



Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

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Summary

Background Global estimates of the effect of common modifiable risk factors on cardiovascular disease and mortality are largely based on data from separate studies, using different methodologies. The Prospective Urban Rural Epidemiology (PURE) study overcomes these limitations by using similar methods to prospectively measure the effect of modifiable risk factors on cardiovascular disease and mortality across 21 countries (spanning five continents) grouped by different economic levels.

Methods In this multinational, prospective cohort study, we examined associations for 14 potentially modifiable risk factors with mortality and cardiovascular disease in 155 722 participants without a prior history of cardiovascular disease from 21 high-income, middle-income, or low-income countries (HICs, MICs, or LICs). The primary outcomes for this paper were composites of cardiovascular disease events (defined as cardiovascular death, myocardial infarction, stroke, and heart failure) and mortality. We describe the prevalence, hazard ratios (HRs), and population-attributable fractions (PAFs) for cardiovascular disease and mortality associated with a cluster of behavioural factors (ie, tobacco use, alcohol, diet, physical activity, and sodium intake), metabolic factors (ie, lipids, blood pressure, diabetes, obesity), socioeconomic and psychosocial factors (ie, education, symptoms of depression), grip strength, and household and ambient pollution. Associations between risk factors and the outcomes were established using multivariable Cox frailty models and using PAFs for the entire cohort, and also by countries grouped by income level. Associations are presented as HRs and PAFs with 95% CIs.

Findings Between Jan 6, 2005, and Dec 4, 2016, 155 722 participants were enrolled and followed up for measurement of risk factors. 17 249 (11·1%) participants were from HICs, 102 680 (65·9%) were from MICs, and 35 793 (23·0%) from LICs. Approximately 70% of cardiovascular disease cases and deaths in the overall study population were attributed to modifiable risk factors. Metabolic factors were the predominant risk factors for cardiovascular disease (41·2% of the PAF), with hypertension being the largest (22·3% of the PAF). As a cluster, behavioural risk factors contributed most to deaths (26·3% of the PAF), although the single largest risk factor was a low education level (12·5% of the PAF). Ambient air pollution was associated with 13·9% of the PAF for cardiovascular disease, although different statistical methods were used for this analysis. In MICs and LICs, household air pollution, poor diet, low education, and low grip strength had stronger effects on cardiovascular disease or mortality than in HICs.

Interpretation Most cardiovascular disease cases and deaths can be attributed to a small number of common, modifiable risk factors. While some factors have extensive global effects (eg, hypertension and education), others (eg, household air pollution and poor diet) vary by a country's economic level. Health policies should focus on risk factors that have the greatest effects on averting cardiovascular disease and death globally, with additional emphasis on risk factors of greatest importance in specific groups of countries.

Funding Full funding sources are listed at the end of the paper (see Acknowledgments).

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Introduction

It is estimated that 55 million deaths occurred in the world in 2017, of which 17·7 million were from cardiovascular disease.^{1,2} Documenting the consistency or variations in the associations between risk factors and cardiovascular disease and mortality, both globally

and by countries grouped by economic levels, will help the development of global and context-specific strategies for prevention.

Thus far, the most comprehensive global estimates of the associations between risk factors and adult deaths and cardiovascular disease are from the Global Burden

Published Online
September 3, 2019
[http://dx.doi.org/10.1016/S0140-6736\(19\)32008-2](http://dx.doi.org/10.1016/S0140-6736(19)32008-2)

See Online/Articles
[http://dx.doi.org/10.1016/S0140-6736\(19\)32007-0](http://dx.doi.org/10.1016/S0140-6736(19)32007-0)

See Online/Comment
[http://dx.doi.org/10.1016/S0140-6736\(19\)32034-3](http://dx.doi.org/10.1016/S0140-6736(19)32034-3)

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Research in context

Evidence before this study

Previous epidemiological studies relating risk factors with cardiovascular disease and mortality have been restricted to populations from individual countries, most of which were high-income countries, and from North America, western Europe, or China. There are few prospective data from other middle-income or low-income countries, or from other regions of the world. The Global Burden of Disease Study is a compilation of findings from existing studies, but it is limited by the fact that estimates are derived through combining data from diverse studies with differing methods of data collection and analyses, conducted at differing time periods (so they might not reflect current patterns of risk factors), and with relatively few data from low-income and middle-income countries. These are the best data currently available, but the reliability of some of the estimates can be improved by large, prospective studies involving multiple countries from different continents and at different economic levels, conducted in a standardised manner and simultaneously assessing the associations of several risk factors with incident diseases and mortality.

Added value of this study

We quantified and compared the associations of risk factors for cardiovascular disease and mortality in 155 722 participants enrolled from 21 countries who did not have a prior history of cardiovascular disease, using standard methods to enrol

participants, and collect and analyse data. Over 70% of the population-attributable fraction (PAF) for cardiovascular disease and mortality in the overall cohort was attributable to 14 modifiable risk factors. Metabolic risk factors were the predominant individual-level risk factors for cardiovascular disease, with hypertension being the largest, accounting for 22.3% of the PAF. As a cluster, behavioural risk factors contributed most to deaths, although the single largest risk factor for death was low education (PAF of 12.5%). Household air pollution (PAF of 6.7%) had a moderate effect. Ambient air pollution (PAF of 13.9%) appeared to have a large effect on cardiovascular disease. Compared with middle-income or high-income countries, there was a higher proportion of cardiovascular disease and deaths in low-income countries. In middle-income and low-income countries, household air pollution, poor diet, low education, and low grip strength had a stronger effect on death than in high-income countries.

Implications of all the available evidence

Most cases of cardiovascular disease or death are attributable to a small number of potentially modifiable risk factors. While some risk factors have a large global effect (eg, hypertension, tobacco, education), the effect of other risk factors (eg, poor diet, household air pollution) varies by the economic level of the countries. Global health policies should be adapted to different groups of countries on the basis of risk factors with the greatest impact in each setting.

of Disease Study (GBD), the largest meta-analytic repository of epidemiologic data relating risk factors to mortality and cardiovascular disease.^{1,2} However, estimates are derived through combining data from diverse studies which used different methods to enrol participants, record information, and analyse the data. Furthermore, there were relatively few data from low-income and middle-income countries (LICs and MICs). To complement, validate, and extend information derived from GBD, large international studies involving MICs and LICs are needed which employ standardised methods of sampling, and standardised measurement of exposures and outcomes. For cardiovascular disease, multinational case-control studies^{3,4} have provided global comparative data on the associations of risk factors with myocardial infarction and stroke, but these had mainly non-fatal events, and are prone to potential biases inherent to case-control studies (eg, reverse causality or recall bias).

The Prospective Urban Rural Epidemiology (PURE) study is an attempt to provide standardised and contemporaneous information across several countries, especially those outside North America and western Europe.⁵ The objectives of this report are to quantify and compare the associations and population-attributable fractions of 14 common modifiable risk factors on

cardiovascular disease and mortality. We also report whether these associations vary between groups of countries at different economic levels.

Methods

Study design and participants

PURE is a prospective cohort study that was designed to include countries across a broad range of economic levels, social circumstances, and health policies, with a proportionally larger representation from MICs and LICs. The study's design has been previously published. The study included four high-income countries (HICs; Canada, Saudi Arabia, Sweden, and United Arab Emirates), 12 MICs (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, Philippines, Poland, Turkey, and South Africa), and five LICs (Bangladesh, India, Pakistan, Tanzania, and Zimbabwe). In participating countries, urban and rural communities were selected using pre-specified criteria (appendix pp 1–3).⁵ Within each community, households and individuals were selected using sampling strategies that would minimise the selection of individuals that could potentially bias any associations between risk factors and outcomes.⁵ The study was approved by local ethics committees in each study centre, and all participants provided written informed consent. Socioeconomic

characteristics and mortality of the study population were comparable to national statistics from participating countries.⁶

This analysis was done on findings of the first two phases of the PURE study, in which individuals were enrolled from 21 countries and had completed at least one cycle of follow-up visits. Information on vital status was available in 161454 (98.4%) of 164007 participants, and information on cardiovascular disease in 154290 (94.1%) participants. This report includes the 155722 participants without a prior history of cardiovascular disease (table 1; figure 1; appendix pp 15, 22). Countries were categorised into HICs, MICs, and LICs based on their World Bank country income classification at the time of inclusion.

Procedures

A detailed summary of each risk factor, its method of measurement, and its categorisation for the calculation of population-attributable fractions (PAFs) is available in the appendix (pp 16–19). Baseline data were collected using standardised methods at the community, household, and individual levels. We evaluated the individual and population-level risk associated with 14 potentially modifiable risk factors. Behavioural risk factors were tobacco use, alcohol consumption, diet quality, physical activity, and sodium intake. Metabolic clusters of risk factors were elevated blood pressure or history of hypertension, dysglycaemia, or history of diabetes, non HDL-cholesterol, and abdominal obesity measured using waist-to-hip ratio.^{7–9} Hypertension was defined as a baseline systolic and diastolic blood pressure of at least 140/90 mm Hg, self-reported history of hypertension, or treatment with anti-hypertensive medications. Diabetes was defined as a baseline fasting glucose greater than or equal to 7 mmol/L, self-reported history of diabetes, or treatment with a glucose-lowering agent. Grip strength was measured with a JAMAR dynamometer.¹⁰ Air pollution was examined both as household (eg, kerosene or solid fuels for cooking), and ambient, which was measured at the community level. Household air pollution was defined as the primary use of kerosene or solid fuels for cooking. To measure ambient pollution at the community level, we integrated information on particulate matter with a diameter of <2.5 µm (PM_{2.5}) from a combination of satellite observations, chemical transport models, and ground level monitoring.¹¹ Symptoms consistent with depression were our primary psychosocial variable of interest. Depression was measured as a score of at least five on an eight-symptom depression score, which was based on the Composite International Diagnostic Interview. Education was our primary socioeconomic variable of interest, because education was a stronger socioeconomic predictor of cardiovascular disease and mortality than wealth or income in a previous PURE study.¹²

For overall diet quality, we used a composite diet score which has been replicated in five independent studies

and was at least as good or superior to previous diet risk scores (unpublished). Non-HDL cholesterol was chosen as our primary lipid value because it had the strongest association with cardiovascular disease (appendix p 19). Fasting urinary sodium excretion was estimated using the Kawasaki formula, and used as a surrogate for sodium intake in 101609 individuals with available data.¹³

Outcomes

The primary outcomes for this paper were composites of cardiovascular disease events (defined as cardiovascular death, myocardial infarction, stroke, and heart failure) and all-cause death. During follow-up, these events were collected using standardised case-report forms and reported based on common definitions (appendix pp 4–13).

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	Overall (n=155 722)	High-income countries (n=17 249)	Middle-income countries (n=102 680)	Low-income countries (n=35 793)
Baseline characteristics				
Sex				
Female	90 811 (58.3%)	9376 (54.4%)	60 822 (59.2%)	20 613 (57.6%)
Male	64 911 (41.7%)	7873 (45.6%)	41 858 (40.8%)	15 180 (42.4%)
Area of residence				
Urban	81 897 (52.6%)	12 506 (72.5%)	52 134 (50.8%)	17 257 (48.2%)
Rural	73 825 (47.4%)	4743 (27.5%)	50 546 (49.2%)	18 536 (51.8%)
Age	50.2 (9.9)	51.6 (9.4)	50.7 (9.7)	48.3 (10.3)
Behavioural risk factors				
Tobacco use				
Current	31 821 (20.4%)	2279 (13.3%)	21 635 (21.3%)	7907 (22.2%)
Former	17 225 (11.2%)	5261 (30.6%)	10 422 (10.2%)	1542 (4.3%)
Never	105 387 (68.2%)	9660 (56.2%)	69 624 (68.5%)	26 103 (73.4%)
Alcohol use				
Never	108 133 (71.0%)	5253 (30.8%)	72 035 (72.3%)	30 845 (86.7%)
Former	6446 (4.2%)	940 (5.5%)	4533 (4.5%)	973 (2.7%)
Current: low	28 314 (18.6%)	7790 (45.7%)	17 770 (17.8%)	2754 (7.7%)
Current: moderate	6466 (4.2%)	2333 (13.7%)	3572 (3.6%)	561 (1.6%)
Current: high	2959 (1.9%)	747 (4.4%)	1788 (1.8%)	424 (1.2%)
PURE diet score	3.9 (1.9)	5.6 (1.6)	4.1 (1.8)	2.5 (1.5)
Physical activity (MET min per week)				
Low: <600	26 691 (18.5%)	2861 (17.9%)	17 342 (17.9%)	6488 (20.9%)
Moderate: 600–3000	53 489 (37.2%)	5661 (35.4%)	37 461 (38.7%)	10 367 (33.4%)
High: >3000	63 731 (44.3%)	7471 (46.7%)	42 044 (43.4%)	14 216 (45.8%)
Sodium				
Urine sodium excretion (g per day)	4.7 (1.9)	4.1 (1.5)	5.0 (1.9)	3.4 (1.7)
Sodium <4 g per day	37 099 (36.5%)	7717 (52.1%)	23 358 (29.9%)	6024 (69.0%)
Sodium 4–6 g per day	42 226 (41.6%)	5980 (40.4%)	34 219 (43.8%)	2027 (23.2%)
Sodium >6 g per day	22 284 (21.9%)	1120 (7.6%)	20 483 (26.2%)	681 (7.8%)

(Table 1 continues on next page)

	Overall (n=155 722)	High-income countries (n=17 249)	Middle-income countries (n=102 680)	Low-income countries (n=35 793)
(Continued from previous page)				
Metabolic risk factors				
Hypertension	57 303 (39.4%)	6315 (37.9%)	40 583 (42.2%)	10 405 (31.9%)
Systolic blood pressure (mm Hg)	130.9 (22.3)	129.1 (19.6)	132.7 (22.6)	126.6 (21.9)
Diastolic blood pressure (mm Hg)	81.7 (15.2)	81.5 (12.2)	82.3 (16.3)	80.2 (13.1)
Diabetes	15 900 (10.2%)	1824 (10.6%)	9767 (9.5%)	4309 (12.0%)
Lipid measures (mmol/L)				
Total cholesterol	4.9 (1.1)	5.3 (1.1)	4.9 (1.1)	4.6 (1.0)
LDL cholesterol	3.1 (1.0)	3.3 (0.9)	3.0 (0.9)	3.2 (1.2)
HDL cholesterol	1.2 (0.4)	1.4 (0.4)	1.2 (0.3)	1.2 (0.4)
Non-HDL cholesterol	3.7 (1.0)	3.9 (1.0)	3.7 (1.0)	3.4 (1.0)
Body-mass index	25.7 (5.3)	27.8 (5.5)	26.2 (5.1)	23.2 (5.0)
Waist-to-hip ratio (men)	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)
Waist-to-hip ratio (women)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Waist-to-hip ratio >0.9 in men or >0.85 in women	73 272 (50.1%)	8865 (53.3%)	48 943 (50.7%)	15 464 (46.9%)
Socioeconomic and psychosocial risk factors				
Education				
Primary or less	66 353 (42.7%)	2264 (13.2%)	44 857 (43.8%)	19 232 (54.0%)
Secondary	59 081 (38.1%)	4962 (28.8%)	42 257 (41.3%)	11 862 (33.3%)
Trade, college, or university	29 819 (19.2%)	9977 (58.0%)	15 308 (14.9%)	4534 (12.7%)
Depression	17 450 (11.3%)	2826 (16.4%)	10 204 (10.0%)	4420 (12.5%)
Grip strength (kg)	30.4 (11.1)	35.6 (12.4)	31.0 (11.0)	25.9 (9.1)
Air pollution				
Household air pollution	31 447 (25.1%)	2 (0%)	20 382 (23.3%)	11 063 (50.0%)
Ambient PM _{2.5} (µg/m ³) air pollution	47.3 (32.5)	20.9 (32.3)	47.9 (29.3)	58.4 (34.3)

Data are n (%) or mean (SD). MET=metabolic equivalent of task. PM_{2.5}=particulate matter with a diameter of <2.5 µm.

Table 1: Baseline characteristics of the study population

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For the PURE study protocol see
www.phri.ca/pure

Statistical analysis

Categorical variables are presented as proportions, and continuous variables as means with SDs. Associations between risk factors and the outcomes were established using multivariable Cox frailty models for the entire cohort, and also by countries grouped by income level. To account for variations in outcomes due to differences between centres, random intercept effects were included in the models. For the Cox frailty models, proportionality assumptions were assessed, as was residual heterogeneity after inclusion of the frailty term (ie, random intercept effects) into each model (appendix p 13). For 12 risk factors (other than sodium and ambient air pollution), each model was mutually adjusted for all other risk factors, in addition to age, sex, and area of residence (urban or rural). Analyses were done for

participants with complete data (appendix p 21). Information on sodium excretion was only available in two-thirds of the study population, and air pollution was analysed as a community-level variable, so for these two risk factors hazard ratios (HRs) were calculated separately from the other 12 risk factors (appendix p 20). Associations are presented as HRs with 95% CIs. To estimate the population-level risk attributable to each risk factor (or cluster of risk factors), we calculated average PAFs in R (version 3.4.4) using the approach described by Eide and Gefeller⁴⁴ and the averisk R package developed by Ferguson and colleagues¹⁵ (see appendix p 14 for methods). Consistent with our HR calculations, PAFs for 12 risk factors were calculated together using a single model, while the PAFs for sodium excretion and ambient air pollution were calculated separately.

Role of the funding source

External funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or submitting of the report for publication. Four authors (SY, PJ, SR, and SI) had full access to the data, and had final responsibility for the decision to submit for publication.

Results

Between Jan 5, 2005, and Dec 4, 2016, 155 722 participants were enrolled and followed up for measurement of risk factors. The age of participants at enrolment ranged between 35 and 70 years, and median follow-up of the cohort was 9.5 years. Baseline characteristics of the study population are summarised in table 1. The mean age of the population was 50.2 (SD 9.9) years, and 90 811 (58.3%) of 155 722 participants were women. 81 897 (52.6%) participants were from urban areas. During follow-up, 10 234 deaths occurred (2917 were due to cardiovascular disease), there were 7980 incident cardiovascular disease cases, 3559 participants had myocardial infarction, and 3577 had a stroke. Events in the overall cohort and by groups of countries based on income status are summarised in the appendix (p 20).

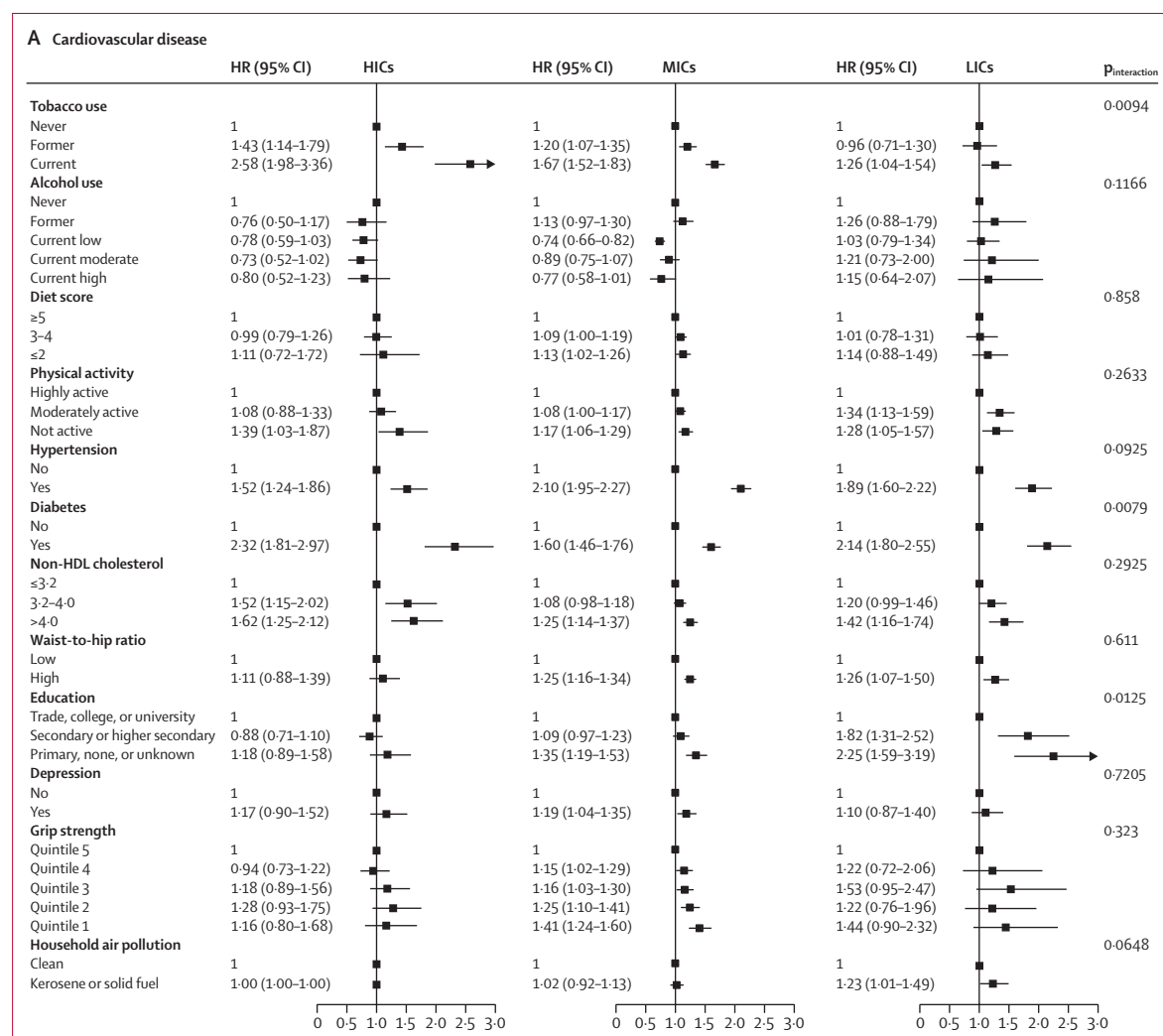
Of the behavioural risk factors, 31 821 (20.4%) participants reported current tobacco use, 6466 (4.2%) were consuming moderate amounts of alcohol, and 2959 (1.9%) were consuming high amounts of alcohol. 26 691 (18.5%) reported low physical activity. Mean PURE diet score was 3.9 (SD 1.9; a lower score indicates worse diet) and mean sodium excretion was 4.7 (SD 1.9) g per day, with 22 284 (21.9%) participants measured at more than 6 g per day. 17 450 (11.3%) participants reported symptoms consistent with depression in the year before enrolment. With respect to metabolic risk factors, 57 303 (39.4%) had hypertension and 15 900 (10.2%) had diabetes. Mean non-HDL cholesterol was 3.7 (SD 1.0) mmol/L, mean body-mass index (BMI) was 25.7 (SD 5.3) and mean waist-to-hip ratio was 0.87 (SD 0.1).

Important variations in baseline characteristics and risk factors were observed between populations across groups of countries categorised by income (table 1). MICs and LICs had more individuals from rural areas compared with HICs. The mean age was lowest in LICs (48·3 years [10·3], intermediate in MICs (50·6 years [9·7]) and highest in HICs (51·6 years [9·4]). Primary education was the highest level of education obtained by most participants from LICs (19232 [54·0%]), followed by 44857 (43·8%) from MICs and 2264 (13·2%) from HICs. By contrast, the proportion of participants with a college, trade, or university education was highest in HICs (9977 [58·0%]), followed by MICs (15308 [14·9%]) and LICs (4534 [12·7%]). A greater proportion of participants in HICs reported a history of smoking or alcohol consumption compared with MICs or LICs, although current smoking was higher in MICs and LICs compared with HICs. Diet quality scores indicated healthiest diet in those from HICs, followed by MICs and then LICs.

Sodium consumption was highest in MICs (driven by high amounts in China). Of the metabolic risk factors, mean BMI, waist-to-hip ratio, and non-HDL cholesterol concentrations were highest in HICs, prevalence of hypertension was highest in MICs, and prevalence of diabetes was highest in LICs. Grip strength was highest in HICs, followed by MICs and lowest in LICs. Household air pollution from kerosene or solid fuels was highest in LICs (11063 [50·0%]), followed by MICs (20382 [23·3%]), and close to zero in HICs. Mean ambient PM_{2.5} was 20·9 (SD 32·3) µg/m³ in HICs, 47·9 (29·3) µg/m³ in MICs, and 58·4 (34·3) µg/m³ in LICs.

See Online for appendix

Of the behavioural risk factors, tobacco use was most strongly associated with cardiovascular disease, followed by physical activity, and low-quality diet (table 2). Of the metabolic risk factors, hypertension had the strongest association with cardiovascular disease, followed by diabetes, elevated non-HDL cholesterol, and increased



(Figure 1 continues on next page)

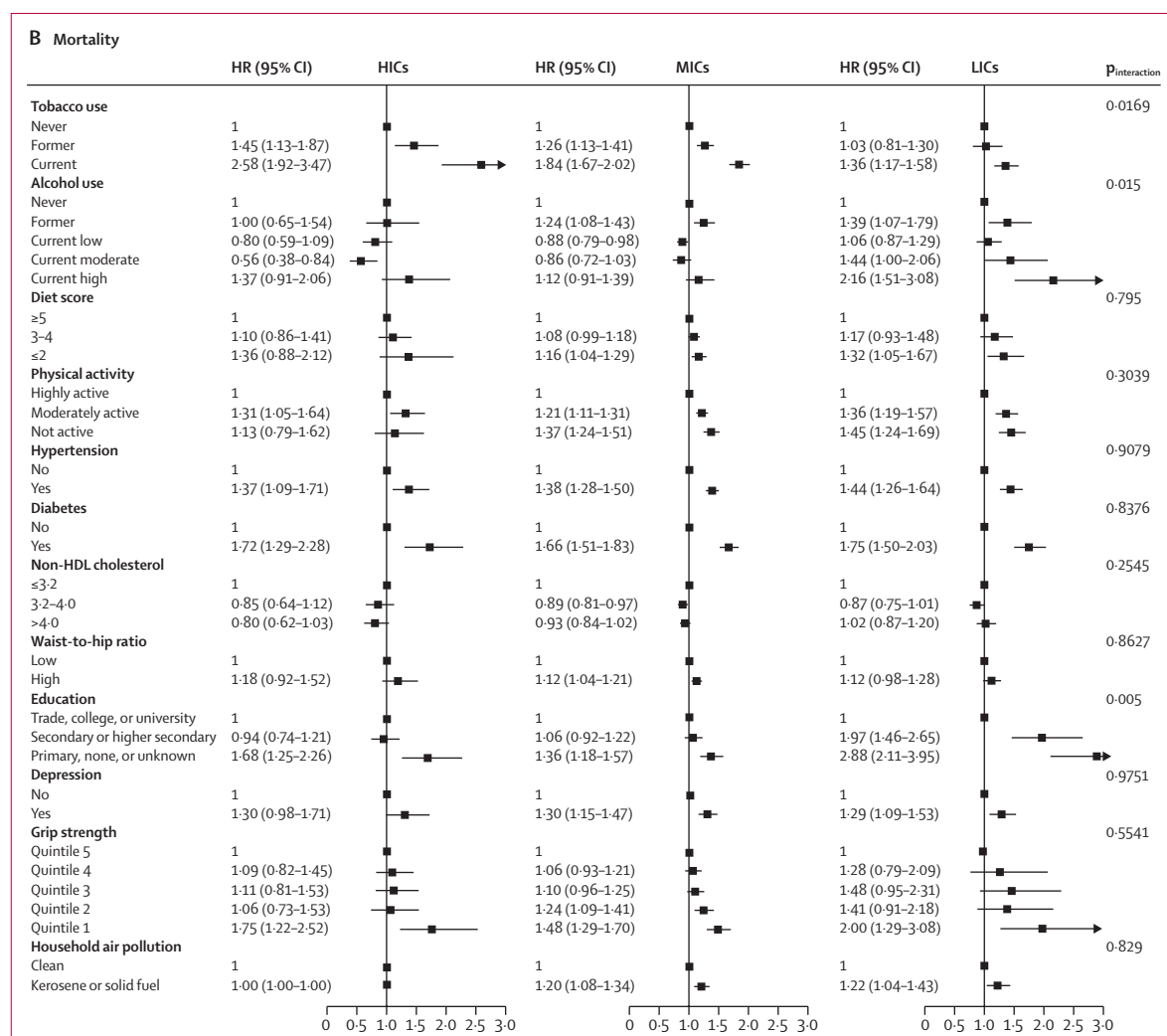


Figure 1: Variations in the associations between 12 modifiable risk factors and (A) cardiovascular disease or (B) death in HICs, MICs, and LICs

p values are for testing the interaction between country income and each exposure category. HICs=high-income countries. HR=hazard ratio. LICs=low-income countries. MICs=middle-income countries.

waist-to-hip ratio. Low education levels, symptoms of depression, low grip strength, and household air pollution were also associated with a higher risk of cardiovascular disease. The risk of cardiovascular disease associated with low education levels was highest in LICs, the risk associated with tobacco was highest in HICs, and the risk associated with diabetes was highest in HICs and LICs (figure 1A).

Of the behavioural risk factors, tobacco use showed the strongest association with death, followed by high alcohol consumption, low physical activity, and poor diet (table 2). Of the metabolic risk factors, diabetes was the strongest risk factor for death, followed by hypertension and abdominal obesity. Compared with the lowest tertile of non-HDL cholesterol, higher tertiles were associated with a lower risk of death (appendix p 23). This is likely related to unmeasured confounding or reverse causality, as

similar findings have been observed in some observational studies, but not in clinical trials of cholesterol lowering.¹⁶ Education and household air pollution were also strongly associated with a risk of death. Lower education and alcohol consumption had the strongest associations with death in LICs, while tobacco had the strongest association with death in HICs (figure 1B).

Hypertension was a stronger risk factor for stroke compared with myocardial infarction, whereas diabetes, non-HDL cholesterol, and current tobacco use were stronger risk factors for myocardial infarction compared with stroke (appendix p 24).

Metabolic risk factors tended to have a stronger association with cardiovascular death compared with non-cardiovascular death (appendix p 23). Elevated non-HDL cholesterol concentrations were associated with a higher risk of cardiovascular death, but an apparent lower

risk of non-cardiovascular death. As previously described, this might be due to reverse causality caused by lower lipid values being associated with some chronic diseases.

	Cardiovascular disease	Death
Behavioural risk factors		
Tobacco use		
Never	1 (ref)	1 (ref)
Former	1.19 (1.08–1.31)	1.22 (1.11–1.34)
Current	1.64 (1.51–1.77)	1.74 (1.61–1.88)
Alcohol use		
Never	1 (ref)	1 (ref)
Former	1.08 (0.96–1.23)	1.27 (1.12–1.43)
Current: low	0.77 (0.70–0.84)	0.92 (0.84–1.01)
Current: moderate	0.88 (0.77–1.02)	0.89 (0.77–1.03)
Current high	0.83 (0.67–1.02)	1.41 (1.20–1.66)
PURE diet score		
Score 5 or higher	1 (ref)	1 (ref)
Score 3–4	1.07 (1.00–1.16)	1.10 (1.02–1.19)
Score ≤ 2	1.13 (1.03–1.24)	1.22 (1.11–1.33)
Physical activity (MET min per week)		
High: >3000	1 (ref)	1 (ref)
Moderate: 600–3000	1.11 (1.04–1.19)	1.26 (1.18–1.35)
Low: <600	1.20 (1.10–1.30)	1.39 (1.28–1.50)
Metabolic risk factors		
Hypertension	2.00 (1.87–2.14)	1.40 (1.31–1.50)
Diabetes	1.74 (1.61–1.88)	1.68 (1.55–1.81)
Non-HDL cholesterol (mmol/L)		
<3.2	1 (ref)	1 (ref)
3.2–4.0	1.12 (1.04–1.21)	0.87 (0.81–0.94)
>4.0	1.31 (1.21–1.41)	0.93 (0.86–1.00)
Waist-to-hip ratio		
High waist-to-hip ratio*	1.26 (1.18–1.34)	1.13 (1.05–1.20)
Socioeconomic and psychosocial risk factors		
Education		
Trade, college, or university	1 (ref)	1 (ref)
Secondary	1.11 (1.01–1.22)	1.15 (1.03–1.29)
Primary or less	1.37 (1.23–1.52)	1.55 (1.39–1.74)
Depression	1.17 (1.05–1.29)	1.31 (1.19–1.43)
Grip strength (kg)		
Quintile 5	1 (ref)	1 (ref)
Quintile 4	1.12 (1.01–1.24)	1.09 (0.97–1.23)
Quintile 3	1.18 (1.07–1.31)	1.16 (1.04–1.30)
Quintile 2	1.21 (1.09–1.35)	1.25 (1.11–1.40)
Quintile 1	1.36 (1.21–1.52)	1.60 (1.42–1.79)
Air pollution		
Household air pollution	1.09 (1.00–1.19)	1.24 (1.14–1.36)

Data are hazard ratios (95% CI). Sodium and ambient air pollution results are presented separately. All models for the remaining 12 individual and household-level covariates were mutually adjusted for each risk factor, in addition to age, sex, and location. A variable for each participating PURE centre was also included as a random effect. MET=metabolic equivalent of task. * >0.9 in men or >0.85 in women.

Table 2: Risk of major cardiovascular disease and death associated with 12 modifiable risk factors in the overall population

Approximately 71% of the PAFs for cardiovascular disease, 79% for myocardial infarction, and 65% for stroke were attributed to individual and household-level risk factors (figure 2; figure 3). Risk factors contributed to a larger proportion of the PAF for cardiovascular disease in LICs compared with MICs or HICs (figure 2). Across all groups of countries categorised by income, the largest contribution to cardiovascular disease was from the cluster of metabolic factors.

In the overall cohort, hypertension was the largest risk factor for cardiovascular disease, contributing to 22.3% of its PAF. This was followed by high non-HDL cholesterol, household air pollution, tobacco use, poor diet, low education, abdominal obesity, and diabetes (each contributing to 5–10% of the PAF for cardiovascular disease; figure 3). Other risk factors each contributed less than 5% of the PAF for cardiovascular disease. High-non HDL cholesterol was the largest risk factor for myocardial infarction, followed by hypertension and tobacco use. Hypertension was the largest risk factor for stroke, followed by household air pollution and poor diet. Compared with HICs, PAFs for cardiovascular disease attributable to low education, poor diet, and household

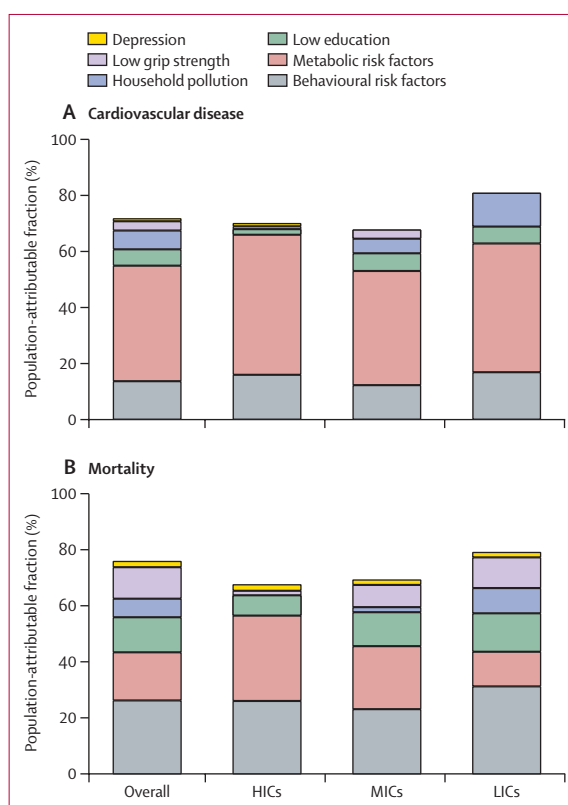


Figure 2: Population-attributable fractions for (A) cardiovascular disease and (B) death associated with 12 individual risk factors or clusters of modifiable risk factors

Estimates for individual risk factors were truncated at a lower limit of 0, as this is the lowest threshold to demarcate a relationship with increased risk. HICs=high-income countries. LIC=low-income countries. MICs=middle-income countries.

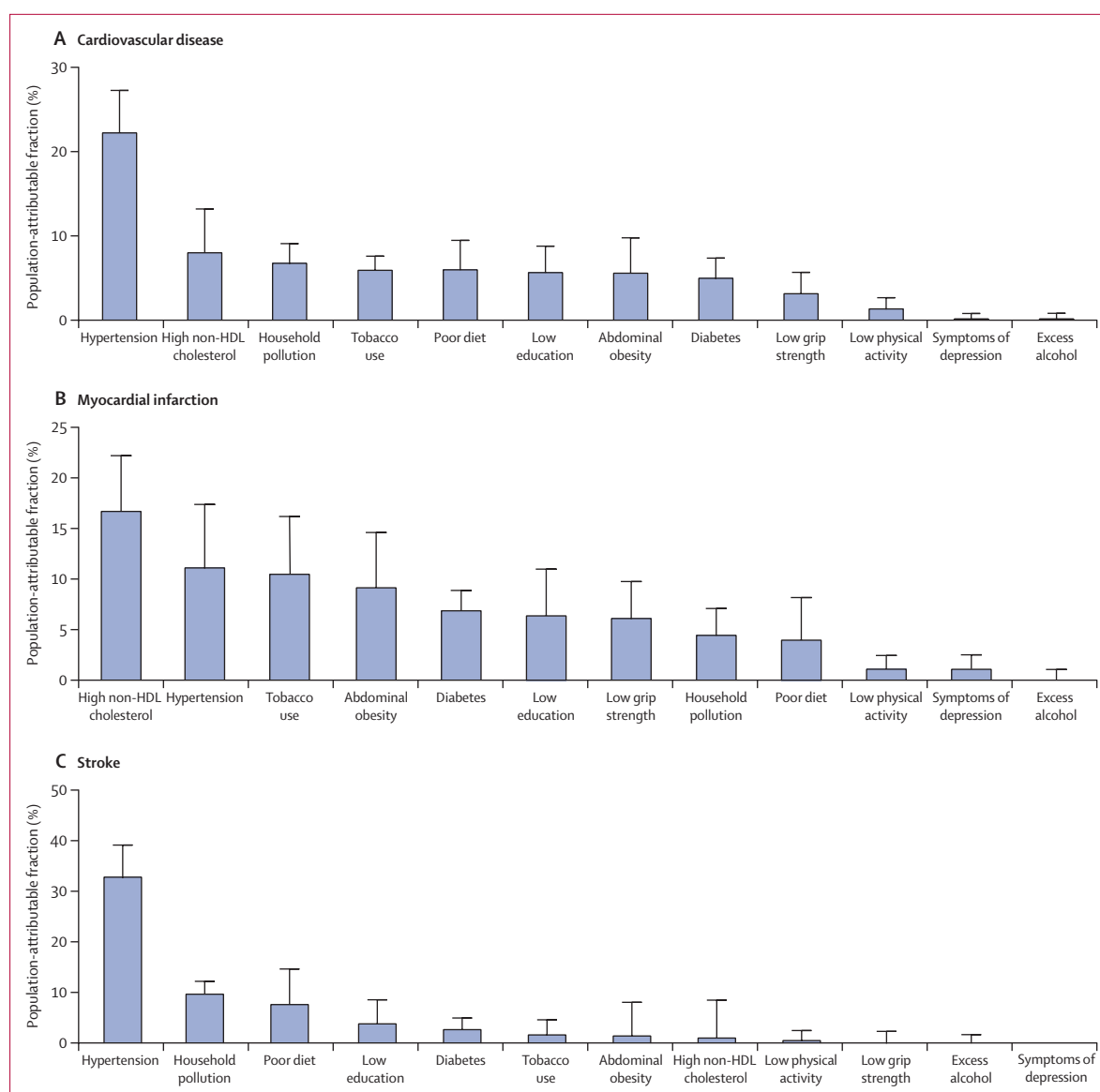


Figure 3: Population-attributable fractions for 12 individual and population-level risk factors with (A) cardiovascular disease, (B) myocardial infarction, and (C) stroke

Estimates for individual risk factors were truncated at a lower limit of 0, as this is the lowest threshold to demarcate a relationship with increased risk.

air pollution were relatively larger in MICs and LICs (figure 2; table 3)

Approximately 75% of deaths were attributable to individual and household-level risk factors (figure 2). Low education had the largest PAF for death in the overall population, followed closely by tobacco use, low grip strength, and a poor diet (each contributing to >10% of the PAF for death; figure 4). Hypertension, household air pollution, and diabetes each contributed to 5–10% of the PAF for death in the overall population. Large variations were observed as to which factors were associated with the highest PAFs between country groups. In HICs, metabolic risk factors contributed most

to deaths, but their relative effect was lower in MICs and LICs, while the effects of behavioural risk factors (driven by the effects of a poor diet), low education, low grip strength, and household air pollution were greater in MICs and LICs compared with HICs (figure 2; table 4).

For cardiovascular death, hypertension was the risk factor with the highest PAF, with several additional risk factors each contributing to more than 5% of its PAF. Tobacco use was the largest risk factor for non-cardiovascular death, followed closely by low education, low grip strength, poor diet, and household pollution. Other risk factors each contributed to less than 5% of the PAF for non-cardiovascular death.

Overall PAF (95% CI)	High-income country PAF (95% CI)	Middle-income country PAF (95% CI)	Low-income country PAF (95% CI)
1 Hypertension 22.3 (17.4 to 27.2)	High non-HDL cholesterol 20.7 (7.7 to 33.6)	Hypertension 26.5 (22.2 to 30.9)	Hypertension 14.3 (7.4 to 21.2)
2 High non-HDL cholesterol 8.1 (3.1 to 13.2)	Tobacco use 15.7 (3.3 to 28.0)	Low education 6.3 (3.0 to 9.5)	High non-HDL cholesterol 14.2 (9.0 to 19.3)
3 Household air pollution 6.9 (4.7 to 9.1)	Hypertension 14.6 (6.2 to 23.0)	Tobacco use 5.9 (2.6 to 9.3)	Household air pollution 12.0 (6.5 to 17.5)
4 Tobacco use 6.1 (4.5 to 7.6)	Diabetes 7.8 (3.9 to 11.7)	Household air pollution 5.2 (2.6 to 7.8)	Diabetes 10.4 (4.7 to 16.2)
5 Poor diet 6.1 (2.8 to 9.5)	Abdominal obesity 6.8 (−6.5 to 20.1)	Abdominal obesity 5.2 (1.8 to 8.6)	Poor diet 10.0 (−5.3 to 25.2)
6 Low education 5.8 (2.8 to 8.8)	Low education 2.0 (−2.4 to 6.4)	High non-HDL cholesterol 5.0 (2.0 to 8.1)	Abdominal obesity 7.0 (0.2 to 13.9)
7 Abdominal obesity 5.7 (1.7 to 9.8)	Depression 1.1 (−3.5 to 5.8)	Poor diet 4.6 (0.9 to 8.3)	Low education 6.0 (−4.5 to 16.5)
8 Diabetes 5.1 (2.9 to 7.4)	Low grip strength 1.0 (−4.2 to 6.1)	Diabetes 4.0 (2.9 to 5.1)	Tobacco use 4.5 (−1.6 to 10.6)
9 Low grip strength 3.3 (0.9 to 5.7)	Poor diet 0.2 (−6.4 to 6.9)	Low grip strength 3.2 (0.5 to 5.9)	Low physical activity 2.2 (−0.7 to 5.2)
10 Low physical activity 1.5 (0.3 to 2.7)	Excess alcohol 0.1 (−5.8 to 6.0)	Low physical activity 1.7 (0.2 to 3.1)	Excess alcohol 0.2 (−1.5 to 2.0)

In our subgroup analysis of country groups stratified by income, estimates for some risk factors within each category with very modest effects became more sensitive to changes using different analytic approaches. Therefore, we limited our results to the ten largest risk factors for cardiovascular disease based on PAFs for each outcome, as these estimates were the most robust. Sodium was not ranked because it was analysed in a subset of the population. Ambient air pollution was not ranked because it is a community-level risk factor. PAF=population-attributable fraction.

Table 3: Rank order for the top ten risk factors for cardiovascular disease in high-income, middle-income, and low-income countries along with their PAFs

Compared with a reference of 4–6 g per day, sodium excretion above 6 g per day was associated with a HR of 1.12 (95% CI 1.03–1.22) risk of cardiovascular disease, 1.16 (1.00–1.34) risk of myocardial infarction, 1.09 (0.98–1.21) risk of stroke, and 1.18 (1.07–1.29) risk of death. We estimated that high sodium consumption (above 6 g per day) accounted for 3.2% of the PAF for cardiovascular disease, 2.7% for myocardial infarction, 3.3% for stroke, and 3.9% for death.

For each 10-unit increase in outdoor PM_{2.5} there was a HR of 1.05 (95% CI 1.02–1.08) in the risk of cardiovascular disease, with a larger effect with stroke (HR 1.08 [1.05–1.11]) than with myocardial infarction (HR 1.03 [1.00–1.06]; appendix p 21). The associations of PM_{2.5} with death and non-cardiovascular death were inverse; however, in sensitivity analyses controlling for additional geographical factors (using a centre-based urban and rural fixed effect), the estimates changed to increased and null associations, respectively. In these analyses, a 10-unit increase in PM_{2.5} was associated with a HR of 1.07 (1.01–1.15) for death, 1.13 (1.02–1.55) for cardiovascular death, 1.04 (0.97–1.12) for non-cardiovascular death, 1.11 (1.03–1.19) for cardiovascular disease events, 1.11 (1.01–1.21) for myocardial infarction, and 1.14 (1.02–1.27) for stroke. Based on these results, PAFs were only estimated for cardiovascular disease outcomes, as these were consistent across analyses (appendix p 21). 14% of the PAF for cardiovascular disease, 9% for myocardial infarction, and 21% for stroke were attributable to ambient PM_{2.5} air pollution. However, the statistical approach used to calculate PAF for ambient air pollution (as a community level risk factor) differed from the approach used to calculate the effect of all other risk factors (which were based on individual-level data) and so they are not strictly comparable.

Discussion

Our overall findings indicate that over 70% of cardiovascular disease cases can be attributed to a small

cluster of modifiable risk factors. The largest proportion of PAFs for cardiovascular disease, stroke, and myocardial infarction globally were attributed to metabolic risk factors, with hypertension being the largest risk factor for cardiovascular disease, accounting for just over a fifth of the PAF for cardiovascular disease. Hypertension had a larger effect on stroke than on myocardial infarction. High non-HDL cholesterol, household air pollution, tobacco use, poor diet, low education, abdominal obesity, and diabetes each contributed to 5–10% of the PAF for cardiovascular disease. Physical activity, symptoms of depression, and excess alcohol consumption each had relatively modest contributions to cardiovascular disease at the global level.

Approximately two-thirds of deaths in the study were from non-cardiovascular causes. Most deaths were associated with low education, behavioural factors (tobacco use and poor diet), low grip strength, household air pollution, hypertension, and diabetes (with other factors each contributing to <5% of the PAF for death). While low education levels are associated with greater clustering of adverse health-related behaviours, this association persists after adjusting for health behaviours.¹⁷ The association of education with death is also larger than that observed with wealth or income.¹² Education affects multiple conditions from childhood onwards, including exposures to community-level factors (such as living or working in healthier environments), and better access to health and social resources. Our findings are also consistent with studies which observed that educational reforms can lead to reductions in cardiovascular and non-cardiovascular related mortality.¹⁸ It is therefore likely that with improvements in education, the number of deaths from several different conditions will also decline, indicating that investment in education can have broad health benefits.

The effect of low grip strength as a risk factor for death was comparable with the effect of several conventional

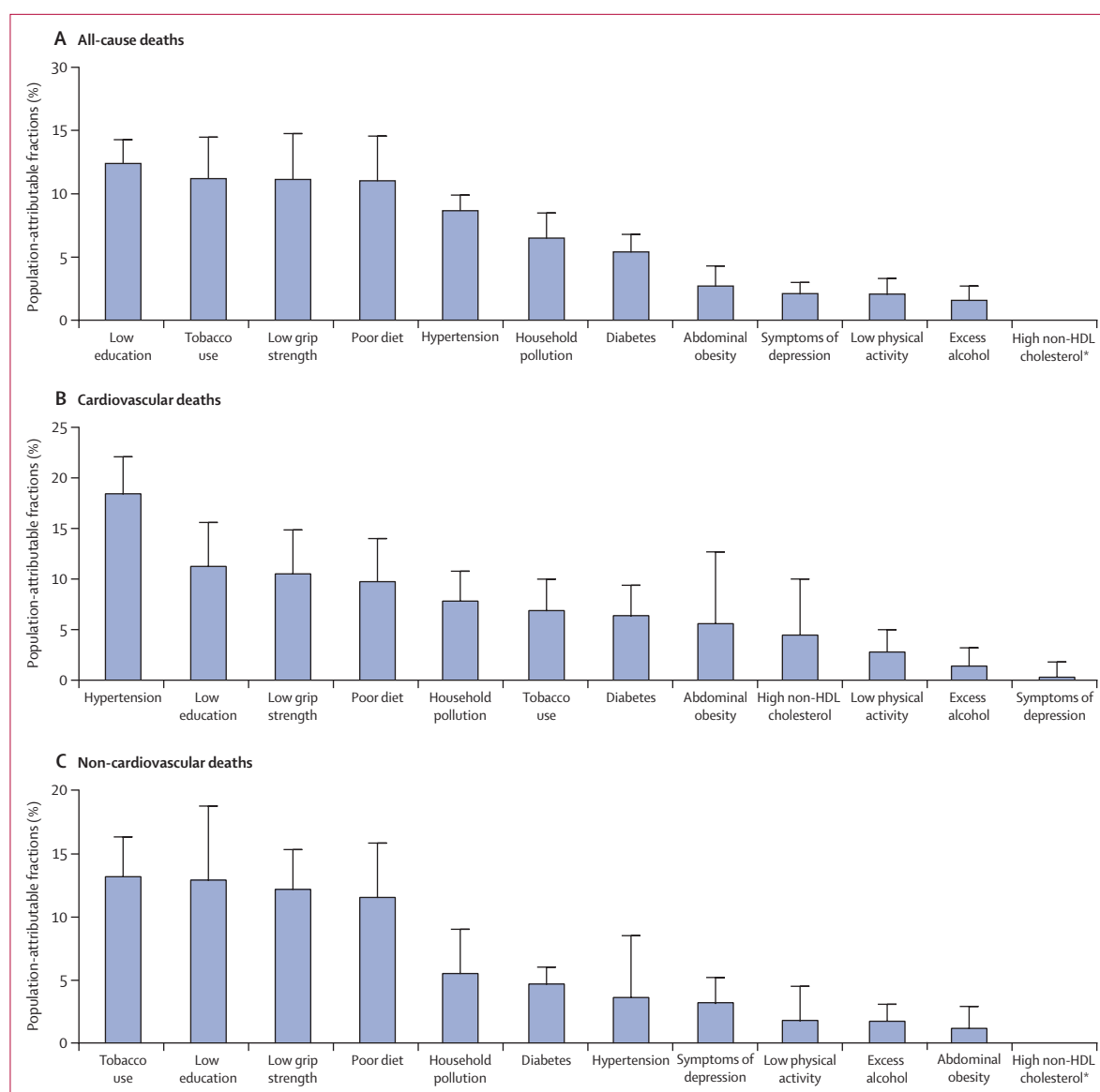


Figure 4: Population-attributable fractions for individual risk factors and (A) all-cause deaths, (B) cardiovascular deaths, and (C) non-cardiovascular deaths
 Estimates for individual risk factors were truncated at a lower limit of 0, as this is the lowest threshold to demarcate a relationship with increased risk. *Not included in analyses because population-attributable fractions and 95% CIs were negative, but potentially related to reverse causality.

risk factors. It is not known whether modifying strength in itself would directly affect mortality, but addressing the underlying processes (such as frailty) could result in greater resilience during acute or chronic illnesses, or injury. Consistent with this, in PURE low grip strength was strongly associated with a higher risk of death, and case fatality after acute illnesses (independent of multimorbidity; unpublished data), but had weaker associations with the actual development of disease.¹⁰ A greater understanding of how grip strength affects survival in people with disease, and learning how these processes can be modified to prolong survival, can lead to new interventions to reduce deaths.

The PAFs for high sodium consumption (>6 g per day) for cardiovascular disease (3.2%) and death (3.9%) were relatively small in the overall cohort, consistent with other studies that have observed modest associations when examining the direct association of sodium excretion with cardiovascular disease or death.^{13,19–21} We did not include data of those with sodium consumption below 4 g per day in our calculations of PAFs for sodium consumption, because those participants showed more cardiovascular disease and deaths compared with participants consuming between 4–6 g per day—and we are uncertain of the implications of this result. However, including those with a sodium consumption below 4 g per day would

	Overall PAF (95% CI)	High-income country PAF (95% CI)	Middle-income country PAF (95% CI)	Low-income country PAF (95% CI)
1	Low education 12.5 (10.7 to 14.3)	Tobacco use 17.9 (1.2 to 34.6)	Hypertension 13.2 (11.2 to 15.1)	Poor diet 19.2 (9.0 to 29.4)
2	Tobacco use 11.3 (8.1 to 14.5)	Hypertension 13.1 (-7.4 to 33.6)	Tobacco use 12.6 (8.9 to 16.3)	Low education 13.7 (7.7 to 19.7)
3	Low grip strength 11.6 (7.3 to 16.0)	Abdominal obesity 11.4 (-6.1 to 28.9)	Low education 12.1 (6.2 to 18.0)	Low grip strength 10.9 (4.4 to 17.5)
4	Poor diet 11.1 (7.7 to 14.6)	Low education 7.2 (1.7 to 12.7)	Low grip strength 7.9 (5.0 to 10.7)	Household air pollution 9.0 (3.7 to 14.2)
5	Hypertension 8.8 (7.6 to 9.9)	Diabetes 5.9 (-0.4 to 12.2)	Poor diet 6.1 (-1.1 to 13.2)	Tobacco use 7.6 (0.7 to 14.5)
6	Household air pollution 6.6 (4.7 to 8.5)	Excess alcohol 5.5 (-0.5 to 11.5)	Abdominal obesity 4.7 (1.3 to 8.0)	Diabetes 6.7 (4.0 to 9.4)
7	Diabetes 5.5 (4.2 to 6.8)	Poor diet 2.7 (-3.8 to 9.1)	Diabetes 4.5 (4.1 to 4.8)	Hypertension 5.6 (0.5 to 10.7)
8	Abdominal obesity 2.8 (1.3 to 4.3)	Depression 2.3 (-3.0 to 7.6)	Low physical activity 3.0 (1.7 to 4.3)	Low physical activity 2.7 (0.4 to 5.0)
9	Depression 2.2 (1.4 to 3.0)	Low grip strength 1.6 (-8.1 to 11.4)	Depression 1.9 (0.6 to 3.2)	Depression 1.9 (0.4 to 3.4)
10	Low physical activity 2.2 (1.0 to 3.3)	Household air pollution 0 (-1.5 to 1.5)	Household air pollution 1.8 (-1.8 to 5.3)	Excess alcohol 1.8 (0.5 to 3.1)

In our subgroup analysis of country groups stratified by income, estimates for some risk factors within each category with very modest effects became more sensitive to changes using different analytic approaches. Also, for high non-HDL cholesterol, it is likely that the inverse association with all-cause mortality we observed is a result of unmeasured confounding or reverse causality, as this observation has been reported in some observational studies, but not in clinical trials. Therefore, we limited our results to the ten largest risk factors for mortality based on PAFs for each outcome, as these estimates were the most robust. Sodium was not ranked because it was analysed in a subset of the population. Ambient air pollution was not ranked because it is a community-level risk factor. PAF=population-attributable fraction.

Table 4: Rank order for the top ten risk factors for death in high-income, middle-income, and low-income countries along with their PAFs

decrease the overall impact of a strategy of extreme sodium reduction. Strategies to reduce sodium may have larger benefits in regions where sodium consumption is high (eg, China or central Asia) or in specific populations who may be sensitive to the effects of sodium (eg, people with hypertension).²² Therefore, targeted or contextually appropriate approaches to reduce sodium intake are preferable to attempting universal reductions.

Our findings also highlight the importance of addressing both household and ambient air pollution to reduce cardiovascular disease and death. Exposure to both forms of air pollution were higher in MICs and highest in LICs, so it is likely that strategies to reduce air pollution have the largest effect in these countries. Ambient air pollution was primarily associated with a higher risk of cardiovascular disease, while household air pollution was also strongly associated with a higher risk of death. This might be related to the greater levels of pollution that result from cooking with kerosene or solid fuels. Our data indicate that a large proportion of premature deaths could be averted globally by focusing on reducing household air pollution from kerosene or solid fuel use in MICs or LICs. We also estimated that 13.9% of cardiovascular disease cases globally could be attributed to ambient air pollution, but since it is a community-level exposure, we were not able to make direct comparisons to other risk factors (as the average PAF method generally results in lower risk estimates). Although we were not able to quantify PAFs for ambient air pollution by country groups, our findings still suggest that it plays an important role in the varying risk of cardiovascular disease observed at different levels of economic development. A 10 µg increase in PM_{2.5} is associated with a 3% increase in the risk of death related to cardiovascular disease, a 5% increase in cardiovascular disease events, a 3% increase in myocardial infarction, and an 8% increase in stroke. To put this in perspective, there is a 2.5-fold difference in PM_{2.5} between HICs and

MICs and 3.7-fold difference between HICs and LICs. Given the pervasiveness of ambient air pollution, if these relatively modest associations between PM_{2.5} and cardiovascular disease are causal, this would account for a substantial proportion of the differences in cardiovascular disease between HICs and MICs or LICs.

The comparative effect of some of our risk factors varied between countries grouped by their economic levels, which could be for several reasons. First, we observed that for some risk factors, (eg, smoking and education) associations with cardiovascular disease or mortality differed between country groups. For example, the association of low education with cardiovascular disease and death was strongest in MICs and LICs, which may be due to the greater support provided to those with low education in HICs or greater disparities between those educated and not educated in poorer countries. Second, the comparative effect of risk factors on cardiovascular disease or deaths would be expected to vary between country groups depending on the prevalence of each risk factor, the relative incidences of different diseases (eg, myocardial infarction vs stroke), and the predominant causes of death (eg, cardiovascular disease, cancers, or infections). This also means that the relative effect of different risk factors on specific diseases and specific causes of death might change over time, if the risk factors change or if effective treatments (eg, lipid-lowering or anti-hypertensive drugs) are more widely used. Third, the relative frequency of deaths from cardiovascular disease versus other causes varies between countries grouped by economic level, and so the relative effect of risk factors on overall deaths will also vary if the prevalence of risk factors (which predominantly affect cardiovascular mortality, but not other causes of death) changes over time.

In HICs, about 70% of cardiovascular disease cases were attributable to modifiable risk factors (excluding ambient air pollution), with the largest contributors being metabolic risk factors and tobacco use. This is

consistent with the findings of previous epidemiological studies conducted across North America and Europe. Modifiable risk factors also accounted for about 70% of cardiovascular disease cases in MICs, with hypertension being the leading risk factor for cardiovascular disease. While metabolic (ie, abdominal obesity, elevated non-HDL cholesterol) and behavioural risk factors (ie, tobacco use) remained significant, the effect of low education was larger in MICs compared with HICs. In LICs modifiable risk factors accounted for about 80% of cardiovascular disease cases, with the largest risks attributed to metabolic risk factors, household air pollution, and poor diet. Household air pollution was the third largest individual risk factor for cardiovascular disease in LICs, probably due to the high prevalence of exposure in these countries. Poor diet was the leading behavioural risk factor for cardiovascular disease in LICs, and at least as important as tobacco use, if not more. This is in keeping with a larger proportion of the population with poor diet, and very low rates of smoking among women, as well as lower risks of cardiovascular disease and death associated with smoking in LICs.

Approximately 65% of deaths in HICs were attributable to modifiable risk factors. The largest contributor to mortality in HICs was tobacco use, likely related to its effect on several non-communicable diseases including cardiovascular disease, cancer, and respiratory disease, as well as the high prevalence of current or past smoking in both men and women in the population. Hypertension and abdominal obesity were the next largest risk factors for death in HICs, reflecting the large contribution of cardiovascular disease to death in these countries. Low education was the fourth largest cause of death in HICs, emphasising the need to improve education even in some HICs.

About 70% of deaths in MICs and 80% of deaths in LICs were attributable to the modifiable risk factors. In these regions, the comparative effect of several risk factors (ie, low education, low grip strength, poor diet, household air pollution) were larger than their effects in HICs. This highlights the need for direct data from MICs and LICs to better guide prevention efforts in these countries, rather than extrapolating data from HICs.

Our study has some potential limitations. First, since our data are based on 21 countries, our results may not be generalisable to all countries. In particular we have no data from west Africa, north Africa, or Australia; the number of participants from the Middle East is modest; and data from LICs are predominantly from south Asia with a few African countries. We will attempt to overcome these limitations by enrolling participants from these regions, or by developing collaborative analyses with independent cohorts in the future. Second, within countries, recruitment of participants was from one or two specific provinces, although in some countries (eg, China, India, Canada, Malaysia, Turkey, and Colombia) participants

were recruited from several provinces. Therefore, the data in PURE from each country might not be applicable to the whole population in these countries. Third, while biases have been minimised in the selection of individuals within a community, the countries and centres within each country were selected based on feasibility and the willingness of investigators to participate in a large, long-term cohort study. However, the inclusion of nearly 900 urban and rural communities from multiple countries in different regions of the world provides substantial diversity of risk factors and contextual variables and makes it likely that the PURE results are more broadly applicable than most previous studies, and might be applicable to many more countries than the 21 included in the study. Fourth, although most risk factors were derived or supplemented with objective measures (eg, blood pressure, plasma lipid concentration, grip strength, anthropometry, ambient air pollution, sodium excretion), or self-reported based on validated instruments (eg, physical activity, diet), some misclassification is possible. We did collect repeat information at 3 and 6 years on the above risk factors in about 20–30% of participants and used this information to correct for regression dilution biases for continuous variables, making the HRs stronger. However, repeat analyses were not possible for categorical variables and moreover as far as we are aware, there is no method to incorporate such measurement errors in the estimations of PAF. Therefore, we present the data without these corrections, so they might be an underestimate of the associations of several of these risk factors with cardiovascular disease and death. Fifth, the only risk factor we report in this paper at the community level is ambient air pollution, and it is likely that other community-level factors (eg, built environment, chemical exposures, noise pollution) and differences in access to health care have important effects on cardiovascular disease and death. Some of these will be incorporated in future analyses from PURE. Finally, only large differences in PAF between risk factors should be taken as evidence that one risk factor is more important than another. PAF estimates by subgroup (ie, by disease type or by country income level) might be more prone to error, particularly if effect sizes are modest. In general, when PAFs are within a few percentages of each other, they should be interpreted as being of similar importance, especially if the CIs of the estimates also overlap.

The findings reported in this paper are complementary to other studies on the importance of risk factors for cardiovascular disease and death. For example, Stringhini and colleagues²³ observed that socioeconomic status (defined by occupation) was the third largest risk factor for death in a meta-analysis of cohorts from seven HICs. In PURE, low education was the fourth leading risk factor for death in HICs, but the largest disparities were observed in MICs and LICs, suggesting that improving education, or addressing the barriers to health in these populations, should be among the highest health

priorities to reduce premature death, particularly in MICs and LICs. Consistent with estimates from GBD, we found that modifiable risk factors account for the majority of deaths globally.²⁻⁴ Both PURE and GBD studies highlight the large effects elevated blood pressure, tobacco use, and poor diet quality have on death at the global level, although our observations also emphasise the need to consider education and strength as key modifiable factors for improving health. Data such as ours will help refine future estimates from GBD and other pooled analyses. Furthermore, our findings indicate that reducing cardiovascular disease and premature death will require both general and context-specific approaches that target risk factors at the individual (eg, behavioural and metabolic), community, and environmental levels. While tobacco avoidance, hypertension control, and reducing elevated lipids are important global strategies, substantial additional benefits can be potentially achieved by addressing socioeconomic factors such as improving education, and reducing environmental factors such as air pollution. Additionally, strategies that improve household access to clean fuels, strength, and diet quality are likely to have particularly large effects in MICs or LICs, and need to be considered as major health priorities in these countries. Such context-specific strategies are likely to have a greater effect in reducing premature cardiovascular disease or mortality than global strategies based mostly on information from HICs.

In conclusion, PURE indicates that a large proportion of cardiovascular disease and premature deaths could be averted by targeting a few modifiable risk factors. While some risk factors warrant global policies (eg, hypertension control, tobacco control, or improved education), the importance of several risk factors varies between countries at different economic levels, highlighting the need for additional context-specific priorities for prevention of premature cardiovascular disease and deaths.

Contributors

SY designed the study, obtained funding, and oversaw its conduct since its inception 18 years ago. SY and PJ wrote the various drafts. SR coordinated the worldwide study, and SI led the statistical analysis. All other authors coordinated the study in their respective countries and all commented on drafts of the paper.

Declaration of interests

SY, PJ, SR, SI, AM, DL, and KT report grants from the Canadian Institutes of Health Research and the Ontario Ministry of Health and Long-Term Care during the conduct of the study. MB reports a grant from the Canadian Institutes of Health Research during the conduct of the study. SY reports a grant from the Marion W Burke Endowed Chair of the Heart and Stroke Foundation of Canada. All other authors declare no competing interests.

Data sharing

Data from PURE are not available for public use.

Acknowledgments

We thank Patrick Sheridan for additional statistical support and Matthew McQueen for supervising and standardising the laboratory analyses. The PURE study is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute, the Canadian Institutes of Health Research (including through the Strategy for

Patient-Oriented Research via the Ontario SPOR Support Unit), the Heart and Stroke Foundation (ON, Canada), the Ontario Ministry of Health and Long-Term Care. The PURE-AIR study is funded by the Canadian Institutes for Health Research (grant 136893) and by the Office of the Director, National Institutes of Health (award DP5OD019850). It is also funded by unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier Laboratories, and GlaxoSmithKline, and additional contributions from Novartis, King Pharma, and from several national and local organisations in participating countries. Further details on the funding and participating countries and institutions, and on collaborating staff, are shown in the appendix (pp 24–31).

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