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

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Short Title: Modifiable risk factors for cardiovascular disease and mortality

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.

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.

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Key Words: 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).[1] [2] 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

277 in MIC (50·6 years) and highest in HIC (51.6 years). Only primary education level or less was
278 attained in the majority of participants from LICs (54·0%), in 43·8% from MICs, and 13·2% in
279 HICs. By contrast, the proportion of participants with a college, trade, or university education was
280 highest in HIC (58·0%), followed by MIC (14·9%) and lowest in LIC (12·7%). A greater
281 proportion of participants in HIC reported a history of smoking or alcohol consumption compared
282 with MIC or LIC, although current smoking was higher in MIC and LIC compared to HIC. Diet
283 quality scores indicated healthiest diet in those from HIC, followed by MIC and then LIC. Sodium
284 consumption was highest in MIC (driven by higher levels in China, but not other MIC). Of the
285 metabolic risk factors, mean BMI, WHR, and non-HDL cholesterol levels were highest in HIC,
286 hypertension prevalence was highest in MIC, and diabetes prevalence was highest in LIC. Grip
287 strength was highest in HIC, followed by MIC and lowest in LIC. Household air pollution from
288 solid fuel use was highest in LIC (50·0%), followed by MIC (23·3%), and nearly zero in HIC.
289 Mean PM 2·5 levels were 20·9, 47·9, and 58·4 µg/m3 respectively in HIC, MIC and LIC.
290
291 **Risk of CVD and death associated with 12 individual or household level risk factors:**
292 Of the behavioural risk factors, tobacco use was the most strongly associated with CVD, followed
293 by physical activity, and low-quality diet (table 2). Of the metabolic risk factors, hypertension had
294 the strongest association with CVD, followed by diabetes, elevated non-HDL cholesterol and
295 increased WHR. Low education levels, depression symptoms, low grip strength, and household
296 air pollution were also associated with a higher risk of CVD. The risk associated with low
297 education was highest in LIC; risk with tobacco was highest in HIC; and risk with diabetes was
298 highest in HIC and LIC (Figure 1a).
299

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

369 factor) differed from that used for the impact of all other risk factors (which were based on
370 individual level data) and so they are not strictly comparable.
371
372 **4 DISCUSSION**
373 Our overall findings indicate that over 70% of CVD cases can be attributed to a small cluster of
374 modifiable risk factors. The largest proportion of PAF for CVD, stroke and MI globally were
375 attributed to metabolic risk factors, with hypertension being the largest risk factor for CVD, and
376 accounting for just over one fifth of the PAF for CVD. Hypertension had a larger impact on stroke
377 than on MI. After hypertension, 5-10% of the PAF for CVD could be attributable to each of several
378 metabolic, behavioural and other risk factors. Physical activity, symptoms of depression, and
379 excess alcohol consumption, each had relatively modest contributions to CVD at the global level.
380
381 Approximately two-thirds of deaths in the study were from non-cardiovascular causes. The
382 majority of total deaths were associated with low education, behavioural factors (poor diet and
383 tobacco use), low grip strength, household air pollution, hypertension and diabetes (with other
384 factors each contributing to <5% of its PAF). While lower education levels are associated with
385 greater clustering of adverse health related behaviours, this association persists after adjusting
386 for health behaviours.[17] The association of education with mortality is larger than what is
387 observed with wealth or income.[10] Education influences multiple conditions from childhood
388 onwards, including exposures to community level factors (such as living or working in healthier
389 environments), and better access to health and social resources. Our findings are also consistent
390 with studies which observed that educational reforms can lead to reductions in CV and non-CV
391 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

414 contextually appropriate approaches to reduce sodium intake is preferable to attempting universal
415 reductions.
416
417 Our findings also highlight the importance of addressing both household and ambient air pollution
418 to reduce CVD and mortality. Exposure to both forms of air pollution were higher in MIC and
419 highest in LIC, so it is likely that strategies to reduce air pollution will have the largest impact in
420 these countries. Ambient air pollution was primarily associated with a higher risk of CVD, while
421 household air pollution was associated with higher risks of both CVD and death, which may be
422 related to the greater levels of pollution when cooking with solid fuels. Our data indicate an
423 important proportion of deaths globally are attributed to household air pollution, despite essentially
424 no exposure to solid fuels in HIC. We estimated that 13.9% of CVD cases globally could be
425 attributed to ambient air pollution, but since it is a community level exposure, we were not able to
426 make direct comparisons to other risk factors (as the average PAF method generally results in
427 lower risk estimates). A 10 microgram increase in PM 2·5 is associated with a 3% increase in the
428 risk of CVD deaths, a 5% increase in CVD events, a 3% increase in MI and a 7% increase in stroke.
429 To put this in perspective, there is a 2.5 fold difference in $PM_{2.5}$ between HIC and MIC and 3.7
430 fold difference between HIC and LIC. Given the pervasiveness of ambient air pollution, if these
431 relatively modest associations between PM 2·5 and CVD are causal, this would account for a
432 significant proportion of the differences in CVD rates between HIC and MIC or LIC.
433
434 The comparative impact of some of our risk factors varied between groups of countries by their
435 economic levels, which could be for several reasons. First, we observed that for some risk factors,
436 (e.g. smoking, education) associations with CVD or mortality differed between groups of

437 countries. For example, the association of low education with CVD and mortality was strongest
438 in MIC and LIC; which may be due to the greater support provided to those with low education in
439 HICs or greater disparities between those educated and not educated in poorer countries. Second,
440 the comparative impact of risk factors on CVD or deaths would be expected to vary between
441 country groups depending on the prevalence of each risk factor, the relative incidences of different
442 diseases (e.g. MI versus strokes) and the predominant causes of death (e.g. CVD, cancers, or
443 infections). This also means that the relative impact of different risk factors on specific diseases
444 and specific causes of death may change over time as the levels of risk factors change or if effective
445 treatments (e.g. lipid lowering or anti-hypertensive drugs) are more widely used. Third, the relative
446 frequency of deaths from CVD versus other causes varies between countries at different economic
447 levels, and so the relative impact of risk factors on total mortality will also vary if the prevalence's
448 of risk factors which predominantly affect CV mortality, but not other causes of death, change
449 over time.
450
451 In HIC, about 70% of CVD cases were attributed to modifiable risk factors (excluding ambient air
452 pollution), with the largest contributors being metabolic risk factors and tobacco use. This is
453 consistent with the findings of prior epidemiologic studies conducted in North America and
454 Europe. Modifiable risk factors also accounted for about 70% of CVD cases in MICs, with
455 hypertension being the leading risk factor for CVD. While metabolic (i.e. abdominal obesity,
456 elevated cholesterol) and behavioural (i.e. tobacco use) risk factors remained significant, the
457 impact of low education was larger in MIC compared with HIC. In LIC modifiable risk factors
458 accounted for about 80% of CVD cases, with the largest risks attributed to modifiable risk factors,
459 household air pollution, and poor diet. Household air pollution was the third largest individual risk

460 factor for CVD in LIC, likely due to the high prevalence of exposure in these countries. Poor diet
461 was the leading behavioural risk factor for CVD in LICs, and at least as important as, if not more
462 than, tobacco use. This is in keeping with a larger proportion of the population with poor diet, and
463 very low rates of smoking among women, as well as lower risks of CVD and mortality associated
464 with smoking in LIC.
465 Approximately 65% of deaths in HIC were attributable to these modifiable risk factors. The largest
466 contributor to mortality in HIC was tobacco use, likely related to its impact on several non-
467 communicable diseases including CVD, cancer and respiratory disease, as well as the high
468 prevalence of current or past smoking in both men and women in the population. Hypertension
469 and abdominal obesity were the next largest risk factors for death in HICs, reflecting the large
470 contribution of CVD to overall mortality in these counties. Low education was the fourth largest
471 cause of death in HIC, emphasizing the need to improve education even in HIC.
472
473 In MIC, about 70% of deaths were attributable to individual level risk factors. The comparative
474 importance of education was higher in these countries, and it was the third largest individual risk
475 factor for death, after hypertension and tobacco. About 80% of deaths in LIC were explained by
476 the modifiable risk factors. Aside from tobacco use and low education, other leading risk factors
477 for death (poor diet, low grip strength, and household air pollution) had much larger impacts in
478 LIC compared with MIC or HIC. This highlights the need for direct data from LIC to better guide
479 prevention efforts in these countries, rather than extrapolating data from HIC.
480 Our study has some potential limitations. Since our data are based on 21 countries, it may not be
481 generalizable to all countries. In particular we have no data from West Africa and North Africa or
482 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.

Authors and contributors: SY designed the study, obtained funding and oversaw its conduct since inception for 18 years. 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.

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Michael Brauer reports grant from Canadian Institutes of Health Research during the conduct of the study. SY also received grants for the conduct of PURE from several other sources which are listed below. All other authors have nothing to disclose, other than financial support for the conduct of PURE in their respective countries which is also described below.

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Data sharing statement: Data from PURE are not available for public use.

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Figure Legend:

Figure 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.

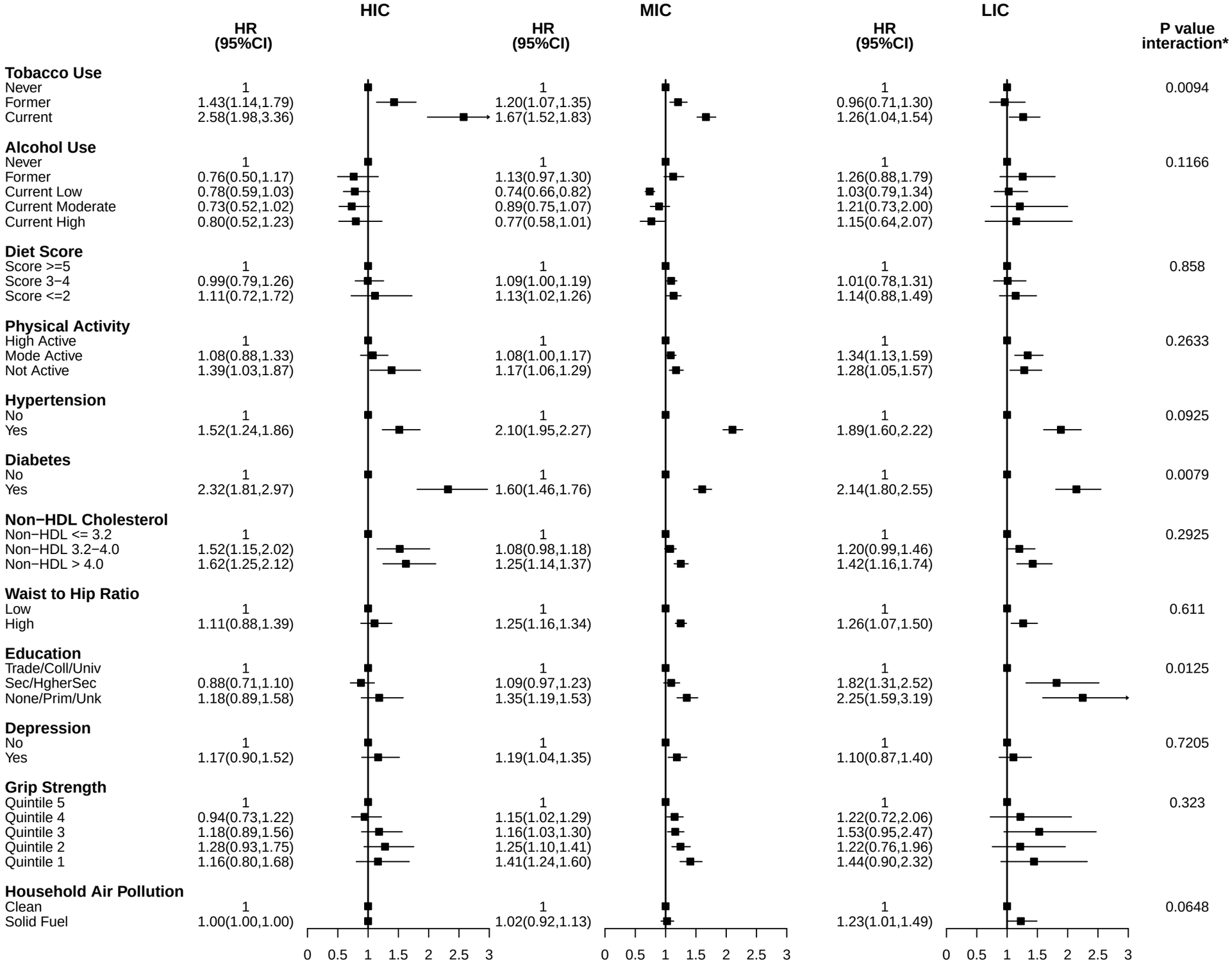
Figure 3: Risk of CV death and Non-CV death associated with 12 individual or household level modifiable risk factors. CV = cardiovascular, HDL = high density lipoprotein, HR = hazard ratio, MI = myocardial infarction.

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.

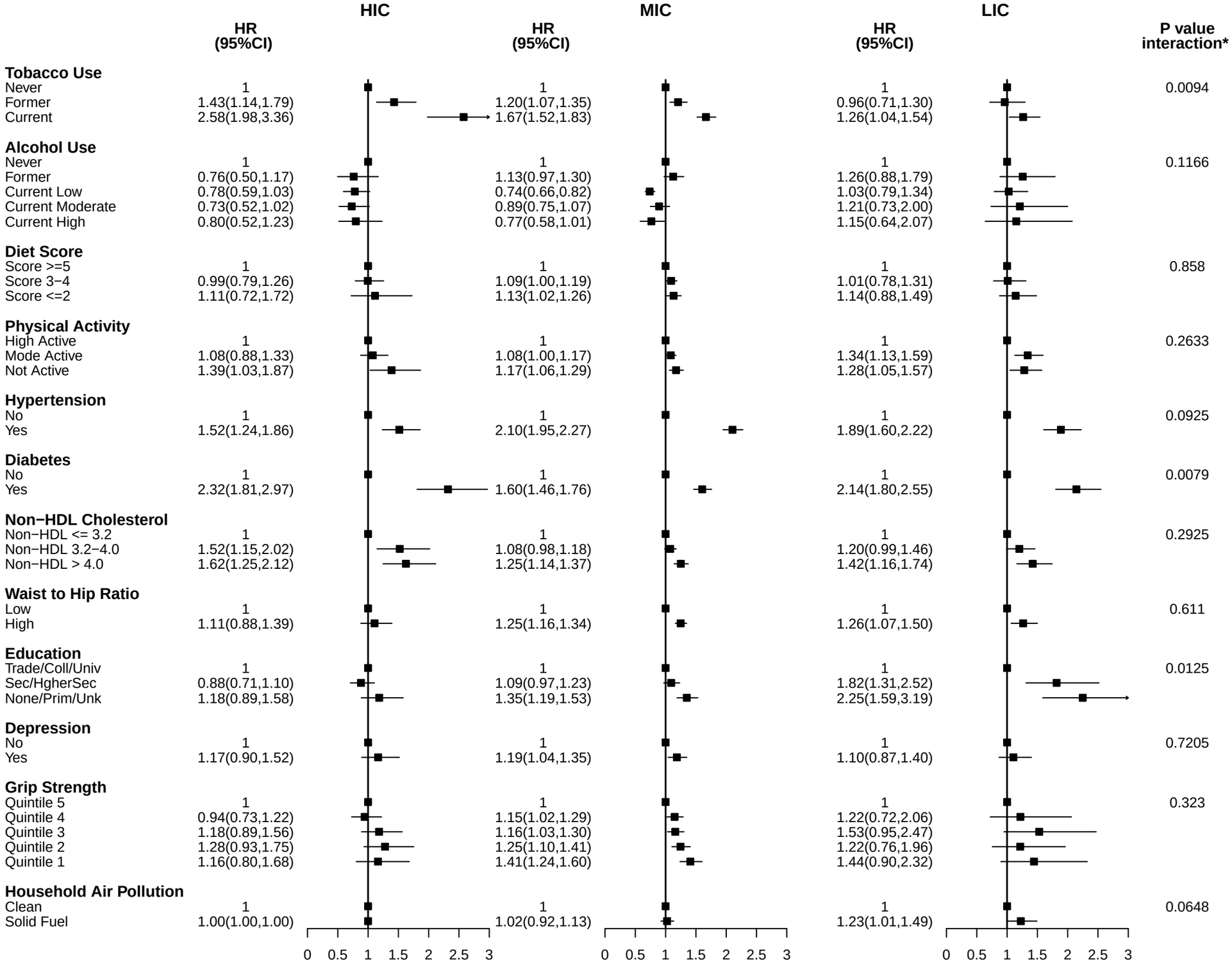
Figure 6: Population attributable fractions for individual risk factors and all-cause mortality, CV deaths and non-CV death. ** Not included as PARs and 95% confidence intervals were negative, but potentially related to reverse causality. Estimates for individual risk factors were truncated at a lower 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.

CARDIOVASCULAR DISEASE

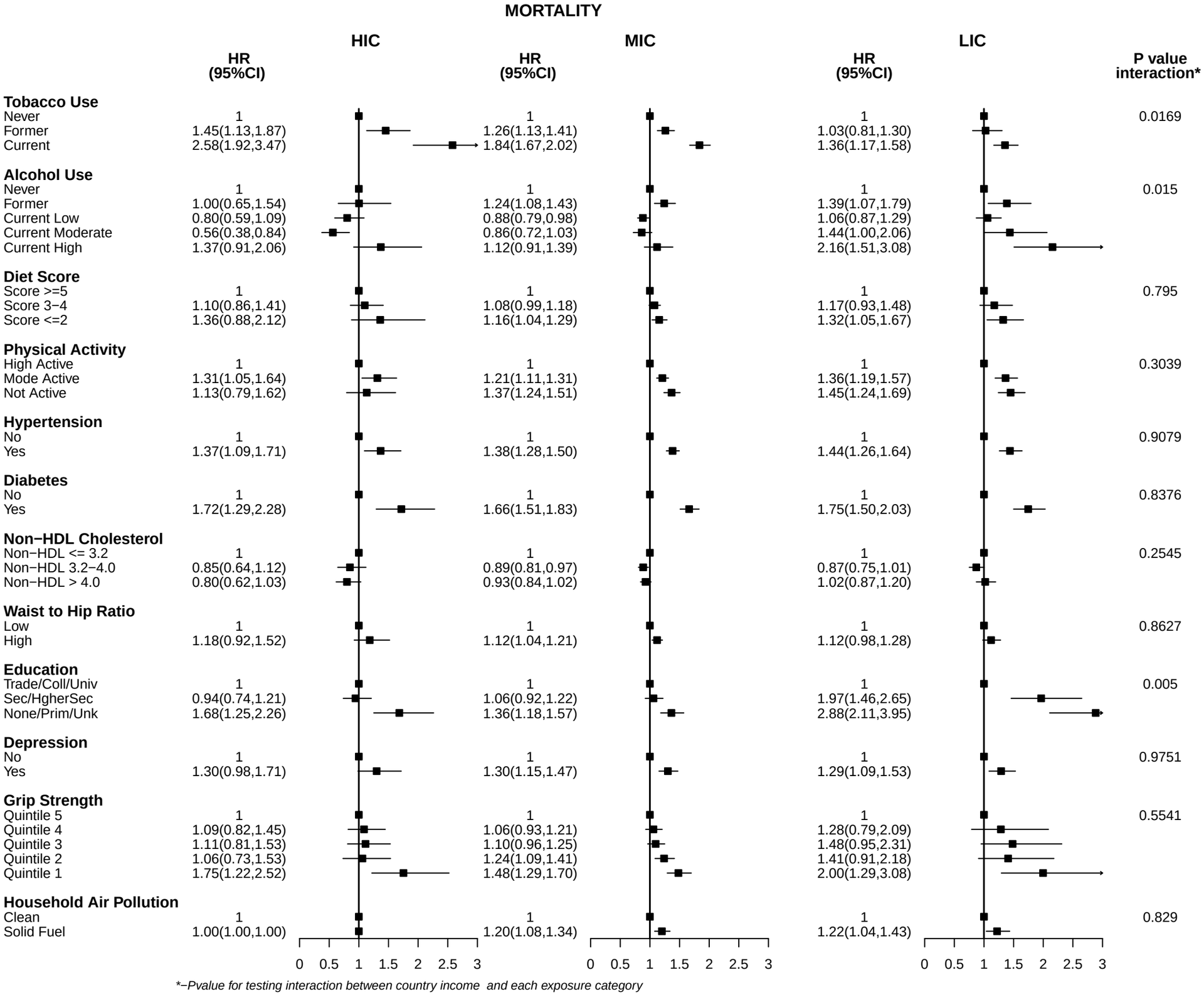


*−Pvalue for testing interaction between country income and each exposure category

CARDIOVASCULAR DISEASE



*−Pvalue for testing interaction between country income and each exposure category



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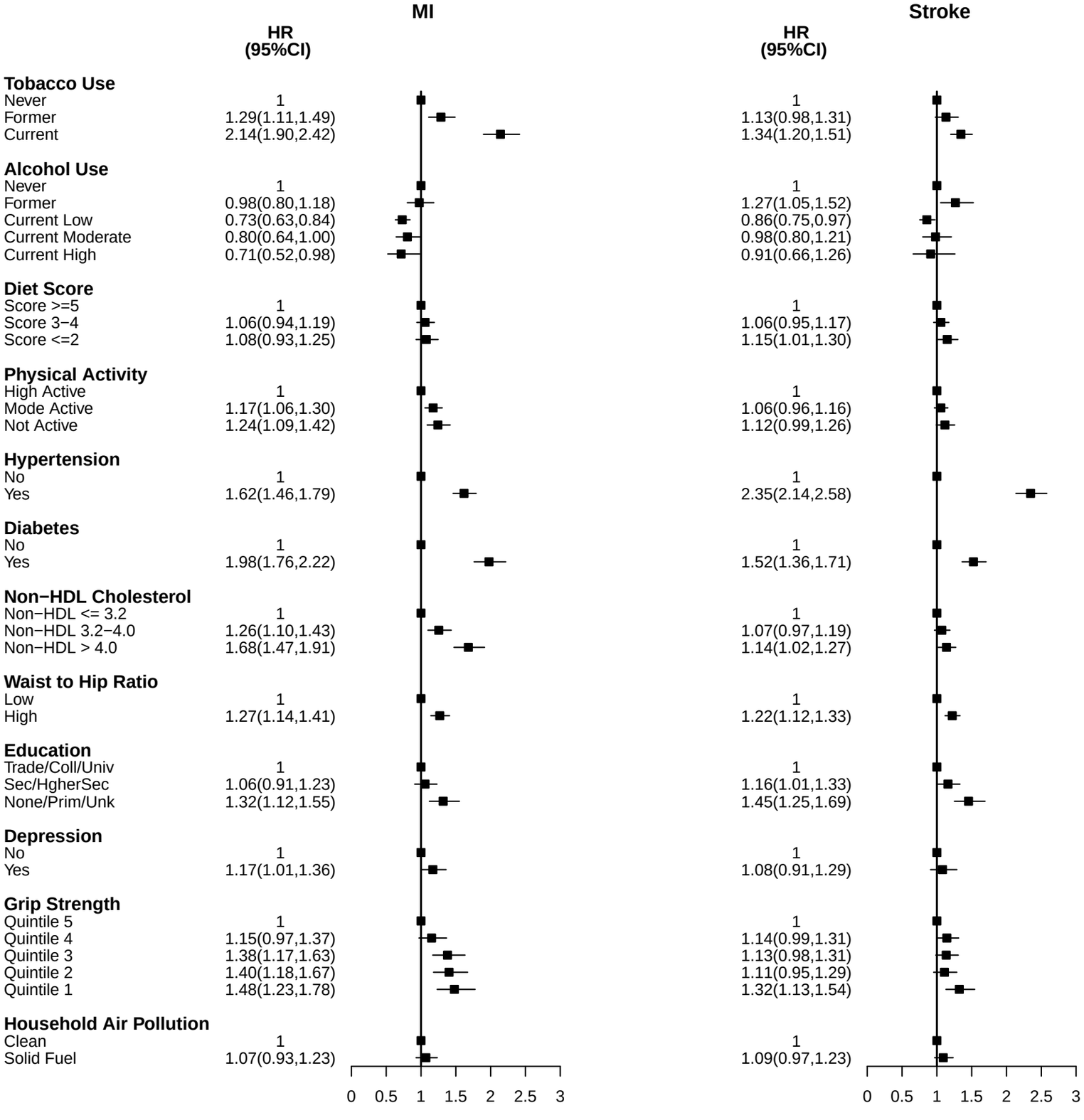

MI
HR
(95%CI)
Tobacco Use
Never 1
Former 1.29(1.11,1.49)
Current 2.14(1.90,2.42)
Alcohol Use
Never 1
Former 0.98(0.80,1.18)
Current Low 0.73(0.63,0.84)
Current Moderate 0.80(0.64,1.00)
Current High 0.71(0.52,0.98)
Diet Score
Score >=5 1
Score 3−4 1.06(0.94,1.19)
Score <=2 1.08(0.93,1.25)
Physical Activity
High Active 1
Mode Active 1.17(1.06,1.30)
Not Active 1.24(1.09,1.42)
Hypertension
No 1
Yes 1.62(1.46,1.79)
Diabetes
No 1
Yes 1.98(1.76,2.22)
Non−HDL Cholesterol
Non−HDL <= 3.2 1
Non−HDL 3.2−4.0 1.26(1.10,1.43)
Non−HDL > 4.0 1.68(1.47,1.91)
Waist to Hip Ratio
Low 1
High 1.27(1.14,1.41)
Education
Trade/Coll/Univ 1
Sec/HgherSec 1.06(0.91,1.23)
None/Prim/Unk 1.32(1.12,1.55)
Depression
No 1
Yes 1.17(1.01,1.36)
Grip Strength
Quintile 5 1
Quintile 4 1.15(0.97,1.37)
Quintile 3 1.38(1.17,1.63)
Quintile 2 1.40(1.18,1.67)
Quintile 1 1.48(1.23,1.78)
Household Air Pollution
Clean 1
Solid Fuel 1.07(0.93,1.23)
0 0.5 1 1.5 2 2.5 3
Stroke
HR
(95%CI)
1
1.13(0.98,1.31)
1.34(1.20,1.51)
1
1.27(1.05,1.52)
0.86(0.75,0.97)
0.98(0.80,1.21)
0.91(0.66,1.26)
1
1.06(0.95,1.17)
1.15(1.01,1.30)
1
1.06(0.96,1.16)
1.12(0.99,1.26)
1
2.35(2.14,2.58)
1
1.52(1.36,1.71)
1
1.07(0.97,1.19)
1.14(1.02,1.27)
1
1.22(1.12,1.33)
1
1.16(1.01,1.33)
1.45(1.25,1.69)
1
1.08(0.91,1.29)
1
1.14(0.99,1.31)
1.13(0.98,1.31)
1.11(0.95,1.29)
1.32(1.13,1.54)
1
1.09(0.97,1.23)
0 0.5 1 1.5 2 2.5 3

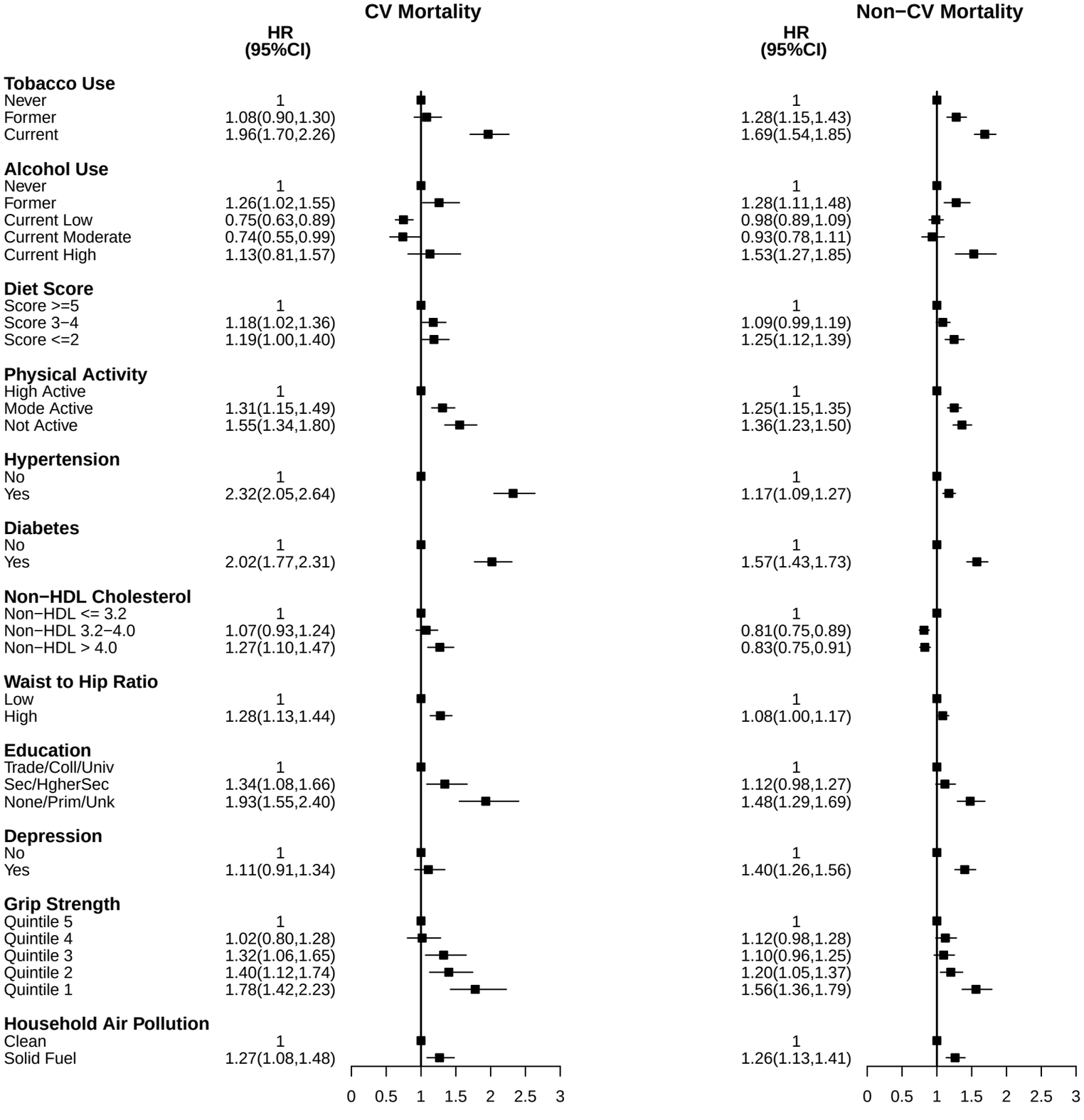
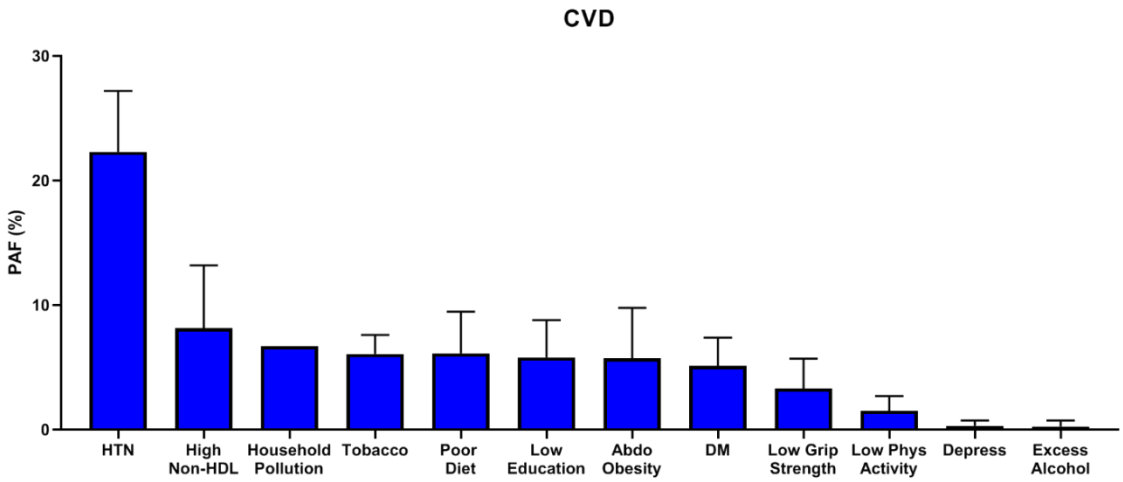
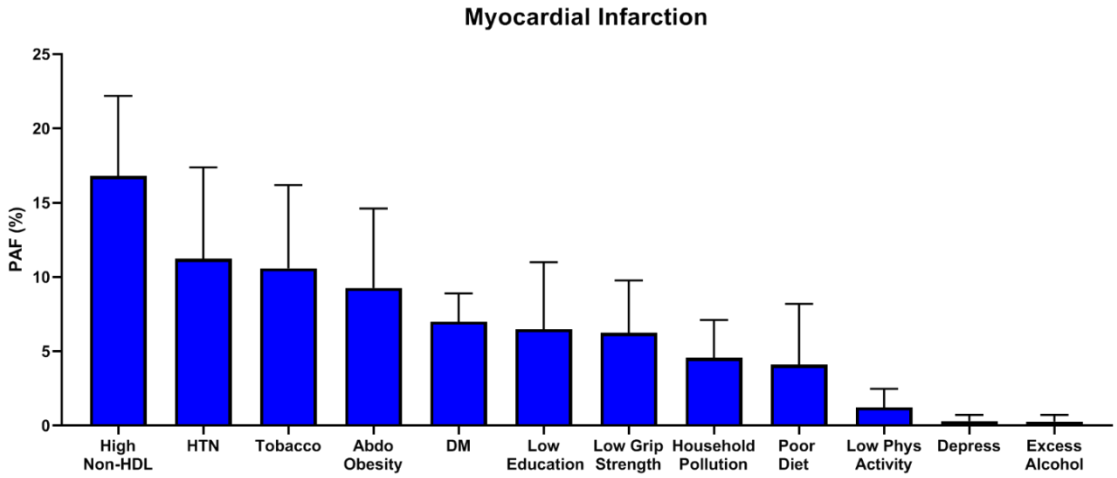

CV Mortality
HR
(95%CI)
Tobacco Use
Never 1
Former 1.08(0.90,1.30)
Current 1.96(1.70,2.26)
Alcohol Use
Never 1
Former 1.26(1.02,1.55)
Current Low 0.75(0.63,0.89)
Current Moderate 0.74(0.55,0.99)
Current High 1.13(0.81,1.57)
Diet Score
Score >=5 1
Score 3−4 1.18(1.02,1.36)
Score <=2 1.19(1.00,1.40)
Physical Activity
High Active 1
Mode Active 1.31(1.15,1.49)
Not Active 1.55(1.34,1.80)
Hypertension
No 1
Yes 2.32(2.05,2.64)
Diabetes
No 1
Yes 2.02(1.77,2.31)
Non−HDL Cholesterol
Non−HDL <= 3.2 1
Non−HDL 3.2−4.0 1.07(0.93,1.24)
Non−HDL > 4.0 1.27(1.10,1.47)
Waist to Hip Ratio
Low 1
High 1.28(1.13,1.44)
Education
Trade/Coll/Univ 1
Sec/HgherSec 1.34(1.08,1.66)
None/Prim/Unk 1.93(1.55,2.40)
Depression
No 1
Yes 1.11(0.91,1.34)
Grip Strength
Quintile 5 1
Quintile 4 1.02(0.80,1.28)
Quintile 3 1.32(1.06,1.65)
Quintile 2 1.40(1.12,1.74)
Quintile 1 1.78(1.42,2.23)
Household Air Pollution
Clean 1
Solid Fuel 1.27(1.08,1.48)
0 0.5 1 1.5 2 2.5 3
Non−CV Mortality
HR
(95%CI)
1
1.28(1.15,1.43)
1.69(1.54,1.85)
1
1.28(1.11,1.48)
0.98(0.89,1.09)
0.93(0.78,1.11)
1.53(1.27,1.85)
1
1.09(0.99,1.19)
1.25(1.12,1.39)
1
1.25(1.15,1.35)
1.36(1.23,1.50)
1
1.17(1.09,1.27)
1
1.57(1.43,1.73)
1
0.81(0.75,0.89)
0.83(0.75,0.91)
1
1.08(1.00,1.17)
1
1.12(0.98,1.27)
1.48(1.29,1.69)
1
1.40(1.26,1.56)
1
1.12(0.98,1.28)
1.10(0.96,1.25)
1.20(1.05,1.37)
1.56(1.36,1.79)
1
1.26(1.13,1.41)
0 0.5 1 1.5 2 2.5 3

Figure 5


CVD
PAF (%)
30
20
10
0
HTN
High Non-HDL
Household Pollution
Tobacco
Poor Diet
Low Education
Abdo Obesity
DM
Low Grip Strength
Low Phys Activity
Depress
Excess Alcohol


Myocardial Infarction
PAF (%)
25
20
15
10
5
0
High Non-HDL
HTN
Tobacco
Abdo Obesity
DM
Low Education
Low Grip Strength
Household Pollution
Poor Diet
Low Phys Activity
Depress
Excess Alcohol

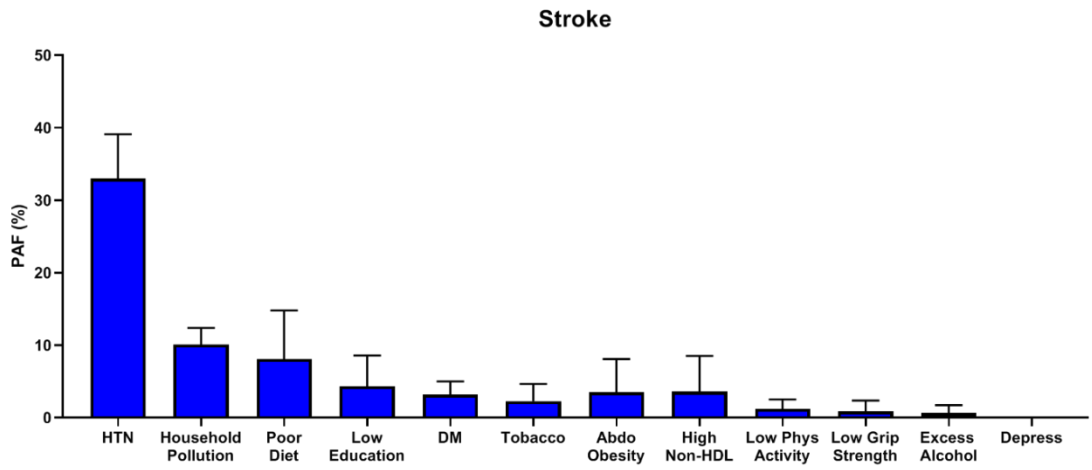
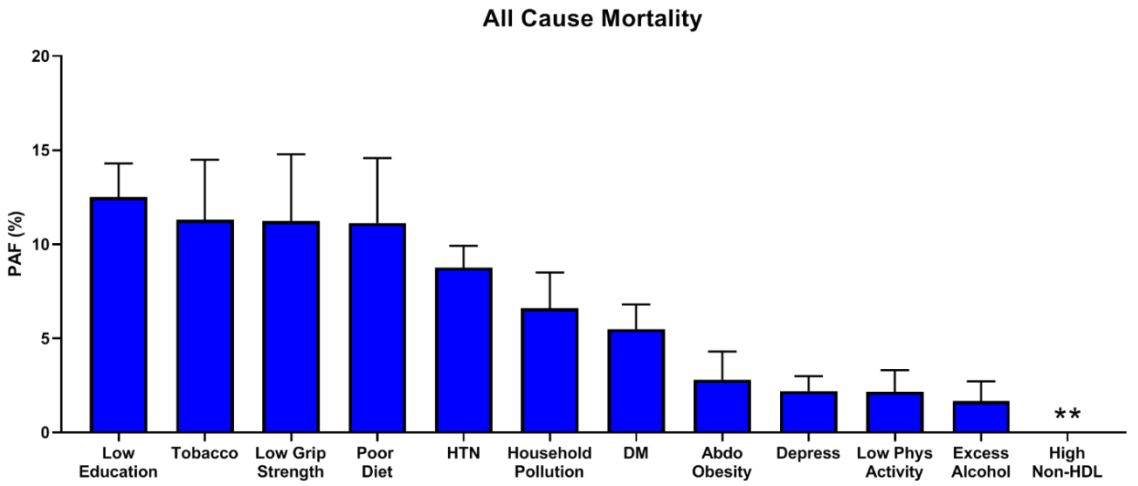
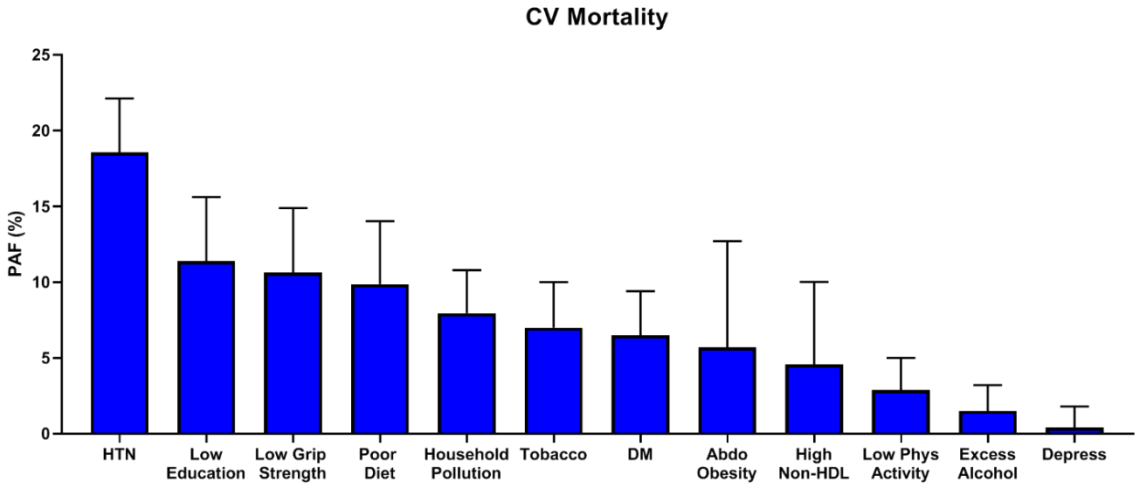

Stroke
PAF (%)
50
40
30
20
10
0
HTN
Household Pollution
Poor Diet
Low Education
DM
Tobacco
Abdo Obesity
High Non-HDL
Low Phys Activity
Low Grip Strength
Excess Alcohol
Depress

Figure 6


All Cause Mortality
PAF (%)
20
15
10
5
0
Low Education
Tobacco
Low Grip Strength
Poor Diet
HTN
Household Pollution
DM
Abdo Obesity
Depress
Low Phys Activity
Excess Alcohol
High Non-HDL
**


CV Mortality
PAF (%)
25
20
15
10
5
0
HTN
Low Education
Low Grip Strength
Poor Diet
Household Pollution
Tobacco
DM
Abdo Obesity
High Non-HDL
Low Phys Activity
Excess Alcohol
Depress

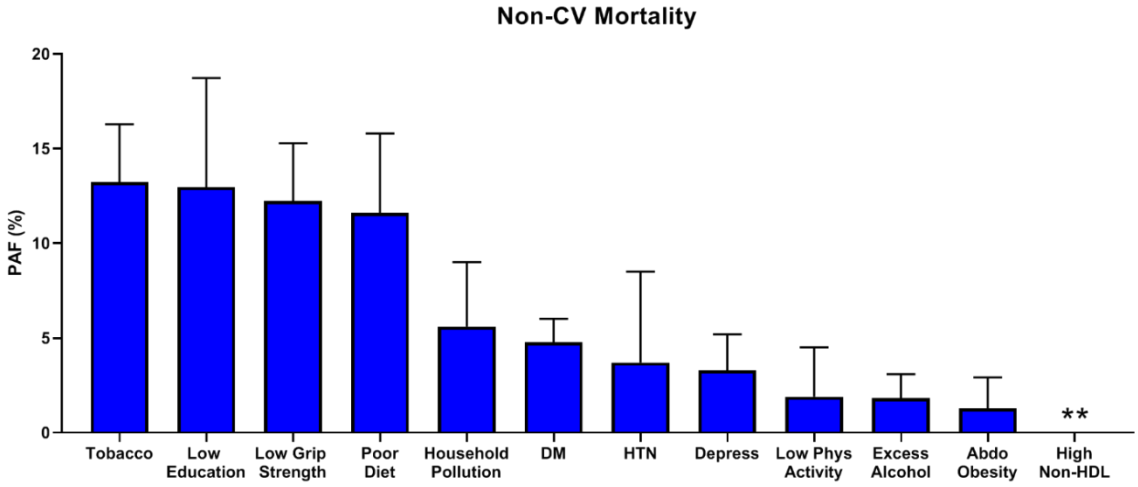

Non-CV Mortality
PAF (%)
20
15
10
5
0
Tobacco
Low Education
Low Grip Strength
Poor Diet
Household Pollution
DM
HTN
Depress
Low Phys Activity
Excess Alcohol
Abdo Obesity
High Non-HDL
**

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)
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		
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**	**HIC**	**MIC**	**LIC**

	PAF (95% Confidence Interval)	PAF (95% Confidence Interval)	PAF (95% Confidence Interval)	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

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

Supplementary Appendix A: Supplementary Methods:

Appendix A1: PURE Study Participant Selection Methodology as Excerpted from Teo et al. Am Heart J. 2009 Jul;158(1):1-7

Selection of Countries
The choice and number of countries selected in PURE reflects a balance between involving a large number of communities in countries at different economic levels, with substantial heterogeneity in social and economic circumstances and policies, and the feasibility of centers to successfully achieve long-term follow-up (see Table S2). Thus, PURE included sites in which investigators are committed to collecting good-quality data for a low-budget study over the planned 10-year follow-up period and did not aim for a strict proportionate sampling of the entire world.

Selection of Communities
Within each country, urban and rural communities were selected based on broad guidelines (see Guidelines for Selection of Countries, Communities, Households, and Individuals Recruited to PURE). A common definition for "community" that is applicable globally is difficult to establish. In PURE, a community was defined as a group of people who have common characteristics and reside in a defined geographic area. A city or large town was not usually considered a single community, rather communities from low-, middle-, and high-income areas were selected from sections of the city and the community area defined according to a geographical measure (e.g., a set of contiguous postal code areas or a group of streets or a village). The primary sampling unit for rural areas in many countries was the village. The reason for inclusion of both urban and rural communities is that for many countries, urban and rural environments exhibit distinct characteristics in social and physical environment, and hence, by sampling both, we ensured considerable variation in societal factors across PURE communities.

The number of communities selected in each country varied, with the aim to recruit communities with substantial heterogeneity in social and economic circumstances balanced against the capacity of local investigators to maintain follow-up. In some countries (e.g., India, China, Canada, and Colombia), communities from several states/provinces were included to capture regional diversity, in policy, socioeconomic status, culture, and physical environment. In other countries (e.g Iran, Poland, Sweden, and Zimbabwe), fewer communities were selected.

Selections of Households and Individuals
Within each community, sampling was designed to achieve a broadly representative sample of that community of adults aged between 35 and 70 years (see Table S2). The choice of sampling frame within each center was based on both "representativeness" and feasibility of long-term follow-up, following broad study guidelines. Once a community was identified, where possible, common and standardized approaches were applied to the enumeration of households, identification of individuals, recruitment procedures, and data collection.

The method of approaching households differed between regions. For example, in rural areas of India and China, a community announcement was made to the village through contact of a community leader, followed by in-person door-to-door visits of all households. In contrast, in Canada, initial contact was by mail followed by telephone inviting members of the households to a central clinic. Households were

eligible if at least 1 member of the household was between the ages of 35 and 70 years and the household members intended to continue living in their current home for a further 4 years.

For each approach, at least 3 attempts at contact were made. All individuals within these households between 35 and 70 years providing written informed consent were enrolled. When an eligible household or eligible individual in a household refused to participate, demographics and self-reported data about CVD risk factors, education, and history of CVD, cancers and deaths in the households within the 2 previous years were recorded.

To ensure standardization and high data quality, we used a comprehensive operations manual, training workshops, DVDs, regular communication with study personnel and standardized report forms. We entered all data in a customized database programmed with range and consistency checks, which was transmitted, electronically to the Population Health Research Institute in Hamilton (Ontario, Canada) where further quality checks were implemented.

Guidelines for Selection of Countries, Communities, Households, and Individuals Recruited to PURE

Countries
1. High-income countries, middle-income countries, and low-income countries, with the bulk of the recruitment from low- and middle-income regions.
2. Committed local investigators with experience in recruiting for population studies.
Communities
1. Select both urban and rural communities. Use the national definition of the country to determine urban and rural communities.
2. Select rural communities that are isolated (distance of >50 km or lack easy access to commuter transportation) from urban centers. However, consider ability to process bloods samples, e.g., villages in rural developing countries should be within 45-min drive of an appropriate facility.
3. Define community to a geographical area, e.g., using postal codes, catchment area of health service/clinics, census tracts, areas bordered by specific streets or natural borders such as a river bank.
4. Consider feasibility for long-term follow-up, e.g., for urban communities, choose sites that have a stable population such as residential colonies related to specific work sites in developing countries. In rural areas, choose villages that have a stable population. Villages at greater distance from urban centers are less susceptible to large migration to urban centers.

5. Enlist a community organization to facilitate contact with the community, eg, in urban areas, large employers (government and private), insurance companies, clubs, religious organizations, clinic or hospital service regions. In rural areas, local authorities such as priests or community elders, hospital or clinic, village leader, or local politician.
Individual
1. Broadly representative sampling of adults 35 to 70 years within each community unit.
2. Consider feasibility for long-term follow-up when formulating community sampling framework, e.g., small percentage random samples of large communities may be more difficult to follow-up because they are dispersed by distance. In rural areas of developing countries that are not connected by telephone, it may be better to sample entire community (i.e., door-to-door systematic sampling).
3. The method of approach of households/individuals may differ between sites. In MIC and HIC, mail, followed up by phone contact may be the practical first means of contact. In LIC, direct household contact through household visits may be the most appropriate means of first contact.
4. Once recruited, all individuals are invited to a study clinic to complete standardized questionnaires and have a standardized set of measurements.

Appendix A2: Standardized Event Definitions in PURE

Prospective Follow-up for Cardiovascular Events and Mortality: History of disease was collected at baseline from every participant with standardized questionnaires regarding history of a) hypertension, b) diabetes c) stroke d) angina/myocardial infarction/coronary artery disease e) heart failure f) other heart disease.

Information on specific events (death, myocardial infarction, stroke, heart failure, cancer, hospitalizations, new diabetes, injury, tuberculosis, human immunodeficiency viral infections, malaria, pneumonia, asthma, chronic obstructive pulmonary disease) were obtained from participants or their family members (events were reported by the participants if alive or by a relative if the individual had died). This information was adjudicated centrally in each country by trained physicians using standardized definitions. Because the PURE study involves urban and rural areas from middle- and low-income countries, supporting documents to confirm cause of death and/or event varied in degrees of completion and availability. In most of middle- and low-income countries there was no central system of death or event registration. Therefore, information was obtained about prior medical illness and medically certified cause of death where available, and, second, best available information was captured from reliable sources in those instances where medical information was not available in order to be able to arrive at a probable diagnosis or cause of death. Event documentation was based on information from household interviews and medical records, death certificates and other sources. Verbal autopsies were

also used to ascertain cause of death in addition to medical records which were reviewed by a health professional. This approach has been used in several studies conducted in middle- and low-income countries.

To ensure a standard approach and accuracy for classification of events across all countries and over time, the first 100 CVD events (deaths, MI, strokes, heart failure or cancers) for China and India, and 50 cases for other countries were adjudicated both locally and also by the adjudication chair, and if necessary further training was provided. Thereafter, every year, 50 cases for China and India and 25 cases for each of the remaining countries were adjudicated as above.

FATAL EVENTS

Cardiovascular Death – Definitions

01.00 DEATH DUE TO CARDIOVASCULAR EVENTS

01.10 Sudden unexpected Cardiovascular Death (SCVD)

Without evidence of other cause of death, death that occurred suddenly and unexpectedly (examples: witnessed collapse, persons resuscitated from cardiac arrest who later died) or persons seen alive less than 12 hours prior to discovery of death (example persons found dead in his/her bed).

- SCVD is either definite, probable or possible according to the following characteristics:

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
01.11: Definite	One of the following in persons with: • known cardiovascular disease, or • diabetes with an additional risk factor such as hypertension, smoking, dyslipidemia, micro albuminuria, serum creatinine 50% above upper limit of normal, or • 3 of the above risk factors, or • 2 of the above risk factors in men aged 60 and more and women aged 65 and more	No ICD-10 Code
01.12: Probable	One of the following in persons with: • diabetes, or • 2 of the above risk factors in men aged less than 60 and in women less than 65, or	

	• one of the above risk factor in men aged 60 and more and in women aged 65 and more, or • typical of chest pain or sudden severe dyspnea of less than 20-minute duration preceding the event	
01.13: Possible	In persons without risk factor	
For SCVD, the patient was well or had a stable CVD (example stable angina) when last seen alive. The event of a sudden death occurring during the hospitalization of MI is considered a fatal MI and not sudden death.		

01.30 Fatal Myocardial Infarction (MI)

Symptoms of Myocardial Infarction:

Typical symptoms or suggestive symptoms of MI according to physician are characterized by severe anterior chest pain as tightness, crushing, burning, lasting at least 20 minutes, occurring at rest, or on exertion, that may radiate to the arms or neck or jaw and may be associated with dyspnea, diaphoresis and nausea. However, death associated with nausea and vomiting with or without chest pain not due to another cause may be considered as possible MI if ECG and cardiac markers are not done. These symptoms may have occurred the last month before death.

Fatal myocardial infarction is either definite, probable or possible according to the following characteristics:

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
01.31: Definite	1. Autopsy demonstrating fresh myocardial infarction and/or recent coronary occlusion, or 2. ECG showing new and definite sign of MI (Minnesota code 1-1-1) or 3. Symptoms typical or atypical or inadequately described but attributed to cardiac origin lasting at least 20 minutes and by troponin or cardiac enzymes (CKMB, CK, SGOT, SLDH) above center laboratory ULN 4. ECG with new ischemic changes (new ST elevation/depression or T wave inversion ≥ 2 mm) and by	

	troponin or cardiac enzymes (CKMB, CK, SGOT, SLDH) above center laboratory ULN	I21- I22
01.32: Probable	1. ECG with sign of probable MI (Minnesota code 1-2-1), or 2. Typical symptoms lasting at least 20 minutes considered of cardiac origin, with only new ST-T changes (new ST elevation/depression or T wave inversion ≥ 1 but < 2mm) without documented increased cardiac markers or enzyme as in PURE definition 1.31 (above), or 3. Increased cardiac enzymes as in PURE definition 1.31 (above) showing a typical pattern of MI as above without symptoms or significant ECG changes	
01.33: Possible	1. ECG with sign of possible MI (Minnesota code 1-3-1) or 2. Typical symptoms or symptoms suggestive of MI according to the physician lasting at least 20 minutes without documented ECG or cardiac marker.	

The Minnesota codes for MI is taken from Rose and Blackburn and published in their book "Evaluation Methods of Cardiovascular Disease WHO 1969".

- Definite MI is Q/R ratio ≥1/3 and Q duration ≥ 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-1-1)
- Probable MI is Q/R ratio ≥1/3 and Q duration between 0.02 and 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-2-1)
- Possible MI is Q/R ratio between 1/5 and 1/3 and Q duration between 0.02 and 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-3-1)

<u>01.40 Fatal Stroke</u>

Fatal stroke is either definite or possible according to the following characteristics:

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes

01.41: Definite	Stroke death is defined as death within 30 days from an acute focal neurological deficit *diagnosed by a physician* and thought to be of vascular origin (without other cause such as brain tumor) with signs and symptoms lasting >= 24 hrs. Stroke death is also considered if death occurred within 24 hrs. of onset of persisting signs and symptoms, or if there is evidence of a recent stroke on autopsy. N.B. • In a subject with a stroke <= 30 days: If death occurred with a pneumonia due to possible aspiration, death will be considered to be due to stroke. • In a subject with a stroke > 30 days: If death occurred with a pneumonia due to possible aspiration, the adjudicator will make a decision according to his/her clinical judgment if death is related to stroke or not. • Subarachnoid hemorrhage death manifested by sudden onset headache with/without focal signs and imaging (CT or MRI) evidence of bleeding primarily in the subarachnoid space is considered a fatal stroke in absence of trauma or brain tumor or malformation • Subdural hematoma death is not considered as a stroke death and may be related to previous trauma or other cause.	I60- I64, I69
01.43: Possible	Death in a participant with a history of sudden onset of focal neurological deficit of one or more limbs, loss of vision or slurred speech lasting about 24 hours.	

01.50 Fatal Congestive Heart Failure

Fatal congestive heart failure is either definite or possible according to the following characteristics:

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes

01.51: Definite	The diagnosis of congestive heart failure may be an autopsy finding in absence of other cause or requires signs (rales, increased jugular venous pressure or ankle edema) or symptoms (nocturnal paroxysmal dyspnea, dyspnea at rest or ankle edema) of congestive heart failure and one or both of the following: • radiological signs of pulmonary congestion, • treatment of heart failure with diuretics *If sudden death occurred in a patient with chronic severe heart failure, it should be adjudicated as fatal congestive heart failure.*	I50
01.52: Probable	Progressive shortness of breath on lying down or at night, improving on sitting up AND any of the following signs or symptoms: swelling of feet, distension of abdomen, progressive cough in a person with known hypertension or a history of previous MI/angina or other heart disease	
01.53: Possible	Progressive shortness of breath on lying down or at night, improving on sitting up AND any of the following signs or symptoms: swelling of feet, distension of abdomen, progressive cough	

01.60 Death Due to Other Cardiovascular Deaths *(other causes [1.10 to 1.50 above] having been excluded)*

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
01.61	Arterial rupture of aneurysm	I71- I72
01.62	Pulmonary embolism *NOTE: Death associated with pulmonary embolism occurring within 2 weeks after a fracture such as hip, femur should attributed to death due to injury. Refer to Injury, Section 6.0*	I26

01.63	Arrhythmic death (A-V block, sustained ventricular tachycardia in absence of other causes)	I44- I45, I47- I49
01.64	Death after invasive cardiovascular intervention: a perioperative death extending to 30 days after coronary or arterial surgical revascularization and to 7 days after a coronary or arterial percutaneous dilatation (angioplasty) with or without a stent or an invasive diagnostic procedure.	I97
01.65	Congenital heart disease	Q20-Q28
01.66	Heart valve disease (including rheumatic heart disease)	I01, I05- I09, I34- I37
01.67	Endocarditis	I33, I38
01.68	Myocarditis	I40
01.69	Tamponade (pericarditis)	I30, I31, I32
01.70	Other cardiovascular events *(Excluding 1.61 to 1.69 above)* *Valid ICD-10 codes would include the following:* *I11, I12, I13, I23, I24, I25, I27, I28, I42, I51, I52, I65-I68, I73, I74, I96, I98, I99 (Refer to ICD-10 Listing for associated definitions for each code)*	Any valid 'I' (Cardiovascular) ICD-10 code that can be classified as underlying cause of death, not specified above

NON-FATAL EVENTS

Cardiovascular Events – Definitions

10.00 NON-FATAL CARDIOVASCULAR EVENTS

10.10 Non-Periprocedural Myocardial Infarction (MI)

MI is considered either definite, probable or possible according to the following characteristics:

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
10.11: Definite	1. ECG showing new and definite sign of MI (Minnesota code 1-1-1) or 2. Symptoms typical or atypical or inadequately described but attributed to cardiac origin lasting at least 20 minutes and by troponin or cardiac enzymes (CKMB, CK, SGOT, SLDH) above center laboratory ULN 3. ECG with new ischemic changes (new ST elevation/depression or T wave inversion ≥ 2 mm) and by troponin or cardiac enzymes (CKMB, CK, SGOT, SLDH) above center laboratory ULN Please note that increased markers may occur in trauma (CK, AST, myoglobin and CK MB to a lesser degree); renal insufficiency, heart failure, pulmonary embolism (troponin), cardioversion (all)	I21-I22
10.12: Probable	1. ECG with new and probable sign of MI (Minnesota code 1-2-1), or 2. Typical symptoms lasting at least 20 minutes considered of cardiac origin, with only new ST-T changes (new ST elevation/depression or T wave inversion ≥ 1 but < 2mm) without documented increased cardiac markers as in PURE definition 10.11 (above), or 3. Increased cardiac enzymes showing a typical pattern of MI as above without symptoms or significant ECG changes.	
10.13: Possible	1. ECG with new and possible sign of MI (Minnesota code 1-3-1), or 2. Typical symptoms lasting 20 minutes and more considered to be of cardiac origin without documented ECG or cardiac marker.	

10.20 Periprocedural Myocardial Infarction

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
10.21: Definite	1. ECG showing new and definite sign of MI (Minnesota code 1-1-1), or 2. Increased cardiac markers within 48 hours of procedure: • percutaneous coronary intervention: CKMB should be ≥ 5 X ULN or troponin ≥ 5 X above lower level of necrosis OR > 20% increase in cardiac markers if elevated at the beginning of the procedure in a patient with symptoms suggestive of myocardial ischemia • Coronary surgery: Increased cardiac markers CKMB should be ≥ 10X ULN or troponin ≥ 10X above lower limit of necrosis.	I21-I22

The Minnesota codes for MI is taken from Rose and Blackburn and published in their book "Evaluation Methods of Cardiovascular Disease WHO 1969".

- Definite MI is Q/R ratio ≥1/3 and Q duration ≥ 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-1-1)
- Probable MI is Q/R ratio ≥1/3 and Q duration between 0.02 and 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-2-1)
- Possible MI is Q/R ratio between 1/5 and 1/3 and Q duration between 0.02 and 0.03 second in one of the following leads: I, II, V2, 3, 4, 5, 6. (code 1-3-1)

10.30 Stroke/Transient Ischemic Attack (TIA)

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
10.31: Definite	Stroke is defined as an acute focal neurological deficit *diagnosed by a physician* and thought to be of vascular origin (without other case such as brain tumor) with signs and symptoms lasting ≥ 24 hrs.	

	N.B. • Subarachnoid hemorrhage manifested by sudden onset headache with/without focal signs and imaging (CT or MRI or lumbar puncture) showing evidence of bleeding primarily in the subarachnoid space is considered a stroke in absence of trauma or brain tumor or malformation • Subdural hematoma is not considered as a stroke and may be related to previous trauma or other cause.	I60-I64, I69
10.33: Possible	Stroke is possible if there is a history of sudden onset of focal neurological deficit of one or more limbs, loss of vision or slurred speech lasting about 24 hours or more	
10.34: TIA	The diagnosis of TIA requires the presence of acute focal neurological deficit thought to be of vascular origin with signs and symptoms lasting less than 24 hours	G45

10.40 Congestive Heart Failure

PURE Adjudication Code	Event Type	Acceptable ICD-10 codes
10.41: Definite	The diagnosis of congestive heart failure requires signs (rales, increased jugular venous pressure or ankle edema) or symptoms (nocturnal paroxysmal dyspnea, dyspnea at rest or ankle edema) of congestive heart failure and one or both of the following: • radiological signs of pulmonary congestion, • Treatment of heart failure with diuretics.	
10.42: Probable	Progressive shortness of breath on lying down or at night, improving on sitting up AND any of the following signs or symptoms: swelling of feet, distension of abdomen, progressive cough in a person with known hypertension or a history of previous MI/angina or other heart disease	I50

10.43: Possible	Congestive heart failure is considered possible when there is progressive shortness of breath on lying down or at night, improving on sitting up AND any of the following signs or symptoms: swelling of feet, distension of abdomen, progressive cough	

Appendix A3: Assumptions examined in Cox Frailty Models: The proportionality assumption of the Cox model was assessed by visual inspection of (1) initial stratified Kaplan-Meier curves by the variables in the model, and by (2) log(-log survival) vs log time plots after fitting Cox models. We did not see any meaningful departures from the proportionality assumption.

We examined the residual heterogeneity, assessing the proportional reduction in the covariance parameter from the null model with inclusion of frailty terms (i.e. the application of random effects intercepts in the cox frailty model). Residual heterogeneity was reduced by 24% at the country level and when we included a frailty term at the community level, it was reduced by a further 54% in the final Cox models.

Appendix A4: Note on sodium analysis: Because information on urinary sodium was available in only 113,078 participants, its associations with CVD and mortality were calculated separately using Cox frailty models mutually adjusted for age, sex, and all risk factors other than hypertension, which is considered to be the primary mediating factor for the effects of sodium on CVD and mortality. Sodium analyses were also adjusted by China versus other countries as a covariate because of the clustering of communities with high sodium excretion values in China. Sodium excretion between 4-6g/day was used as the reference category in our hazard ratio calculations because in our previous analyses this range was associated with the lowest risk.

Since we were primary interested in estimating the PAF related to high sodium excretion, and we did not consider the effects of low sodium excretion (i.e. less than 4 g/day) with increased CVD and mortality. Therefore, participants with a sodium of <4g/day were excluded in the PAF calculation. Therefore the impact on CVD and deaths of a downward shift in the entire distribution of sodium intake in the whole population may be overestimated by our approach.

Appendix A5: Note on $PM_{2.5}$ ambient air pollution: Since ambient PM2.5 air pollution was estimated at the community level, the associations of PM2.5 with CVD and mortality were also calculated separately after adjusting for both individual and additional community level risk factors. The model was 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 satellite data (indicator of local economic activity), national or regional healthcare access & quality index and community random effect.

We estimated a separate PAF using the fully adjusted linear HRs and the PM2.5 exposure distribution for PURE participants. The PAF was calculated using 10 μg/m3 as a counterfactual (based on the World Health Organization guidelines for PM2.5).Therefore, the PAFs for ambient air pollution is not strictly comparable to the estimates for the other risk factors.

Appendix A6: Note on calculation of the Average Population Attributable Fractions: Mutually adjusted, average population attributable fractions (APAFs) and their 95% confidence intervals were calculated using the approach described by Eide and Olaf. In this approach, APAF for each risk factor are determined using logistic regression, all risk factors of interest are added to the model in every possible order, and the average of all PAFs are then calculated using the R package called 'averisk' developed by Ferguson et. al. Estimates of PAF were further adjusted for age, sex and urban/rural location. This APAF calculation allows for an estimation of the individual contribution of each risk factor (or group of risk factors) to the overall PAF, and generally provides a smaller estimate for PAF for individual risk factors than more conventional methods used by GBD, and in INTEREART and INTERSTROKE, for which the sum of individual risk factor PAFs exceed the cumulative PAF. The 'averisk' package also computes confidence intervals based on Monte Carlo simulation. Consistent with our hazard ratio calculations, PAFs for 12 risk factors (excluding sodium and ambient air pollution) were calculated together using a single model. For sodium excretion was only available in two-thirds of the study population, intake and air pollution was analyzed as a community level variable, and for these reasons both hazard ratios and PAFs were calculated separately from the other 12 risk factors

Supplementary Appendix B: Supplementary Tables and Figures:

Appendix B, Table 1: List of 21 countries participating in phase 1 and 2 of PURE, and number of participants eligible, enrolled, included in the analysis

Country Name (grouped by county income status)	Number of participants approached that were eligible to participate in core study	Number of participants who consented for core study	Number of participants in the current analysis*
HIC	23039	18105 (78.6%)	17249 (95.3%)
UAE	2158	1498	1427
Sweden	5243	4152	3990
Canada	13038	10409	9855
Saudi Arabia	2600	2046	1977
MIC	150838	110905 (73.5%)	102680 (92.6%)
China	63878	47534	44300
South Africa	7647	4541	3882
Colombia	10904	7490	7258
Brazil	8000	6075	5662
Chile	4787	3573	3473
Iran	7321	6013	5654
Argentina	9062	7514	7242
Poland	2577	1951	1896
Malaysia	20834	15377	15347
Turkey	5196	4221	3761
Palestine	3062	1634	1554
Philippines**	7570	4982	2651
LIC	61303	38058 (62.1%)	35793 (94.0%)
India	49908	29168	28204
Zimbabwe	1700	1213	1190
Bangladesh	3461	2934	2856
Pakistan	3093	2714	1621
Tanzania	3141	2029	1922
All Countries	235180	167068 (71.0%)	155722 (93.2%)

*Analyses were limited to participants with at least one follow-up visit and without a prior history of CVD
** In Philippines, only 2331 had reached the time point for the first follow-up, which is ongoing.

Appendix B, Table 2: Summary of modifiable risk factors

Risk Factor	Definition or method of measurement	Risk category used for calculation of PAF	Reference category used for calculation of PAF
Behavioural cluster of risk factors:			
Tobacco use	Self-reported tobacco consumption using a standard tobacco use frequency questionnaire, categorized as never, former or current.	History of current or former tobacco use	No history of tobacco use
Alcohol[1]	Self-reported alcohol consumption using a standard alcohol consumption frequency questionnaire. Consumption was categorized as former, never and current. Current consumption is further categorized as low (<=7 drinks/week), moderate (8-14 drinks/week in women or 8-21 drinks/week in men), or high-consumption (> 14 drinks/week in women or >21 drinks/week in men).	Excess alcohol use defined as either high current use or former use	No history of alcohol consumption, low current use, or moderate current use.
Diet[2–4]	Diet was measured using country specific, food frequency dietary questionnaires (FFQ). Using these, a comprehensive diet score was created based on eight food types associated with a lower risk of CVD or mortality in PURE: fruits, vegetables, legumes, nuts, fish, dairy, unprocessed red meat and poultry; with each classified into high-consumption (1 point) or low-consumption (0 points) based on the median amount consumed in PURE (in	Diet score $\leq$ 4	Diet score $\geq$ 5**

	grams/day), then added to a final score (with lower scores representing a lower quality diet)		
Physical activity[5]	Physical activity was measured using the International Physical Activity Questionnaire, and classified as low (<600 metabolic equivalents [MET] × minutes per week or <150 minutes per week of moderate intensity physical activity), moderate (600–3000 MET × minutes or 150–750 minutes per week) or high (>3000 MET × minutes or >750 minutes per week)	Low physical activity level	Moderate or high physical activity**
Urine sodium excretion[6,7]	Urine sodium excretion was estimated by the Kawasaki formula using morning fasting urine samples.	Estimated urine sodium excretion > 6g /day	Estimated urine sodium excretion $\leq$ 6g/day
Metabolic cluster of risk factors:			
Hypertension	Blood pressure was measured in all participants at baseline, and hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, a self-reported history of hypertension, or treatment with anti-hypertensive medications.	Definition of hypertension was met	Definition of hypertension was not met
Diabetes	Diabetes was defined as either a fasting glucose > 7 mmol/dl or self-reported history of diabetes, on treatment for diabetes.	Definition of diabetes was met	Definition of diabetes was not met
Non-HDL cholesterol[8]	Total cholesterol minus HDL, measured using fasting lipid values	Highest two tertiles, corresponding to a value of >3.2 mmol/L	Lowest tertile of TC-HDL
Abdominal obesity	Waist and hip circumference was measured routinely in participants at baseline, and used to calculate the waist to hip ratio (WHR)	WHR > 0.9 in men or 0.85 in women*	WHR $\leq$ 0.9 in men or 0.85 in women

Socio-economic and psychosocial cluster of risk factors:			
Education[9]	Education was self-reported, and classified as low (primary education level or less), intermediate (secondary school education) or high (college, trade school, or university education)	Low education	Moderate or high education**
Symptoms of Depression[10,11]	Symptoms of depression were reported based on adapted version of the Short-Form Composite International Diagnostic Interview (CIDI-SF) for major depressive disorders, using an 8 point depression score based self-reported symptoms associated with depression. Symptoms consistent with depression was defined as a score ≥ 5	Symptoms consistent with depression	No depression
Grip strength[12]	Measured using JAMAR dynamometer	Lowest two quintiles of grip strength	Highest three quintiles of grip strength**
Air pollution cluster of risk factors:			
Household air pollution from solid fuel use for cooking	Self-reported primary use of solid fuels (i.e. charcoal, coal, wood, agriculture/crop, animal dung, shrub/grass) for cooking	Primary use of any solid fuel)	Primary use of gas or electricity for cooking
Fine particulate matter $(PM)_{2.5}$ ambient air pollution	3-year average $PM_{2.5}$ concentration assigned to each PURE community of residence. Please refer to main text for details on method of measurement.	Community level exposure > 10 $\mu g/m^3$ *	Community level exposure $\leq$ 10 $\mu g/m^3$

Prior publications from INTERHEART and PURE by Rosengren et al. demonstrated that education level was superior to other markers of socioeconomic status such as wealth index and so only education was used in this analysis as a marker of socio-economic status.[9] *Thresholds for waist to hip ratio and $PM_{2.5}$ ambient air pollution were selected based on WHO criteria.[13,14] **

For several risk factors where the associated risk was along a continuum, choosing extreme counterfactuals or reference values would inflate their impact by a modest degree, but would be difficult to achieve in any population based strategy (i.e. shifting all individuals to a college/university of trade school education, or shifting all individuals to a high physical activity level). Therefore, we considered more conservative reference categories for our primary analyses.

For alcohol, we observed that high and former alcohol consumption were both associated with higher risk of mortality, suggesting that in the former group, participants stopped alcohol consumption after suffering the adverse health effects of alcohol. Therefore, our risk group for calculation of the PAF related to alcohol combined the harmful effects from former and high alcohol consumption.

For sodium intakes less than 4 g/d was associated with higher mortality and CVD compared to 4 to 6g/d.We excluded these with low sodium as the implications of the above findings is unclear. Inclusion of the group with low sodium would counterbalance the effects of increased risks of sodium >6 g/d and would essentially nullify any potential excess of sodium as a risk factor.

Appendix B, Table 3: Comparison of different lipid markers with the risk of major CVD

Lipid measurement	Hazard ratio (95% confidence interval)				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Total cholesterol	Reference	1.11 (1.00,1.23)	1.08 (0.97,1.20)	1.22 (1.10,1.35)	1.35 (1.22,1.51)
Non-HDL (total cholesterol – HDL)	Reference	1.23 (1.10,1.37)	1.19 (1.07,1.33)	1.30 (1.17,1.45)	1.50 (1.34,1.67)
LDL cholesterol	Reference	1.04 (0.93,1.15)	1.07 (0.96,1.18)	1.05 (0.95,1.17)	1.32 (1.19,1.47)
Total cholesterol /HDL ratio	Reference	1.06 (0.95,1.19)	1.14 (1.03,1.27)	1.11 (0.99,1.24)	1.40 (1.26,1.56)

HDL = high density lipoprotein, LDL = low density lipoprotein

Appendix B, Table 4: Summary of levels of completeness of data for each risk factor

	Overall	HIC	MIC	LIC
Sample size	155722	17249	102680	35793
Risk factor of interest	**Number (%) of participants with complete data**			
Hypertension	145357(93.3)	16641(96.5)	96081(93.6)	32635(91.2)
Diabetes	155722(100)	17249(100)	102680(100)	35793(100)
Non-HDL cholesterol	120148(77.2)	15538(90.1)	82896(80.7)	21714(60.7)
Waist to hip ratio	146125(93.8)	16633(96.4)	96509(94.0)	32983(92.1)
Tobacco use	154433(99.2)	17200(99.7)	101681(99.0)	35552(99.3)
Alcohol consumption	152318(97.8)	17063(98.9)	99698(97.1)	35557(99.3)
Diet Score	141164(90.7)	16293(94.5)	92720(90.3)	32151(89.8)
Physical activity	143911(92.4)	15993(92.7)	96847(94.3)	31071(86.8)
Sodium excretion	101609(65.3)	14817(85.9)	78060(76.0)	8732(24.4)*
Education	155253(99.7)	17203(99.7)	102422(99.7)	35628(99.5)
Depression	154316(99.1)	17189(99.7)	101871(99.2)	35256(98.5)
Grip strength	141843(91.1)	16221(94.0)	94742(92.3)	30880(86.3)
Household air pollution from solid fuel use for cooking	125460(80.6)	15701(91.0)	87616(85.3)	22143(61.9)
$PM_{2.5}$ level	154646(99.3)	16744(97.1)	102236(99.6)	35666(99.6)

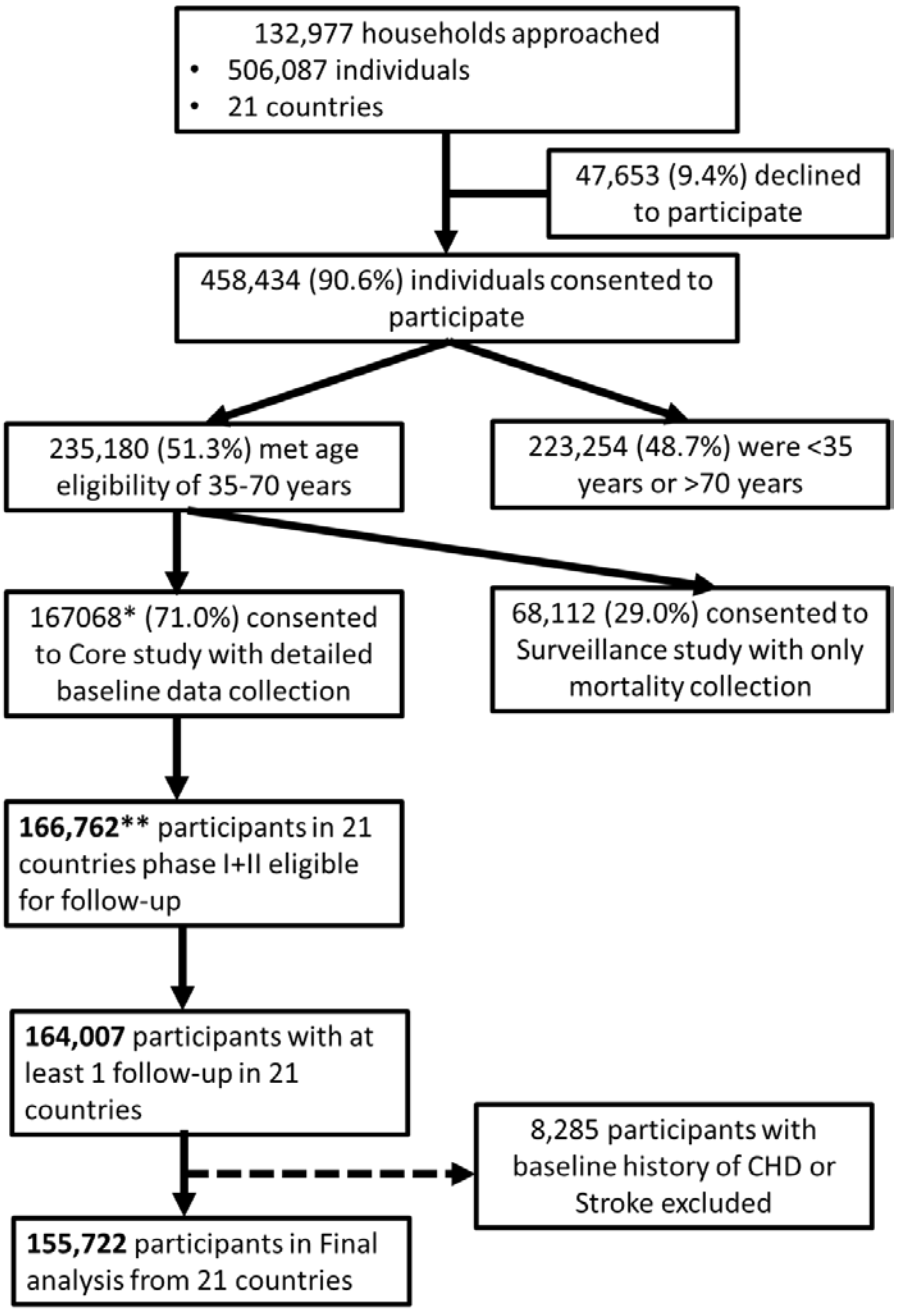
*All stored samples in India degraded during storage and so were not analyzed. HDL = high density lipoprotein.

Appendix B, Table 5: Total number of events, and age and sex standardized event rates per 1000 person years: Overall and by Country Income Status

Event	**Overall (rate per 1000 person years)**	**HIC (rate per 1000 person years)**	**MIC (rate per 1000 person years)**	**LIC (rate per 1000 person years)**
CVD	7980 (4.57)	624 (2.87)	5167 (4.62)	2189 (5.22)
MI	3559 (2.08)	307 (1.48)	1909 (1.75)	1343 (3.25)
Stroke	3577 (1.99)	237 (1.05)	2671 (2.34)	669 (1.52)
All-Cause Mortality	10234 (5.44)	501 (2.00)	5543 (4.70)	4190 (9.13)
CV Mortality	2917 (1.51)	75 (0.31)	1613 (1.32)	1229 (2.67)
Non-CV Mortality	7317 (3.93)	426 (1.69)	3930 (3.38)	2961 (6.46)

CVD = cardiovascular disease, MI = myocardial infarction

Supplementary Figure 1: Consort Diagram of Participants Included in the Current Analysis



*2805 were excluded due missing values in age, gender
**306 recruited participants are not yet due for a follow-up visit

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