Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment

*The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration**

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Summary

Background High blood pressure, blood glucose, serum cholesterol, and BMI are risk factors for cardiovascular diseases and some of these factors also increase the risk of chronic kidney disease and diabetes. We estimated mortality from cardiovascular diseases, chronic kidney disease, and diabetes that was attributable to these four cardiometabolic risk factors for all countries and regions from 1980 to 2010.

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

Findings In 2010, high blood pressure was the leading risk factor for deaths due to cardiovascular diseases, chronic kidney disease, and diabetes in every region, causing more than 40% of worldwide deaths from these diseases; high BMI and glucose were each responsible for about 15% of deaths, and high cholesterol for more than 10%. After accounting for multicausality, 63% (10·8 million deaths, 95% CI 10·1–11·5) of deaths from these diseases in 2010 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 from 1980 to 2010. At the country level, age-standardised death rates from these diseases attributable to the combined effects of these four risk factors surpassed 925 deaths per 100 000 for men in Belarus, Kazakhstan, and Mongolia, but were less than 130 deaths per 100 000 for women and less than 200 for men in some high-income countries including Australia, Canada, France, Japan, the Netherlands, Singapore, South Korea, and Spain.

Interpretation The salient features of the cardiometabolic disease and risk factor epidemic at the beginning of the 21st century are high blood pressure and an increasing effect of obesity and diabetes. The mortality burden of cardiometabolic risk factors has shifted from high-income to low-income and middle-income countries. Lowering cardiometabolic risks through dietary, behavioural, and pharmacological interventions should be a part of the global response to non-communicable diseases.

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Introduction

Cardiovascular diseases, chronic kidney disease, and diabetes are among leading global and regional causes of death.[1,2] Between 1990 and 2010, the total number of deaths caused by cardiovascular diseases increased by more than 25% and those of chronic kidney disease and diabetes nearly doubled.[1] Adiposity and high blood pressure, cholesterol, and glucose are important modifiable risk factors for cardiovascular diseases and (except for cholesterol) for chronic kidney disease.[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 BMI and blood glucose have increased in most countries and worldwide,[8,9] mean blood pressure has fallen in high-income and some middle-income regions; it has remained unchanged or even increased in some low-income and middle-income countries.[10] Mean serum total cholesterol has also fallen in many parts of Europe, north America, and Australasia while increasing in east and southeast Asia, especially China, Japan, and Thailand.[11]

Previous comparative risk assessments[12,13] have reported global and some regional estimates of the effects of cardiometabolic risk factors on mortality. However, these studies did not analyse the combined effects of the risk factors, partly because reliable estimates of how much of the effect of adiposity on cardiovascular diseases is mediated through blood pressure, blood glucose, and serum cholesterol concentration were unavailable at the time.[14] The only analysis[15] of the combined effects of these risks divided the world into

three large regions and did not include high blood glucose as a risk factor. Additionally, previous studies used broad disease categories—for example, all cardiovascular diseases, rather than specific diseases of public health or clinical relevance such as stroke subtypes. Finally, very little is known about how much the effects of these risk factors on mortality have changed over time, even though both the prevalence of risk factors and cardiometabolic death rates have changed enormously, sometimes in opposite directions. We estimated cause-specific mortality from cardiovascular diseases, chronic kidney disease, and diabetes attributable to the effects of high BMI, blood pressure, blood glucose, and serum cholesterol, individually as well as in combination, by country and region from 1980 to 2010.

Methods

Data sources

We used measures of exposure to cardiometabolic risk factors for which the most comprehensive worldwide data were available—namely, BMI, fasting plasma glucose, systolic blood pressure, and serum total cholesterol. We derived population exposure to risk factors by country, year, sex, and age group from pooled analyses of population-representative health surveys as described in detail elsewhere.[8–11] Briefly, we collated population-based data from published and unpublished national, subnational, and community surveys and studies done between 1980 and 2010. We used 960 data sources across countries and years for BMI, 786 for systolic blood pressure, 370 for fasting plasma glucose, and 321 for total cholesterol.[8–11] About 50% of data for BMI in low-income and middle-income countries were from the 2000s and another 34% from the 1990s, whereas for high-income regions, data were evenly distributed over time.[9] The data for systolic blood pressure were distributed almost equally among the three decades of analysis, but more than 60% of national sources were from the 2000s.[10] About 40% of all data for total cholesterol and two-thirds of all national data were from the 2000s.[11] Half of the data for fasting plasma glucose and 68% of the national data, were from the 2000s, and another 35% from the 1990s.[8]

We used a Bayesian hierarchical model to estimate the levels of risk factors by sex and age group for all countries and years, sharing and borrowing information across space, time, and age as well as through covariates that helped predict risk factor levels.[8–11,16] The uncertainties of the estimates incorporated the sampling error of the data, as well as uncertainty resulting from some data sources not being nationally representative and from missing data. We estimated the standard deviations (SDs) of distributions of risk factors for each country-year-age-sex unit using the population mean and the coefficients of a regression that related SD to mean. We corrected SDs for systolic blood pressure, total cholesterol, and fasting plasma glucose for the error associated with one-off measurements by use of coefficients from prospective studies with multiple measurements.[17–19]

We quantified the effects of each risk factor on specific cardiovascular disease outcomes (ischaemic heart disease, ischaemic and haemorrhagic strokes, hypertensive heart disease, and other cardiovascular diseases), diabetes, and chronic kidney disease when there was evidence of a convincing or probable causal association.[3] For each risk factor–disease pair, we used the age-specific relative risk (RR) from meta-analyses of prospective studies that had adjusted for major confounders and to the extent possible for regression dilution bias. The RRs for effects on cardiovascular diseases and diabetes are reported elsewhere, as is the RR for the effect of high BMI on chronic kidney disease.[3,4,20] The RR for the effect of high blood pressure on chronic kidney disease from pooled analysis of prospective cohorts was 1·28 (1·18–1·39) per 10 mm Hg higher systolic blood pressure (unpublished data).

We estimated what proportion of the effects of BMI on ischaemic heart disease and stroke was mediated through the other three risk factors from a pooled analysis of 97 prospective cohort studies.[14] This pooled analysis showed that 46% (95% CI 42–50) of the excess RR of BMI on ischaemic heart disease and 76% (65–91) on stroke were mediated through the other three risk factors.[14] We assumed that the effect of high BMI on hypertensive heart disease is fully mediated through blood pressure, on diabetes through fasting plasma glucose concentration, and on chronic kidney disease through the combination of systolic blood pressure and fasting plasma glucose concentration.

We used estimates of the number of deaths by underlying cause from the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study, with data sources and methods described in detail elsewhere.[1] Briefly, total and cause-specific death rates were estimated from 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 re-distributed, and statistical models were used to estimate cause-specific death rates by country, year, sex, and age group, with specific models selected on the basis of data quality and performance of the model. Like risk factors, there were substantially more data for causes of death in recent years than for the 1980s.[1]

Statistical analysis

We calculated population attributable fractions, which quantify 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. We calculated population attributable fractions as described elsewhere,[12,13,21] using data for exposure distributions and RRs for each risk factor–disease pair. The number of

deaths attributable to each risk factor is a product of the population attributable fraction and the cause-specific deaths for each country-year-sex-age group unit. The optimal levels were based on the levels corresponding to lowest all-cause mortality from reliable epidemiological studies.[3] To account for the uncertainty of these optimal distributions, we allowed them to take a range with means of 110–115 mm Hg (SDs 4–6) for systolic blood pressure; 3·8–4·0 mmol/L (0·50–0·65) for total cholesterol; 21–23 kg/m² (1·1–1·8) for BMI; and 4·9–5·3 mmol/L (0·4–0·6) for fasting plasma glucose.[3] The benefits of lowering BMI for haemorrhagic stroke were estimated only for values above 25 kg/m², because there seems to be no reduction in risk below this level.[4]

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 are the result of more than one risk factor (multicausality), and because some of the effects of BMI are mediated through the other three risk factors.[14] In the absence of mediation, effect modification, and risk factor correlation, the combined effects of multiple risk factors can be calculated on the basis of their individual population attributable fractions using a simple relationship that incorporates multicausality as described elsewhere.[15] To use this relationship in the presence of mediation, we calculated the direct effect of BMI on the relevant disease outcomes (ie, the part not mediated by the other three risks). We then tested the sensitivity of our findings to the correlation between risk factors. We used both an empirical correlation matrix from the continuous US National Health and Nutrition Examination Survey 1999–2010 (with pairwise correlation coefficients of between 0·11 and 0·31) and another correlation matrix with substantially larger pairwise correlation coefficients of 0·8.

For the **US National Health and Nutrition Examination Survey 1999–2010** see http://www.cdc.gov/nchs/nhanes.htm

Our analysis covered 187 countries for which estimates of deaths by cause were available. We obtained regional and worldwide results by population weighting country estimates. We combined age-specific death rates into broader ages (25–69 and ≥70 years). We calculated age-standardised death rates with use of the WHO standard population.[22]

We propagated the uncertainties of all inputs (risk factor exposure distributions, RRs, proportion of excess risk from BMI mediated through the other three risks, and cause-specific deaths) to the final estimates with a simulation approach. Specifically, we used 1000 draws from the uncertainty distributions of each input, and repeated the calculations with these draws. The resulting 1000 population attributable fractions and attributable deaths characterised the distributions of the outputs. We report the median of these draws as the central estimates and their 2·5th and 97·5th percentiles as the 95% credible or confidence interval. Draws for different analysis units might be correlated (eg, in two age groups or countries for risk factor exposures and cause-specific deaths because they came from a common statistical model). We took these correlations into account by taking correlated draws across countries, age groups, and years. We did all statistical analyses with Stata (version 12.0) and R (version 3.02).

Role of the funding source

The funders 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

Between 1980 and 2008, age-standardised global mean BMI increased by 0·4 kg/m² per decade (95% CI 0·2 to 0·6) for men and 0·5 kg/m² per decade (0·3 to 0·7) for women. Mean BMI for men increased in every region except central Africa and south Asia, 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 did not change for women in central and eastern Europe and central Asia. Between 1980 and 2008, worldwide systolic blood pressure fell by 0·8 mm Hg per decade (95% CI –0·4 to 2·2) for men and 1·0 mm Hg per decade (–0·3 to 2·3) for women. Systolic blood pressure decreased most in high-income countries for men and women. Systolic blood pressure rose in Oceania, east Africa, south Asia, and southeast Asia for both sexes, and in west Africa for women. Globally, mean serum total cholesterol concentration changed little between 1980 and 2008, falling by less than 0·1 mmol/L per decade for men and women. Total serum cholesterol fell in Europe, Australasia, and north America but increased in east and southeast Asia and Pacific. We found little evidence of a change in Latin America and the Caribbean, the Middle East and north Africa, south Asia, and sub-Saharan Africa. Global age-standardised mean fasting plasma glucose increased by 0·07 mmol/L per decade (95% CI –0·02 to 0·15) for men and 0·09 mmol/L per decade (0·00 to 0·17) for women, with increases or, at best, no change in every region. The largest increase in fasting plasma glucose occurred in Oceania. Risk factor trends by country and region are described in detail elsewhere.[8–11]

In 2010, cardiovascular diseases, chronic kidney disease, and diabetes were together responsible for 17·6 million (33%) of 52·8 million deaths worldwide.[1] The number of deaths from these causes attributable to individual cardiometabolic risks ranged between 2·0 (1·5–2·5) million for high serum cholesterol and 7·7 (6·9–8·4) million for high blood pressure. After accounting for multicausality, the four risk factors together were responsible for 63% (10·8 million, 95% CI 10·1–11·5) of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes, accounting for one in every five deaths worldwide. 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 was 7·1 million (67%) of 10·6 million deaths worldwide (95% CI 6·6–7·6) in 1980, increasing steadily throughout the three decades of analysis, driven by population growth and aging. Although high blood pressure was the leading risk factor throughout the analysis period, high cholesterol was responsible for the second most deaths until 1990. High BMI and blood glucose had smaller effects in 1980, each responsible for around 1·2 million deaths; this number had doubled by 2010.

After accounting for population size and aging, age-standardised deaths attributable to the four risk factors fell steadily worldwide, and in high-income regions, Latin America and the Caribbean, and the Middle East and north Africa, between 1980 and 2010 (figure 2). In high-income regions, this fall was caused by a combination of decreasing population attributable fractions (themselves driven by lower systolic blood pressure and total serum cholesterol) and lower cardiovascular death rates; elsewhere, falling mortality was the main driver.[23,24] Age-standardised death rates attributable to risk factors increased in south Asia because both risk factor levels and total death rates increased; they did not change in sub-Saharan Africa and decreased only slightly in central and eastern Europe and central Asia. There was, however, a steeper decline in central and eastern Europe and central Asia after 2000.

In 1980, the number of deaths attributable to these four risk factors in high-income regions was larger than that in any of the low-income and middle-income regions; high-income regions accounted for 35% (2·5 milion of 7·1 million) of deaths attributable to the combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol, whereas low-income and middle-income regions accounted for the remaining 65% (figure 1A). By 2010, low-income and middle-income regions accounted for 82% (8·8 million of 10·8 million) of attributable deaths, and the two regions with the largest number of attributable deaths were east and southeast Asia and Pacific (3 million deaths or 28% of all deaths attributable to these risks), followed by central and eastern Europe and central Asia (2 million deaths). In fact, from 1980 to 2010, the number of deaths attributable to high blood pressure and cholesterol fell in high-income regions, despite population increase and aging, and those attributable to high BMI and blood glucose increased only slightly. In low-income and middle-income regions, the number of deaths attributable to these four risk factors increased or remained stable over time. In 2010, east and southeast Asia and Pacific also had the largest mortality burden of high blood glucose and blood pressure—30% of deaths attributable to high blood pressure worldwide occurred in this region. However, mortality burden of high BMI and serum cholesterol were still largest in high-income regions and in central and eastern Europe and central Asia in 2010.

40% (4·3 million of 10·8 million) of deaths attributable to these four risk factors in 2010 occurred in people aged younger than 70 years and thus caused greater loss of life years than deaths of older people (figure 1B). Deaths before age 70 years made up a smaller proportion of the mortality burden of the four risk factors in high-income regions (21% of all attributable deaths) and in central and eastern Europe and central Asia (33%) than in other regions. The share of attributable deaths before age 70 years was greatest in south Asia (55%) and sub-Saharan Africa (58%). Deaths attributable to the four risk factors shifted to older ages over time in high-income regions, where 31% of deaths attributable to the risk factors occurred in people younger than age 70 years in 1980 (compared with 21% in 2010). A similar shift occurred in Latin America and the Caribbean but not in other regions.

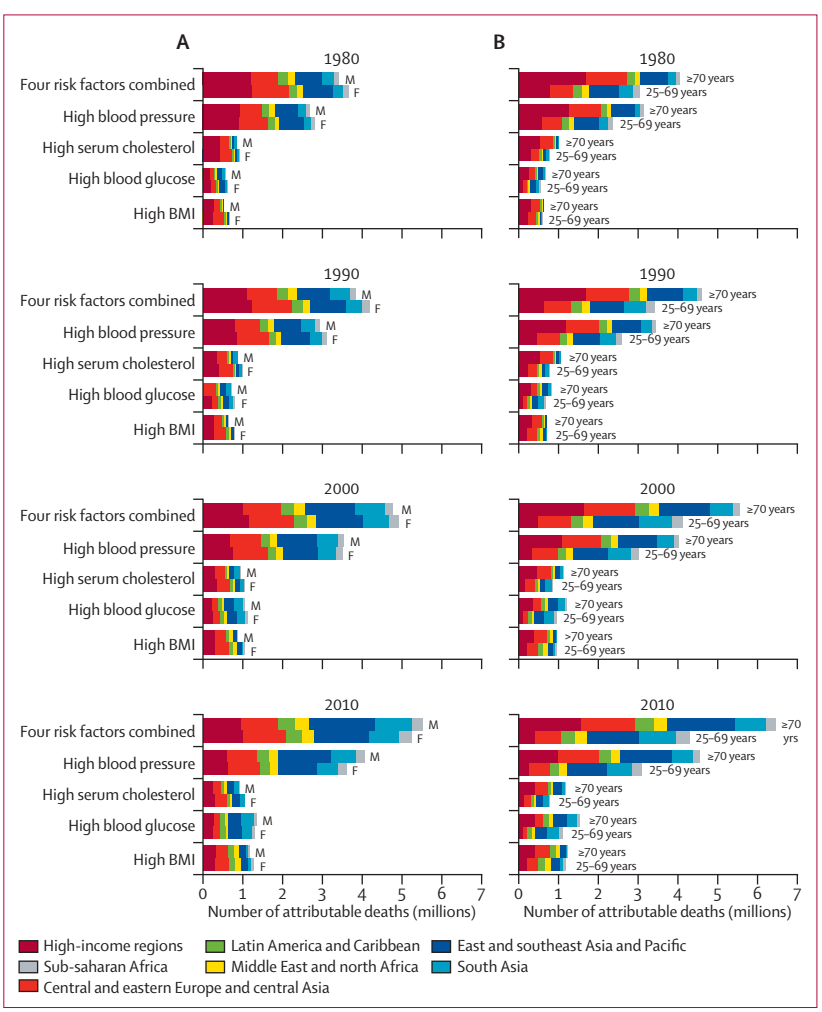

Figure 1: **Deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to the individual and combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose by region and sex (A) and age group (B), 1980–2010**
M=male. F=female.

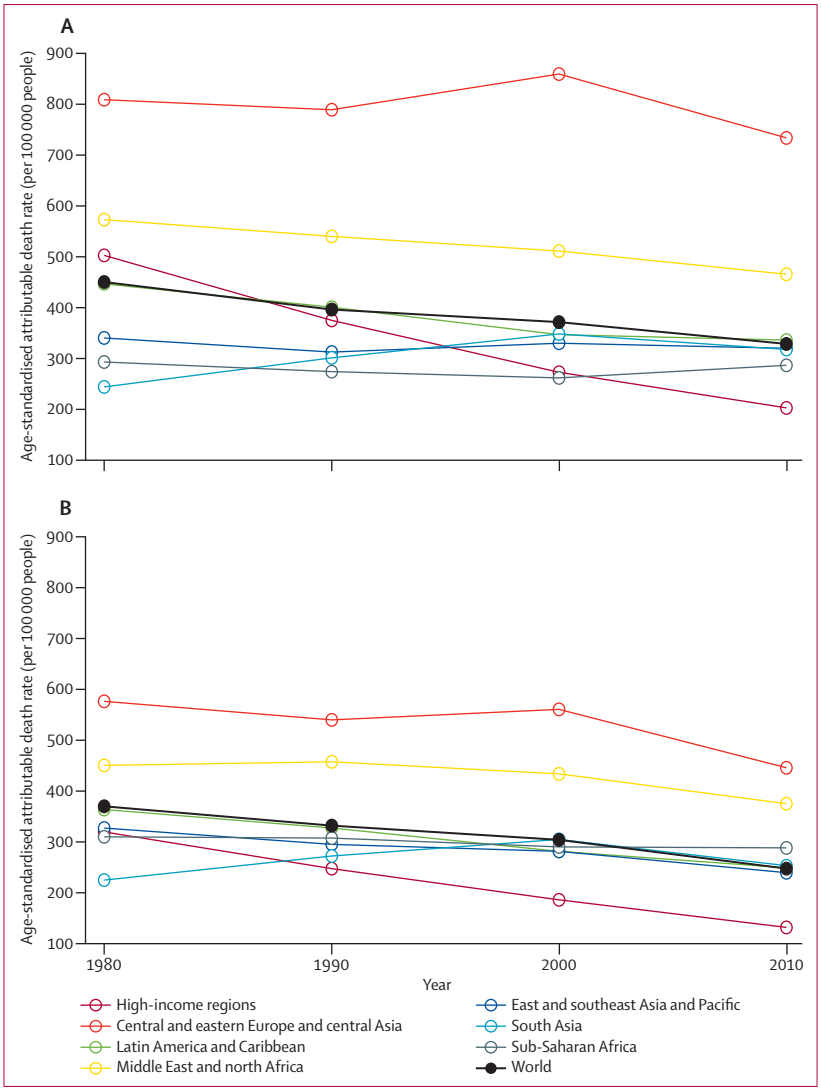

Figure 2: **Age-standardised death rates from cardiovascular diseases, diabetes, and chronic kidney disease attributable to the combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose by region for men (A) and women (B)**

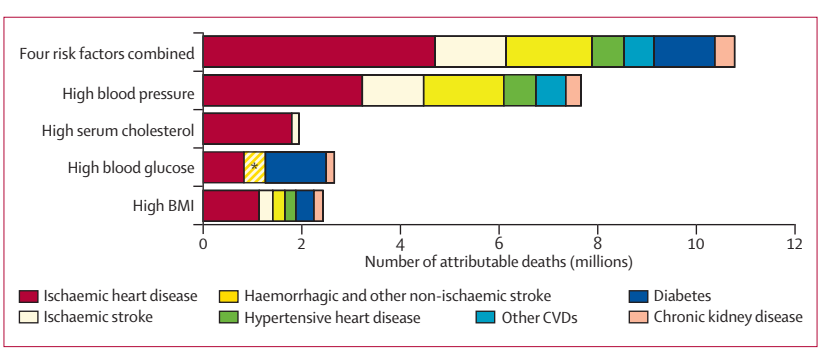

Figure 3: **Deaths attributable to the individual and combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose in 2010, by disease**
CVD=cardiovascular disease. *For total stroke (RRs were for association between blood glucose and total stroke).

In every region and through the whole analysis period, high blood pressure was the leading risk factor for mortality, but the relative importance of other risks varied by region and over time (appendix). In 1980, high blood pressure was followed by either high cholesterol or high glucose for every region and sex, except for women in the Middle East and north Africa, for whom high BMI was the second leading risk factor. By 2010, the relative importance of high cholesterol fell, and its mortality burden was in the third or fourth greatest for every region and sex; blood pressure was followed by either high BMI or high blood glucose, a result of the worldwide rise in excess weight and hyperglycaemia. The increasing importance of high BMI as a risk factor accelerated after 1990.

Overall, 44% (4·7 million of 10·8 million) of deaths attributable to the combined effects of these risk factors in 2010 were from ischaemic heart disease, followed by 30% from stroke, and 11% from diabetes (figure 3). Ischaemic heart disease was the single most dominant cause of death attributable to high cholesterol (92% [1·80 of 1·95] of all deaths attributable to this risk factor), whereas about the same number of deaths caused by ischaemic heart disease and stroke were attributable to high blood pressure. Deaths directly assigned to diabetes accounted for only 46% (1·24 million of 2·66 million) of deaths caused by high blood glucose, with the remainder having ischaemic heart disease, ischaemic stroke, or chronic kidney as the underlying clinical causes of death.

After accounting for multicausality, 63% (CI 59–67) of all deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes among men and 62% (56–67) among women were attributable to the four risk factors together in 2010 (table). In 1980, the population attributable fractions were 67% (62–72) for men and 66% (61–72) for women (detailed results not shown). High blood pressure alone was responsible for more than 40% of deaths caused by these three diseases, high BMI and glucose concentration were each responsible for about 15% of deaths, and cholesterol for more than 10%. Although high cholesterol was responsible for fewer deaths from the combination of cardiovascular diseases, chronic kidney disease, and diabetes in 2010 compared to the other three risk factors, it caused the second most deaths caused by ischaemic heart disease, about twice that of high glucose. High BMI and glucose were responsible for fewer deaths caused by ischaemic heart disease than was high cholesterol, but were also associated with deaths from haemorrhagic stroke, diabetes, and chronic kidney disease, none of which are affected by high cholesterol. The combined population attributable fraction of the four risk factors together was about three quarters for hypertensive heart disease, about two thirds for ischaemic heart disease, and just more than a half for stroke and chronic kidney disease. The population attributable fraction for the effects of all four risk factors combined increased by only 1 percentage point when we introduced a pairwise correlation between

	Number of deaths (95% CI; thousands)	PAF of risk factor (95% CI)				
		High blood pressure	High BMI	High blood glucose	High serum cholesterol	Four risk factors combined
Men						
All CVDs, diabetes, and CKD	8716 (8291–9201)	46% (42–51)	13% (12–15)	15% (13–18)	10% (8–13)	63% (59–67)
Hypertensive heart disease	387 (325–467)	76% (71–80)	24% (17–30)	0%	0%	76% (71–80)
Ischaemic heart disease	3705 (3341–3951)	48% (39–56)	16% (14–18)	12% (9–17)	23% (17–28)	67% (60–73)
Total stroke	2816 (2516–3226)	53% (46–59)	8% (7–10)	8% (6–11)	2% (1–6)	58% (52–65)
Haemorrhagic and other non-ischaemic stroke	1585 (1263–1952)	57% (49–66)	7% (5–9)	..	0%	61% (53–70)
Ischaemic stroke	1221 (1114–1593)	48% (40–55)	10% (8–12)	..	5% (3–13)	54% (46–63)
Other CVDs	891 (822–964)	37% (33–40)	0%	0%	0%	37% (33–40)
Diabetes	569 (409–603)	0%	27% (11–43)	100%	0%	100%
Chronic kidney disease	357 (298–393)	45% (39–50)	24% (19–29)	23% (19–28)	0%	57% (52–62)
Women						
All CVDs, diabetes, and CKD	8568 (8142–9005)	43% (35–49)	15% (12–17)	15% (13–18)	12% (8–17)	62% (56–67)
Hypertensive heart disease	469 (328–668)	75% (70–80)	28% (19–38)	0%	0%	75% (70–80)
Ischaemic heart disease	3263 (3063–3455)	45% (28–57)	17% (13–21)	11% (8–15)	29% (19–39)	69% (57–76)
Total stroke	2995 (2708–3246)	47% (38–55)	10% (8–12)	7% (5–10)	2% (1–12)	52% (44–62)
Haemorrhagic and other non-ischaemic stroke	1439 (1205–1589)	52% (41–64)	10% (8–12)	..	0%	56% (46–68)
Ischaemic stroke	1559 (1476–1719)	42% (29–52)	9% (7–13)	..	4% (2–22)	49% (35–62)
Other CVDs	860 (807–905)	33% (27–37)	0%	0%	0%	33% (27–37)
Diabetes	667 (513–696)	0%	33% (14–51)	100%	0%	100%
Chronic kidney disease	345 (236–392)	46% (39–52)	29% (24–35)	23% (19–28)	0%	58% (53–63)

CVD=cardiovascular disease. CKD=chronic kidney disease. PAF=population attributable fraction.

Table: **Proportion of deaths attributable to the individual and combined effects of high BMI, blood pressure, blood glucose, and serum total cholesterol in 2010**

See Online for appendix

risk factors in two different sensitivity analyses (with empirical and low *vs* high correlation; data not shown).

At the country level (figure 4), the proportion of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes that were attributable to the combined effect of the four risk factors was lowest in Japan (<50%), followed by some other Asian countries (eg, Cambodia and South Korea), some western European countries, Canada, and Peru; it was highest in the Pacific islands and in some countries in the Middle East, such as Bahrain and Qatar, reaching 80% or more in Marshall Islands, Fiji, and Kiribati. The population attributable fraction for risk factors tended to be low or high for both men and women in the same country (correlation coefficient between population attributable fractions for the two sexes was 0·81).

The geographical patterns of population attributable fractions for individual risk factors differed from their combined effect. High blood pressure was responsible for more than 55% of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes in central Asia, eastern Europe, and sub-Saharan Africa. By contrast, it was responsible for a third or less of such deaths in some high-income countries—including 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 population attributable fraction 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 population attributable fractions surpassing a third. High BMI was responsible for 5% or less of deaths from cardiovascular diseases, chronic kidney disease, and diabetes in some south and southeast Asian countries (eg, Vietnam, Bangladesh, Nepal, Cambodia, and India), Japan, and a few African countries, such as Ethiopia, DR Congo, Eritrea, and Burkina Faso. The largest population attributable fractions for high blood glucose occurred in the Pacific islands, Mexico, a few Caribbean countries (eg, Trinidad and Tobago and Barbados), and some Middle Eastern countries (eg, Bahrain, Qatar, and Jordan). For example, in Samoa, Kiribati, and Marshall Islands, one half or more of deaths from cardiovascular diseases, chronic kidney disease, and diabetes were attributable to high blood glucose alone. Finally, the proportion of deaths attributable to high serum cholesterol ranged from less than 5% in much of sub-Saharan Africa, Vietnam, and Bangladesh to 20% or more in central and northern

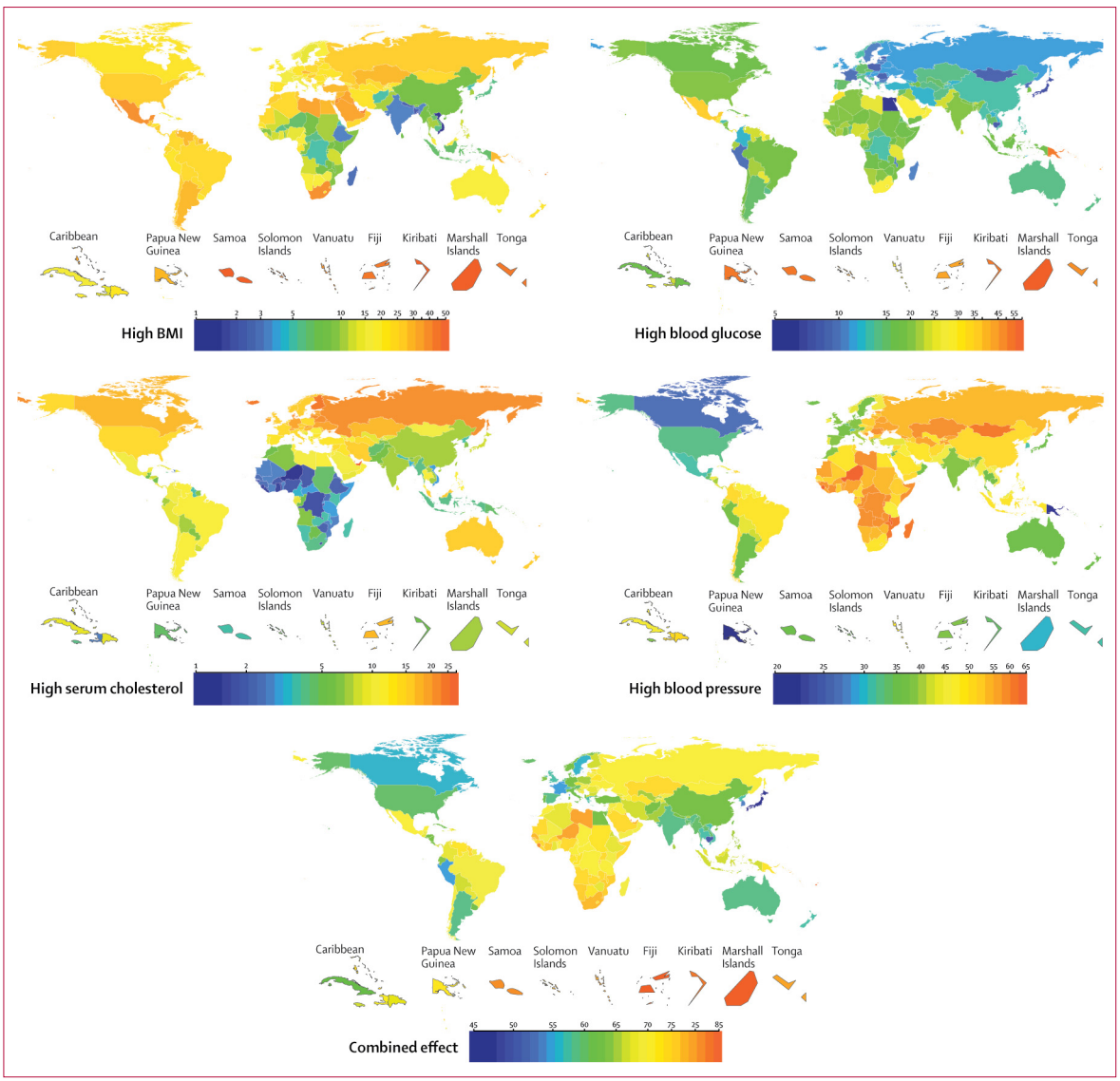

Figure 4: **Proportion of deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to individual and combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol in 2010**
Note that the scales differ by panel.

Europe (Iceland, Finland, Belarus, Russia, Denmark, Lithuania, Russia, Estonia, and Germany) and wealthier Middle Eastern countries such as Kuwait and United Arab Emirates.

In 2010, age-standardised death rates attributable to these four risk factors were highest in countries in central Asia and eastern Europe (figure 5), where population attributable fractions were large (because of high exposure) and mortality from cardiovascular diseases was high. For example, these four risk factors together were responsible for more than 925 deaths from cardiovascular diseases, chronic kidney disease, and diabetes per 100 000 men in Belarus, Mongolia, and Kazakhstan. The attributable death rates were lowest in high-income countries—Japan, Singapore, South Korea, France, Spain, the Netherlands, Australia, and Canada all had fewer than 130 deaths per 100 000 women and fewer than 200 deaths per 100 000 men. These countries had low adult mortality and low population attributable fractions because some metabolic factors are low compared with in other countries. Attributable death rates were also low in Senegal, Peru, Niger, and The Gambia, where death rates from non-communicable diseases were low because these countries are still in the early phases of the demographic and epidemiological transition. From 1980 to 2010, age-standardised death rates attributable to the combined effects of these risk factors decreased in more than 120 countries, especially

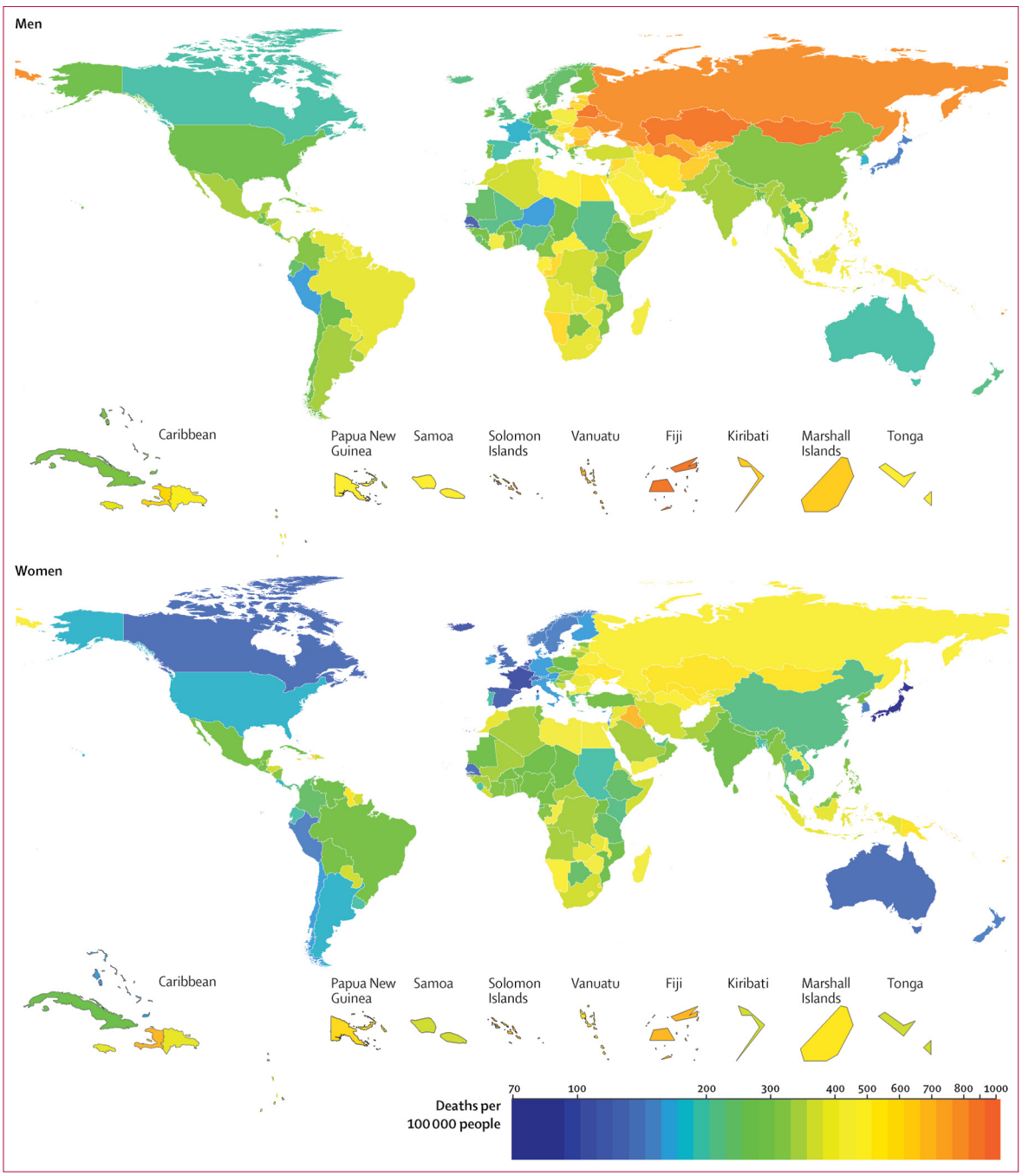

Figure 5: **Age-standardised death rates from cardiovascular diseases, diabetes, and chronic kidney disease attributable to combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol by sex in 2010**

Results are not shown for women in Afghanistan because despite relatively low population attributable fractions (figure 4), they had the highest worldwide death rates attributable to these risk factors. This occurred because of very high cardiovascular death rates in the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. The appendix shows results for women in Afghanistan.

in high-income countries (data not shown). Although some of this decrease was caused by falling population attributable fractions (eg, because of declining trends for systolic blood pressure), the main driver was a decrease in overall cardiovascular disease mortality.

62% of all deaths attributable to the combined effects of these four risk factors in 2010 occurred in ten countries, led by China, India, Russia, and USA (figure 6), because they had large populations or high age-standardised death rates, or both. These four

countries also accounted for the most deaths attributable to each individual risk factor, with the exception of the mortality burden of high BMI, for which India had the eighth highest burden. Over time, middle-income countries such as Mexico, Turkey, Egypt, and Indonesia have replaced high-income European countries such as the UK and France as places where a large number of deaths are attributable to these risk factors (figure 6).

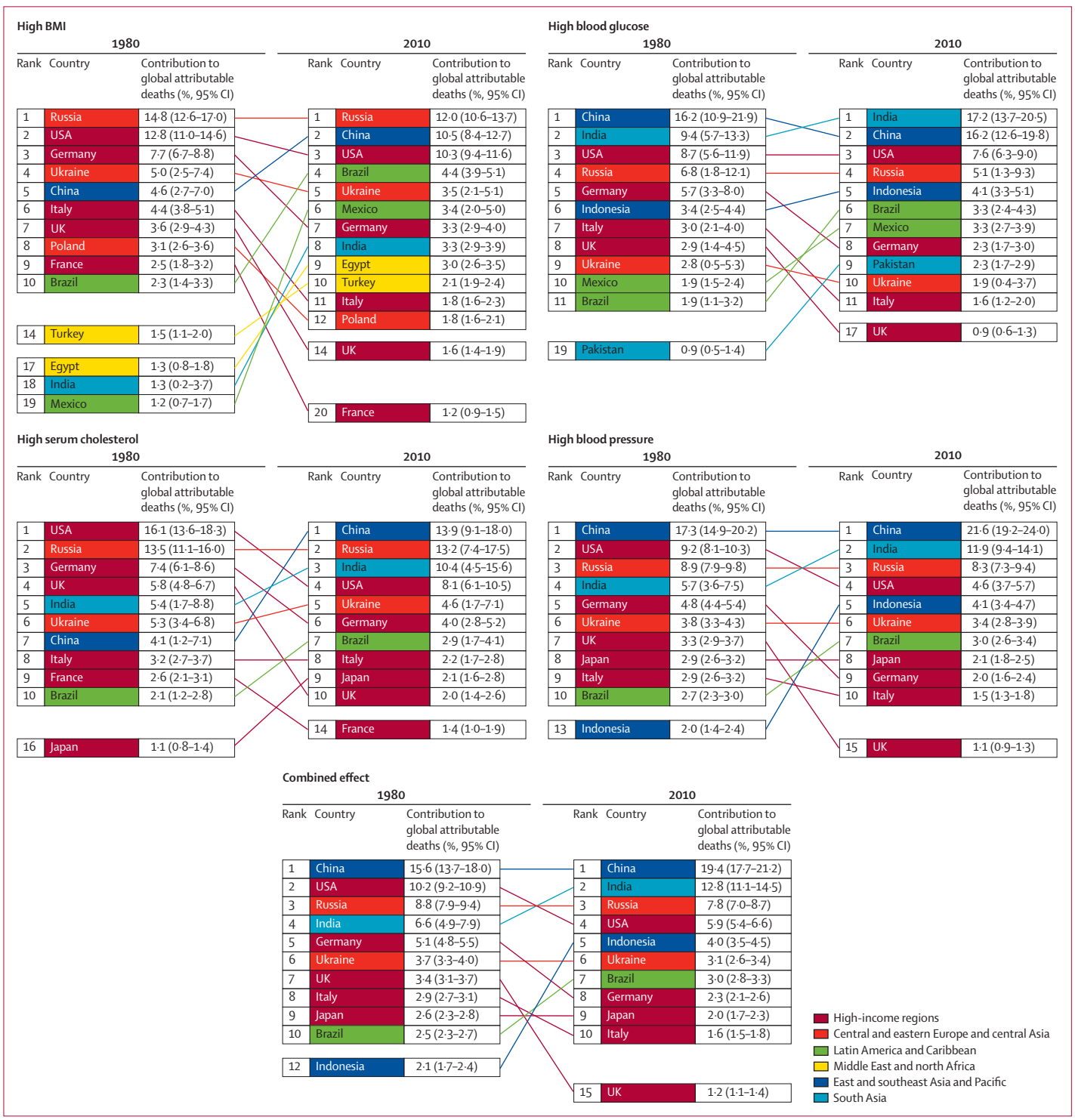

Figure 6: **Ten countries with most deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to high BMI, blood pressure, serum cholesterol, and blood glucose in 1980 and 2010**

Other high-income countries such as Italy and Germany had lower ranks in 2010 in terms of number of deaths attributable to these risk factors, with increasing importance of middle-income countries such as Brazil and Ukraine.

Discussion

More than 60% of worldwide deaths from cardiovascular diseases, chronic kidney disease, and diabetes in 2010 were attributable to four preventable cardiometabolic risk factors, with high blood pressure having the largest effect. Over time, high blood pressure has maintained its role as the leading risk factor while the mortality burdens 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 serum cholesterol nonetheless remains the second leading risk factor for deaths from ischaemic heart disease.

At present, the mortality burden of most of these risk factors is largest in east and southeast Asia and Pacific and in central and eastern Europe and central Asia, where many people die of cardiovascular diseases (predominantly stroke in east and southeast Asia and Pacific and ischaemic heart disease in central and eastern Europe and central Asia); central and eastern Europe and central Asia also have high levels of most cardiometabolic risk factors compared with other regions.[8–11] The mortality burden has shifted from high-income to low-income and middle-income countries because of a combination of demographic factors (faster population growth and aging) and divergent epidemiological trends (decreasing blood pressure and cholesterol, and cardiovascular death rates in high-income countries while risk factors increased or remained unchanged in low-income and middle-income regions). Deaths attributable to these risk factors occurred in younger people in low-income and middle-income regions than in high-income countries.

Our study is the most detailed analysis of the worldwide mortality burden of cardiometabolic 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 (panel). We used data for risk factor exposure, individual and joint associations of risk factors with disease-specific mortality, and cause-specific deaths from comprehensive up-to-date pooling studies.[1,3,8–11,14] We also quantified the uncertainties of our estimates.

Our study also has some limitations. Despite using much more data than previous analyses, risk factor exposures and deaths in some regions were affected by data shortages and had large uncertainty. Second, we used RRs from observational studies, which could have been affected by residual confounding. For high blood pressure and serum cholesterol, overwhelming evidence from randomised trials of antihypertensive and cholesterol-lowering drugs support the relative risks from observational studies.[17,33,34] The causal effects of high BMI are supported by follow-up of patients after bariatric surgery and randomised trials of lifestyle and diet interventions that have shown that weight loss helps to prevent diabetes.[35] Results of some randomised trials showed that intensive glucose lowering did not significantly reduce cardiovascular disease mortality of patients with diabetes.[36] The reasons for these findings might be that intensive glucose lowering was compared with usual care (rather than with placebo), participants were generally old and frail, patients had had diabetes for a long time at baseline, the high prevalence of existing atherosclerotic disease at trial entry, and low incidence of cardiovascular disease in the trial populations because of concurrent treatment with statins, aspirin, and antihypertensive drugs, which reduced the power of the trials to detect an effect.[36] Subsequently, several meta-analyses[37–39] of randomised trials of intensive versus moderate glucose lowering for patients with diabetes have shown that such treatment significantly reduces the risk of myocardial infarction and other major cardiovascular events. In particular, a meta-analysis of the four largest randomised trials concluded that highly intensive glucose lowering causes a modest but significant cardiovascular benefit in the short to medium term.[38] For these reasons, and in view of the overwhelming evidence from observational studies of the graded increase in risk of cardiovascular disease caused by impaired glucose metabolism, we included ischaemic heart disease and stroke as outcomes of high blood glucose. Nevertheless, for both high BMI and blood glucose, residual confounding remains a concern.

We used the same RRs for all countries. Although the results of large cohort pooling studies[3,7,14] suggest that RRs (and mediation of the excess risk of BMI by other cardiometabolic risk factors) are similar for populations in western and Asian cohorts, further evidence about the size of RRs would be useful—for example, from Africa and Latin America. In addition to mediation, the combined population attributable fractions for multiple risk factors 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 total cholesterol to measure population exposure to high cholesterol because substantially more data were available for total cholesterol than for other measures such as LDL-cholesterol or non-HDL-cholesterol and for apolipoproteins.[11] Findings in countries with data for both total cholesterol and LDL-cholesterol (each with a corresponding RR) show that the estimated attributable deaths are comparable.[21] Similarly, we used BMI as our measure of adiposity to take advantage of decades of worldwide data for height and weight. 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.[40]

Panel: **Research in context**

Systematic review

We searched PubMed with the terms "comparative risk assessment" AND ("cardiovascular disease" OR "chronic kidney disease" OR "diabetes") for articles in English published before April 9, 2014. We also identified articles thorough the references for comparative risk assessment studies. We found some articles that had reported the mortality burden of individual or multiple cardiometabolic 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.[12,13,15,21,25–31]

Interpretation

Our study shows that more than 60% of deaths worldwide from cardiovascular diseases, chronic kidney disease, and diabetes are attributable to four cardiometabolic risk factors—high BMI, blood pressure, blood glucose, and serum cholesterol—which can be prevented through a combination of population-based and personal interventions. The largest mortality burden was caused by high blood pressure but mortality caused by high BMI and high blood glucose has increased more quickly since 1980 than those of the other two risks. Successful initiatives to reduce population blood pressure and cholesterol should be replicated on a wider scale, and effective and scalable interventions need to be developed to curb or reverse the rising trends of BMI and hyperglycaemia.[32] Periodic representative country data for cardiometabolic risk factors are needed to improve the estimates and monitor trends.

Our analysis focused on effects on only cardiovascular diseases, chronic kidney disease, and diabetes which are causally related. High BMI is also a risk factor for some types of cancer and responsible for an estimated 320 000 cancer deaths worldwide in 2010.[12] High glucose concentration is associated with increased risk of tuberculosis.[41] Finally, the remaining deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes—which ranged from 20% to more than 50% in different countries—might be a result of factors not considered in our analysis, independently or in interaction with genetic factors. For example, more than 10% of all deaths caused by cardiovascular diseases are attributable to smoking,[42] which would make the combined effects of cardiometabolic risk factors and smoking about 70% worldwide. Unhealthy diets, insufficient physical activity, and harmful alcohol use are risk factors for cardiovascular diseases and diabetes, with their effects partly or fully mediated through the cardiometabolic factors covered in the present work. Fetal and early childhood undernutrition increases the risk of cardiovascular diseases and diabetes; infections and environmental pollutants are also risk factors for chronic kidney disease.[43] Inflammation, caused by infections and other environmental factors, is a risk factor for cardiovascular diseases, chronic kidney disease, and possibly diabetes.[44,45] There is increasing evidence that stress, insufficient sleep, and other psychosocial factors are independent risk factors for cardiovascular and other non-communicable diseases.

Our results have important implications for the prevention and control of non-communicable diseases throughout the world.[32] Interventions to lower blood pressure, such as reducing dietary salt and better diagnosis and treatment, have successfully reduced blood pressure in high-income countries,[46–48] which has in turn been an important determinant of the fall in deaths from cardiovascular diseases.[49] Interventions to reduce blood pressure are urgently needed for low-income and middle-income countries, where salt intake remains high and coverage of treatment with anti-hypertensive drugs is low.[50–52] Salt from packaged and prepared foods is a relatively small component of total salt intake in these countries, therefore alternative locally accepted approaches to reduce salt intake are needed.[53,54] Similarly, scaling up drug treatments requires a universal and high-quality primary care system as well as national guidelines for identification of people who are in need of intervention, either based on the presence of a single risk factor or on their absolute risk of an adverse event.[51,55]

High-income countries in Europe, north America, and Australasia have also reduced the prevalence of high serum cholesterol concentrations through a combination of replacing saturated fats with unsaturated fats and higher coverage of treatment.[11,56–58] Although high cholesterol had the lowest mortality burden of these risk factors worldwide, it has increased in east and southeast Asian countries such as Japan, China, and Thailand, possibly as a result of increased intake of meat, animal fats, and dairy.[11,59] The number of deaths from cardiovascular diseases attributable to high serum cholesterol increased by about 250% in the east and southeast Asia and Pacific regions between 1980 and 2010, more than those attributable to blood pressure and glucose but less than BMI. Dietary and health-care interventions for lowering serum cholesterol are needed in this region. Finally, access to and quality of health care is one of the most important determinants of variation in mortality caused by cardiovascular diseases, chronic kidney disease, and diabetes both across and within countries.

Unlike national successes for reducing blood pressure and cholesterol, most countries have had increases of BMI and blood glucose;[8–11] a trend shown by the larger increase of their mortality burden than those of high blood pressure and cholesterol. Randomised studies of diet and lifestyle change have shown that moderate weight loss can be beneficial for up to 2 years,[60–62] and reduces diabetes incidence.[63] However, the long-term and community effectiveness of such interventions is not clear.[64] Simple advice and exercise alone have not been efficacious, even in randomised trials.[62] The rising burdens of high BMI and glucose, which can be only partly addressed through interventions to reduce blood

pressure and cholesterol, shows the urgent need for developing and testing new approaches to prevention of obesity. These approaches would have to go beyond health promotion at the individual level, and use fiscal and regulatory mechanisms to motivate changes in diet and lifestyle.[46,65] Actions to reduce exposure to cardiometabolic risk factors (and smoking) will also contribute significantly towards achieving the global 25×25 target for non-communicable disease mortality.[32]

Contributors

GD and ME designed the study. YL, GMS, 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 data for exposure and effect size. ME and GD wrote the first draft of the paper, with input from other members of the writing group and collaborating group. GD, SSL, and ME oversaw research.

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Declaration of interests

DM has received honoraria from Quaker Oats, Pollock Institute, and Bunge, has consulted for Foodminds, Nutrition Impact, Amarin, Astra Zeneca, Winston and Strawn, and Life Sciences Research Organization,

has sat on advisory boards for Unilever, and has received royalties from UpToDate. The other authors declare no competing interests. GAS, MJC, and LMR are staff members of the WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the WHO.

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