
The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration

Summary

Background—Elevated blood pressure and glucose, serum cholesterol, and body mass index (BMI) are risk factors for cardiovascular diseases (CVDs); some of these factors also increase the risk of chronic kidney disease (CKD) and diabetes. We estimated CVD, CKD, and diabetes mortality attributable to these four cardio-metabolic risk factors for all countries and regions between 1980 and 2010.

Methods—We used data on risk factor exposure by country, age group, and sex from pooled analysis of population-based health surveys. Relative risks for cause-specific mortality were obtained from pooling of large prospective studies. We calculated the population attributable fractions (PAF) for each risk factor alone, and for the combination of all risk factors, accounting for multi-causality and for mediation of the effects of BMI by the other three risks. We calculated attributable deaths by multiplying the cause-specific PAFs by the number of disease-specific deaths from the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. We propagated the uncertainties of all inputs to the final estimates.

Findings—In 2010, high blood pressure was the leading risk factor for dying from CVDs, CKD, and diabetes in every region, causing over 40% of worldwide deaths from these diseases; high BMI and glucose were each responsible for about 15% of deaths; and cholesterol for 10%. After accounting for multi-causality, 63% (10.8 million deaths; 95% confidence interval 10.1–11.5) of deaths from these diseases were attributable to the combined effect of these four metabolic risk factors, compared with 67% (7.1 million deaths; 6.6–7.6) in 1980. The mortality burden of high BMI and glucose nearly doubled between 1980 and 2010. At the country level, age-standardised death rates attributable to these four risk factors surpassed 925 deaths per 100,000 among men in Belarus, Mongolia, and Kazakhstan, but were below 130 deaths per 100,000 for women and below 200 for men in some high-income countries like Japan, Singapore, South Korea, France, Spain, The Netherlands, Australia, and Canada.

Conflict of interest
None

Author contribution
GD and ME designed the study concept. YL, GMD, EC, GAS, MC, FF, JKL, MMF, and MR analysed exposure and effect size data. YL and EC analysed attributable fractions and deaths. Collaborating group members contributed exposure and effect size data. ME and GD wrote the first draft of the paper, with input from other writing group and collaborating group members. GD, SSL, and ME oversaw research.
**Interpretations**—The salient features of the cardio-metabolic epidemic at the beginning of the twenty-first century are the large role of high blood pressure and an increasing impact of obesity and diabetes. There has been a shift in the mortality burden from high-income to low- and middle-income countries.

**Introduction**

Cardiovascular diseases (CVDs), chronic kidney disease (CKD) and diabetes are among leading global and regional causes of death.\(^1,2\) The number of CVD deaths in the world increased by over 25% and those of CKD and diabetes nearly doubled between 1990 and 2010.\(^1\) Adiposity and high blood pressure, cholesterol, and glucose are important modifiable risk factors for CVDs and (except for cholesterol) for CKD.\(^3-6\) Adiposity is also the most important modifiable risk factor for diabetes.\(^3,4,7\) Over the past few decades, these risk factors have had divergent trajectories in many countries. While body mass index (BMI) and diabetes prevalence have increased in most countries and globally,\(^8,9\) blood pressure has declined in high-income and some middle-income regions; it has remained unchanged or even increased in some low- and middle-income countries.\(^10\) Cholesterol has also declined in western countries while increasing in East and Southeast Asia, especially China, Japan, and Thailand.\(^11\)

Global and some regional mortality effects of cardio-metabolic risk factors were estimated in previous comparative risk assessment (CRA) studies.\(^12,13\) However, these studies did not analyse the combined effects of the risk factors partly because much of the effects of adiposity on CVDs are mediated through blood pressure, cholesterol, and glucose and reliable estimates of the mediated proportion was not available.\(^14\) The only analysis of the combined effects of these risks divided the world into only three large regions and did not include high blood glucose.\(^15\) In addition, prior studies used broad disease categories, e.g. all CVDs, as opposed to specific diseases of public health or clinical relevance, e.g. stroke subtypes. Finally, very little is known about how much the mortality effects of these risk factors have changed over time, even though both risk factor levels and cardio-metabolic death rates have changed enormously, sometimes in opposite directions. We report cause-specific mortality from CVDs, CKD, and diabetes attributable to the effects of high BMI, blood pressure, cholesterol, and glucose, individually as well as in combination, by country and region between 1980 and 2010.

**Methods**

**Data sources**

**Risk factor exposure by country, year, sex, and age group**—We measured population exposure to cardio-metabolic risk factors using metrics that had the most comprehensive global data. These were BMI, fasting plasma glucose (FPG), systolic blood pressure (SBP), and serum total cholesterol (TC). Risk factor exposures by country, year, sex, and age group were derived from pooled analyses of population-representative health surveys as described in detail elsewhere.\(^8-11\) In brief, population-based data were collated from published and unpublished population-based national, sub-national and community surveys and studies. There were 960 data sources across countries and years for BMI, 786
for SBP, 370 for FPG, and 321 for TC. About half of BMI data in low- and middle-income countries were from the 2000s and another 34% from the 1990s, whereas in high-income regions data were evenly distributed over time. The SBP data were spread almost equally among the three decades of analysis, but more than 60% of national sources were from the 2000s. About 40% of all TC data and two-thirds of all national data were from the 2000s. Half of the FPG data, and 68% of the national data, were from the 2000s, and another 35% from the 1990s.

A Bayesian hierarchical model was used to estimate risk factor levels by sex and age group for all countries and years, borrowing information across space, time, and age as well as through covariates that helped predict risk factor levels. The uncertainties of the estimates incorporated the sampling error of the data, as well as uncertainty due to having some data sources that were not nationally representative, and due to missing data for many country years. Standard deviations (SD) of risk factor distributions for each country-year-age-sex unit were estimated using the population mean and the coefficients of a regression that related SD to mean. Estimated SDs for SBP, TC, and FPG were corrected for the error associated with one-off measurements using coefficients from prospective studies with multiple measurements.

**Associations of risk factors with disease-specific mortality**—We quantified the effects of each risk factor on specific CVD outcomes (ischemic heart disease (IHD), ischemic and hemorrhagic stroke, hypertensive heart disease, and other CVDs), diabetes, and CKD when there was evidence of a convincing or probable causal association. For each risk factor-disease pair, we used the age-specific relative risk (RR) from meta-analyses of prospective studies which had adjusted for major confounders and to the extent possible for regression dilution bias.

The proportion of the effects of BMI on IHD and stroke mediated through the other three risk factors was based on a pooled analysis of 97 prospective cohorts. This pooling study found that 46% (95% confidence interval 42–50) of the excess RR of BMI on IHD and 76% (65–91) on stroke are mediated through the other three risks. We assumed that the effect of BMI on hypertensive heart disease is fully mediated through blood pressure, on diabetes through FPG, and on CKD through the combination of SBP and FPG.

**Cause-specific deaths by country, year, age, and sex group**—Data on the number of deaths by underlying cause were from the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study, with data sources and methods described in detail elsewhere. Briefly, total and cause-specific death rates were estimated using data from vital registration, sample death registration systems, verbal autopsy studies, censuses, household surveys, and mortuaries. Deaths assigned to impossible and improbable causes of death were redistributed, and statistical models were used to estimate cause-specific death rates by country, year, sex, and age group, with specific models selected based on data quality and out-of-sample performance of the model. Like risk factors, there were substantially more data on causes of death in recent years than around 1980.
Statistical methods

Deaths attributable to individual risk factors—We calculated the Population Attributable Fraction (PAF), which quantifies the proportion of deaths from each cause that would have been prevented if the risk factor distribution had been set to an optimal level in the population. PAFs were calculated as described elsewhere, using data on exposure distributions and relative risks (RRs) for each risk factor-disease pair. The number of deaths attributable to each risk factor is a product of PAF and the cause-specific deaths for each country-year-age group-sex unit. The optimal levels were chosen based on the levels corresponding to lowest all-cause mortality in well-conducted epidemiological studies. To account for the uncertainty of these optimal distributions, we allowed them to take a range with means (SD) of 110–115 (4–6) mmHg for SBP; 3.8–4.0 (0.5–0.65) mmol/L for TC; 21–23 (1.1–1.8) kg/m\(^2\) for BMI; and 4.9–5.3 (0.4–0.6) mmol/L for FPG. The benefits of lowering BMI for haemorrhagic stroke were estimated only for levels above 25 kg/m\(^2\), as there seems to be no reduction in risk below this level.

The number of cause-specific deaths attributable to multiple risk factors is often less than the sum of those attributable to individual risk factors because some deaths may be due to more than one risk factor (multi-causality), and because some of the effects of BMI are mediated through the other three metabolic risk factors. In the absence of mediation, effect modification, and risk factor correlation, the combined effects of multiple risk factors can be calculated based on their individual PAFs using a simple relationship that incorporates multi-causality as described elsewhere. To use this relationship in the presence of mediation, we calculated the direct effect of BMI on the selected disease outcomes (i.e. the part not mediated by the other three risks). We then examined the sensitivity of our findings to the correlation among risk factors. We used both an empirical correlation matrix from the US National Health and Nutrition Examination Survey (continuous NHANES 1999–2010) (with pairwise correlation coefficients ranging between 0.11 and 0.31) as well as another correlation matrix with substantially larger pairwise correlation coefficients of 0.8.

All analyses were done by sex, age group, country, and year for 187 countries for which estimates of deaths by cause were available. Regional and global results were obtained by population weighting. Age-specific death rates were combined into broader ages (25–69 and 70+ years) through age standardisation with the WHO standard population.

Uncertainty analysis—We propagated the uncertainties of all inputs (risk factor exposure distributions, RRs, proportion of BMI excess risk mediated through the other three risks, and cause-specific deaths) to the final estimates using a simulation approach. Specifically, we used 1,000 draws from the uncertainty distributions of each input, and repeated the calculations using these draws. The resulting 1,000 PAFs and attributable deaths characterised the uncertainty distributions of the outputs. When draws for two analysis units were correlated (e.g. in two age groups or countries for risk factor exposures and cause-specific deaths because they came from a common statistical model), these correlations were taken into account. All statistical analyses were conducted using Stata 12.0 and R 3.02.
Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. YL, GMS, and EC together had full access to all data used in this study. ME was responsible for submitting the article for publication.

Results

Risk factor trends by country and region are described in detail elsewhere. In summary, between 1980 and 2008, age-standardized global mean BMI increased by 0.4 (0.2–0.6) kg/m²/decade for men and 0.5 (0.3–0.7) kg/m²/decade for women. Mean BMI for men increased in every subregion except Central Africa and South Asia (SA), with the largest increase in Oceania. The largest rise in women’s BMI also occurred in Oceania, followed by Southern and Central Latin America. BMI trends for women in Central and Eastern Europe and Central Asia (CEE-CA) were indistinguishable from being flat. Between 1980 and 2008, SBP declined by 0.8 (−0.4, 2.1) mmHg/decade among men and 1.0 (−0.3, 2.3) mmHg/decade among women globally. Women’s SBP declined most in Western Europe and Australasia; SBP among men declined most in high-income North America, followed by Australasia and Western Europe. SBP rose in Oceania, East Africa, SA, and Southeast Asia for both sexes, and in West Africa for women. Global mean TC changed little between 1980 and 2008, declining by less than 0.1 mmol/L/decade in men and women. TC declined in Europe and high-income Australasia and North America but increased in East and Southeast Asia and Pacific (ESEA-P). There was little evidence of change in TC in Latin America and Caribbean (LAC), Middle East and North Africa (MENA), SA, and sub-Saharan Africa (SSA). Global age-standardized mean FPG increased by 0.07 (−0.02, 0.15) and 0.09 (0.00, 0.17) mmol/L/decade respectively with FPG increasing or at best remaining unchanged in virtually every region. The largest increase in FPG occurred in Oceania.

In 2010, CVDs, CKD, and diabetes were together responsible for 17.6 million (33%) of worldwide deaths. The number of deaths from these causes attributable to individual cardio-metabolic risks ranged between 2.0 (1.5–2.5) million for high cholesterol and 7.8 (6.9–8.4) million for high blood pressure (Figure 1). After accounting for multi-causality, the four risk factors were together responsible for 10.8 (10.1–11.5) million deaths from CVDs, diabetes and CKD, accounting for one in every five deaths in the world. These deaths were divided almost equally between men (5.5 million; 5.0–5.9) and women (5.3 million; 4.7–5.8) (Figure 1A). The combined mortality burden of the four risk factors had been 7.1 (6.6–7.6) million in 1980, increasing steadily throughout the three decades of analysis, driven by population growth and aging (see below). While high blood pressure was the leading risk factor throughout the analysis period, cholesterol had been responsible for the second largest number of deaths until 1990. High BMI and glucose had smaller effects in 1980, each responsible for around 1.2 million deaths. This number was doubled in 2010.

After accounting for population size and aging, age-standardised death rates attributable to risk factors declined globally, and in high-income regions, LAC, and MENA (Figure 2). In high-income regions, this decline was due to a combination of declining PAFs (itself driven by lower SBP and TC) and decreasing CVD death rates; elsewhere, declining death rate was the main driver. Age-standardised death rates attributable to risk factors increased in
SA because both risk factor levels and total death rates increased; they did not change in SSA and decreased only slightly in CEE-CA.

In 1980, the number of deaths attributable to these four risk factors in high-income regions was larger than that of any low- and middle-income region; in that year, high-income regions accounted for 35% of deaths attributable to the combined effects of high BMI, blood pressure, cholesterol, and glucose, and low- and middle-income regions for the remaining 65% (Figure 1A). By 2010, low- and middle-income regions accounted for 82% of attributable deaths, and the two regions with the largest number of attributable deaths were ESEA-P (3 million deaths or 28% of all deaths attributable to these risks), followed by CEE-CA (2 million deaths). In fact, between 1980 and 2010, the number of deaths attributable to high blood pressure and cholesterol declined in high-income regions, despite population increase and aging, and those attributable to high BMI and glucose increased only slightly. In low- and middle-income regions, the number of deaths attributable to every risk factor increased or remained stable over time. In 2010, ESEA-P also had the largest mortality burden of high blood pressure (30% of global blood-pressure-attributable deaths were in this region) and glucose, whereas those of high BMI and cholesterol were still largest in high-income regions.

Forty percent of deaths attributable to these four risk factors in 2010 occurred below 70 years of age, and hence caused larger loss of life years than deaths in older ages (Figure 1B). The share of these premature deaths was lowest in high-income regions (21% of all attributable deaths) and in CEE-CA (33%) and highest in SA (55%) and sub-Saharan Africa (SSA) (58%). Deaths attributable to these four risk factors shifted to older ages over time in high-income regions, where 31% of attributable deaths had occurred below age 70 in 1980. A similar shifting of attributable deaths to older ages occurred in LAC but not in other regions.

In every region and through the whole analysis period, high blood pressure was the leading risk factor for mortality, but there were differences across regions and over time in the relative importance of other risks (Webtable 1). In 1980, high blood pressure was followed by either high cholesterol or high glucose in every region and sex, except among women in MENA, for whom high BMI was the second leading risk factor. By 2010, cholesterol’s relative importance declined, and its mortality burden was in the 3rd or 4th place in every region and sex. Rather, blood pressure was followed by either BMI or FPG, reflecting the worldwide rise in excess weight and glycaemia. The increasing importance of BMI as a risk factor accelerated after 1990.

Overall 44% of deaths attributable to the combined effects of these risk factors in 2010 were from IHD, followed by 30% from stroke, and 11% from diabetes disease (Figure 3). IHD was the single most dominant cause of death attributable to high cholesterol (92% of all deaths attributable to this risk factor) whereas about the same number of IHD and stroke deaths were attributable to high blood pressure. Direct diabetes deaths accounted for only 46% of deaths due to non-optimal blood glucose levels, with the remainder having IHD, ischemic stroke, or CKD as the underlying causes of death.
After accounting for multi-causality, 63% (59–67) of all deaths from CVDs, CKD, and diabetes among men and 62% (56–67) among women were attributable to these risk factors together in 2010 (Table 1). The attributable proportions were 67% (62–72) and 66% (61–72) in 1980 (detailed results not shown). High blood pressure alone was responsible for over 40% of deaths from these causes, and the other three risks for between 10% and 15% each. Although TC was responsible for fewer deaths from CVDs, CKD, and diabetes taken together in 2010, it caused the second largest number of IHD deaths, about twice that of high glucose. High BMI and glucose were responsible for fewer IHD deaths than TC, but are associated with deaths from haemorrhagic stroke, diabetes, and CKD, none of which is affected by high cholesterol. The combined PAF of the four risk factors together was about three quarters for hypertensive heart disease, about two thirds for IHD, and just over one half for stroke and CKD. The PAF for the effects of all four risk factors combined increased by only 1 percentage point when we introduced a pairwise correlation between risk factors in two different sensitivity analyses (with empirical and low vs. high correlation, results not shown).

At the country level (Figure 4), the proportion of deaths from CVDs, CKD, and diabetes attributable to the combined effect of the four risks was lowest in Japan (< 50%), followed by some other Asian countries (e.g., Cambodia and South Korea), some western European countries, Canada and Peru; it was highest in Pacific islands and in some countries in the Middle East like Bahrain and Qatar, reaching 80% or more in Marshall Islands, Fiji, and Kiribati. The PAF for risk factors tended to be low or high for both men and women in the same country (correlation coefficient of 0.81).

The geographical patterns of PAFs for individual risk factors differed from their combined effect. High blood pressure was responsible for > 55% of deaths from CVDs, CKD, and diabetes in Central Asia, Eastern Europe, and sub-Saharan Africa, vs. one third or less in some high-income countries like Canada, Switzerland, South Korea, USA, and Taiwan; in Mexico; and in Papua New Guinea and a few other Pacific islands. Some of the countries with relatively low PAF for high blood pressure, including Pacific islands and Mexico were disproportionately affected by high BMI, as were some Middle Eastern countries and South Africa, with PAFs surpassing one third. High BMI was responsible for 5% or less of deaths from CVDs, CKD, and diabetes in some South and Southeast Asian countries (e.g., Vietnam, Bangladesh, Nepal, Cambodia, and India), Japan, and a few African countries like Ethiopia, DRC, Eritrea, and Burkina Faso. The largest PAFs for high blood glucose were also observed in the Pacific islands, Mexico and a few Caribbean countries (e.g., Trinidad and Tobago and Barbados), and some Middle Eastern countries like Bahrain, Qatar, and Jordan; at the extreme, in Samoa, Kiribati, and Marshall Islands, one half or more of deaths from CVDs, CKD, and diabetes were attributable to high glucose alone. Finally, the proportion of deaths attributable to high serum cholesterol ranged between < 5% in much of sub-Saharan Africa, Vietnam, and Bangladesh to 20% or more in central and northern Europe (Iceland, Finland, Belarus, Russia, Denmark, Lithuania, Russia, Estonia, and Germany) and wealthier Middle Eastern countries like Kuwait and UAE.

Age-standardized death rates attributable to these four risks were highest in countries in Central Asia and Eastern Europe (Figure 5), where PAFs are large (due to high exposure).
and CVD mortality is high. For example, in 2010 these four risks together were responsible for over 925 deaths per 100,000 men in Belarus, Mongolia, and Kazakhstan. The attributable death rates were lowest in high-income countries like Japan, Singapore, South Korea, France, Spain, The Netherlands, Australia and Canada, all below 130 deaths per 100,000 for women and below 200 for men. These countries have low adult mortality and lower PAFs because some risk factors are at relatively low levels. Attributable death rates were also low in countries like Senegal, Peru, Niger and The Gambia where death rates from non-communicable diseases are low because they are still in the early phases of the demographic and epidemiological transition. Between 1980 and 2010, age-standardized death rates attributable to these risk factors decreased in over 120 countries, especially in high-income countries (detailed results not shown). While some of this decrease was due to lower PAFs (e.g., due to declining SBP trends), the main driver was a decline in overall CVD mortality.

Sixty one percent of all deaths attributable to these risks in 2010 were in ten countries, led by China, India, Russia, and USA (Figure 6); this was due to a combination of large population and/or high age-standardised death rates. These four countries also accounted for the largest number of deaths attributable to each individual risk factor, with the exception of the mortality burden of high BMI for which India was in the 8th place. Over time, middle-income countries like Mexico, Turkey, Egypt, and Indonesia have replaced high-income European countries like the UK and France as places where large number of deaths are attributable to these risk factors (Figure 6). Other high-income countries like Italy and Germany have lower ranks in 2010 in terms of number of deaths attributable to these risks, with increasing importance of middle-income countries like Brazil and Ukraine.

Discussion

We found that over 60% of global deaths from CVDs, CKD, and diabetes in 2010 were attributable to four preventable cardio-metabolic risk factors, with high blood pressure having the largest effect. Over time, high blood pressure maintained its role as the leading risk while the mortality burden of high BMI and glucose increased faster than that of high cholesterol, such that these two risks are now responsible for more deaths than high cholesterol. High cholesterol nonetheless remains the second leading risk factor for IHD mortality.

Currently the mortality burden of most of these risk factors is largest in ESEA-P and in CEE-CA where there are a large number of CVD deaths (stroke in ESEA-P and IHD in CEE-CA); CEE-CA also has particularly high levels of most cardio-metabolic risks compared to other regions. There has been a shift in the mortality burden from high-income to low- and middle-income countries due to a combination of demographic factors (faster population growth and aging) and divergent epidemiological trends (declining blood pressure, cholesterol, and CVD death rates in high-income countries while risk factors increased or remained unchanged in low- and middle-income regions). Deaths attributable to these risks occurred in younger ages in low- and middle-income regions compared to high-income countries.
Our study is the most detailed analysis of the worldwide mortality burden of cardio-metabolic risk factors, and the only study to analyse trends in mortality burden over a period of three decades and to report the individual and combined effects of risk factors at the country level. We used data on risk factor exposure, individual and joint aetiological effects, and cause-specific deaths from recent comprehensive pooling studies.\textsuperscript{1, 3, 8–11, 14} We also quantified the uncertainties of our estimates.

Our study also has some limitations. Despite using significantly more data than previous analyses, risk factor exposures and deaths in some regions were affected by data shortage and had larger uncertainty. Second, our RRs were from observational studies, and may be affected by residual confounding. For blood pressure and cholesterol, overwhelming evidence from randomized trials of anti-hypertensive and cholesterol-lowering drugs support the evidence from observational studies on the magnitude of effects.\textsuperscript{17, 25, 26} The causal effects of high BMI are supported by follow-ups of patients after bariatric surgery and randomized lifestyle and diet interventions that have shown benefits of weight loss for diabetes prevention.\textsuperscript{27} Some recent randomized trials have not found a significant beneficial effect of intensive glucose lowering in diabetic patients on CVD mortality. The reasons for these findings may be because intensive glucose lowering was compared with usual care (vs. with placebo), relatively old age and frailty of participants, long duration of diabetes at baseline and high prevalence of existing atherosclerotic disease at trial entry, and relatively low incidence of CVD in trial populations due to concurrent treatment with statins, aspirin and antihypertensives which reduced the power of the trials to detect an effect.\textsuperscript{28} Subsequently, several meta-analyses of randomized trials of intensive versus moderate glucose lowering in diabetic patients have shown significant reduction in the risk of myocardial infarction and other major cardiovascular events.\textsuperscript{29–31} In particular, a meta-analysis of the 4 largest randomized trials concluded that more intensive glucose lowering causes a “modest but significant cardiovascular benefit in the short to medium term”.\textsuperscript{30} For these reasons, and considering the overwhelming evidence from observational studies of the graded increase in risk of CVD with higher blood glucose levels, we included IHD and stroke as outcomes of high blood glucose. Nonetheless, for both BMI and glucose, residual confounding remains a concern. We used the same RRs for all countries. Although similarity of RRs (and of mediation of the excess risk of BMI by other cardio-metabolic risks) between East Asian and Western populations is supported by results of large cohort pooling studies,\textsuperscript{3, 7, 14} it would be desirable to have further evidence on the magnitude of RRs, e.g. from Africa and Latin America. In addition to mediatiion, the combined PAFs for multiple risks depend on correlation of exposures and on effect size modification, for which we did not have data. In sensitivity analyses, our results were robust to correlations of risk factor exposures. We used serum TC to measure population exposure to high cholesterol because there were substantially more data available for TC than for subtypes such as LDL or non-HDL cholesterol and for apolipoproteins.\textsuperscript{11} Findings in countries with data on both total and LDL cholesterol (each with its corresponding RR) show that the estimated attributable deaths are comparable using the two metrics.\textsuperscript{21} Similarly, we used BMI as our measure of adiposity to take advantage of decades of worldwide anthropometric data. However, measures of abdominal obesity such as waist circumference and waist-to-hip ratio seem to have independent effects on mortality even after accounting for BMI.\textsuperscript{32}
focused only on effects on CVDs, CKD, and diabetes which are aetiologically related. High BMI is also a risk factor for some types of cancer, responsible for an estimated 320,000 cancer deaths worldwide in 2010.\textsuperscript{12} High glucose is associated with increased risk of tuberculosis.\textsuperscript{33} Finally, the remaining CVD, CKD and diabetes deaths, which ranged between 20\% and over 50\% in different countries, may be due to a range of factors not considered in our analysis, independently or in interaction with genetic factors. For example, over 10\% of all CVDs are attributable to smoking,\textsuperscript{34} which would make the combined effects of the cardio-metabolic risks and smoking about 70\% at the global level. Unhealthy diets, insufficient physical activity, and harmful alcohol use are risk factors for CVDs and diabetes, with their effects partially or fully mediated through the cardio-metabolic factors covered in our work. Foetal and early childhood undernutrition increases the risk of CVDs and diabetes; infections and parasitic diseases are also risk factors for CKD. Inflammation, caused by infections as well as by other environmental factors, is a risk factor for CVDs, CKD, and possibly diabetes. There is increasing evidence on the role of stress, sleep patterns, and other psychosocial factors as independent risk factors for CVDs and other noncommunicable diseases (NCDs).

Our results have important implications for NCD prevention and control throughout the world. Interventions for lowering blood pressure such as reducing salt in diet and better diagnosis and treatment have been successful in reducing blood pressure in high-income countries,\textsuperscript{35–37} which has in turn been an important determinant of decline in CVD mortality.\textsuperscript{38} Blood pressure interventions are urgently needed in low- and middle-income countries, where salt intake remains high and coverage of anti-hypertensive drugs is low.\textsuperscript{39–41} Salt from packaged and prepared foods is a relatively small component of total salt intake in these countries, which necessitates alternative locally-acceptable approaches to salt reduction.\textsuperscript{42, 43} Similarly, scaling up pharmacological treatments requires a universal and high-quality primary care system as well as national guidelines for identifying those who are in need of intervention, either based on the level of a single risk factor or based on their absolute risk of an adverse event.\textsuperscript{40, 44} Western high-income countries have also lowered serum cholesterol, through a combination of replacing saturated fats with unsaturated fats and increased treatment.\textsuperscript{11, 45–47} While at the global level high cholesterol had the lowest mortality burden among these risk factors, it has increased in East/Southeast Asian countries like Japan, China, and Thailand, possibly due to increased intake of animal-source foods.\textsuperscript{11, 48} The number of CVD deaths attributable to serum cholesterol increased by about 250\% in the ESEA-P between 1980 and 2010, more than blood pressure and glucose but less than BMI. Dietary and healthcare interventions for lowering serum cholesterol are needed in this region. Finally, healthcare access and quality is one of the most important determinants of variation in mortality from CVDs, CKD, and diabetes both across and within countries.

Unlike national successes in reducing blood pressure and cholesterol, BMI and blood glucose have increased in most countries,\textsuperscript{8–11} a trend reflected in the larger increase in their mortality burden than those of high blood pressure and cholesterol. Randomised studies of diet and lifestyle change have shown moderate weight loss benefits for up to 2 years,\textsuperscript{49–51} and have reduced diabetes incidence.\textsuperscript{52} However, long-term and community effectiveness of such interventions is not clear.\textsuperscript{53} Simple advice and exercise alone have not been efficacious, even in randomised trials.\textsuperscript{51} The rising burdens of BMI and glucose, which can
be only partially addressed through blood pressure and cholesterol interventions, demonstrates the urgent need for developing and testing new approaches to obesity prevention. These approaches would have to go beyond individual-level health promotion, and use fiscal and regulatory tools to motivate changes in diet and lifestyle.35 54

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Research in context

Systematic review

We searched in PubMed using the search words “comparative risk assessment” AND ("cardiovascular disease" OR "chronic kidney disease" OR “diabetes”) for articles in English published before 09 April 2014. We also identified articles thorough the reference accessed for Comparative Risk Assessment studies. We found some articles that had reported the mortality burden of individual or multiple cardio-metabolic risk factors for one or more countries (including subnationally), for specific diseases or all cause mortality, for one or at most two points in time.12, 13, 15, 21, 55–61

Interpretation

Our study shows that over 60% of worldwide deaths from cardiovascular diseases, chronic kidney disease and diabetes are attributable to four cardio-metabolic risk factors – elevated blood pressure and glucose, serum cholesterol, and BMI – which can be prevented through a combination of population-based and personal interventions. The largest mortality burden was due to high blood pressure but those of high BMI and blood glucose increased faster than that of the other two risks over time. There is a need to replicate successful experiences in reducing population blood pressure and cholesterol, and to identify effective and scalable interventions that may curb or reverse the rising trends of BMI and glycaemia. There is a need for periodic representative country data on cardio-metabolic risk factors to improve the risk factor estimates and monitor risk factor trends.
Figure 1.
Deaths attributable to the individual and combined effects of high body mass index, blood pressure, cholesterol, and glucose by region and (A) sex and (B) age group.
Figure 2.
Age-standardised death rates attributable to the combined effects of high body mass index, blood pressure, cholesterol, and glucose by region.
Figure 3.
Deaths attributable to the individual and combined effects of high body mass index, blood pressure, cholesterol, and glucose in 2010, by disease.
Figure 4.
Percent of deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to individual and combined effects of high body mass index, blood pressure, cholesterol, and glucose by country in 2010.
Note that the scales differ by panel to enhance visibility.
Figure 5.
Age-standardized death rates from cardiovascular diseases, diabetes, and chronic kidney disease attributable to individual and combined effects of high body mass index, blood pressure, cholesterol, and glucose by country and sex, in 2010.
Results are not shown for women in Afghanistan because despite relatively low PAFs (Figure 4), they had the highest worldwide death rates attributable to these risk factors due to very high CVD death rates in the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. See Webfigure 1 for the version of figure that also includes results for women in Afghanistan.
Figure 6.
Ten countries with the largest number of deaths attributable to high BMI, blood pressure, cholesterol, and glucose in 1980 and 2010.
Table 1
Percent of deaths attributable to the individual and combined effects of body mass index, fasting plasma glucose, serum total cholesterol, and systolic blood pressure by sex in 2010.

<table>
<thead>
<tr>
<th></th>
<th>Number of death, median (95% CI), thousand</th>
<th>Contributing risk factor (individual PAF, median (95% CI), percentage point)</th>
<th>Joint PAF, median (95% CI), percentage point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High blood pressure</td>
<td>High body mass index</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart</td>
<td>387 (325 – 467)</td>
<td>76 (71 – 80)</td>
<td>24 (17 – 30)</td>
</tr>
<tr>
<td>disease</td>
<td>Ischemic heart disease</td>
<td>3705 (3341 – 3951)</td>
<td>48 (39 – 56)</td>
</tr>
<tr>
<td>Total stroke</td>
<td>2816 (2516 – 3226)</td>
<td>53 (46 – 59)</td>
<td>8 (7 – 10)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1585 (1263 – 1952)</td>
<td>57 (49 – 66)</td>
<td>7 (5 – 9)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1211 (1114 – 1593)</td>
<td>48 (40 – 55)</td>
<td>10 (8 – 12)</td>
</tr>
<tr>
<td>Other CVDs</td>
<td>891 (822 – 964)</td>
<td>37 (33 – 40)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>569 (409 – 603)</td>
<td>0</td>
<td>27 (11 – 43)</td>
</tr>
<tr>
<td>Chronic kidney</td>
<td>357 (298 – 393)</td>
<td>45 (39 – 50)</td>
<td>24 (19 – 29)</td>
</tr>
<tr>
<td>disease</td>
<td>All CVDs, diabetes and CKD</td>
<td>8716 (8291 – 9201)</td>
<td>46 (42 – 51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart</td>
<td>469 (328 – 668)</td>
<td>75 (70 – 80)</td>
<td>28 (19 – 38)</td>
</tr>
<tr>
<td>disease</td>
<td>Ischemic heart disease</td>
<td>3263 (3063 – 3455)</td>
<td>45 (28 – 57)</td>
</tr>
<tr>
<td>Total stroke</td>
<td>2995 (2708 – 3246)</td>
<td>47 (38 – 55)</td>
<td>10 (8 – 12)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1439 (1205 – 1589)</td>
<td>52 (41 – 64)</td>
<td>10 (8 – 12)</td>
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<tr>
<td>Ischemic stroke</td>
<td>1559 (1476 – 1719)</td>
<td>42 (29 – 52)</td>
<td>9 (7 – 13)</td>
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<tr>
<td>Other CVDs</td>
<td>860 (807 – 905)</td>
<td>33 (27 – 37)</td>
<td>0</td>
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<tr>
<td>Diabetes</td>
<td>667 (513 – 696)</td>
<td>0</td>
<td>33 (14 – 51)</td>
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<tr>
<td>Chronic kidney</td>
<td>345 (236 – 392)</td>
<td>46 (39 – 52)</td>
<td>29 (24 – 35)</td>
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<tr>
<td>disease</td>
<td>All CVDs, diabetes and CKD</td>
<td>8568 (8142 – 9005)</td>
<td>43 (35 – 49)</td>
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</table>