegetables) in the original CRA Study in 2000, to 11 in recent analyses (diet low in fruits, vegetables, wholegrains, nuts and seeds, fiber, and polyunsaturated and omega 3 fatty acids from seafood; diet high in processed meat, trans fats, and salt) (three other dietary factors included in recent CRA analyses, namely diets low in milk and calcium and high in red meat, were associated with cancers but not CVDs).[9, 13] This increase in the number is partly driven by the increasing number of epidemiological studies on associations between various food groups, nutrients, and dietary patterns and CVDs.[95] Most of the food groups in recent CRA analyses have good

observational evidence in relation to increased risk of CVD, including low intakes of vegetables and fruits,[96, 97] nuts and seeds,[98] whole grains,[99] fiber, and fish;[100] and high intakes of processed meat,[101] trans fats,[102] sugar-sweetened beverages and other highly processed carbohydrates,[95], and salt.[103] However, these diet-CVD associations tend to be affected by multiplicity of comparisons, high correlation among various components of diet, systematic and random measurement errors, and often selective reporting. The limitations impede robust elucidation of the presence and magnitudes of causal associations, perhaps even more so than those of BMI and blood glucose.[23, 104]

Randomization is increasingly used to assess the effects of dietary factors on clinical CVD outcomes. Yet, owing to the difficulties of dietary trials, even some large trials, such as the Lyon Diet Heart Study and the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet,[105, 106] are affected by poor compliance and poorly defined comparator diets, early termination, and low event rates. These limitations could lead to imprecise and possibly biased effect estimates, and hence undermine robust quantification of the CVD burden of these factors. Nonetheless, the distinction between true causal and confounded associations is being sought out in an increasing number of well-designed randomized trials. For example, a number of well-designed trials have demonstrated the CVD benefits of replacing saturated fats with unsaturated fats.[107, 108] In contrast, for fish oil, trials have collectively found null effects[109]. For salt intake, there is evidence from trials for adverse effects on blood pressure, i.e. higher salt intake is associated with higher blood pressure.[110] The blood pressure benefits of lower salt intake continue to levels that are below the currently recommended amounts.[111] Evidence for increased risk of CVD events and deaths associated with high salt intake, however, come from prospective studies, which are affected by limitations related to exposure measurement and reverse causation.[112] As a result, there is

broad agreement about the CVD harms of high levels of salt use but debate continues about the optimal low levels of consumption.[113]

Global and regional CVD effects

Global analyses have attributed millions of deaths from CVDs to various dietary factors – with the largest being due to low intake of fruits (4.3 million CVD deaths), nuts and seeds (2.5 million CVD deaths), whole grains (1.7 million CVD deaths), vegetables (1.7 million CVD deaths), and high salt intake (2.9 million CVD deaths).[13] These figures are of the same magnitude as, or larger than, the effects of high BMI, blood glucose, and serum cholesterol. It is however important to note that various dietary traits can be correlated either due to behavioral and socioeconomic factors – i.e., preference for or affordability of more or less healthy foods – or because some foods simply substitute others. For example, eating more whole grains, unsaturated fats, and fresh fruits and vegetables may imply eating less processed carbohydrates, saturated fats and meat.[114] Therefore the effects of different dietary factors are not additive, not only because of their etiological overlaps (which affects all risk factors) but also because of the potential for substitution.

In terms of regional variations, fruit consumption in most regions is much lower than the 300 grams/day used as the counterfactual (optimal) level in global analyses.[13] Fruit consumption may be low because fruits are only available seasonally in many countries or have high prices relative to local purchasing power. Salt intake levels are high in most regions of the world, and particularly in central and east Asia and in eastern Europe.[115-118] Trans fats intake is high in parts of the Middle East and north Africa, north America, and south Asia, whereas saturated fats are highest in the Pacific Islands, countries in southeast Asia where palm oil is used for cooking, and some central, eastern, and northern European countries.[119]

Physical inactivity

Causal effects of physical inactivity

The association between sedentary life styles or low physical activity and the risk of CVDs is largely based on observational studies, and hence may be affected by the same sources of error and bias as those discussed for diet and BMI. Nonetheless, the associations have been largely consistent since the early studies in the 1950s.[120-122] The benefits of additional activity seem larger at low baseline activity levels than among people who are currently active indicating a non-linear dose-response relationship.[123, 124] Meta-analysis of clinical trials also shows that medically prescribed and supervised exercise can reduce mortality rates of persons with pre-existing coronary artery disease.[125]

Whilst the early evidence on this relationship was from studies of occupational activity, the great majority of studies since the 1980's have been based on leisure time activity, which is important in industrialized societies. Leisure time activity has limited relevance to countries where most energy expenditure occurs during transportation by walking and cycling, and paid and domestic work.[126, 127] The role of activity in domains other than leisure means that measuring the extent of physical inactivity in countries with diverse patterns of daily activity remains a major challenge.[128] Further, the findings on the association between occupational physical activity and CVDs have been inconsistent, in particular regarding heavy occupational physical activity which has been associated with increased CVD risk.[129] If the adverse effect of heavy occupational activity is confirmed in additional studies, there will a need for more emphasis on the domain (and perhaps social circumstances) of activity in public health recommendations and surveillance.

Global and regional CVD effects

Worldwide 2.5 million CVD deaths have been attributed to physical inactivity and insufficient activity.[13] Inactivity is particularly prevalent, and its CVD burden is largest, in high-income countries, Middle East and north Africa, parts of Latin America, and Pacific islands.[13]

Environmental risk factors

A few environmental exposures associated with CVDs have been included in global CRA analyses, including exposure to lead and to pollutants in the ambient air and from household burning of biomass and coal for cooking and heating.[9, 13]

Ambient air pollution

Short- and long-term exposures to many pollutants in the ambient air have been associated with increased incidence, morbidity and mortality from CVDs.[130] Particulate matter (PM), especially fine PM ($PM_{2.5}$), has so far been used as the proxy marker for the hazardous effects of air pollution in global analyses.[13, 131-134] $PM_{2.5}$ concentrations in ambient air have been associated with increased risk of IHD and stroke (as well as heart failure which is a sequelae of a number of CVDs).[130]

The effect sizes for PM-CVD association are smaller than those of smoking and the other established factors, and may be affected by residual confounding. More importantly, the great majority of prospective cohort studies on air pollution as a CVD risk factor are from Europe and north America,[134] where concentrations are much lower than those in east and south Asia (**Figure 6**). Therefore, there is little data on concentration-response relationships at high pollution levels, typical of many Asian cities. The absence of direct studies has necessitated

extrapolating the concentration-response relationships beyond the levels measured in epidemiological studies.[134] The estimated global and regional CVD burdens of air pollution are highly sensitive to how this extrapolation is done.[133, 134] Further, PM in different parts of the world is emitted by different sources – including vehicle and industrial emissions, residential coal and biomass burning, crustal dust, and even sea salt.[136, 137] There is growing evidence that the health effects of PM depend on its source and chemical composition.[138, 139]. Therefore, we should expect differences in toxicity across the world, which is not reflected in current estimates.

With all of these assumptions and knowledge gaps taken into consideration, ambient PM was estimated to be responsible for nearly 2.5 million CVD deaths in the world in 2010. Over 900,000 of these deaths occurred in east Asia and another 560,000 in south Asia.[13] PM levels in these regions are substantially higher than in other regions, not only in cities but also spreading to rural areas (**Figure 6**).

Household air pollution

There are no direct studies of household air pollution from burning of biomass and coal as a risk factor for CVDs. Nonetheless, tens of studies have shown that household PM concentrations are the same or substantially higher than those in the ambient air. Therefore, global analyses have applied the same concentration-response as for ambient PM to household air pollution. Attributing some CVD burden to household air pollution is supported by the emerging evidence about its effect on blood pressure, and more recently on markers of inflammation.[140, 141] In 2010, an estimated 2.1 million CVD deaths were attributable to household air pollution; over 1.3 million of these deaths occurred in east Asia and south Asia.[142, 143]

Lead exposure

Long-term exposure to lead, measured as bone lead level, has been associated with raised blood pressure as well as with clinical CVD outcomes.[144, 145] In high-income countries, leaded fuel and many other sources of lead exposure have been eliminated for decades.[146] Phasing out leaded fuel began much later in many low- and middle-income countries, and other sources such as battery recycling, paint, and lead-glazed ceramics, persist.[146] Populations in Middle East and north Africa, central and south America, and south Asia have some of the highest bone or blood lead concentrations.[146] In 2010, accumulated life-course exposure to lead was estimated to be responsible for over 650,000 CVD deaths in the world.[13]

Other environmental risk factors

CVDs have also been associated, with varying degrees of evidence, with a number of other environmental factors which have so far not been quantified in global analyses because global exposure data are very limited. These risks include noise, cold and warm temperatures, and chemicals such as cadmium and arsenic.

Noise from road traffic and aircraft has been associated with increased risk of IHD and hypertension.[147-149] There is little data on population noise exposure other than in some high-income countries.[150] Such data, through measurement and modeling studies, are needed to quantify the burden of CVDs and other diseases attributable to noise. Noise exposure is likely to increase with urbanization and increased vehicle and airplane traffic, which will in turn increase its significance as a global CVD risk factor.

Both high and low temperatures are associated with increased risk of CVDs, although the temperatures at which the hazardous effects begin may depend on the overall annual and seasonal average temperatures.[151-153] For mid- to high-latitude populations, the overall effect of low temperatures predominates over that of heat.[153, 154] Therefore, although projected increases in weather variability due to global environmental change are expected to affect CVDs, the consequences will depend on the relative impacts of cold vs. warm temperatures and adaptation measures for each of them. These effects might be particularly relevant to low- and middle-income countries where there is less access to potential modifiers of risks from extreme temperatures such as quality housing, air conditioning and central heating.

Emerging risk factors and omic markers

The so-called emerging risk factors are biomarkers beyond the established risk factors identified in the early epidemiological studies in **Figure 2**. Although emerging risks have so far not been included in global analyses, rapidly-increasing epidemiological research on their role as CVD risk factors will inevitably raise a question on whether they should be included alongside other physiological factors.

Despite intensive research, the evidence for consistent associations independent of the established risk factors is available for very few of these biomarkers.[22] Further, their CVD effect sizes are small to modest, and many of them are affected by large heterogeneity and likely bias.[22] Emerging risk factors with more consistent evidence include non-HDL cholesterol, serum albumin, apolipoprotein B/A1 ratio, glycosylated hemoglobin, lipoprotein-associated phospholipase mass and activity, and nonfasting insulin. Of emerging risk factors, only IL-6 and Lp(a) have evidence from Mendelian randomization studies for a causative association.[155, 156]

Recently interest has also turned to omic technologies as a means of identifying new biomarkers, including genomic, metabolomic and epigenomic markers, for CVDs and their risk factors. Genome-wide association studies (GWAS) have to date identified tens of independent genetic variants associated significantly or suggestively with IHD in European and South Asian populations, with similar magnitudes of associations.[157, 158]. Despite these findings, the inclusion of genetic risk scores has not improved individual prediction of disease risk over and above established risk factors.[159] At the population level, worldwide differences in CVDs are likely to be mainly due to the effects of behavioral, dietary and environmental exposures, healthcare access and quality, and possibly fetal and early life nutrition and environment.[4, 11, 160-162]

Metabolomic profiling, and the identified metabolites, provide a potentially-comprehensive assessment of gene actions, intrinsic metabolism, and exposure to risk factors, which can collectively affect CVDs (or their physiological risks like blood pressure, diabetes and adiposity).[163-166] Similarly, variations in DNA methylation at specific loci have also been associated with adiposity and diabetes.[167, 168] However, similar to emerging risk factors, novel omic markers have not improved CVD risk prediction beyond the established risk factors, and, excepting the GWAS findings, evidence that they are on the casual pathway is either absent or limited.[104, 169, 170] There are however promising new leads, for example evidence for a gut microbial step in choline metabolism related to atherosclerosis.[171] Measurement of omic markers is still relatively specialized and expensive. Therefore, measuring them in worldwide population-based health surveys is for the time being unlikely and their application to CVDs currently remains in a research context for understanding disease mechanisms and identifying new biomarkers of risk factor exposure or therapeutic targets.

Future benefits of reducing major CVD risk factors and the global NCD target

Following the establishment of the global targets for NCDs and their major risk factors, there is a need to estimate how much of future CVD mortality may be avoided if risk factor levels were reduced according to their global targets.[5] The future benefits of risk factor prevention depend on two epidemiological characteristics of CVDs (and other NCDs). First, as seen in Figure 1, CVDs have multiple causes, combined effects from which lead to a particular disease rate in the population. Some of these causes are currently non-modifiable (e.g., genetic determinants), unmeasured or poorly measured (e.g., health-care quality or stress), or even unknown. Therefore, trends for CVDs can be different from that of any single risk factor or small number of risk factors, depending on how the other determinants and medical treatment are changing, and latency of effects.[3] For example, CVD mortality in high-income countries has decreased for decades, during which time some of its risk factors (e.g., blood pressure, serum cholesterol, and, in some countries, smoking) have decreased and others (e.g., obesity and smoking in other countries) have increased.[3, 160] The second characteristic of CVDs is that when exposure to one of its risk factors increases or decreases, the harmful or beneficial impacts on disease risk begin immediately and continue to accumulate gradually until risk reaches the levels of those who have had the higher/lower exposure over a prolonged period (see Table S1).[3, 172, 173] Although the process may take up to 10 years of more,[3, 172, 173] the reversibility of risk after exposure removal seems to occur more steeply than the accumulation of hazardous effect.[3] This asymmetry of rapid benefits vs. more gradual harms may exist because although the development of atherosclerotic plaques or hardening of the arteries is gradual, the risk of a fatal obstruction of the coronary arteries might be reduced fairly quickly, particularly if a risk factor affects late-stage factors, such as clotting and thrombus formation.

It has been projected that if current trends continue, premature CVD mortality (defined as the probability of dying between 30 and 70 years of age from a CVD cause) will continue to decrease in the world as a whole, from 0.101 in 2010 to 0.083 in 2025, i.e., an 18% decrease which is less than the 25% global target (**Figure 7**).[5] High-income countries, which currently have lower CVD death rates than other parts of the world, are projected to have a 29% reduction under current trends.

After accounting for overlaps in the effects of risk factors and the gradual changes in CVD death rates following changes in population exposure, it is projected that the premature CVD mortality will further fall to 34% if targets for six of the seven risk factors with global targets (tobacco smoking, alcohol use, raised blood pressure and glucose, obesity and salt intake) are met (Table S2). The effects of risk factor targets on the projected course of CVD mortality in high-income countries is relatively small because high-income countries are already benefiting from mostly favorable risk factor trends, due to decreases in blood pressure, tobacco smoking, and alcohol use (as well as cholesterol for which there is no global target) although these favorable trends are partially offset by rising obesity and diabetes. Despite the projected decline in CVD death rates, the number of CVD deaths in high-income countries as a whole is projected to rise by a modest 0.2 million between 2010 and 2025, due to population growth and ageing (this increase the net effect of increase in number of deaths in some countries and decrease in others). Achieving the risk factor targets will help compensate for these demographic factors, and reduce the number of CVD deaths in high-income countries in 2025 to being the same as their 2010 levels.

Premature CVD mortality has also been declining in low- and middle-income countries as a whole (although rising in some regions)[173] and is projected to continue this decline, with probability of dying from CVDs between 30 and 70 years of age declining from 0.118 in 2010 to 0.095 in 2025 (**Figure 7**). This 20% decline is not enough to meet the global target. Further, population growth and ageing means that the number of CVD deaths in 2025 is expected to rise by 4.4 million compared to 2010. Achieving the risk factor targets will accelerate the decline in CVDs, leading to a 37% decline, achieve the global target, and avoid 3.5 million deaths in 2025 alone.

Limitations of current data on the health effects of CVD risk factors

As described throughout this review, the estimated CVD burden of many risk factors is affected by the fact that limited data are available regarding population exposure and by likely or potential biases in the magnitudes of their effects. To overcome the limitations of data on population exposure, researchers have used sophisticated statistical methods for pooling worldwide population-based surveys,[174] or proxy measures of risk factors exposure, e.g., lung cancer death rates as a measure of cumulative life-long smoking and satellite-based measurement as a proxy for ambient PM pollution.[6, 175] Nonetheless, the estimated exposures have moderate-to-large uncertainties, even for a risk factor such as diabetes that is commonly used in clinical settings.[79, 81] Further, small effect sizes and publication and reporting bias can undermine the presumed causal associations; even when causality is accepted, these limitations lead to bias in the magnitudes of associations.[104]

The estimated CVD burden of risk factors is relatively robust to these issues for those risks with high prevalence and large causal effects (**Figure 8**), a situation that for CVD risks may be limited to high blood pressure, high cholesterol (for effects on IHD), smoking (among

men), and possibly harmful alcohol use (among Eastern European men). If causal effects are large but risk factor exposure is low, for example in the case of smoking in Asian and African women, the estimated health burden is most sensitive to the quality of, and error in, exposure data. The most common situation for CVD risks, however, is one of small effect sizes and high exposure levels, which applies to most dietary and environmental risks, physical inactivity, and high BMI and glucose. The estimated CVD burden of such high-exposure-and-low-effect-size risks is highly sensitive to bias and residual confounding in their effect sizes. At the extreme, the real estimated CVD burden of such risks can be zero if the causal association is spurious. More likely, the CVD burden may be overestimated by many folds because inadequate adjustment and publication bias often lead to inflated effect sizes.[104] The proportional overestimation of the CVD burden in the presence of bias and confounding is more severe in the case of small effect estimates. For illustration, if one half of the excess relative risk is due to residual confounding, and if the observed relative risk is 1.02, the CVD burden would be overestimated by 98% for those risks with universal exposure. The overestimation would be 67% if the observed relative risk is 1.50 and 50% if it is 2.0.

Further, the CVD burden of risk factors is estimated by comparing their actual levels in worldwide populations with some counterfactual optimal level.[9] Putting aside risks such as smoking, dietary trans fats, and binge drinking for which the optimal level in a population is unequivocally zero, the exposures used as counterfactual optimal levels in global analyses – e.g., a systolic blood pressure of 110-115 mmHg, BMI of 21-23 kg/m^2, vigorous levels of physical activity for the whole population, and a daily fruit intake of 300 grams – [13] tend to be at the extreme levels in most epidemiological studies and hence are uncertain.

Finally, the effect sizes for the associations between risk factors and CVDs tend to attenuate with age, with relative risks approaching 1.0 in older ages.[40] Because most epidemiological studies do not enroll a sufficiently large number of older individuals to robustly estimate small effects at these ages, relative risks in ages above 75 years either are not estimated or have large uncertainty. This gap in data has required extrapolating effect sizes to older ages for population-based analyses.[13, 40] With CVD events and especially deaths increasingly shifting to older ages, this extrapolation increases the uncertainty of estimated CVD burden of risk factors.

Conclusions

Following the expansion of, and advances in, epidemiological research on the behavioral, dietary, environmental, and physiological causes of CVDs, the number of CVD risk factors in global CRA analyses has increased substantially, from a handful in 1990 to tens in recent analyses. The CRA analyses have attributed hundreds of thousands or millions of CVD deaths to the aforementioned risk factors. These numbers have in turn helped draw attention to important global or regional public health issues.

The above-mentioned limitations and gaps in data on risk factor exposure and effect sizes should not overshadow the tremendous advances in understanding the causes of CVDs, and in measuring their levels in worldwide populations, since the first cohort studies were done five or six decades ago. Rather, they should motivate future efforts in collecting new data and re-analyzing existing ones that can improve our knowledge of the worldwide CVD effects of risk factors, as outlined in **Table 2**.

Even with these uncertainties a number of policies and interventions identified in **Table 2**, if successfully implemented, are likely to reduce the worldwide burden of CVDs through primordial prevention at the population level.[176] Together with equitable access to high-quality healthcare for CVD prevention and treatment, these actions can help replicate the successes of high-income countries in reducing CVD events and deaths, and to reduce global inequalities in CVD burden.[3-5, 160, 176]

Finally, we note that CVDs and most of their risk factors are strongly inversely associated with individual and community socioeconomic status, as summarized in prior reviews.[19, 160] The higher CVD incidence and mortality in the poor is at least partly mediated by less favorable risk factor levels and more limited and lower quality healthcare for prevention and treatment,[18, 160, 161] although independent pathways may also exist. Therefore all CVD prevention policies, and scientific analyses that inform them, should take into account their impacts on CVDs on the poor and on inequalities.[160]

Conflict of interest

None

Table 1. Comparison of the effect sizes (hazard ratios) for the associations of physiological risk factors with ischemic heart disease (IHD) and stroke between western and Asian cohorts. All effect sizes are shown at 65-74 years, because hazard ratios for CVDs attenuate with age.

Risk factor	Region	Hazard ratio for IHD	Hazard ratio for ischemic stroke	Hazard ratio for hemorrhagic and other non-ischemic strokes
Blood pressure (per 10 mm Hg higher usual systolic blood pressure)	Asian cohorts	1.37 (1.31-1.42) [a]	1.48 (1.42-1.54) [a]	1.51 (1.46-1.57) [a]
	Western cohorts	1.31 (1.30-1.33) [b]	1.42 (1.37-1.47) [b]	1.41 (1.37-1.45) [b]
Serum cholesterol (per 1 mmol/L higher usual total cholesterol)	Asian cohorts	1.25 (1.21-1.29) [a]	1.10 (1.03-1.17) [a]	No association
	Western cohorts	1.29 (1.26-1.33) [b]	1.06 (0.99-1.13)	No association
Fasting plasma glucose, FPG (per 1 mmol/L higher usual or baseline FPG)	Asian cohorts	1.24 (1.16-1.33) [a]	1.20 (1.10-1.31) [a, d]	
	Western cohorts	1.13 (1.10-1.17) [c]	1.12 (1.07-1.18) [c, d]	
Body mass index, BMI (per 5 kg/m² higher baseline BMI)	Asian cohorts	1.32 (1.24-1.40) [a]	1.30 (1.19-1.42) [a]	Not reported
	Western cohorts	1.36 (1.31-1.42) [b]	1.42 (1.32-1.52) [b]	1.58 (1.46-1.71) [b]

[a] from re-analysis/overview of Asia-Pacific Cohort Studies Collaboration as reported by Singh et al.[40]
[b] from re-analysis/overview of Prospective Studies Collaboration as reported by Singh et al.[40]
[c] from re-analysis/overview of Emerging Risk Factor Collaboration as reported by Singh et al.[40]
[d] Hazard ratios are for total stroke.

Table 2. Research, surveillance, and policy needs to better measure and reduce the cardiovascular disease (CVD) burden of preventable risk factors.

Strategy	Potential benefits
Research	
Form regional and multi-region cohort pooling consortia	Overcomes small sample sizes and unreliable and unstable effects in individual cohorts; partially overcomes publication bias that affects individual cohorts; allows estimates of effects by region, as has been done for established CVD risk factors in Asian and western cohorts.[34, 40, 74]
Enroll older participants in epidemiological studies, and/or re-measure exposure among participants once they reach 70-75 years	Allows better estimation of the associations between risk factors and events in older ages, which is currently largely based on extrapolation,[40] and having more robust age-specific effect sizes throughout the lifecourse.
Develop methods and technologies (e.g., biomarkers and sensors) for better measurement of exposure to dietary and environmental CVD risks	Helps with reducing error in exposures of interest and potential confounders in observational studies.
Conduct randomized studies of dietary and environmental risks	Establishes whether the observed associations are causal and provides unbiased estimates of the magnitude of causal effects. Such studies are however difficult and expensive for clinical CVD outcomes because they require several years of follow-up. The difficulties arise from the fact that in dietary trials, the intervention group may continue to consume at least some of their normal food and it may not be possible to blind intervention.
Find ways to reduce selective reporting of positive findings in observational studies	Investigate the practicality and impacts of registries of observational research where protocols would be registered, and/or requiring reporting of results together with those of the prior studies and formal assessment of publication bias.
Surveillance	
Conduct periodic (e.g., every five years) population-based health examination surveys with measured data on risk factors; report data to the World Health Organization (WHO)	Allows measuring risk factor levels and trends by age and sex, and possibly by other characteristics like rural and urban place of residence or socioeconomic status. Reporting to WHO, as done for mortality statistics, is needed for consistent global reporting.
Use primary care (electronic) data as a source of risk factor exposure information	Can be used in countries with universal health coverage and accessible primary care system, which includes many high-income countries (other than the United States) and several middle-income countries. Provides an efficient system for collecting annual data on risk factors which can be calibrated with periodic health examination surveys.
Develop and deploy low-cost and low-power sensors for measurement of environmental CVD risks such as particulate matter and noise	Allows measuring, and possibly real-time reporting, of environmental risks for CVDs with high spatial resolution.
Policy [a]	
Eliminate or substantially reduce tobacco smoking and harmful alcohol use	Will have substantial benefits for CVDs and other non-communicable diseases (NCDs).
Eliminate manufactured trans fats; identify strategies to increase the intake of fresh fruits and vegetables, whole grains, and	Will lower the burden of CVDs, diabetes, and some cancers.

unsaturated fats and reduce the intake of processed carbohydrates, excessive salt, and saturated fats	
Identify and treat, using combination of blood pressure and lipid lowering medicines and aspirin, people at high risk of CVDs, including those with a history of CVD event, with diabetes, and with high absolute risk [b]	Will lower major physiological risks and the burden of CVDs.
Develop and implement regulations, economic measures and technologies that promote the use of clean fuels for household cooking and heating and reduce ambient air pollution	Will lower the burden of CVDs, other NCDs, and childhood diseases; improves quality of life.

[a] See Ezzati and Riboli[176] for further strategies for prevention of CVDs and others NCDs, and whether and where there are examples of successful implementation of these strategies.

[b] Achieving this aim requires an equitable and high-quality primary care system and availability of essential, and typically low-cost, medicines for CVD prevention and early-stage treatment.[4, 176, 177] In countries with limited healthcare infrastructure, the system may rely on non-physician health workers with appropriate training and guidelines. Examples of such programs have been implemented in some low- and middle-income countries for some CVD risk factors especially for diabetes.[178, 179]

Figure 1. Schematic diagram of the determinants of and risk factors for cardiovascular diseases.

Figure 2. Major milestones and studies of established and emerging cardiovascular disease risk factors. See http://www.epi.umn.edu/cvdepi/ for additional historical studies.

Figure 3. Mean population body mass index (BMI), systolic blood pressure (SBP), and serum total cholesterol (TC), and prevalence of diabetes in different world regions. The estimates are from pooled analysis of hundreds of population based measurement studies, as described in detail elsewhere.[58, 77-79] See www.ncdrisc.org for additional data and interactive visualizations.

Figure 4. Deaths from cardiovascular diseases (CVDs) in people aged 30 years and older, attributable to the individual and combined effects of smoking and high body mass index (BMI), blood pressure and glucose and serum cholesterol by region and (A) sex and (B) age group, 1980–2010. Data sources and methods are described elsewhere.[5, 14] In addition to CVDs, some of these risks are associated with increased risk of diabetes, chronic kidney disease, and cancers.[13, 14] Deaths attributable to individual risk factors show their total CVD burden. Deaths attributable to the combined effects of all risk factors account for multi-causality and for the partial mediation of the effects high BMI through high blood pressure and glucose and serum cholesterol.[14, 34]

Figure 5. Age-standardized cardiovascular death rates among people aged 30 years and older attributable to the combined effects of smoking and high body mass index, blood pressure and glucose and serum cholesterol by region and sex. Death rates were standardized to the World Health Organization standard population.

Figure 6. Average concentration of fine particulate matter ($PM_{2.5}$) over a decade from 2001 to 2010. Reproduced from van Donkelaar et al.[135]

The high concentrations in central Asia and the Middle East and north Africa are largely due to crustal particulate matter (dust).

Figure 7. The impact of achieving globally-agreed targets for six risk factors (tobacco smoking, alcohol use, salt intake, obesity and raised blood pressure and glucose) on the probability of dying prematurely (A) and number of deaths (B) from cardiovascular diseases in high-income versus low- and middle-income countries. Source: re-analysis based on data and methods in Kontis et al.[5]

Figure 8. Population attributable fractions (PAFs) for different risk factor prevalences and effect sizes (relative risks, RR). For each RR, the graph shows PAF at different levels of risk factor prevalence. Differences and errors in prevalence can be characterized by movement along each curve, and those of effect size by moving from one curve to another.

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Genome & metagenome

Prenatal and early life

Clinical cardiovascular disease: ischemic heart disease, stroke, heart failure, peripheral arterial disease, rheumatic heart disease

Subclinical atherosclerosis

Physiological pathways

Raised blood pressure

Raised blood lipids

Diabetes and raised blood glucose

Thrombosis and inflammation

Altered metabolome, epigenome, proteome, transcriptome

Adiposity

Behavioral factors and infections

Physical inactivity

Smoking, alcohol

Infections

Poor diet:
↑processed meat, ↑salt,
↓fruits and vegetables, ↓fiber,
↓whole grain, ↑trans fat

Socioeconomic and environmental conditions

Sanitation and living conditions

Natural and physical environment:
↑air pollution, ↑noise, ↓green space, extreme temperature

Social environment:
↓socioeconomic status,
↓education, poverty, inequality

Examples of major collaborative consortia

Blood Pressure Trialists' Collaboration

Asia Pacific Cohort Studies Collaboration

Prospective Studies Collaboration

AHA Pooling Project

ERFC

Wellcome Trust Case Control Consortium

Cholesterol Treatment Trialists' Collaboration

CARDIOGRAM

Asian Cohort Consortium

Examples of early landmark RCTs

Oslo Study of Diet and Anti-smoking Advice

MRC trial of treatment of mild hypertension

The Oslo Study on Mild Hypertension I

Helsinki Heart Study

VA Cooperative Study on Hypertension

Hypertension Detection and Follow-up Program

UK Prospective Diabetes Study

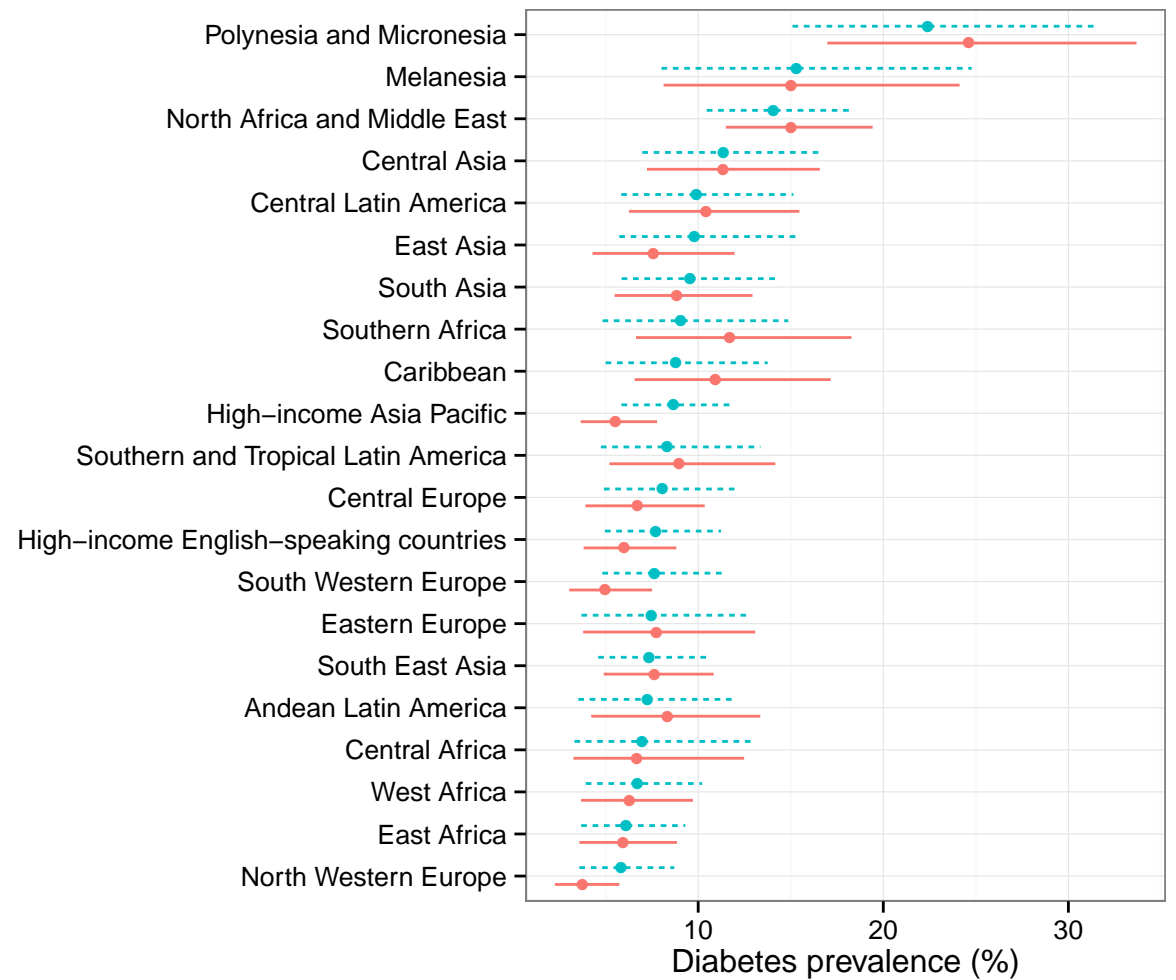Heart Protection Study

WOSCOPS

MRFIT

LRC CPPT

Examples of early CVD cohort studies in western populations, East Asia, South Asia, Africa, Latin America, Eastern Europe, and multi-country studies

CORIS

Lipid Research Clinics Study

Idikan Adult Mortality Study

Yugoslavia cardiovascular disease study

Six Chinese Cities Cohorts Study

Minnesota Business and Professional Men Study

Hisayama study

Tanno - Soubetsu Study

Los Angeles Heart Study

Puerto Rico Heart Health

East Beijing Cohort Study

PURE

Framingham Study

British Doctors Study

Build and BP Study

Seven Countries Study

Xi'an Study

Mumbai Cohort Study

EFRICARD CARMEN

Ni–Hon–San study

MONICA

1934	1939	1944	1949	1954	1959	1964	1969	1974	1979	1984	1989	1994	1999	2004	2009	2014

Examples of major studies of established and other risk factors

Smoking

Systolic Blood Pressure

HDL cholesterol

Diabetes

Serum Cholesterol

Lipoprotein(a)

Apolipoproteins

Lipoprotein-associated phospholipase A2

Fibrinogen

C-reactive protein

Introduction of emerging risk factors

	Men	Women

Columns: High-income regions; Central and eastern Europe and central Asia; Latin America and Caribbean; Middle East and north Africa; East and southeast Asia and Pacific; South Asia; Sub-Saharan Africa

Risk factors (top to bottom): Five risk factors combined; Smoking; High blood pressure; High serum cholesterol; High blood glucose; High BMI

X-axis: Millions of deaths

Legend:
- High-income regions
- Central and eastern Europe and central Asia
- Latin America and Caribbean
- Middle East and north Africa
- East and southeast Asia and Pacific
- South Asia
- Sub-Saharan Africa

	30-69 years	over 70 years

Legend:
- High-income regions
- Central and eastern Europe and central Asia
- Latin America and Caribbean
- Middle East and north Africa
- East and southeast Asia and Pacific
- South Asia
- Sub-Saharan Africa

Risk factors (y-axis):
- Five risk factors combined
- Smoking
- High blood pressure
- High serum cholesterol
- High blood glucose
- High BMI

x-axis: Millions of deaths (0 to 6)

Men | Women

Sub-Saharan Africa	
South Asia	
Central and eastern Europe and central Asia	
Middle East and north Africa	
Latin America and Caribbean	
East and southeast Asia and Pacific	
High-income countries	

Age-standardised death rate per 100,000 people

- Ischaemic heart disease
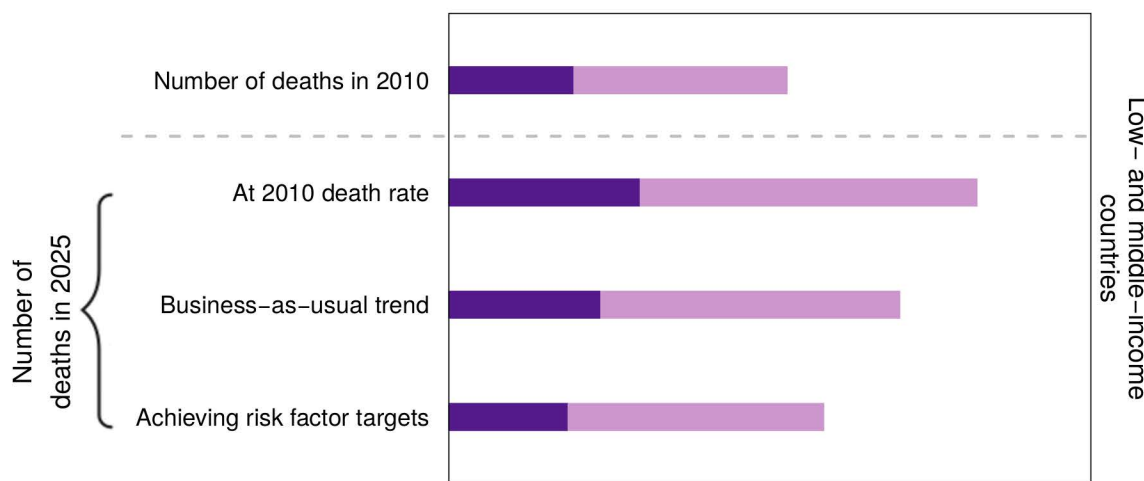- Stroke
- Other cardiovascular diseases

PM$_{2.5}$ [μg/m^3]

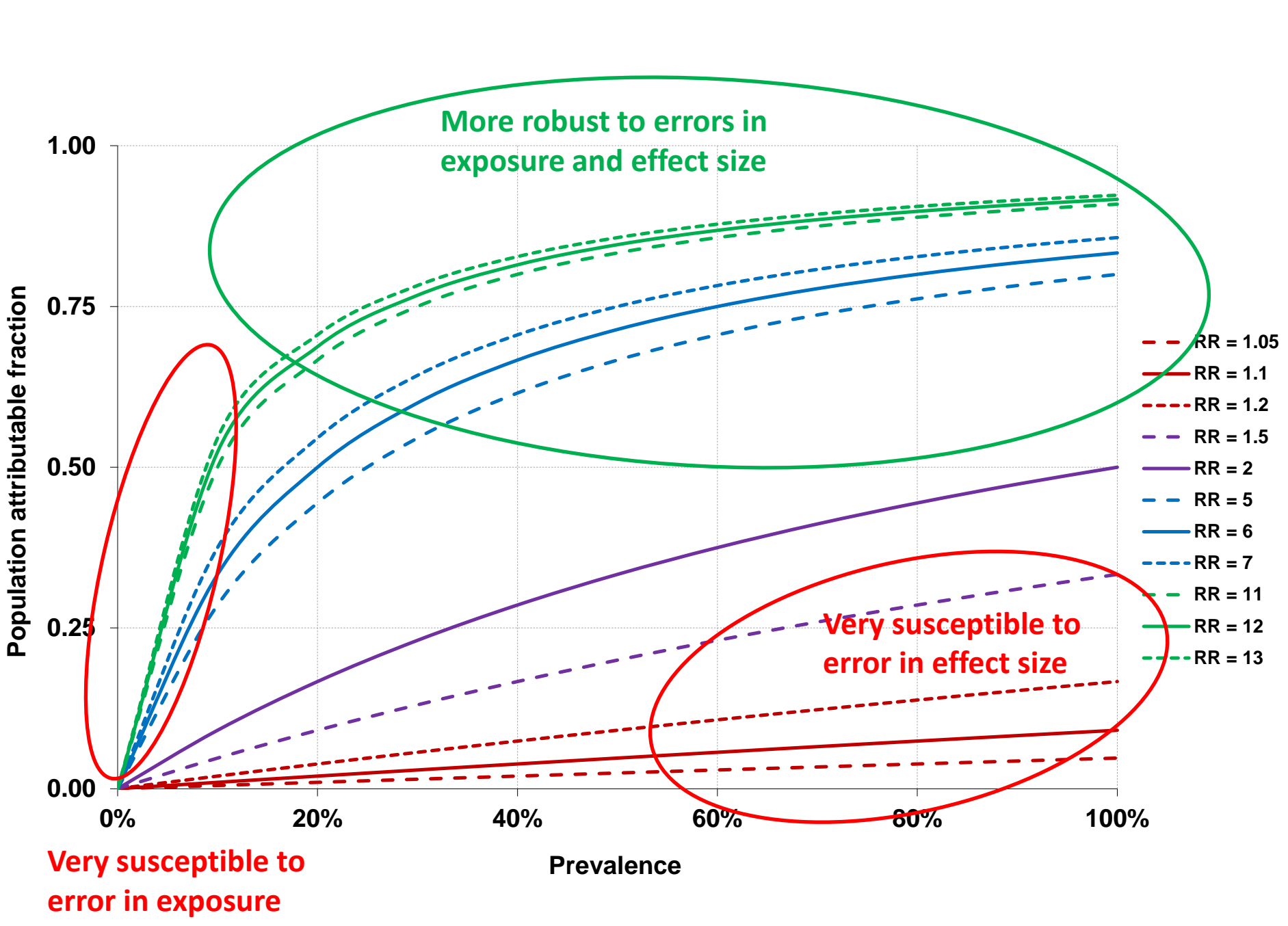**Probability of dying from cardiovascular disease between 30 and 70 years of age**

Number of deaths from cardiovascular disease

World

High-income countries

Low- and middle-income countries

Number of deaths in 2010

Number of deaths in 2025

At 2010 death rate

Business-as-usual trend

Achieving risk factor targets

25% reduction

Year

Probability of dying between 30 and 70 years of age

Millions of deaths

- Business-as-usual trend
- Trend if risk factor targets are achieved

30–69 years
70+ years