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Modifiable risk factors, cardiovascular disease and mortality in 155,722 individuals from 21 high-, middle-, and low-income countries

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Abstract

Background: Global estimates of the impact of common modifiable risk factors on cardiovascular disease (CVD) 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 methodology to prospectively evaluate the impact of modifiable risk factors on CVD and mortality across 21 countries (spanning five continents) at different economic levels.

Methods: In a multi-national, prospective cohort study, we examined associations for 14 potentially modifiable risk factors with mortality and major CVD in 155,722 community-dwelling participants (ages 35–70 years at enrollment) from 21 high-, middle-, or low-income countries (HIC, MIC or LIC) followed for a median of 9·5 years. We describe the prevalence, hazard ratios, and population attributable fractions (PAFs) for CVD and mortality associated with a cluster of behavioural factors (i.e. tobacco, alcohol, diet, physical activity and sodium intake), metabolic factors (i.e. lipids, blood pressure, diabetes, obesity), socioeconomic and psychosocial factors (i.e. education, symptoms of depression), strength, household (solid fuel for cooking) and ambient PM 2·5 air pollution.

Findings: Mean age of the population was 50·2 years of age, 58·3% were female, 52·6% were from urban areas, 11·1% from HIC, 65·9% from MIC, and 23·0% from LIC. Over 70% of CVD cases and deaths in the overall cohort were attributed to modifiable risk factors. Metabolic factors were the predominant risk factors for CVD (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 CVD (although different statistical methods were used for this analysis). In MIC and LIC, the importance of household air pollution, poor diet, low education, and low grip strength were larger compared with HIC.

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

Keywords

Cardiovascular disease; mortality; risk factors

1 INTRODUCTION:

It is estimated that 55 million deaths occurred in the world in 2017, of which 17·7 million were from cardiovascular disease (CVD).[12] Documenting the consistency or variations in the associations between risk factors with CVD 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 CVD are from the Global Burden of Disease (GBD), the largest meta-

analytic repository of epidemiologic data relating risk factors to mortality and CVD .[1,2] However, estimates are derived through combining data from diverse studies with differing methods, at differing time-periods, with relatively little data from low- and middle-income countries (LIC and MIC). To complement, validate and extend information derived from the GBD, large international studies involving MIC and LIC and employing standardized methods of sampling, measurement of exposures and outcomes, are needed. For CVD, a few multi-national case-control studies have provided comparative data on the associations of risk factors with myocardial infarction (MI) and strokes, but these had a majority of non-fatal events, and are prone to potential biases inherent to case-control studies (e.g. reverse causality or recall biases).[3,4]

The Prospective Urban Rural Epidemiology (PURE) study is an attempt to provide standardized and contemporaneous information across several countries, especially those outside North America and Western Europe.[5] The objectives of this report is to quantify and compare the associations and population attributable fractions of 14 common modifiable risk factors on CVD and mortality. We also report whether these associations vary between groups of countries at different economic levels.

2 METHODS:

2.1 Study Design and Participants:

PURE was designed to include countries across a broad range of economic levels, social circumstances and health policies, with a proportionally larger representation from MIC and LIC. The study's design has been previously published. In participating countries, urban and rural communities were selected using pre-specified criteria (Supplementary Appendix A1).[5] Within each community, households and individuals were selected using sampling strategies to minimize the selection of individuals that could potentially bias any associations between risk factors and outcomes.[5] Socioeconomic characteristics and mortality rates of the study population are comparable to national statistics from participating countries.[6] This analysis was limited to the first two phases of PURE, which involved 21 countries between 2003–2014 that completed at least one cycle of follow-up visits. Information on vital status was available in 98·4%, and information on CVD in 94.1%. Median follow up of the cohort is 9.5 years. The population included was between 35–70 years of age at enrollment, and without a prior history of CVD, resulting in 155,722 participants (Supplementary Appendix B, Table 1 and Figure 1). Countries were categorized into HIC, MIC and LIC based on their World Bank country income classification at the time of inclusion. The study was approved by local ethics committees in each center, and all participants provided written informed consent.

2.2 Measurement of Risk Factors:

A detailed summary of each risk factor, its method of measurement, and its categorization for the calculation of population attributable fractions (PAFs) are summarized in Supplementary Appendix B, Table 2. Data were collected using standardized methods. Baseline data were collected at the community, household, and individual levels. For this analysis, 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. The metabolic cluster of risk factors comprised blood pressure/hypertension, dysgyleemia/diabetes, non HDL-cholesterol, and obesity (measured using waist-to-hip ratio [WHR], which was more strongly associated with CVD and mortality than body mass index [BMI] in PURE and several prior studies).[7–9] Education and symptoms consistent with depression was our primary psychosocial variable of interest. Education was included as our primary socioeconomic variable of interest as we have previously shown that education was a stronger socioeconomic predictor of CVD and mortality than wealth or income.[10] Grip strength was measured by JAMAR dynamometer, and has previously been shown to be associated with CVD and mortality.[11] Air pollution was examined both as household (solid fuels for cooking), and ambient, which was estimated at the community level, and obtained from integrating information on particulate matter smaller than 2·5 microns (PM2·5) from a combination of satellite observations, chemical transport models, and ground level monitoring,[12]

For overall diet quality, we used a composite diet score which has been replicated in 5 independent studies and was at least as good, or superior to previous diet risk scores (unpublished data). Non HDL-C was chosen as our primary lipid value because it had the strongest association with CVD (Supplementary Appendix B, Table 3). Fasting urinary sodium excretion was estimated using the Kawasaki formula, and used as a surrogate for sodium intake in 101,609 individuals with available data.[13].

2.3 Outcomes:

The primary outcomes for this paper were composite of CVD events (defined as CV death, myocardial infarction, stroke and heart failure) and mortality. During follow-up, these events were collected using standardized case-report forms, reported based on common definitions and adjudicated. (Supplementary Appendix A2).

2.4 Statistical analysis:

Categorical variables are summarized as proportions, and continuous variables as means with standard deviations (SDs). Associations between risk factor and the outcomes were determined 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 centers, 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 (i.e. random intercept effects) into each model (Supplementary Appendix A3). 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 urban-rural area. Analyses were conducted on participants with complete data (Supplementary Appendix B, Table 4). Information on sodium excretion was available in only two-thirds of the study population, and air pollution was analyzed as a community level variable. Therefore hazard ratios for these two risk factors were calculated separately from the other 12 risk factors (Supplementary Appendix A4 and A5). Associations are presented as hazard ratios with 95% confidence intervals. To estimate the population level risk attributable to each risk factor (or clusters of risk factors), we calculated average population attributable fractions

using the approach described by Eide and Gefeller, and based on the 'averisk' R package developed by Ferguson et al. (see Supplementary Appendix A6 for methods).[14,15] Consistent with our hazard ratio calculations, PAFs for 12 risk factors, excluding sodium and ambient air pollution, were calculated together using a single model, while the latter were calculated separately.

2.5 Role of the funding sources:

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

3 RESULTS:

Characteristics of the study population are summarized in table 1. The mean age of the population was 50·2 (standard deviation [SD] 9·9) years of age, and 58·3% were female. 52·6% of the population were from urban areas. During follow up, 10,234 deaths (of which 2917 were due to a CVD), 7980 incident CVD cases, 3559 MIs, and 3577 strokes occurred. Rates of each outcome are overall and by groupings of countries by income status are summarized in Supplementary Appendix B, Table 5.

Of the behavioural risk factors, 20·6% of the study population reported current tobacco use; 4·2% were consuming moderate and 1·9% were consuming high amounts of alcohol; and 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/day, with 20·9% of the population consuming >6g/day. 11·3% of the population reported symptoms consistent with depression in the prior year to enrollment. With respect to metabolic risk factors, 39.4% had hypertension, and 10·2% had diabetes. Mean non-HDL cholesterol was 3·7 (1·0) mmol/L, mean BMI was 25·7 (SD 5·3) and mean waist-to-hip ratio (WHR) was 0·87 (SD 0·1).

Important variations in baseline characteristics and risk factors were observed between populations across groups of countries categorized by income (table 1). MIC and LIC had more individuals from rural areas compared with HIC. The mean age was lowest in LIC (48·3 years), intermediate in MIC (50·6 years) and highest in HIC (51.6 years). Only primary education level or less was attained in the majority of participants from LICs (54·0%), in 43·8% from MICs, and 13·2% in HICs. By contrast, the proportion of participants with a college, trade, or university education was highest in HIC (58·0%), followed by MIC (14·9%) and lowest in LIC (12·7%). A greater proportion of participants in HIC reported a history of smoking or alcohol consumption compared with MIC or LIC, although current smoking was higher in MIC and LIC compared to HIC. Diet quality scores indicated healthiest diet in those from HIC, followed by MIC and then LIC. Sodium consumption was highest in MIC (driven by higher levels in China, but not other MIC). Of the metabolic risk factors, mean BMI, WHR, and non-HDL cholesterol levels were highest in HIC, hypertension prevalence was highest in MIC, and diabetes prevalence was highest in LIC. Grip strength was highest in HIC, followed by MIC and lowest in LIC. Household air pollution from solid fuel use was highest in LIC (50·0%), followed by MIC (23·3%), and

nearly zero in HIC. Mean PM 2·5 levels were 20·9, 47·9, and 58·4 μg/m3 respectively in HIC, MIC and LIC.

Risk of CVD and death associated with 12 individual or household level risk factors:

Of the behavioural risk factors, tobacco use was the most strongly associated with CVD, followed by physical activity, and low-quality diet (table 2). Of the metabolic risk factors, hypertension had the strongest association with CVD, followed by diabetes, elevated non-HDL cholesterol and increased WHR. Low education levels, depression symptoms, low grip strength, and household air pollution were also associated with a higher risk of CVD. The risk associated with low education was highest in LIC; risk with tobacco was highest in HIC; and risk with diabetes was highest in HIC and LIC (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 factors, diabetes was the strongest risk factor for death, followed by hypertension and abdominal obesity. Compared to the lowest tertile of non HDL-C, higher tertiles were associated with a lower mortality (however it was associated with a higher risk of CVD mortality [figure 3])..[16] Education and household air pollution were also strongly associated with a higher risk of death. Lower education and alcohol consumption had the strongest associations with death in LIC, 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 MI compared to stroke (figure 2).

Metabolic risk factors tended to have a stronger association with CV death compared with non-CV death (figure 3). Elevated non-HDL cholesterol was associated with a higher risk of CV death, but an apparent lower risk of non-CV death, but this may be due to reverse causality due to lower lipid values being associated with some chronic diseases.

Population attributable risks of 12 individual and household level risk factors with CVD and mortality

Approximately 71% of the PAF for CVD, 79% for MI, and 65% for stroke were attributed to individual and household level risk factors ((Figures 4 and 5, and Table 3). Risk factors contributed to a larger proportion of the PAF for CVD in LIC compared with MIC or HIC (figure 4). Across all groups of countries categorized by income levels, the largest contribution to CVD was from the cluster of metabolic factors.

Hypertension was the largest risk factor for CVD, 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 between 5–10% of the PAF for CVD) (figure 5). Other risk factors each contributed less than 5% of the PAF for CVD. High-non HDL cholesterol was the largest risk factor for MI followed by hypertension, and tobacco use. Hypertension was the largest risk factor for stroke, followed by household air pollution and poor diet.

Approximately 75% of deaths were attributed to individual and household level risk factors, with the largest impact observed in LIC. (Figures 4 and 6, and table 3). Behavioural risk factors had the largest PAF for death overall, but large variations were observed as to which factors were associated with the highest PAFs between county groups. In HIC, metabolic risk factors contributed most to deaths, but their relative impact was less in MIC and LIC; while the impacts of behavioural risk factors, education and household air pollution were higher in MIC and LIC compared with HIC.

Low education had the highest 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). Hypertension, household air pollution, and diabetes each contributed between 5–10% of the PAF for death, while other risk factors contributed to less than 5% the PAF. For CV death, hypertension was the risk factor with the highest PAF, with several additional risk factors contributing to > 5% of its PAF. Tobacco use was the largest risk factor for non-CV death, followed closely by low education, low grip strength, poor diet and household pollution. Other risk factors contributed to less than 5% of the PAF for non-CV death.

High sodium versus CVD and mortality:

Compared to a reference of 4–6g/day, excretion of >6g/day of sodium was associated with a 1·12(95% CI 1·03, 1·22) risk of CVD, 1·16(1·00, 1·34) of MI, 1·09 (0·98, 1·21) of stroke, and 1·18(1·07, 1·29) of death. Elevated sodium intake accounted for 3·2% of the PAF for CVD, 2·7% for MI, 3·3% for stroke, and 3·9% for death.

Ambient $PM_{2.5}$ air pollution vs CVD and mortality:

For each 10 unit increase in outdoor PM2·5 there was a HR of 1·05 (95% CI 1·02–1·08) in the risk of CVD, with a larger effect with stroke (HR = 1·08 (95% CI 1·05–1·11) than with MI (HR = 1·03 (95% CI 1·00–1·06)) (Table 4). The association of PM2·5 with overall mortality and non-CV death were inverse; however, in sensitivity analyses controlling for additional geographic factors (using a center urban and rural fixed effect) the estimates changed to increased and null associations, respectively. In these analyses, a 10 unit increase in PM2·5 was associated with a HR of 1·07 (95% CI: 1·01–1·15) for mortality, 1·13 (95% CI: 1·02–1·55) for CVD mortality, 1·04 (95% CI: 0·97–1·12) for non-CV mortality, 1·11 (95% CI: 1·03–1·19) for CVD events, 1·11 (95% CI: 1·01–1·21) for MI, and 1·14 (95% CI: 1·02–1·27) for stroke. Ambient PM2·5 air pollution contributed to 14% of the PAF for CVD, 9% for MI, and 21% of the PAF for stroke. However, the statistical approach to the calculation of PAF for ambient air pollution (as a community level risk factor) differed from that used for the impact of all other risk factors (which were based on individual level data) and so they are not strictly comparable.

4 DISCUSSION

Our overall findings indicate that over 70% of CVD cases can be attributed to a small cluster of modifiable risk factors. The largest proportion of PAF for CVD, stroke and MI globally were attributed to metabolic risk factors, with hypertension being the largest risk factor for CVD, and accounting for just over one fifth of the PAF for CVD. Hypertension had a larger

impact on stroke than on MI. After hypertension, 5–10% of the PAF for CVD could be attributable to each of several metabolic, behavioural and other risk factors. Physical activity, symptoms of depression, and excess alcohol consumption, each had relatively modest contributions to CVD at the global level.

Approximately two-thirds of deaths in the study were from non-cardiovascular causes. The majority of total deaths were associated with low education, behavioural factors (poor diet and tobacco use), low grip strength, household air pollution, hypertension and diabetes (with other factors each contributing to <5% of its PAF). While lower 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 mortality is larger than what is observed with wealth or income.[10] Education influences 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 CV and non-CV related mortality.[18] It is therefore likely that with improving education of the population, mortality rates from several different conditions will also decline, indicating that investment in education can have broad health benefits.

The impact of low grip strength as a risk factor for death was comparable or greater than that of several conventional risk factors. It is not known whether modifying strength in itself will directly impact 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 higher mortality and case fatality rates after acute illnesses (independent of multi-morbidity, unpublished data), but had weaker associations with the development of disease per se.[11] A greater understanding of how grip strength influences survival in people with disease, and learning how these processes can be modified to prolong survival, can lead to new interventions to reduce mortality.

The PAFs of high sodium consumption (i.e. >6 g/day) for CVD and mortality in the global cohort were relatively small (about 3.0%), which is consistent with most studies that have examined the direct association of sodium excretion with CVD or mortality.[13,19–21] We did not incorporate the data in those with sodium consumption below 4 g/d as they showed higher CVD and mortality compared to those with sodium between 4 and 6 g/d—and we are uncertain of their implications. Including those with a sodium below 4 g/d would 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 (e.g. China or Central Asia), or in specific populations who may be sensitive to the effects of sodium (e.g. those with hypertension).[22] Therefore targeted or contextually appropriate approaches to reduce sodium intake is preferable to attempting universal reductions.

Our findings also highlight the importance of addressing both household and ambient air pollution to reduce CVD and mortality. Exposure to both forms of air pollution were higher in MIC and highest in LIC, so it is likely that strategies to reduce air pollution will have the largest impact in these countries. Ambient air pollution was primarily associated with a

higher risk of CVD, while household air pollution was associated with higher risks of both CVD and death, which may be related to the greater levels of pollution when cooking with solid fuels. Our data indicate an important proportion of deaths globally are attributed to household air pollution, despite essentially no exposure to solid fuels in HIC. We estimated that 13.9% of CVD 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). A 10 microgram increase in PM 2·5 is associated with a 3% increase in the risk of CVD deaths, a 5% increase in CVD events, a 3% increase in MI and a 7% increase in stroke. To put this in perspective, there is a 2.5 fold difference in $PM_{2.5}$ between HIC and MIC and 3.7 fold difference between HIC and LIC. Given the pervasiveness of ambient air pollution, if these relatively modest associations between PM 2·5 and CVD are causal, this would account for a significant proportion of the differences in CVD rates between HIC and MIC or LIC.

The comparative impact of some of our risk factors varied between groups of countries by their economic levels, which could be for several reasons. First, we observed that for some risk factors, (e.g. smoking, education) associations with CVD or mortality differed between groups of countries. For example, the association of low education with CVD and mortality was strongest in MIC and LIC; 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 impact of risk factors on CVD or deaths would be expected to vary between country groups depending on the prevalence of each risk factor, the relative incidences of different diseases (e.g. MI versus strokes) and the predominant causes of death (e.g. CVD, cancers, or infections). This also means that the relative impact of different risk factors on specific diseases and specific causes of death may change over time as the levels of risk factors change or if effective treatments (e.g. lipid lowering or anti-hypertensive drugs) are more widely used. Third, the relative frequency of deaths from CVD versus other causes varies between countries at different economic levels, and so the relative impact of risk factors on total mortality will also vary if the prevalence's of risk factors which predominantly affect CV mortality, but not other causes of death, change over time.

In HIC, about 70% of CVD cases were attributed 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 prior epidemiologic studies conducted in North America and Europe. Modifiable risk factors also accounted for about 70% of CVD cases in MICs, with hypertension being the leading risk factor for CVD. While metabolic (i.e. abdominal obesity, elevated cholesterol) and behavioural (i.e. tobacco use) risk factors remained significant, the impact of low education was larger in MIC compared with HIC. In LIC modifiable risk factors accounted for about 80% of CVD cases, with the largest risks attributed to modifiable risk factors, household air pollution, and poor diet. Household air pollution was the third largest individual risk factor for CVD in LIC, likely due to the high prevalence of exposure in these countries. Poor diet was the leading behavioural risk factor for CVD in LICs, and at least as important as, if not more than, tobacco use. 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 CVD and mortality associated with smoking in LIC.

Approximately 65% of deaths in HIC were attributable to these modifiable risk factors. The largest contributor to mortality in HIC was tobacco use, likely related to its impact on several noncommunicable diseases including CVD, 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 CVD to overall mortality in these counties. Low education was the fourth largest cause of death in HIC, emphasizing the need to improve education even in HIC.

In MIC, about 70% of deaths were attributable to individual level risk factors. The comparative importance of education was higher in these countries, and it was the third largest individual risk factor for death, after hypertension and tobacco. About 80% of deaths in LIC were explained by the modifiable risk factors. Aside from tobacco use and low education, other leading risk factors for death (poor diet, low grip strength, and household air pollution) had much larger impacts in LIC compared with MIC or HIC. This highlights the need for direct data from LIC to better guide prevention efforts in these countries, rather than extrapolating data from HIC.

Our study has some potential limitations. Since our data are based on 21 countries, it may not be generalizable to all countries. In particular we have no data from West Africa and 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 (e.g. China, India, Canada, Malaysia, Turkey, and Colombia) participants were recruited from several provinces. Therefore the data in PURE from each country should not be taken as applying to the whole population in these countries. Third, while biases have been minimized in the selection of individuals within a community, the countries and centers 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 the PURE results are more broadly applicable than most previous studies and so the results are also likely applicable to many more countries than the 21 included in the study. Fourth, although the majority of risk factors were derived or supplemented with objective measures (e.g. blood pressure, lipids, grip strength, anthropometry, ambient air pollution, sodium excretion), or self-reported based on validated instruments (e.g. 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 to 30% of participants and using this information to correct for regression dilution biases for continuous variables made the hazard ratios stronger but the same analyses was not possible for categorical variables and moreover there is no method we are aware of how to incorporate such measurement errors in the estimations of PAF.Therefore, we present the data without these corrections, which is likely an underestimate of the associations of several of these risk factors on CVD and mortality. 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 (e.g. built environment, chemical exposures, noise pollution) and differences in access to health care have important impacts on CVD and mortality. 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 in subgroups (i.e. by disease type or by country income level) may be more prone to random error, particularly if effect sizes are modest, which we observed for a few risk factors. In general, when PAFs are within a few percentages of each other, they should be interpreted as being of similar importance, especially if the confidence intervals of the estimates also overlap.

The findings reported in this paper are complementary to other studies on the importance of risk factors for CVD and mortality. For example, Stringhini et al. observed that socioeconomic status (defined by occupation) was the third largest risk factor for mortality in a meta-analysis of cohorts from seven HIC.[23] In PURE, low education was the fourth leading risk factor for death in HIC, but the largest disparities were observed in MIC and LIC, suggesting that improving education, or addressing the barriers to health in these populations, should be among the highest health priorities to reduce premature mortality, particularly in MIC and LIC. Consistent with estimates from the GBD, we found that that modifiable risk factors account for the majority of deaths globally.[2–4] Both studies highlight the large impacts that elevated blood pressure, tobacco use, and poor diet quality have on mortality at the global level, although our observations also emphasize 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. Further, our findings indicate that reducing CVD and premature mortality will require both general and context specific approaches that target risk factors at the individual (e.g. 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. In addition, strategies that improve household access to clean fuels, improve strength, and diet quality are likely to have particularly large effects in MIC or LIC, and need to be considered major health priorities in these countries. Such context specific strategies are likely to have a greater impact in reducing premature CVD or mortality than global strategies based mostly on information from HIC.

In conclusion, PURE indicates that a large proportion of CVD and premature deaths could be averted by targeting a few modifiable risk factors. While some risk factors warrant global policies (e.g. 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 CVD and deaths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1736–88. [PubMed: 30496103]
2. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1923–94. [PubMed: 30496105]
3. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937–52. [PubMed: 15364185]
4. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016; 388: 761–75. [PubMed: 27431356]
5. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, PURE Investigators-Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. Am Heart J 2009; 158: 1–7.e1. [PubMed: 19540385]
6. Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. Am Heart J 2013; 166: 636–646.e4. [PubMed: 24093842]
7. Hotchkiss JW, Davies CA, Leyland AH. Adiposity has differing associations with incident coronary heart disease and mortality in the Scottish population: cross-sectional surveys with follow-up. Int J Obes (Lond) 2013; 37: 732–9. [PubMed: 22751254]
8. Czernichow S, Kengne A-P, Stamatakis E, Hamer M, Batty GD. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev 2011; 12: 680–7. [PubMed: 21521449]
9. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005; 366: 1640–9. [PubMed: 16271645]

10. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. Lancet Glob Health 2019; 7: e748–60. [PubMed: 31028013]
11. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 2015; 386: 266–73. [PubMed: 25982160]
12. Shaddick G, Thomas ML, Amini H, et al. Data Integration for the Assessment of Population Exposure to Ambient Air Pollution for Global Burden of Disease Assessment. Environ Sci Technol 2018; 52: 9069–78. [PubMed: 29957991]
13. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med 2014; 371: 601–11. [PubMed: 25119606]
14. Eide GE, Gefeller O. Sequential and average attributable fractions as aids in the selection of preventive strategies. J Clin Epidemiol 1995; 48: 645–55. [PubMed: 7730921]
15. Ferguson J, Alvarez-Iglesias A, Newell J, Hinde J, O'Donnell M. Estimating average attributable fractions with confidence intervals for cohort and case-control studies. Stat Methods Med Res 2018; 27: 1141–52. [PubMed: 27342575]
16. Ravnskov U, Diamond DM, Hama R, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. BMJ Open 2016; 6: e010401.
17. Skalamera J, Hummer RA. Educational attainment and the clustering of health-related behavior among U.S. young adults. Prev Med 2016; 84: 83–9. [PubMed: 26740348]
18. Lager ACJ, Torssander J. Causal effect of education on mortality in a quasi-experiment on 1.2 million Swedes. Proc Natl Acad Sci USA 2012; 109: 8461–6. [PubMed: 22586112]
19. Welsh CE, Welsh P, Jhund P, et al. Urinary Sodium Excretion, Blood Pressure, and Risk of Future Cardiovascular Disease and Mortality in Subjects Without Prior Cardiovascular Disease. Hypertension 2019; 73: 1202–9. [PubMed: 31067194]
20. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014; 371: 612–23. [PubMed: 25119607]
21. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA 2011; 305: 1777–85. [PubMed: 21540421]
22. Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet 2018; 392: 496–506. [PubMed: 30129465]
23. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. Lancet 2017; 389: 1229–37. [PubMed: 28159391]

Research in context:

Evidence before this study:

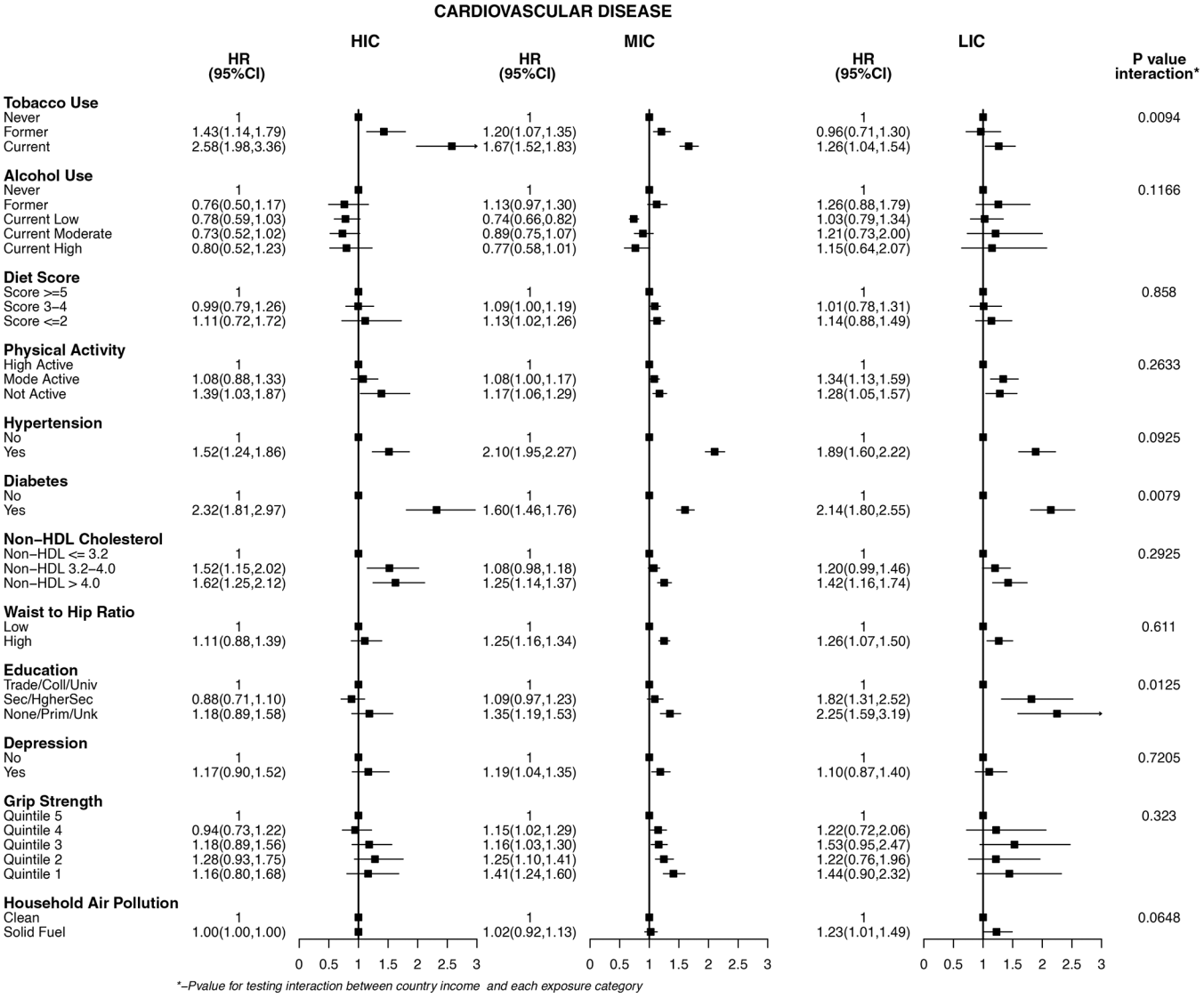
Previous epidemiologic studies relating risk factors with cardiovascular diseases and mortality have been restricted to populations from individual countries most of which were high income and from North America, Western Europe or China. There are few prospective data from other middle- or low-income countries, or from other regions of the world. The Global Burden of Disease (GBD) is a compilation of findings from existing studies, but it is limited by the fact that relatively little high quality data are available from some regions of the world, studies included were conducted over different periods of time (and so may not reflect current patterns of risk factors), used different methods and each study focused only on a limited number of risk factors. While these are the best data currently available, 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 standardized manner and simultaneously assessing the associations of several risk factors with incident diseases and mortality.

Added Value of this study:

We assessed the associations of risk factors for CVD and mortality in 155,722 participants enrolled from 21 countries in the Prospective Urban Rural Epidemiology (PURE) study who did not have a prior history of CVD. Over 70% of the population attributable fraction (PAF) for CVD and mortality in the overall cohort were attributable to fourteen modifiable risk factors (behavioural: smoking, diet, physical activity, alcohol consumption, sodium intake; metabolic: hypertension, lipids, diabetes, abdominal obesity; strength; psychosocial factors: education and symptoms of depression; and environmental factors: household and ambient air pollution). Metabolic risk factors were the predominant individual level risk factors for CVD, 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 impact. Ambient air pollution (PAF 13.9%) appeared to have a large impact on CVD but this estimate uses methods that differed from that used with all other risk factors as it was not an individual level risk factor and so is not comparable. Compared with middle- or high-income countries, a higher proportion of CVD and deaths in low-income countries. The importance of low education, poor diet, household air pollution and low strength were largest in middle- or low-income countries.

Implications of all the available evidence:

The majority of CVD and mortality are attributable to a small number of potentially modifiable risk factors. While some risk factors have large global impacts (e.g. hypertension, tobacco, low education), the impact of others (e.g. poor diet, household air pollution) vary by the economic level of countries. There is a need to adapt global health policies to different groups of countries based on the risk factors of greatest impact in each setting.



1a and b: Variations in the associations between 12 modifiable risk factors and a) cardiovascular disease and b) death in high-, middle-, and low-income countries.

HDL = high density lipoprotein, HIC = high income countries, HR = hazard ratio, LIC = low income countries, MIC = middle income countries.

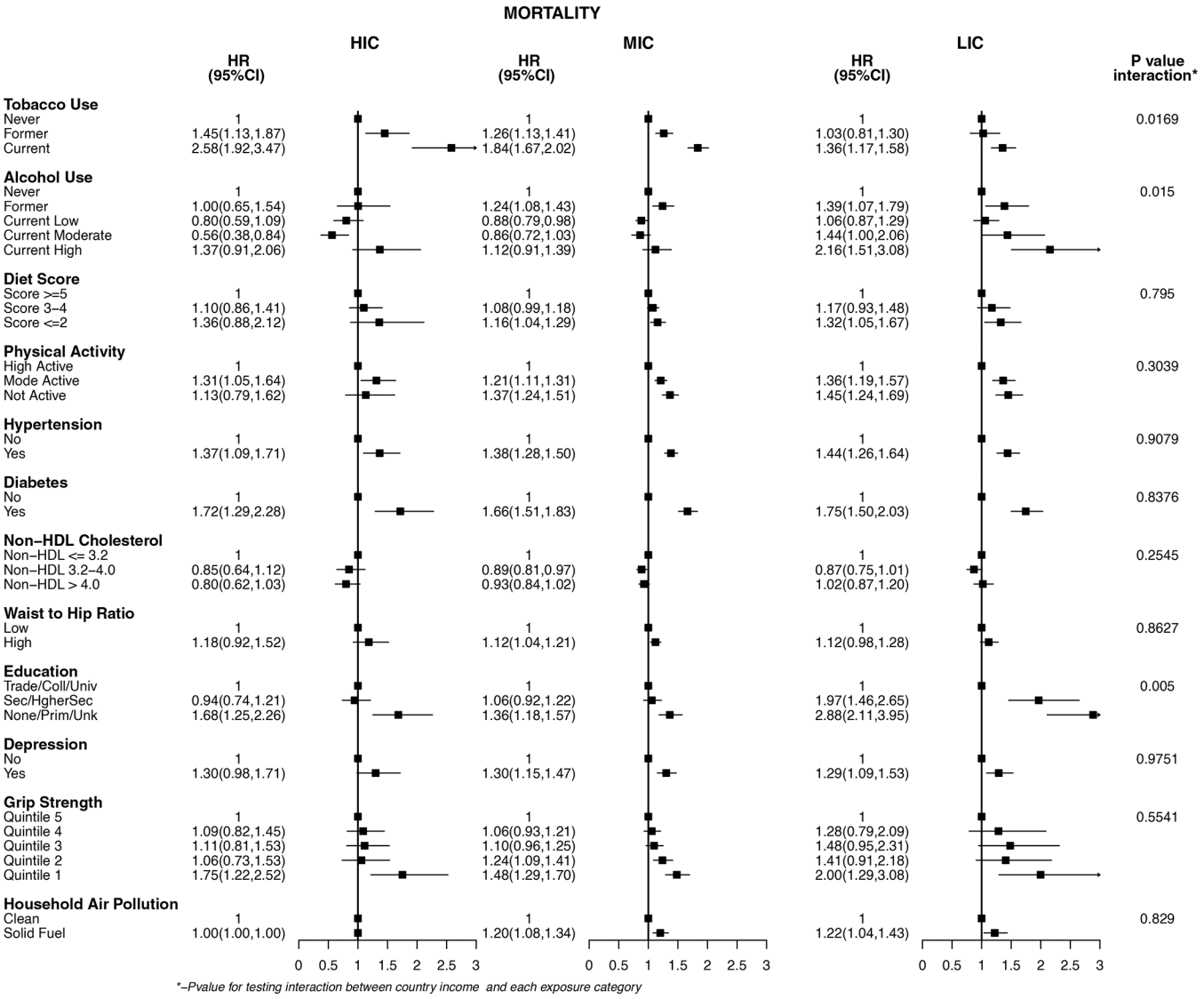


Figure 2: Risk of myocardial infarction and stroke associated with 12 modifiable risk factors.
HDL = high density lipoprotein, HR = hazard ratio, MI = myocardial infarction.

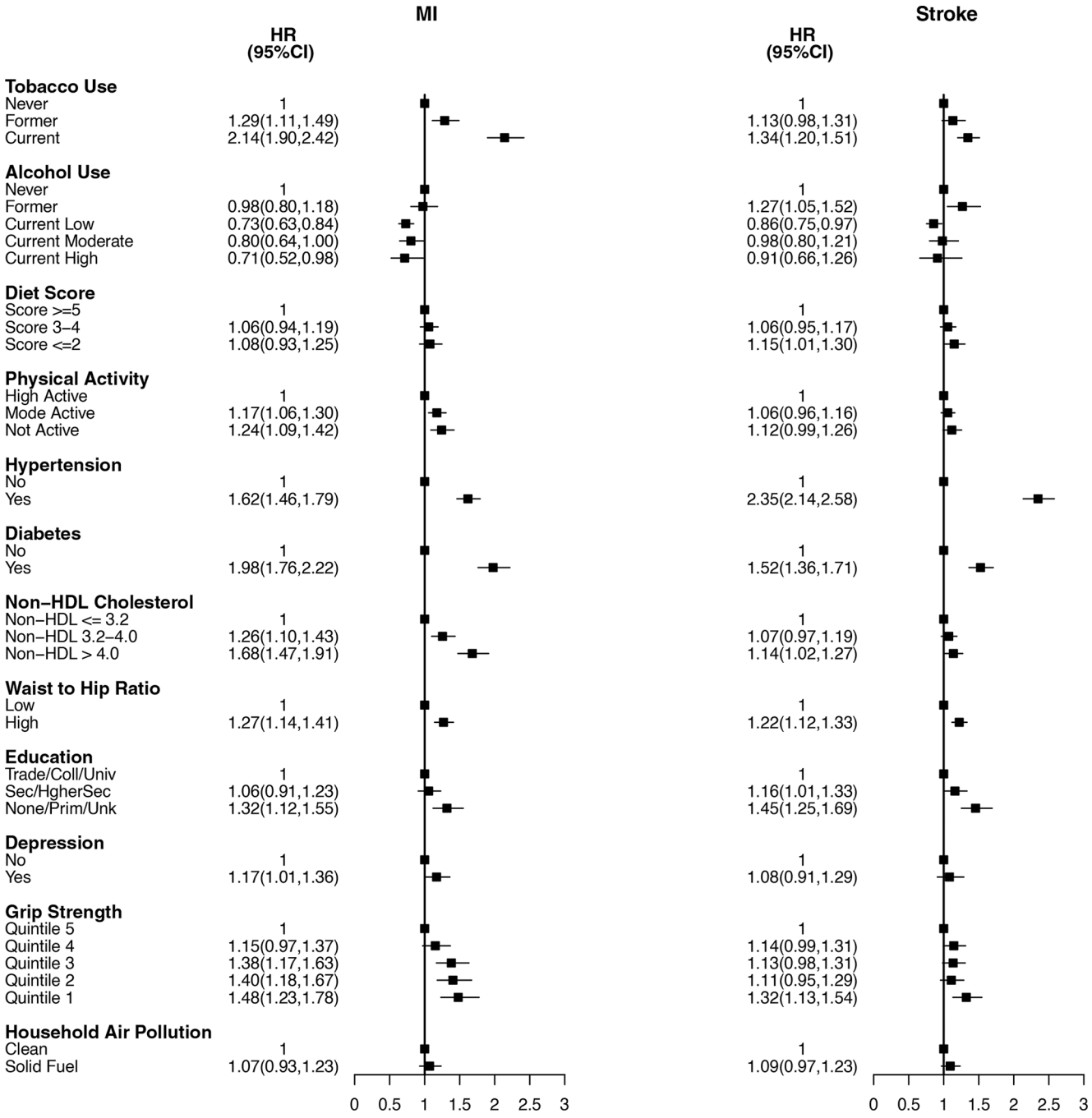


Figure 3: Risk of CV death and Non-CV death associated with 12 individual or household level modifiable risk factors.

CV = cardiovascular, HDL = high density lipoprotein, HR = hazard ratio, MI = myocardial infarction.

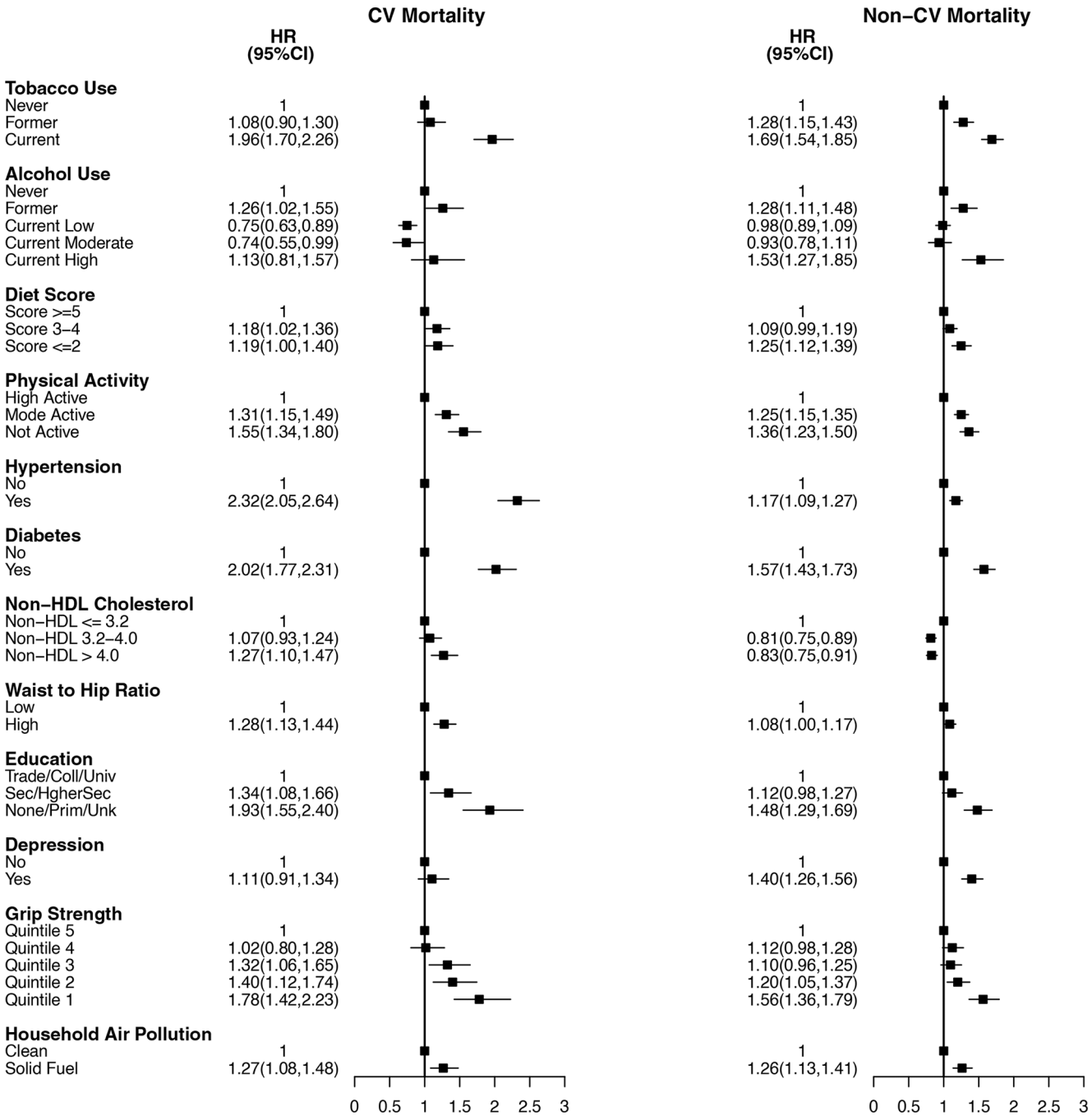


Figure 4: Population attributable fractions for CVD and mortality associated with 12 individual or clusters of modifiable risk factors.

Data are derived from PAF estimates summarized in table 4. 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. HDL = high density lipoprotein, HIC = high income countries, LIC = low income countries, MIC = middle income countries, PAF = population attributable fraction

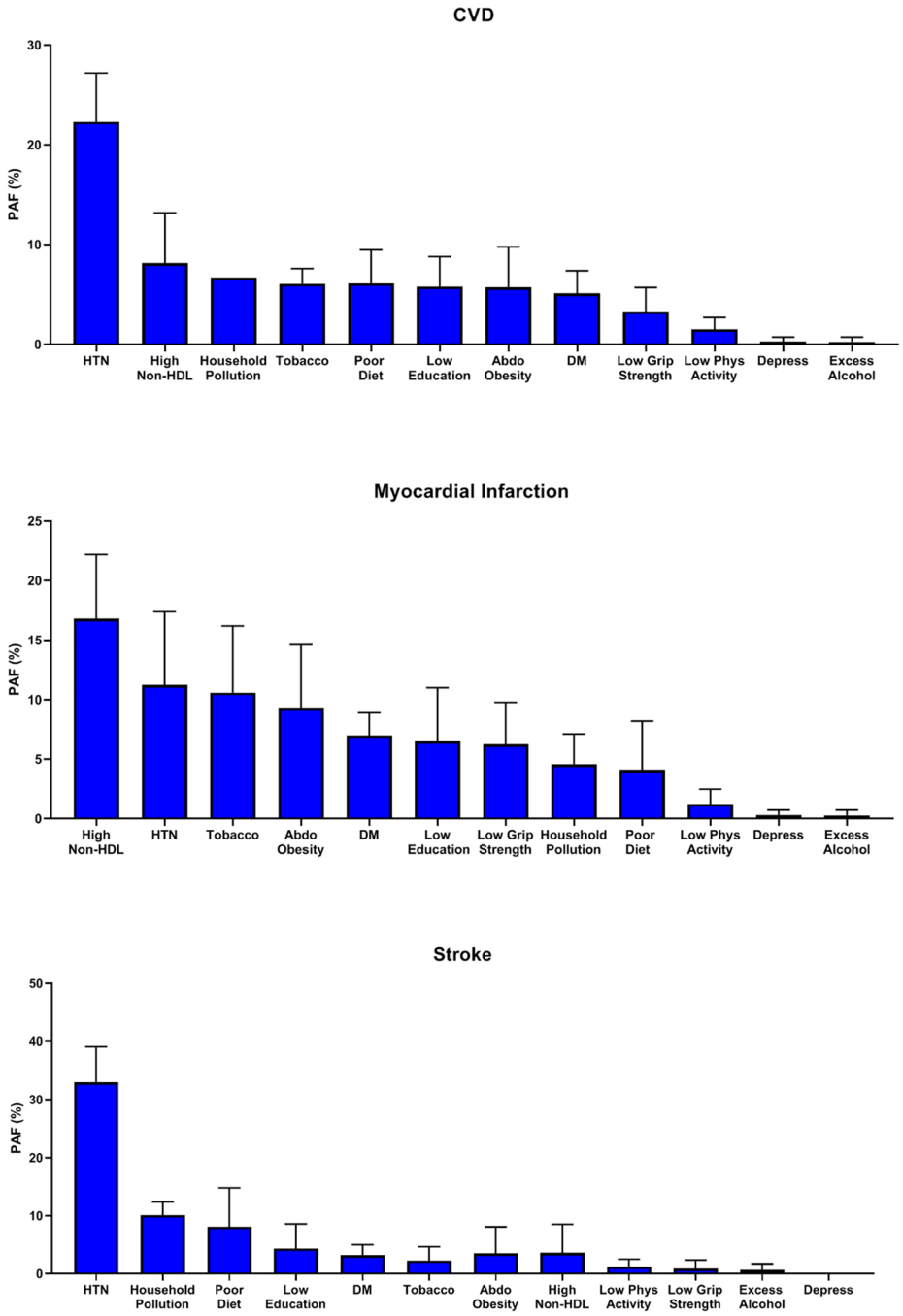


Figure 5: Population attributable fractions for 12 individual and population level risk factors with CVD, MI and Stroke.

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. Depress = symptoms of depression, HDL = high density lipoprotein, MI = myocardial infarction, PAF = population attributable fraction.

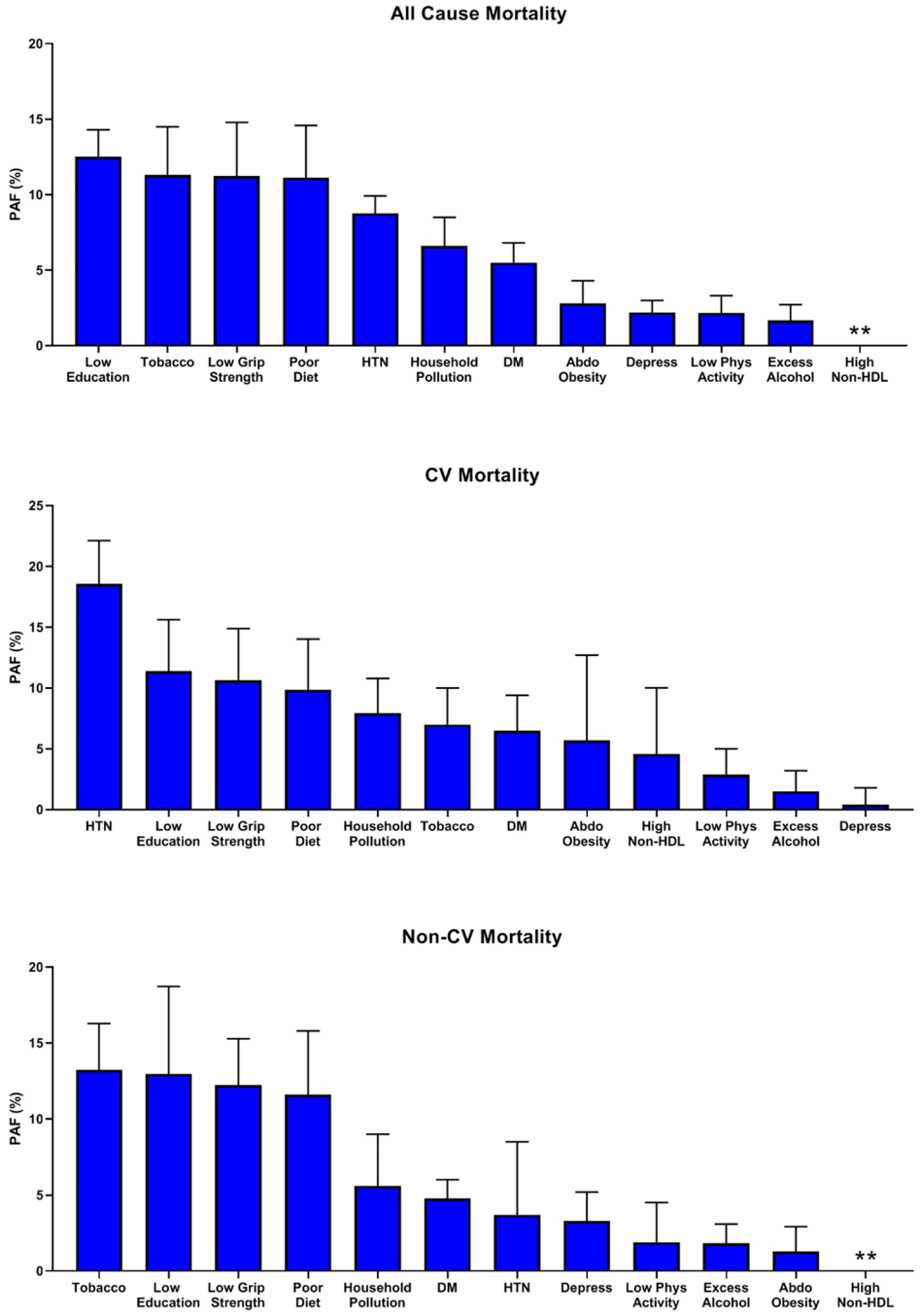


Figure 6: Population attributable fractions for individual risk factors and all-cause mortality, CV deaths and non-CV death.

** Not included as PARs and 95% confidence intervals were negative, but potentially related to reverse causality. 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. CV = cardiovascular, Depress = symptoms of depression, HDL = high density lipoprotein, PAF = population attributable fraction.

Table 1:

Baseline Characteristics of the Study Population Overall and by County Income Groups

Factors	Overall N=155,722	HIC N=17,249	MIC N=102,680	LIC N=35,793
Urban residence	81897(52•6)	12506(72•5)	52134(50•8)	17257(48•2)
Female	90811(58•3)	9376(54•4)	60822(59•2)	20613(57•6)
Age: Mean (SD)	50·22(9•9)	51•60(9•4)	50·65(9•7)	48•32(10•3)
A: Behavioural cluster of risk factors:				
Tobacco Use – N (%)				
Current	31821(20·6)	2279(13•3)	21635(21•3)	7907(22•2)
Former	17225(11•2)	5261(30•6)	10422(10•2)	1542(4•3)
Never	105387(68•2)	9660(56•2)	69624(68•5)	26103(73•4)
Alcohol Use – N (%)				
Never	108133(71•0)	5253(30•8)	72035(72•3)	30845(86•7)
Former	6446(4•2)	940(5•5)	4533(4•5)	973(2•7)
Current: Low	28314(18•6)	7790(45•7)	17770(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 – Mean(SD)	3•94(1•9)	5•60(1•6)	4•14(1•8)	2•53(1•5)
Physical Activity (Met x min/week) – N (%)				
Low: < 600	26691(18•5)	2861(17•9)	17342(17•9)	6488(20•9)
Moderate: 600–3000	53489(37•2)	5661(35•4)	37461(38•7)	10367(33•4)
High: >3000	63731(44•3)	7471(46•7)	42044(43•4)	14216(45•8)
Sodium				
Urine sodium excretion - Mean g/d (SD)	4•71(1•9)	4•06(1•5)	4•99(1•9)	3•38(1•7)
Sodium < 4 g/d	37099(36•5)	7717(52•1)	23358(29•9)	6024(69•0)
Sodium 4–6 g/d	42226(41•6)	5980(40•4)	34219(43•8)	2027(23•2)
Sodium >= 6 g/d	22284(21•9)	1120(7•6)	20483(26•2)	681(7•8)
B: Metabolic cluster of risk factors:				
Hypertension - N (%)	57303(39•4)	6315(37•9)	40583(42•2)	10405(31•9)
SBP (mmHg) – Mean (SD)	130•89(22•3)	129•11(19•6)	132•67(22•6)	126•58(21•9)
DBP (mmHg) – Mean (SD)	81•71(15•2)	81•46(12•2)	82•26(16•3)	80•24(13•1)
Diabetes - N (%)	15900(10•2)	1824(10•6)	9767(9•5)	4309(12•0)
Lipid Measures – (mmol/L)				
Total Cholesterol – Mean (SD)	4•88(1•1)	5•29(1•1)	4•88(1•1)	4•55(1•0)
LDL Cholesterol – Mean (SD)	3•07(1•0)	3•28(0•9)	3•01(0•9)	3•16(1•2)
HDL Cholesterol – Mean (SD)	1•21(0•4)	1•39(0•4)	1•19(0•3)	1•18(0•4)
Non-HDL Cholesterol	3•67(1•0)	3•88(1•0)	3•71(1•0)	3•38(1•0)
BMI - Mean(SD)	25•71(5•3)	27•81(5•5)	26•19(5•1)	23•23(5•0)
Waist to hip ratio (men) - Mean (SD)	0•85(0•1)	0•83(0•1)	0•85(0•1)	0•84(0•1)

Factors	Overall N=155,722	HIC N=17,249	MIC N=102,680	LIC N=35,793
Waist to Hip Ratio (women) - Mean (SD)	0•91(0•1)	0•94(0•1)	0•91(0•1)	0•91(0•1)
Waist to hip ratio >0•9 in men or >0•85 in women	73272(50•1)	8865(53•3)	48943(50•7)	15464(46•9)
C: Socio-economic and psychosocial risk factor cluster:				
Education – N (%)				
Primary or less	66353(42•7)	2264(13•2)	44857(43•8)	19232(54•0)
Secondary	59081(38•1)	4962(28•8)	42257(41•3)	11862(33•3)
Trade/College/University	29819(19•2)	9977(58•0)	15308(14•9)	4534(12•7)
Depression	17450(11•3)	2826(16•4)	10204(10•0)	4420(12•5)
D: Grip Strength (kg) Mean(SD)	30•4 (11•1)	35•6 (12•4)	31•0 (11•0)	25•9 (9•1)
E: Air pollution				
Household air pollution – N (%)	31447(25•1)	2(0•0)	20382(23•3)	11063(50•0)
Ambient $PM_{2.5}$ ($\mu g/m^3$) air pollution	47•3(32•5)	20•9(32•3)	47•9(29•3)	58•4(34•3)

SD = standard deviation, PM = particulate matter, HIC=High Income countries, MIC= Middle Income countries, LIC= Low income countries

Table 2:

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

Exposure	CVD Hazard ratio (95% confidence intervals)	Death Hazard ratio (95% confidence intervals)
A: Behavioral cluster of risk factors:		
Tobacco use		
Never (reference)		
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 intake		
Never (reference)		
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 (reference)		
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		
High activity (reference)		
Moderate activity	1•11(1•04,1•19)	1•26(1•18,1•35)
Low Activity	1•20(1•10,1•30)	1•39(1•28,1•50)
B: Metabolic cluster of 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		
<3.2 (reference)		
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		
--WHR M>0.9/W>0.85	1•26(1•18,1•34)	1•13(1•05,1•20
C: Socio-economic and psychosocial cluster of risk factors:		
Education		
Trade/College/University (reference)		
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
D: Grip strength		

Exposure	CVD Hazard ratio (95% confidence intervals)	Death Hazard ratio (95% confidence intervals)
Quintile 5 (reference)		
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
E: Air pollution		
Household air pollution	1•09(1•00,1•19)	1•24(1•14,1•36

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, and sex. A variable for each participating PURE center was also included as a random effect. HDL = high density lipoproteins, WHR = waist to hip ratio.

Table 3:

Rank order for the top 10 risk factors for major CVD and death overall and in high-, middle, and low-income countries along with their PAFs:

CVD				
RANK	**Overall PAF (95% Confidence Interval)**	**HIC PAF (95% Confidence Interval)**	**MIC PAF (95% Confidence Interval)**	**LIC PAF (95% Confidence Interval)**
1	Hypertension 22•3 (17•4, 27•2)	High Non-HDL cholesterol 20•7 (7•7, 33•6)	Hypertension 26•5 (22•2, 30•9)	Hypertension 14•3 (7•4, 21•2)
2	High Non-HDL cholesterol 8•1 (3•1, 13•2)	Tobacco Use 15•7 (3•3, 28•0)	Low Education 6•3 (3•0,9•5)	High Non-HDL cholesterol 14•2 (9•0, 19•3)
3	Household air pollution 6•9 (4•7, 9•1)	Hypertension 14•6 (6•2, 23•0)	Tobacco Use 5•9 (2•6, 9•3)	Household air pollution 12•0 (6•5, 17•5)
4	Tobacco Use 6•1 (4•5, 7•6)	Diabetes 7•8 (3•9, 11•7)	Household air pollution 5•2 (2•6, 7•8)	Diabetes 10•4 (4•7,16•2)
5	Poor diet 6•1 (2•8, 9•5)	Abdominal obesity 6•8 (−6•5, 20•1)	Abdominal Obesity 5•2 (1•8, 8•6)	Poor Diet 10•0 (−5•3, 25•2)
6	Low Education 5•8 (2•8, 8•8)	Low Education 2•0 (−2•4, 6•4)	High Non-HDL cholesterol 5•0 (2•0, 8•1)	Abdominal Obesity 7•0 (0•2, 13•9)
7	Abdominal Obesity 5•7 (1•7, 9•8)	Depression 1•1 (−3•5, 5•8)	Poor Diet 4•6 (0•9, 8•3)	Low Education 6•0(−4•5, 16•5)
8	Diabetes 5•1 (2•9, 7•4)	Low Grip Strength 1•0 (−4•2, 6•1)	Diabetes 4•0 (2•9, 5•1)	Tobacco Use 4•5 (−1•6, 10•6)
9	Low Grip Strength 3•3 (0•9, 5•7)	Poor diet 0•2 (−6•4, 6•9)	Low Grip Strength 3•2 (0•5, 5•9)	Low Physical Activity 2•2 (−0•7, 5•2)
10	Low Physical Activity 1•5 (0•3, 2•7)	Excess alcohol 0•1 (−5•8, 6•0)	Low Physical Activity 1•7 (0•2, 3•1)	Excess Alcohol 0•2 (−1•5, 2•0)
Mortality				
RANK	**Overall PAF (95% Confidence Interval)**	**HIC PAF (95% Confidence Interval)**	**MIC PAF (95% Confidence Interval)**	**LIC PAF (95% Confidence Interval)**
1	Low Education 12•5 (10•7, 14•3)	Tobacco Use 17•9 (1•2, 34•6)	Hypertension 13•2 (11•2, 15•1)	Poor Diet 19•2 (9•0, 29•4)
2	Tobacco use 11•3 (8•1, 14•5)	Hypertension 13•1 (−7•4, 33•6)	Tobacco Use 12•6 (8•9, 16•3)	Low Education 13•7 (7•7, 19•7)
3	Low grip strength 11•6 (7•3, 16•0)	Abdominal Obesity 11•4 (•6•1, 28•9)	Low Education 12•1 (6•2, 18•0)	Low Grip Strength 10•9 (4•4, 17•5)
4	Poor diet 11•1 (7•7, 14•6)	Low Education 7•2 (1•7, 12•7)	Low Grip Strength 7•9 (5•0, 10•7)	Household air pollution 9•0 (3•7, 14•2)
5	Hypertension 8•8 (7•6, 9•9)	Diabetes 5•9(•0•4, 12•2)	Poor Diet 6•1(−1•1, 13•2)	Tobacco Use 7•6 (0•7, 14•5)
6	Household air pollution 6•6 (4•7, 8•5)	Excess alcohol 5•5 (−0•5, 11•5)	Abdominal Obesity 4•7 (1•3, 8•0)	Diabetes 6•7 (4•0, 9•4)
7	Diabetes 5•5 (4•2, 6•8)	Poor diet 2•7 (−3•8, 9•1)	Diabetes 4•5 (4•1, 4•8)	Hypertension 5•6 (0•5, 10•7)
8	Abdominal obesity 2•8 (1•3, 4•3)	Depression 2•3 (−3•0, 7•6)	Low Physical Activity 3•0 (1•7, 4•3)	Low Physical Activity 2•7 (0•4, 5•0)
9	Depression 2•2 (1•4, 3•0)	Low Grip Strength 1•6 (−8•1, 11•4)	Depression 1•9 (0•6, 3•2)	Depression 1•9 (0•4, 3•4)
10	Low physical activity 2•2 (1•0, 3•3)	Household air pollution 0 (−1•5, 1•5)	Household air pollution 1•8(−1•8, 5–3)	Excess Alcohol 1–8 (0–5, 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 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 10 largest risk factors for CVD and mortality based on PAFs for each outcome as these estimates were the most robust. Sodium was not ranked because it was analyzed in a subset of the population. Ambient air pollution was not ranked because it is a community level risk factor. HDL = high density lipoprotein, HIC = high income countries, HR = hazard ratio, LIC = low income countries, MIC = middle income countries.

Table 4:

Individual and population level risks associated with ambient and household air pollution

Outcome	Hazard Ratio (95% confidence intervals)		Population Attributable Fraction (%)	
	Ambient air pollution (per 10 µg/m3 in PM $_{2.5}$)	Indoor air pollution (yes vs. no)	Ambient air pollution (> 10 µg/m3 in $PM_{2.5}$)[a]	Indoor air pollution (yes vs. no)
All-cause mortality	0•97 (0•96–0•99)	1•24(1•14,1•36)	na*	6•7%
CV deaths	1•03 (1•00–1•05)	1•27(1•08,1•48)	8•7%	7•9%
Non-CV deaths	0•95 (0•93–0•97)	1•26 (1•13,1•41)	na*	5•6%
Major CVD	1•05 (1•03–1•07)	1•09 (1•00,1•19)	13•9%	6•9%
MI	1•03 (1•00–1•06)	1•07 (0•93,1•23)	8•7%	4•6%
Stroke	1•08 (1•05–1•11)	1•09 (0•98,1•21)	21•1%	10•1%

[a]PAF calculated using 10 µg/m3 as a counterfactual (based on the World Health Organization guidelines for $PM_{2.5}$). $PM_{2.5}$ analyses were restricted to individuals without CVD at baseline and with available outdoor $PM_{2.5}$ estimates for 3 years at baseline. Model adjusted for the following covariates: age, sex, baseline year, smoking status, alcohol use, physical activity, waist-hip ratio, PURE diet score, INTERHEART risk score, use of solid fuels for cooking, education level, household wealth index, occupational class, baseline chronic conditions, use of CVD medication, hypertension status, urban/rural status, baseline country GDP per person, community lights at night based on satellite data (as an indicator of local economic activity), national or regional healthcare access & quality index and community random effect.

*Not included as PAF was neutral or negative, potentially related to residual confounding (refer to results section for further description). CV = cardiovascular, CVD = cardiovascular disease, PM = particulate matter