	Overweight		Obesity	
	HR (95% CI)	Excess risk mediated (%, 95% CI)	HR (95% CI)	Excess risk mediated (%, 95% CI)
Coronary heart disease				
None	1·26 (1·22 to 1·30)	..	1·69 (1·58 to 1·81)	..
Blood pressure	1·18 (1·14 to 1·22)	31% (26 to 36)	1·48 (1·39 to 1·57)	31% (27 to 35)
Cholesterol	1·21 (1·18 to 1·25)	18% (13 to 22)	1·64 (1·54 to 1·75)	8% (2 to 12)
Blood glucose	1·23 (1·18 to 1·27)	12% (6 to 18)	1·60 (1·49 to 1·72)	14% (8 to 20)
Blood pressure and cholesterol	1·14 (1·11 to 1·18)	45% (40 to 52)	1·44 (1·36 to 1·53)	36% (33 to 40)
Blood pressure and blood glucose	1·16 (1·12 to 1·20)	38% (32 to 45)	1·42 (1·34 to 1·51)	39% (35 to 44)
Cholesterol and blood glucose	1·19 (1·15 to 1·23)	27% (22 to 33)	1·55 (1·46 to 1·64)	21% (17 to 25)
Blood pressure, cholesterol, and blood glucose	1·13 (1·09 to 1·16)	50% (44 to 58)	1·39 (1·32 to 1·47)	44% (41 to 48)
Stroke				
None	1·13 (1·08 to 1·18)	..	1·47 (1·36 to 1·59)	..
Blood pressure	1·03 (0·99 to 1·07)	76% (61 to 104)	1·21 (1·13 to 1·28)	56% (50 to 64)
Cholesterol	1·11 (1·06 to 1·16)	17% (5 to 30)	1·44 (1·33 to 1·56)	7% (−1 to 14)
Blood glucose	1·09 (1·04 to 1·15)	29% (13 to 55)	1·35 (1·24 to 1·47)	25% (18 to 34)
Blood pressure and cholesterol	1·04 (0·99 to 1·08)	74% (54 to 112)	1·19 (1·12 to 1·27)	59% (52 to 70)
Blood pressure and blood glucose	1·01 (0·96 to 1·06)	93% (67 to 147)	1·15 (1·08 to 1·22)	68% (62 to 76)
Cholesterol and blood glucose	1·09 (1·04 to 1·15)	31% (16 to 56)	1·34 (1·24 to 1·45)	28% (20 to 36)
Blood pressure, cholesterol, and blood glucose	1·00 (0·96 to 1·05)	98% (69 to 155)	1·14 (1·08 to 1·21)	69% (64 to 77)

All HRs are relative to normal weight (BMI ≥20–<25 kg/m²), and were adjusted for confounders. HR=hazard ratio. BMI=body-mass index.

Table 3: **HRs and excess risk of overweight and obesity mediated through different combinations of metabolic risk factors**

4% (−3 to 12) for cholesterol; we noted this non-significant mediation of stroke risk by cholesterol in both Asian and western cohorts. When we adjusted for all three mediators, the excess risk of stroke was attenuated by 76% (65–91).

The HRs of coronary heart disease decreased by 31% for both overweight and obesity after adjustment for blood pressure (table 3). PERM for the association of overweight with coronary heart disease was larger than that of obesity for most combinations of mediators, but the CIs overlapped (table 3). All three mediators together accounted for 50% (44–58) of the excess risk of overweight on coronary heart disease, and 44% (41–48) of the excess risk of obesity. The metabolic factors also mediated more excess risk of overweight on stroke than of obesity, although the CIs overlapped (table 3). 76% of the excess risk of overweight (61–104) and 56% of that of obesity (50–64) on stroke were mediated through blood pressure alone (table 3). When we adjusted for all three mediators, excess risk of stroke decreased by 98% (69–155) for overweight and by 69% (64–77) for obesity.

In subgroup analyses, PERM for all three mediators combined did not differ significantly by most cohort characteristics (ie, 95% CIs overlapped; table 4). The only significant difference in PERM was for coronary heart disease and baseline year of study, for which a larger percentage of excess risk was mediated by the three mediators in cohorts that had enrolled participants before 1990 versus in 1990 or later. Among individual mediators, blood pressure mediated 69% (57–91) of the excess risk of stroke in Asian cohorts versus 60% (48–78) in western cohorts. The role of blood pressure as a mediator for excess risk of coronary heart disease was similar in Asian and western cohorts (32%, 22–44 *vs* 30%, 26–34).

In sensitivity analyses, PERMs were 1 to 8 percentage points higher for waist circumference than for BMI in 16 studies that had measured both, but were 4 to 15 percentage points lower for waist-to-hip ratio than for BMI; these differences were not significant (ie, 95% CIs overlapped). LDL cholesterol was a stronger mediator than was total cholesterol, but the difference in PERM was less than 5 percentage points for both coronary heart disease and stroke (results not shown), possibly because of the high correlation between total cholesterol and LDL cholesterol in these cohorts (Pearson correlation coefficient >0·8). PERM for coronary heart disease by all three mediators was only slightly (3 percentage points) and non-significantly higher in cohorts that used measurements for diabetes (25% of cohorts) compared with continuous glucose (results not shown).

Discussion

In this pooled analysis of 97 prospective cohort studies, we estimated that nearly half of excess risk for coronary heart disease and three-quarters of excess risk for stroke due to high BMI were mediated through three metabolic risk factors: blood pressure, cholesterol, and glucose. The most important mediator was blood pressure, especially for stroke, accounting for two-thirds of the excess risk. Compared with having healthy weight, being overweight or obese was associated with an increased risk of coronary

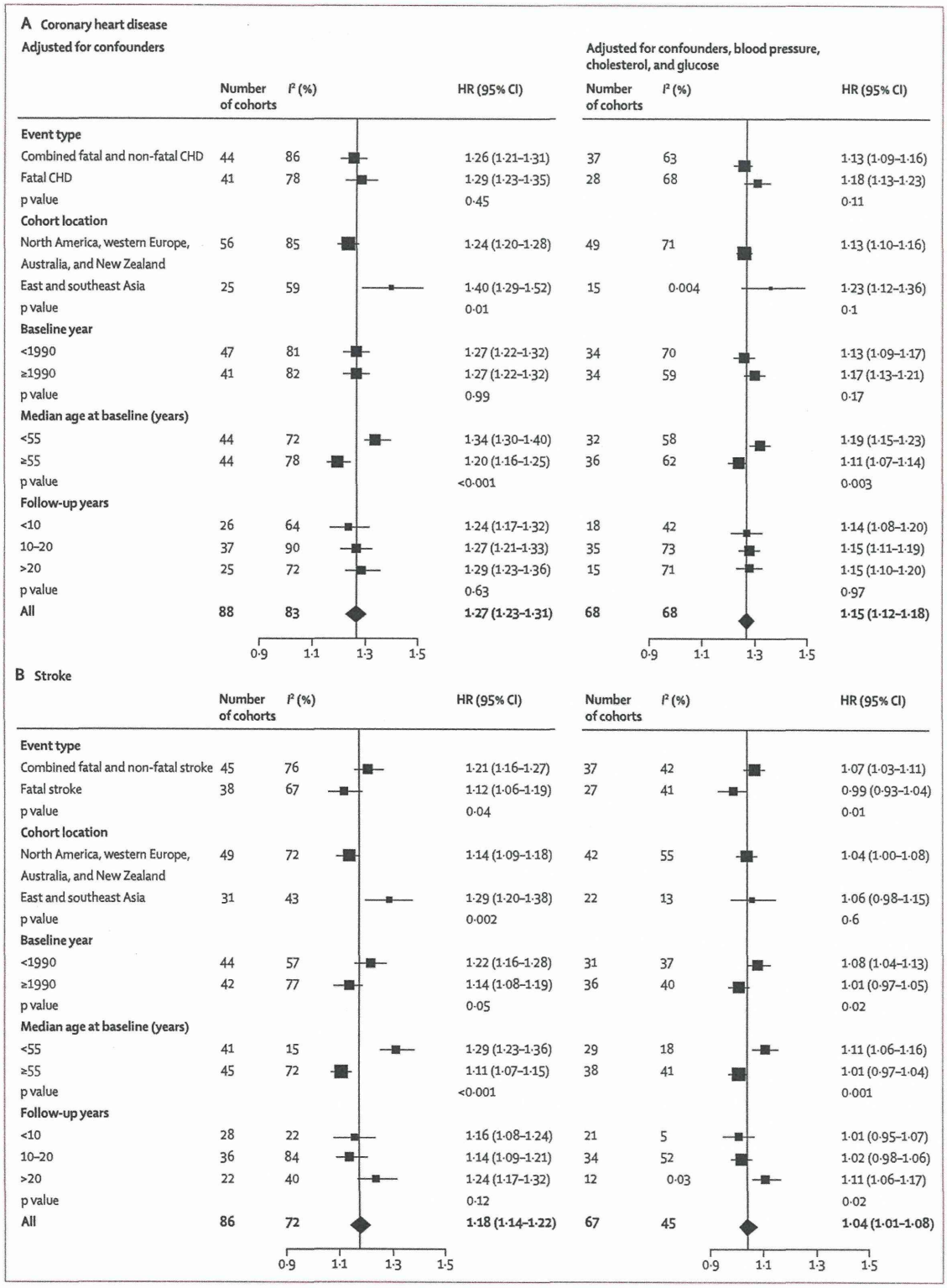

Figure 2: **Stratified analyses of HRs per 5 kg/m² higher body-mass index, with and without adjustment for mediators in CHD (A) and stroke (B)**
p values were meta-regression p values between groups. Results are presented for all three mediators combined. The appendix (pp 73–90) shows HRs with adjustment for combinations of one and two mediators. CHD=coronary heart disease. HR=hazard ratio

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heart disease and stroke, with obesity having a larger effect than overweight.

Our results for the overall association between BMI and coronary heart disease or stroke are consistent with those of other large pooled analyses of prospective cohorts.[2,3,24] Previous studies mostly analysed all mediators combined, and did not assess the role of other combinations of mediators. A meta-analysis[18] of 21 cohorts (including 16 analysed here) reported that 45% of excess risk of coronary heart disease was mediated through blood pressure and total cholesterol, compared with 39% in our analysis (both effects reported for 5 kg/m² higher BMI). Results of another pooled analysis[3] of 58 cohorts (including 15 analysed here) showed that roughly 60% of the excess risk of coronary heart disease and 70% of ischaemic stroke were due to the same three mediators, compared with 46% for coronary heart disease and 76% for stroke in our analysis.

Our lower estimates for coronary heart disease might be the result of a larger number of cohorts that included only fatal coronary heart disease (almost half of our cohorts used only fatal coronary heart disease compared with 9% in the study by Wormser and colleagues[3]) because PERM tended to be lower when fatal events were analysed (table 4). Our lower estimates for coronary heart disease could also be explained by the use of blood glucose measurements versus diabetes as the metric of mediator. The slightly higher estimates for stroke might be due to the larger number of Asian cohorts in our analysis (34% of our cohorts were from Asia compared with 7% in the study by Wormser and colleagues[3]), or the stroke subtypes analysed (we used total stroke whereas Wormser and colleagues[3] used ischaemic stroke).

Our finding that both overweight and obesity were associated with increased risk of coronary heart disease and stroke differed from reports by Flegal and colleagues,[28] who recorded no effects for overweight on either cardiovascular disease mortality in one cohort, or on all-cause mortality in a meta-analysis.[29] Flegal and colleagues' findings for cardiovascular disease[28] might have differed from ours because of inadequate adjustment for pre-existing diseases and their inadequate control of confounding.[30,31] Our results are not directly comparable with those for all-cause mortality.

We noted that metabolic factors mediate a larger proportion of the excess risk for overweight individuals than do those for obese individuals (although the 95% CIs overlapped). This finding suggests that clinical and public health interventions that control blood pressure, cholesterol, and glucose can largely (in coronary heart disease) or fully (in stroke) address the excess risk of coronary heart disease and stroke in overweight individuals. Obese individuals also benefit from interventions on mediators but will continue to have significantly raised risk.

Several pathways link adiposity and excess weight to cardiovascular disease via the mediators analysed in this study. Adiposity can raise blood pressure through increased peripheral vascular resistance and renal salt retention, the latter itself due to higher activity of sympathetic nervous system, leptin concentrations, angiotensin-aldosterone activity, and hyperinsulinaemia.[5,32] Adiposity is also associated with dyslipidaemia, and systemic inflammatory state, which could contribute to the development of insulin resistance and diabetes.[6] Our results also suggest that the association between adiposity and cardiovascular disease is not completely explained by the three mediators in our analysis. The unexplained risk might be caused by other pathways such as endothelial dysfunction, increase in thrombogenic factors, and the remaining effect of increased sympathetic activity and systemic inflammation not related to risk

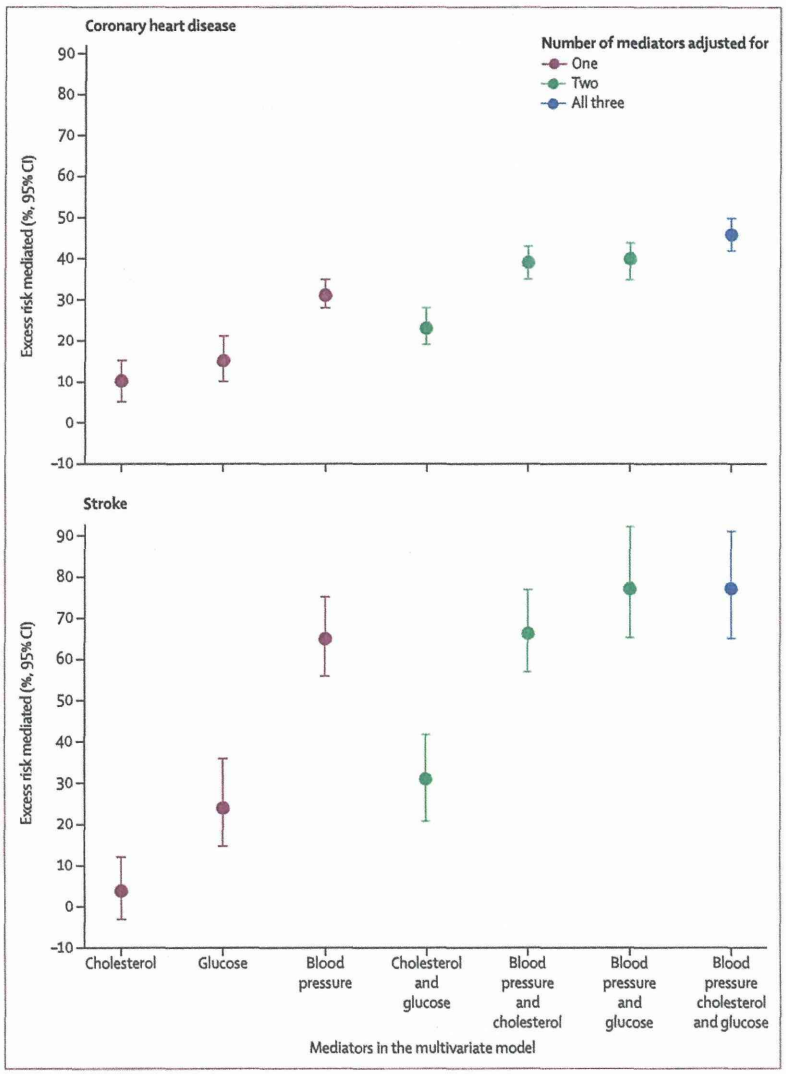

Figure 3: Percentage of excess risk per 5 kg/m² higher body-mass index mediated through different combinations of metabolic risk factors in coronary heart disease and stroke

	CHD	Stroke
Event type*		
Combined fatal and non-fatal event	50% (46–55)	69% (60–81)
Fatal event	39% (31–49)	115%‡ (78–234‡)
Cohort location†		
North America, western Europe, Australia and New Zealand	44% (40–50)	73% (57–96)
East and southeast Asia	39% (31–49)	79% (59–108‡)
Baseline year		
<1990	53% (46–62)	62% (51–78)
≥1990	38% (34–44)	93% (74–141‡)
Median age at baseline (years)		
<55	45% (41–50)	63% (53–74)
≥55	46% (39–56)	95% (73–149‡)
Follow-up years		
<10	43% (35–52)	89% (67–132‡)
10 to 20	45% (40–52)	84% (68–134‡)
>20	49% (40–59)	52% (44–62)

BMI=body-mass index.*Three cohorts reported their results for non-fatal coronary heart disease and non-fatal stroke. †Seven cohorts from other regions reported results for coronary heart disease, and six cohorts from other regions reported results for stroke. ‡Hazard ratios of BMI were less than 1·0 after adjustment for mediators. Therefore, the numerator of percentage of excess risk mediated was greater than the denominator. This possible overadjustment itself could be due to residual and unmeasured confounding.

Table 4: **Stratified analyses of percentage of excess risk (95% CI) per 5 kg/m² higher BMI mediated through the combination of blood pressure, cholesterol, and blood glucose**

Panel: Research in context

Systematic Review

We did a systematic review by searching PubMed and Embase from their inception up to March 23, 2010, using search terms listed in the appendix (pp 2–4). We invited the corresponding authors of eligible cohorts to join the Collaborating Group.

We analysed data from 97 prospective cohort studies to estimate the effects of high body-mass index (BMI) on coronary heart disease and stroke, with and without adjustment for selected metabolic factors (blood pressure, serum cholesterol, and glucose). We pooled hazard ratios (HRs) across cohorts and quantified how much of the excess risk of BMI is mediated through any combination of three metabolic factors.

Interpretation

We found that about half of the excess risk of BMI on coronary heart disease and three-quarters of the excess risk of BMI on stroke was mediated by blood pressure, glucose, and cholesterol collectively. The most important mediator was blood pressure, which mediated a third of the excess risk of BMI on coronary heart disease and two-thirds for stroke. A larger proportion of risk might be mediated for overweight compared with obesity. Interventions that reduce high blood pressure, cholesterol, and glucose might address a substantial proportion of the effect of high BMI on cardiovascular disease. Maintenance of optimum bodyweight is needed to achieve the full benefits.

factors analysed here.[6] These other pathways might play a more important part in obese individuals than in overweight individuals. It would be interesting to probe and quantify the role of these other pathways in subsequent studies, including in relation to overweight versus obese status, although fewer cohorts collect comparable data for these other variables compared with the well known metabolic mediators that we analysed.

Our study is the largest pooling analysis of multiple cardiovascular disease risk factors, with 1·8 million participants, and 57 161 coronary heart disease and 31 093 stroke events. This large sample size allowed us to study the extent of mediation, and how it varies by cohort characteristics. The cohorts covered Asian and western populations, and therefore, showed the role of BMI and the mediators of its effects in these diverse populations. The consistent stratified analysis suggested the important role of blood pressure as a mediator in the effect of BMI on stroke in Asian populations, in whom high blood pressure and large stroke burden have made this risk factor the leading cause of disease burden.[16,33]

Our study has some limitations. First, although we consistently adjusted for age, sex, and smoking as the minimum set of confounders, our results might still be affected by unmeasured and residual confounding. For instance, only a few cohorts were adjusted for diet and physical activity, which are risk factors for coronary heart disease and stroke and are associated with increased BMI. Confounders might have been measured with error, which leads to residual confounding (eg, smoking and socioeconomic status). When we restricted the pooling to cohorts that had adjusted for additional confounders, PERM for the three mediators did not change significantly: it was 6 percentage points higher for coronary heart disease and 1 percentage point lower for stroke than for cohorts with minimum set of confounders, and 95% CIs overlapped. Our analysis did not allow for interactions between BMI and mediators, which might exist.[34] The mediators were not measured consistently across cohorts because of variability in laboratory methods or metrics of mediators. Sensitivity analyses showed that our results were robust to the choice of metrics used for mediators. Additionally, we could not analyse stroke subtypes separately because most cohorts had not reported the stroke outcome by subtype. Finally, despite the large number of cohorts included in the analysis, we could not access data from all eligible cohorts, especially some with enrolment decades ago.

Our findings have implications for clinical prevention of cardiovascular disease as well as for public health programmes. As a clinical example, consider a 70-year-old non-smoking man who does not have diabetes, is 174 cm tall and weighs 100 kg (ie, has a BMI of 33 kg/m²), with a systolic blood pressure of 147 mm Hg, total cholesterol of 5·05 mmol/L, and HDL cholesterol of 0·93 mmol/L. This person represents roughly the 80th percentile of age, BMI, and cholesterol of adult men, and 90th percentile of blood pressure among adult men with BMI of 30 kg/m² or more in the US National Health and Nutrition Examination Survey in 2007–08. According to the Framingham risk score, this man's predicted 10-year

risk of coronary heart disease is 25%.[35] With the assumption that the results of our observational analysis are indicative of the true benefits of losing excess weight, if this patient lost 15 kg of weight through a hypothetical intervention (ie, 5 kg/m² lower BMI), his new estimated 10 year coronary heart disease risk would be 19·7% (25% minus [25% divided by 1·27], because the HR for coronary heart disease per 5 kg/m² BMI is 1·27), which is 5 percentage points lower. Alternatively, if he receives drugs to lower his blood pressure and cholesterol to levels that are expected based on a 15 kg weight loss, his 10 year risk of coronary heart disease would only decrease by 2 percentage points (5% times 39%, because the estimated PERM by blood pressure and cholesterol for coronary heart disease is 39% per 5 kg/m² higher BMI), as he only receives the benefits of reductions in these two risk factors.

Despite the potentially large benefits of weight loss, interventions have had small long-term success, especially at the population level,[7,8] leading to a worldwide rise in overweight and obesity.[14] By contrast, effective clinical and lifestyle interventions are available to control blood pressure and serum cholesterol,[36–39] with evidence that these risk factors have been successfully reduced, in individual patients and whole populations.[16,17,40,41] For example, blood pressure, the most important mediator of the association between BMI and cardiovascular disease, has fallen substantially in high-income countries, central Europe, and parts of Latin America.[16] Serum cholesterol has also fallen in western countries, but has increased in east and southeast Asia.[17] In the USA, decreases in blood pressure and cholesterol have been even larger in overweight and obese individuals, possibly because of more aggressive management.[42] Therefore, control of blood pressure and cholesterol might help to lessen the cardiovascular effects of the global obesity epidemic.

The most important step to leverage this potential is to continue past efforts for the reduction of blood pressure and cholesterol, and to try to replicate these efforts in Asia where blood pressure remains high,[16] serum cholesterol has increased,[17] and stroke is a common cause of death. Despite this potential, and some past successes, further reduction of blood pressure and cholesterol needs major improvements in both primary care and public health programmes.[43] The coverage of blood pressure and lipid-lowering drugs is low in most low-income and middle-income countries, even in patients with cardiovascular disease, and social inequalities in coverage exist.[44,45] To increase diagnosis and treatment will need well developed national guidelines that include these activities in the primary care system, with emphasis on improvement of access in disadvantaged social and economic groups.[44–46] Interventions related to diet that lower the intake of salt, saturated and trans fats, and processed carbohydrates, and increase the consumption of fruits, vegetables, unsaturated fats, and whole grains, can improve the metabolic risk profile even when total calories remain unchanged,[47–50] but access to these interventions needs to be improved worldwide.[43,51] Additionally, adiposity increases the risk of diabetes, and prevalence of blood glucose and diabetes has increased worldwide.[52] Clinical interventions for glycaemic management are not as effective as those for blood pressure and cholesterol.[53] Therefore, reliance on control of the metabolic mediators might be only a partial and temporary response to the obesity epidemic. Rather, creative and bold strategies are needed that can curb and reverse rising adiposity so that the full benefits for cardiovascular disease and diabetes reduction can be achieved.

Contributors

GD and ME developed the study concept and analytical strategy. YL and KH did the systematic review, pooled analysis, and prepared results. YL, KH, and Cohort Collaborating Group analysed cohort data. EBR and MW contributed to the design of the study and interpretation of results. YL, KH, ME, and GD wrote the first draft of the report. All other Collaborating Group members commented on the report draft and have seen and approved of the final text. ME and GD oversaw the research. GD is the study guarantor.

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Conflicts of interest

The members of the Writing and Pooling Group declare that they have no conflicts of interest.

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