Metabolic, behavioural, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study

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Summary

Background There is a paucity of data on the prevalence of risk factors and their associations with incident cardiovascular disease in women compared with men, especially from low-income and middle-income countries.

Methods In the Prospective Urban Rural Epidemiological (PURE) study, we enrolled participants from the general population from 21 high-income, middle-income, and low-income countries and followed them up for approximately 10 years. We recorded information on participants' metabolic, behavioural, and psychosocial risk factors. For this analysis, we included participants aged 35–70 years at baseline without a history of cardiovascular disease, with at least one follow-up visit. The primary outcome was a composite of major cardiovascular events (cardiovascular disease deaths, myocardial infarction, stroke, and heart failure). We report the prevalence of each risk factor in women and men, their hazard ratios (HRs), and population-attributable fractions (PAFs) associated with major cardiovascular disease. The PURE study is registered with ClinicalTrials.gov, NCT03225586.

Findings In this analysis, we included 155 724 participants enrolled and followed-up between Jan 5, 2005, and Sept 13, 2021, (90 934 [58·4%] women and 64 790 [41·6%] men), with a median follow-up of 10·1 years (IQR 8·5–12·0). At study entry, the mean age of women was 49·8 years (SD 9·7) compared with 50·8 years (9·8) in men. As of data cutoff (Sept 13, 2021), 4280 major cardiovascular disease events had occurred in women (age-standardised incidence rate of 5·0 events [95% CI 4·9–5·2] per 1000 person-years) and 4911 in men (8·2 [8·0–8·4] per 1000 person-years). Compared with men, women presented with a more favourable cardiovascular risk profile, especially at younger ages. The HRs for metabolic risk factors were similar in women and men, except for non-HDL cholesterol, for which high non-HDL cholesterol was associated with an HR for major cardiovascular disease of 1·11 (95% CI 1·01–1·21) in women and 1·28 (1·19–1·39) in men, with a consistent pattern for higher risk among men than among women with other lipid markers. Symptoms of depression had a HR of 1·09 (0·98–1·21) in women and 1·42 (1·25–1·60) in men. By contrast, consumption of a diet with a PURE score of 4 or lower (score ranges from 0 to 8), was more strongly associated with major cardiovascular disease in women (1·17 [1·08–1·26]) than in men (1·07 [0·99–1·15]). The total PAFs associated with behavioural and psychosocial risk factors were greater in men (15·7%) than in women (8·4%) predominantly due to the larger contribution of smoking to PAFs in men (ie, 1·3% [95% CI 0·5–2·1] in women *vs* 10·7% [8·8–12·6] in men).

Interpretation Lipid markers and depression are more strongly associated with the risk of cardiovascular disease in men than in women, whereas diet is more strongly associated with the risk of cardiovascular disease in women than in men. The similar associations of other risk factors with cardiovascular disease in women and men emphasise the importance of a similar strategy for the prevention of cardiovascular disease in men and women.

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Introduction

Whether risk factors for cardiovascular disease have similar or variable associations among women and men is unclear. Few studies to date have examined a comprehensive list of risk factors encompassing metabolic, behavioural, and psychosocial risk factors, and related them to cardiovascular disease in women and men. Existing studies, mostly from high-income countries, have reported that hypertension, diabetes, and smoking are more strongly associated with cardiovascular disease in women than in men.[1–5] Such findings would imply that women would benefit to a greater extent in

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Research in context

Evidence before this study

We searched MEDLINE databases, without language or publication date restrictions, on Sept 10, 2021, and again on June 8, 2022, for studies reporting on cardiovascular disease risk factors in women and men. Our key search terms included ("risk factors" OR "hypertension" OR "diabetes" OR "dyslipidaemia" OR "cholesterol" OR "smoking" OR "tobacco use" OR "diet" OR "depression" OR "alcohol" OR "physical activity" OR "waist-to-hip ratio" OR "abdominal obesity" OR "obesity") AND "cardiovascular disease" AND ("women" OR "gender" OR "sex differences"). Previous studies have emphasised that some risk factors, such as hypertension, diabetes, and smoking, are more strongly associated with cardiovascular disease in women than men. These findings would suggest that women would benefit from more intensive management of these risk factors to reduce their risk of cardiovascular disease. However, much of the existing evidence was from high-income countries (mainly North America and Europe). There is a paucity of prospective data from low-income and middle-income countries. We did not find any study that reported on differences between women and men in the levels of metabolic, behavioural, and psychosocial risk factors, and also whether the associations between these risk factors and cardiovascular disease differ between women and men using a community-based sample from high-income, middle-income, and low-income countries.

Added value of this study

To our knowledge, this is the first comprehensive overview of the prevalence of metabolic, behavioural, and psychosocial risk factors, their hazard ratios (HRs), and population-attributable fractions for cardiovascular disease in women and men aged 35–70 years. Our results extend previous studies by reporting on a geographically diverse population from five continents, who did not have a history of cardiovascular disease and were followed up for a median of 10·1 years. Compared with men, women presented with a more favourable cardiovascular risk profile. The HRs for metabolic risk factors were similar in women and men, except for non-HDL cholesterol, for which larger HRs for cardiovascular disease were observed in men. Larger HRs for symptoms of depression were observed for men than for women. By contrast, diet was more strongly associated with cardiovascular disease in women than in men, which has not been described previously and requires independent confirmation. The total PAFs associated with behavioural and psychosocial risk factors were greater in men than in women due to the larger contribution of smoking to the overall PAFs in men.

Implications of all the available evidence

Our results emphasise the importance of a similar strategy for the prevention of cardiovascular disease in both sexes. However, the increased risk of cardiovascular disease in men might be substantially attenuated with better reductions in tobacco use and lipid concentrations.

reducing cardiovascular disease risk from control of these risk factors than would men. However, the burden of cardiovascular disease is greatest in low-income and middle-income countries, for which prospective data on the association of risk factors with cardiovascular disease are sparse, with a paucity of analysis by sex.[6] For instance, a recently published commission review[7] of the literature on risk factors and cardiovascular disease in women relied almost exclusively on the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study, which combines disparate data sources. To date, no study has comprehensively examined risk factors and cardiovascular disease in women and men from predominantly low-income and middle-income countries using standardised methods for enrolment and data collection. We used data from the Prospective Urban Rural Epidemiological (PURE) study, which was conducted in 21 high-income, middle-income, and low-income countries, to examine the prevalence of metabolic, behavioural, and psychosocial risk factors and their associations with cardiovascular disease in the general population.

Methods

Study design and participants

The PURE study is an ongoing, multicountry, prospective cohort study that involves participants who live in high-income countries (11%) and low-income and middle-income countries (89%). These proportions closely reflect the global population distribution by economic levels. The PURE study's design has been published previously[8–10] and is also described in the appendix (pp 12–15). Briefly, participants were enrolled in three phases, which began in 2003. In phase one, 157719 participants were recruited from 17 countries; in phase two, an additional 10794 participants were recruited from four additional countries; and in phase three, an additional 9322 participants were recruited from four more countries (a list of the countries and their centres categorised by country income classification is in the appendix [p 12]). The countries and communities in PURE were selected with the aim of obtaining a socioeconomically heterogeneous study sample while also ensuring feasibility of detailed data collection and long-term follow-up. Households within communities were selected so that participants were broadly representative of their communities' sociodemographic compositions. The PURE study was coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University (Hamilton, ON, Canada). Ethics committees at each participating centre approved the study[9–11] and all participants provided written informed consent.[10]

For this analysis, we present data on 155724 PURE participants aged 35–70 years at baseline, without a history of cardiovascular disease, with at least one follow-up visit (at 3 years). We excluded participants with implausible or extreme values of risk factors. Countries were categorised into high-income countries, upper-middle-income countries, lower-middle-income countries, and low-income countries on the basis of their World Bank country income classification at the time of inclusion in the study.

Data collection

We used standardised methods to collect information on risk factors at baseline.[12] Blood samples were drawn from each participant and frozen between –20°C and –70°C. All blood samples were shipped in ambient packaging with the use of STP-250 shipping boxes (Fat-T-Pak, AnInmark Company, Edmonton, AB, Canada) to the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital (Hamilton, ON, Canada) or regional laboratories in Beijing (China), Bangalore (India), or Kocaeli (Türkiye) for analysis. Fasting and non-fasting blood samples were analysed for triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, apolipoprotein B (ApoB [Apo B-100]), apolipoprotein A1 (ApoA1 [Apo-AI]), and blood glucose. The blood samples were analysed using validated and standardised methods.

Every 3 years, information on clinical events was obtained by in-person visits or by telephone from participants or family members of deceased participants. Events were adjudicated in each country using standardised definitions and, depending on the country, information from verbal autopsies and reviews of additional documents (eg, medical records and hospital or physician reports).[12]

Here, we analysed the following metabolic risk factors: systolic blood pressure, hypertension, fasting plasma glucose concentration, diabetes, waist-to-hip ratio, abdominal obesity, and non-HDL cholesterol. Sitting blood pressure was taken by trained research assistants using a standardised procedure with an Omron digital blood pressure measuring device (Omron HEM-757, Toronto, ON, Canada). Hypertension was defined as a baseline systolic blood pressure of at least 140 mm Hg and diastolic blood pressure of at least 90 mm Hg, self-reported history of hypertension, or treatment with blood pressure-lowering medicines. Diabetes was defined as a baseline fasting plasma glucose concentration of 7·0 mmol/L or higher, self-reported history of diabetes, or treatment with glucose-lowering medicines. Abdominal obesity was defined as a waist-to-hip ratio of more than 0·90 in men or 0·85 in women. Elevated non-HDL cholesterol was defined as total cholesterol minus HDL cholesterol, using fasting lipid measurements, corresponding to a concentration of more than 3·1 mmol/L, which represents the upper two-thirds of the distribution.

Behavioural risk factors were smoking (current, former, or never), alcohol consumption (current, former, or never), physical activity (measured using the long-form International Physical Activity Questionnaire[13]), and diet (measured using the PURE diet score[12]). Psychosocial risk factors were symptoms of depression and education. Low physical activity was defined as having done less than 600 metabolic equivalents×min per week.[13] We dichotomised the PURE diet score at 4 or less or 5 to 8.[12] Presence of symptoms of depression was defined as having five or more symptoms of depression based on the Short-Form International Diagnostic Interview Schedule for Major Depressive Disorder.[14] Low education was defined as primary education level or less. We also included grip strength and household air pollution as risk factors because our previous study[12] showed that both grip strength and household air pollution were strongly associated with cardiovascular disease, particularly in low-income and middle-income countries. Low grip strength (measured using a JAMAR dynamometer [Performance Health Canada, China]), was defined as being in the lowest two quintiles of grip strength in the overall population.[12] Presence of household air pollution was defined as primarily using kerosene or solid fuel for cooking.[12]

Lipid measures included total cholesterol, triglycerides, LDL particles (LDL cholesterol), HDL particles (HDL cholesterol), the ratio of total cholesterol to HDL particles, ApoA1, ApoB, and their ratio (ApoB:ApoA1). Presence of elevated total cholesterol was defined as a fasting blood cholesterol concentration of at least 5·2 mmol/L. Presence of elevated triglycerides was defined as a fasting blood triglyceride concentration of at least 1·7 mmol/L. Presence of elevated LDL cholesterol was defined as a fasting concentration of at least 3·4 mmol/L.

Outcomes

The primary outcome of this study was major cardiovascular disease, which was a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure. Secondary outcomes were each of cardiovascular disease death, myocardial infarction, and stroke. Heart failure was not included as a secondary outcome because relatively few participants developed incident heart failure during follow-up.

Statistical analysis

We present continuous variables as means (SD) and categorical variables as counts and proportions. We used direct standardisation, according to the age and sex distribution of the PURE cohort, to calculate age-standardised incidence rates with corresponding 95% CIs (per 1000 person-years) for cardiovascular events. We estimated the mean and 95% CI levels of metabolic risk factors (ie, systolic blood pressure, fasting plasma glucose concentrations, waist-to-hip ratio, non-HDL cholesterol) and blood lipids (ie, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol:HDL cholesterol ratio, ApoA1, ApoB, and ApoB:ApoA1 ratio) separately for women and men using multilevel

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See Online for appendix

	Women (n=90 934)	Men (n=64 790)
Sociodemographic characteristics		
Mean (SD) age, years	49·8 (9·7)	50·8 (9·8)
Living in high-income or upper-middle-income country*	33 923 (37·3%)	24 347 (37·6%)
Living in low-income or lower-middle-income country†	57 011 (62·7%)	40 443 (62·4%)
Living in rural community	42 520 (46·8%)	31 150 (48·1%)
Number of events		
Major cardiovascular disease	4280 (4·7%)	4911 (7·6%)
Myocardial infarction	1794 (2·0%)	2490 (3·8%)
Stroke	2126 (2·3%)	2108 (3·3%)
Cardiovascular disease death	1563 (1·7%)	2072 (3·2%)
Age-standardised incidence rate (95% CI) per 1000 person-years		
Major cardiovascular disease	5·0 (4·9–5·2)	8·2 (8·0–8·4)
Myocardial infarction	2·1 (2·0–2·2)	4·1 (4·0–4·3)
Stroke	2·5 (2·4–2·6)	3·5 (3·3–3·6)
Cardiovascular disease death	1·8 (1·7–1·9)	3·4 (3·3–3·6)

Data are n (%), unless otherwise stated. Major cardiovascular disease is a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure. *Includes Argentina, Brazil, Canada, Chile, Malaysia, Poland, Saudi Arabia, South Africa, Sweden, Türkiye, and United Arab Emirates. †Includes Bangladesh, China, Colombia, India, Iran, Pakistan, Palestine, Philippines, Tanzania, and Zimbabwe.

Table 1: **Baseline characteristics, number of events, and incidence rates during follow-up**

mixed-effects linear regression models. We adjusted these models for age, urban or rural residence, education level, smoking status, and physical activity. We additionally adjusted systolic blood pressure for waist-to-hip ratio, and the use of blood pressure-lowering medicines. We additionally adjusted fasting plasma glucose concentrations for glucose-lowering medicines and blood lipid concentrations for use of lipid-lowering medicines. In the multilevel structure of the linear regression models, we considered that the individual participant was nested in a centre and considered each centre as a random intercept effect. After each multilevel mixed-effects linear regression model, we then obtained the adjusted means holding age fixed at three levels: age 35–44 years, 45–54 years, and 55–70 years.

We used shared frailty Cox proportional hazards models to estimate the hazard ratio (HR) for each risk factor with cardiovascular disease outcomes, with interaction terms between each variable and sex.[15] Centre was specified as a random intercept to account for within-centre clustering of participants. We adjusted these models for age, urban or rural residence, and the use of lipid-lowering medicines, and they were mutually adjusted for other relevant risk factors. We additionally adjusted smoking for pack-years of smoking.[16] We also estimated the HR for each risk factor with major cardiovascular disease by countries grouped by income level, combining high-income and upper-middle-income countries, and low-income and lower-middle-income countries. Additional details of models are in the appendix (pp 26–28). We assessed the proportionality of hazards by visual inspection of log-log survival plots. $P_{interaction}$ values were calculated using likelihood ratio tests. Given the multiplicity of comparisons, p values should be interpreted cautiously, except when they are small (eg, $p<0·01$) or consistent across several different related analyses.

In a post-hoc sensitivity analysis, we estimated the HR for each risk factor with major cardiovascular disease in the subgroup of individuals aged 50 years and younger, and older than 50 years. Post hoc, we also did multiple imputations by chained equations for missing blood lipids, household air pollution, and grip strength using the method of multiple imputations by chained equations with ten imputations for each missing variable. We also did a competing risks regression analysis for major cardiovascular disease, with death unrelated to cardiovascular disease as the competing risk. These results are presented as subdistribution HRs and corresponding 95% CIs. Other post-hoc sensitivity analyses were estimating the HR for each risk factor with major cardiovascular disease: (1) when major cardiovascular disease excluded incident heart failure from the composite outcome; (2) in the subset of participants not taking lipid-lowering medicines at baseline; (3) for different cutoffs of non-HDL cholesterol; and (4) when current alcohol consumption was further categorised into low, moderate, and high intake.

We calculated the population-level risk attributable for 12 risk factors (hypertension, abdominal obesity, diabetes, non-HDL cholesterol, smoking, alcohol consumption, physical activity, diet, symptoms of depression, education, grip strength, and household air pollution) using the approach described by Eide and Gefeller[17] and the averisk R package developed by Ferguson and colleagues.[18] Population-attributable fractions (PAFs) and associated 95% CIs quantify the proportional reduction in disease prevalence that would be achieved if the risk factor is theoretically removed from the population.

We used R (version 4.2.1) to estimate PAFs and STATA (version 16.0) for all other analyses. The PURE study is registered with ClinicalTrials.gov, NCT03225586.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or submitting of the report for publication.

Results

In the current analysis, we included data for 155724 individuals enrolled and followed up between Jan 5, 2005, and Sept 13, 2021, including 90934 (58·4%) women and 64790 (41·6%) men (appendix p 16). The

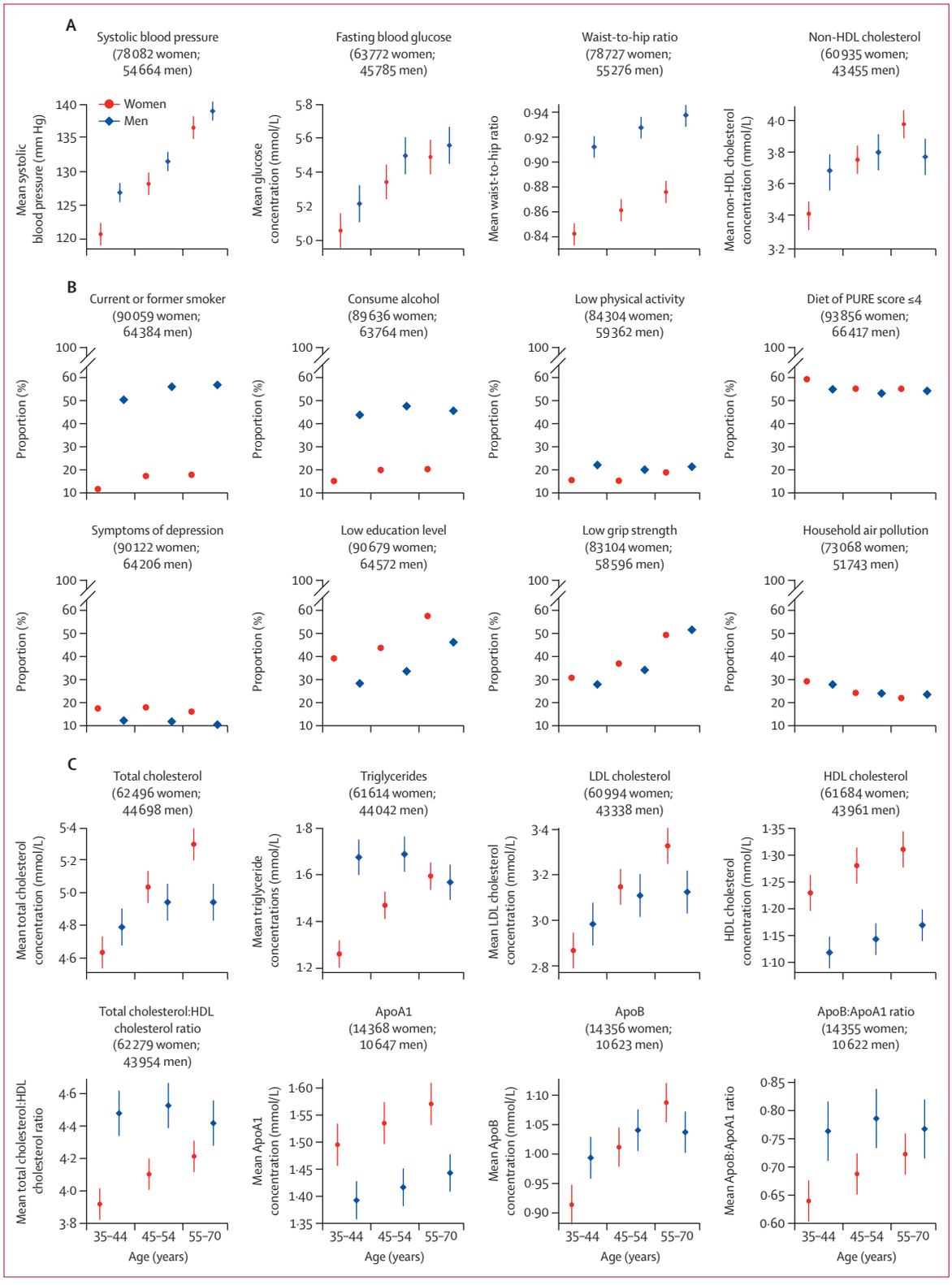

Figure 1: **Mean levels of risk factors at baseline by age category in women and men**
(A) Metabolic risk factors. (B) Behavioural, psychosocial, physical, and environmental risk factors. (C) Lipid concentrations and lipid ratios. Datapoints are means, with error bars showing 95% CIs; 95% CIs for part B are shown in the appendix (p 59) because they were too narrow to be seen clearly on the figure. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B.

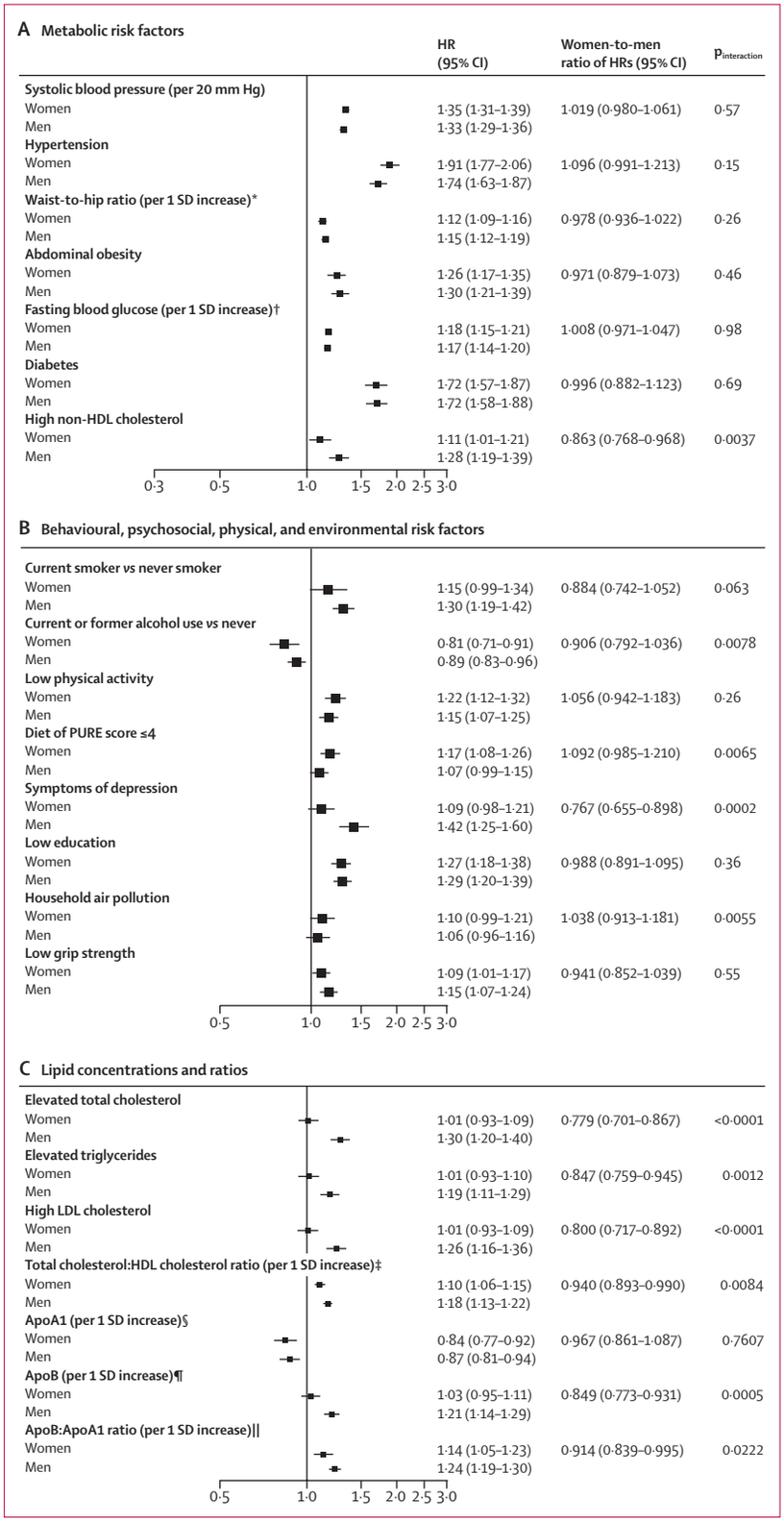

Figure 2: **Associations between metabolic risk factors (A); behavioural, psychosocial, physical, and environmental risk factors (B); and lipid concentrations and ratios (C) and cardiovascular disease in women *vs* men**
Major cardiovascular disease is a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure. p values are based on tests of interaction using a likelihood ratio test. HR=hazard ratio. ApoA1=apolipoprotein A1. ApoB=apolipoprotein B. *1 SD increase in waist-to-hip ratio is 0·09. †1 SD increase in fasting blood glucose is 1·8 mmol/L. ‡1 SD increase in total cholesterol:HDL cholesterol ratio is 1·18. §1 SD increase in ApoA1 is 0·34. ¶1 SD increase in ApoB is 0·28. ||1 SD increase in ApoB:ApoA1 ratio is 0·27.

median follow-up was 10·1 years (IQR 8·5–12·0) and the mean age at baseline was 49·8 years (SD 9·7) in women and 50·8 years (9·8) in men (table 1). A similar proportion of women and men lived in high-income or upper-middle-income countries, low-income or lower-middle-income countries, and in rural communities. As of data cutoff (Sept 13, 2021), 4280 (4·7%) women and 4911 (7·6%) men had major cardiovascular disease events. The age-standardised incidence rate of major cardiovascular disease was 5·0 (95% CI 4·9–5·2) per 1000 person-years in women and 8·2 (8·0–8·4) per 1000 person-years in men.

Mean systolic blood pressure increased with age in both sexes; however, the mean levels tended to be lower in women than in men within each age group (figure 1A). Similarly, fasting plasma glucose concentrations increased with age in both sexes and was slightly lower in women than in men until age 55–70 years. Mean waist-to-hip ratios were consistently lower in women than in men in all age categories. By contrast, the mean concentrations of non-HDL cholesterol increased with age in women, but not in men.

A higher proportion of men than women were current or former smokers, consumed alcohol, and had low physical activity (figure 1B). By contrast, a higher proportion of women than men had symptoms of depression and low educational status in all three age categories. A similar proportion of women and men consumed a diet with a PURE score of 4 or less, had low grip strength, and were exposed to household air pollution.

In women, the mean concentrations of all lipids and lipid ratios increased with increasing age. This pattern was not observed in men. The mean concentrations of total cholesterol, LDL cholesterol, and ApoB were higher for men than for women for the age 35–44 years group, and were similar between the sexes in the age 45–54 years group, but higher for women than for men in the age 55–70 years group. By contrast, triglycerides, the total cholesterol:HDL cholesterol ratio, and the ApoB:ApoA1 ratio were substantially higher in men than in women aged 35–44 years and 45–54 years, but quite similar in women and men aged 55–70 years.

Associations of each risk factor with incident major cardiovascular disease in women and men are shown in figure 2. High non-HDL cholesterol was more strongly associated with major cardiovascular disease in men than in women, whereas the HRs for other metabolic risk

factors were similar among women and men (figure 2A). A diet score of 4 or less was more strongly associated with cardiovascular disease in women than in men (figure 2B). By contrast, symptoms of depression were more strongly associated with cardiovascular disease in men than in women, with the HRs for symptoms of depression being higher in men than in women (figure 2B). The HRs of other behavioural and psychosocial risk factors, as well as grip strength and household air pollution, were similar among women and men. Larger HRs for major cardiovascular disease were observed in men than women for elevated total cholesterol, elevated triglycerides, high LDL cholesterol, and total cholesterol:HDL cholesterol ratio (per 1 SD increase; figure 2C). ApoB (per 1 SD increase) was also more strongly associated with major cardiovascular disease in men than in women. By contrast, the association of ApoA1 (per 1 SD increase) with major cardiovascular disease was similar in women and in men (figure 2C). Results of the post-hoc sensitivity analyses are shown in the appendix (pp 44–57). Post-hoc sensitivity analysis of the associations of each risk factor with incident major cardiovascular disease in the subgroup of participants aged 50 years and younger compared with those older than 50 years did not materially alter our findings (appendix pp 42–44), nor did the imputations for missing values (appendix pp 54–56). The patterns by sex for the adjusted subdistribution HR from competing risk regression were similar to the adjusted HR from the shared frailty Cox proportional hazards models (appendix pp 49–50).

Similar patterns of associations between women and men for risk factors and major cardiovascular disease were observed in high-income and upper-middle-income countries and in low-income and lower-middle-income countries (appendix p 29–31).

Approximately 58·0% (95% CI 52·4–63·6) of the PAFs for cardiovascular disease were attributed to the measured risk factors in women and 65·4% (61·0–69·7) in men (table 2). Among the metabolic risk factors, hypertension contributed substantially and similarly to the risk of major cardiovascular disease in women and men, followed by abdominal obesity in women and high non-HDL cholesterol in men. Among the behavioural and psychosocial risk factors, diet had the largest contribution to the overall PAFs in women, whereas current smoking had the largest contribution in men. By contrast, alcohol consumption (current or former) contributed to negative PAF in both women and men, given the reduced risk associated with alcohol consumption and major cardiovascular disease.[19] Household air pollution also had an important contribution to the overall PAFs, which was larger for women than for men. For the secondary outcomes, the age-standardised incidence rates per 1000 person-years of myocardial infarction, stroke, and cardiovascular disease-related death are shown in table 1.

The associations between women and men for risk factors and myocardial infarction followed a pattern similar to the results for major cardiovascular disease, with the exceptions of systolic blood pressure (per 20 mm Hg), hypertension, and household air pollution, for which larger HRs were observed in women than in men (appendix pp 32–34). The HRs for a 20 mm Hg increase in systolic blood pressure were 1·28 (95% CI 1·23–1·35) in women versus 1·21 (1·15–1·26) in men (women-to-men ratio of HRs: 1·07 [95% CI 1·00–1·13]; $p_{interaction}$=0·014), for hypertension the HRs were 1·73 (95% CI 1·54–1·95) in women versus 1·43 (1·29–1·58) in men (women-to-men ratio of HRs: 1·21 [95% CI 1·04–1·41]; $p_{interaction}$=0·0074), and for household air pollution the HRs were 1·24 (95% CI 1·06–1·46) in women versus 0·97 (0·84–1·12) in men (women-to-men ratio of HRs: 1·28 [95% CI 1·05–1·56]; $p_{interaction}$<0·0001). By contrast, for incident stroke, the associations of all risk factors were of similar magnitude in women and men (appendix pp 35–37). Similar magnitudes of association in women and men were also observed for cardiovascular disease death (appendix pp 38–40), except for elevated total cholesterol, for which smaller HRs were observed in women than in men (0·92 [95% CI 0·79–1·05] *vs* 1·23 [1·08–1·39]; women-to-men ratio of HRs: 0·75 [95% CI 0·62–0·90]; $p_{interaction}$=0·0018).

Approximately 69·1% (95% CI 62·1–76·2) of the PAFs in women and 68·3% (61·3–75·3) in men for myocardial

	Women	Men
Metabolic risk factors		
Hypertension	23·3% (20·6 to 26·0)	23·1% (20·1 to 26·2)
Abdominal obesity	8·8% (5·5 to 12·2)	4·0% (1·0 to 7·1)
Diabetes	4·6% (3·4 to 5·9)	4·4% (3·2 to 5·6)
High non-HDL cholesterol	3·2% (–0·6 to 7·1)	8·6% (4·4 to 12·7)
Total	39·9% (36·4 to 43·4)	40·1% (35·7 to 44·5)
Behavioural, psychosocial, physical, and environmental risk factors		
Behavioural and psychosocial		
Current smoker	1·3% (0·5 to 2·1)	10·7% (8·8 to 12·6)
Alcohol consumption (current or former)	–5·0% (–6·4 to –3·6)	–5·4% (–8·0 to –2·8)
Low physical activity	2·1% (0·8 to 3·5)	0·8% (–0·3 to 2·0)
Diet of PURE score of ≤4	6·5% (3·3 to 9·8)	4·8% (2·3 to 7·3)
Symptoms of depression	–1·1% (–2·0 to –0·1)	0·7% (–0·1 to 1·5)
Low education	4·6% (1·7 to 7·5)	4·1% (2·4 to 5·9)
Total	8·4% (2·9 to 13·9)	15·7% (10·4 to 21·0)
Low grip strength	1·2% (–1·1 to 3·6)	3·6% (1·3 to 5·9)
Household air pollution	8·3% (6·4 to 10·3)	5·9% (3·9 to 7·9)
Total	58·0% (52·4 to 63·6)	65·4% (61·0 to 69·7)

Data are population-attributable fractions with 95% CIs in parentheses. Major cardiovascular disease is a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure.

Table 2: **Population-attributable fractions for 12 risk factors with major cardiovascular disease in women and men**

infarction, 47·1% (38·2–56·0) in women and 63·1% (56·2–70·0) in men for stroke, and 79·3% (73·1–85·5) in women and 82·5% (78·5–86·5) in men for cardiovascular disease death were attributed to the measured risk factors (appendix p 41).

Of the metabolic risk factors, hypertension had the largest contribution to the overall PAFs in women for myocardial infarction (15·2% in women *vs* 10·1% in men), whereas in men, the largest contributor was high non-HDL cholesterol (10·4% in women *vs* 17·4% in men). For stroke and cardiovascular disease death, hypertension was the largest contributing risk factor in both women and men (29·5% in women *vs* 33·5% in men for stroke; 21·1% in women *vs* 20·3% in men for cardiovascular disease death; appendix p 41). Of the behavioural and psychosocial risk factors, in women, diet was the largest contributing risk factor for myocardial infarction (7·6% in women *vs* 0·4% in men) and stroke (6·5% in women *vs* 9·3% in men), and low education was the largest contributing risk factor for cardiovascular disease death (11·6% in women *vs* 10·3% in men). By contrast, in men, smoking was the largest contributing behavioural and psychosocial risk factor for myocardial infarction (3·0% in women *vs* 13·1% in men), stroke (–0·4% in women *vs* 9·8% in men), and cardiovascular disease death (2·2% in women *vs* 11·1% in men). Household air pollution also had important contributions to overall PAFs in both women and men for myocardial infarction (8·9% in women *vs* 3·0% in men), stroke (8·7% in women *vs* 9·6% in men), and cardiovascular disease death (9·9% in women *vs* 6·3% in men).

Discussion

Our study has four major findings. First, women have a more favourable cardiovascular risk profile than do men, especially at younger ages. This finding was supported by lower rates of incident major cardiovascular disease in women than in men. Second, despite sex differences in risk factor levels at baseline, the magnitude of the associations with major cardiovascular disease for most risk factors were similar in women and in men. Third, high concentrations of non-HDL cholesterol, and of related lipids, and symptoms of depression were more strongly associated with the risk of cardiovascular disease in men than in women. By contrast, diet was more strongly associated with the risk of cardiovascular disease in women than in men. Finally, the patterns of these findings were generally similar in high-income countries and upper-middle-income countries, and in low-income and lower-middle-income countries.

We observed that men had higher levels of metabolic risk factors than did women in younger age groups (ie, younger than 55 years). This implies that efforts at risk factor control should be initiated at an even younger age in men than in women. Findings similar to our observations were reported by Jousilahti and colleagues[20] in their analysis of risk factors (ie, smoking, serum total cholesterol, HDL cholesterol, blood pressure, BMI, and diabetes) and coronary heart disease in a Finnish cohort. A higher risk factor burden among men than women at younger ages (ie, <60 years) was also reported in the INTERHEART study.[21] The increases in the mean levels of some risk factors (eg, lipid ratios) observed in women at older ages have been postulated to be due to decreases in endogenous oestrogen that occur during natural menopause. Studies that followed up women who were pre-menopausal or peri-menopausal at the initial examination, reported increases in total cholesterol, LDL cholesterol, and ApoB after menopause that were more substantial than could be attributable to age alone.[22] However, the importance of menopause as an independent risk factor of cardiovascular disease remains uncertain.[23] Examining the role of menopause independent of ageing is beyond the scope of the current analysis. As the mean age of populations increase, and with the increased lifespans of women, differences in the levels of cardiovascular disease risk factors and rates of cardiovascular disease events between women and men might lessen in older individuals.

We found that high concentrations of total cholesterol, triglycerides, high LDL cholesterol, and ApoB (per 1 SD increase), and the ratio of total cholesterol to HDL cholesterol (per 1 SD increase) were more strongly associated with cardiovascular disease in men than in women. Larger HRs for lipids in men than for women were also observed in the subgroup of participants aged 50 years and younger and those who were older than 50 years. A systematic review of cohort studies of total cholesterol with cardiovascular disease also reported a significantly stronger association in men than in women when comparing the highest total cholesterol category to the lowest (relative risk of 1·55 [95% CI 1·37–1·76] in women *vs* 1·77 [1·58–1·99] in men; women-to-men relative risk ratio: 0·87 [95% CI 0·79–0·96]).[24] Although elevated total cholesterol (and its individual components) and elevated triglycerides were associated with an increased risk of myocardial infarction in both women and men (with larger HRs in men than in women), they were not associated with an increased risk of stroke or cardiovascular disease death in women. In a systematic review of cohort studies, Peters and colleagues[24] also found no association between total cholesterol and risk of stroke in women. Moreover, a meta-analysis of 22 trials of statin therapy[25] reported that, in individuals without a history of cardiovascular disease, a 1 mmol/L reduction in LDL cholesterol reduced cardiovascular disease events by 15% in women and 28% in men ($p_{heterogeneity}$=0·02),[25] which is consistent with our findings. Furthermore, the GBD study recently reported that the total disability-adjusted life-years due to LDL cholesterol in 2019 were significantly higher in men than in women, and that they were especially high in men younger than 65 years.[6] Taken together, these findings suggest that lipid levels are stronger risk factors in men than in women and suggest

that more effort is needed to reduce lipid levels in men, especially those who are relatively younger.

We found that the magnitude of association of most other metabolic risk factors with incident major cardiovascular disease were generally similar in women and men. Millett and colleagues[2] reported higher HRs for systolic blood pressure, hypertension, and diabetes with incident myocardial infarction in women than in men using data from the UK Biobank Study, a prospective cohort study of women and men aged 40–69 years from the UK who had been followed up for 7 years. Similarly, Anand and colleagues[21] reported that self-reported hypertension and diabetes were more strongly associated with myocardial infarction in women than in men in the INTERHEART study. We also found that systolic blood pressure and hypertension are more strongly associated with incident myocardial infarction in women than in men; however, we did not observe between-sex differences for the association of diabetes or fasting plasma glucose concentrations with major cardiovascular disease. In studies where the presence of diabetes was self-reported and also by using actual measurements, the associations with cardiovascular disease were stronger among women than among men only for those with self-reported diabetes, and not for those with actual measurements. For instance, although de Jong and colleagues[26] found self-reported diabetes to be more strongly associated with myocardial infarction in women than in men using the UK Biobank cohort, sex differences were not observed when examining the association of glycated haemoglobin with myocardial infarction in the same cohort. Using data from the China Kadoorie Biobank, Bragg and colleagues[27] reported a higher rate ratio of self-reported diabetes with cardiovascular disease death in women than men (rate ratio: 2·72 [95% CI 2·49–2·98] in women *vs* 1·93 [1·77–2·10] in men), but did not find significant sex differences when assessing the association of screening-detected diabetes with cardiovascular disease death (1·91 [1·70–2·14] in women *vs* 1·79 [1·59–2·02] in men). The absence of a sex difference in the association of fasting plasma glucose concentrations with cardiovascular disease we observed in PURE is consistent with these previous studies. The stronger association described in previous studies for self-reported diabetes and cardiovascular disease in women than in men might be driven by differences in the rates of diagnosis and differences in health-seeking behaviour between sexes, whereby women are more likely to have their diabetes detected than are men.

We have previously reported a stronger association between symptoms of depression and cardiovascular disease in men than in women,[14] which has also been observed by others.[28] By contrast, the stronger association of diet quality and risk of cardiovascular disease in women than in men has not been previously described, but few large studies have examined this before. Previous studies, mostly from high-income countries, have suggested that poor diet is associated with increased risk of cardiovascular disease in both sexes.[29] Our observations require independent replication in large prospective studies conducted in multiple countries.

Alcohol consumption (current or former) was associated with a reduced risk of major cardiovascular disease in both women and men, and contributed a negative PAF for major cardiovascular disease. We previously reported the protective effects of alcohol consumption with cardiovascular disease, whereas excess alcohol consumption was associated with an increased risk of alcohol-related cancers, injury, and mortality.[12,19] Therefore, the net health benefits of alcohol consumption should consider the potentially protective effects of moderate alcohol consumption alongside harmful effects of excess consumption associated with other clinical outcomes.

The significantly higher PAF associated with smoking in men than in women is a result of the higher prevalence of smoking in men. We did not observe significant sex differences in the HRs for smoking, which is in contrast with the conclusions of a systematic review and meta-analysis[5] of mostly prospective cohort studies in high-income countries in which smoking in women was associated with a 25% greater relative risk of coronary heart disease than in men. Studies from high-income countries using more contemporaneous populations have also reported larger HRs for cardiovascular disease in women who smoked than in men who smoked.[2,30] By contrast, a case-control study of 1·1 million homes in India reported similar risk ratios of death due to heart disease in women (1·7 [95% CI 1·3–2·1]) and in men (1·6 [1·5–1·8]).[31] Furthermore, data from the Framingham Heart Study Offspring Cohort[32] showed consistently larger HRs in men who smoked than in women who smoked over a 30 year observation period (1976–2006). We recently reported that smokers in high-income countries started smoking at younger ages and smoked more products per day and for a longer duration than smokers in middle-income and low-income countries.[16] The heterogeneity in conclusions across studies might reflect the distinct smoking behaviours in women and men from different regions of the world, rather than differential biological effects, as has been argued by some.[33] The well established harmful effects of smoking highlight the importance of initiatives aimed at increasing smoking cessation rates and decreasing initiation rates in all smokers, irrespective of biological sex.

Our study has some limitations. First, in our analysis we used risk factors measured at baseline and did not account for changes in the risk factors over time, which might have introduced time-varying confounding to our estimates. However, studies in which repeated measures of risk factors are available have generally found the same pattern of association of the risk factor with cardiovascular disease,[32] although the associations are stronger in analyses that include repeat measures.[34] We do not expect this limitation to materially affect the differential effect of risk factors on cardiovascular disease between women and

men. Furthermore, we report HRs, but HRs are conditional on the observations still under risk at each timepoint, and therefore they are conditional on survival. However, given the relatively low mortality rates (less than 10% over 10 years), we expect there would be little effect on mortality as a competing issue. Second, there were too few events to examine the association between each risk factor separately in women and men within several geographical regions. With additional follow-up in the PURE study, we expect to be able to provide more robust results within most geographical regions over the next 5–10 years. Third, we are unable to discriminate between ST-elevation myocardial infarction and non-ST-elevation myocardial infarction. However, we are not aware of any previous data indicating that the associations of risk factors in women compared with men vary according to the type of acute coronary syndrome. Fourth, relatively few participants developed heart failure during follow-up (ie, <1300 incident cases), and so analyses of heart failure subdivided by sex and by country economic groups would be unreliable. Fifth, although most risk factors were measured using validated methods, measurement error is possible, especially when data are self-reported. Given the observational nature of our study, our empirical approach might not have accounted for all sources of bias that could result in unmeasured confounding. Additionally, model misspecification might have occurred. Sixth, some participants had missing data, but this proportion was low for most variables. Lipoprotein measurements (measured locally) to estimate non-HDL-cholesterol were available in 70% of participants. Apolipoproteins were only intended to be analysed in 20% of samples[35] that could be shipped frozen from countries to the central laboratory in Canada, because regulations in several countries prevented shipping samples internationally. The proportion of variables with missing values were similar in women and men (data not shown), and so little bias will have been introduced by the missing data. Moreover, imputations for missing values did not change our results.

In this global study, the risk associated with most risk factors of cardiovascular disease was similar in women and men. However, the PAF associated with elevated lipids and smoking were higher in men than in women. Although our results suggest that the higher risks of cardiovascular disease in men than in women can be substantially attenuated with improved reductions in tobacco use and lipids, these measures and control of all other risk factors is important for both women and men in high-income, middle-income, and low-income countries.

Contributors

SY designed the study, obtained the funding, and oversaw study conduct since its inception. MW-A wrote the analysis plan and did all study analyses. MW-A and SY wrote manuscript drafts. SR coordinated the worldwide study. SSA reviewed and commented on several drafts of the manuscript. All other authors coordinated the study in their respective countries, and all commented on drafts of the manuscript. MW-A, SR, and SY accessed and verified the underlying study data, and were responsible for the decision to submit the manuscript for publication. All country coauthors have access to their country data.

Declaration of interests

LMP-V received a grant from the Philippine Council for Health Research and Development to support this study. AW received funding support from the Population Health Research Institute for participation in the study as site principal investigator and is a member of the Board of Directors of the InterAmerican Heart Foundation. SSA received speaker and consulting fees from both Bayer AG and Janssen Pharma for work conducted outside the scope of this study. All other authors declare no competing interests.

Data sharing

The Population Health Research Institute (PHRI) is the sponsor of this study. The PHRI believes the dissemination of research results is vital and sharing of data is important. PHRI prioritises access to data to researchers who have worked on the PURE study for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the study. Data will be disclosed to these individuals upon request for specific proposals after review and approval of the proposed use of the data by a PURE Review Committee. Specific collaborative projects may be developed with external groups with similar data for joint analyses as long as there is an exchange of data and the proposal enhances the findings from PURE. The underlying data for this clinical study contain personal information and personal health information of participants who were involved, which is protected under Canada's privacy laws, the Health Insurance Portability and Accountability Act of 1996 (USA) and General Data Protection Regulation, among other international laws governing privacy. Consent for public disclosure of this information was not obtained and could pose a threat to confidentiality and violate privacy laws. Therefore, sharing of individual data is usually not possible, except for with PURE investigators. PHRI has no objection to sharing the information under confidentiality and with appropriate data protection and privacy. PHRI follows this procedure and does not share or link data from clinical studies publicly when such data are or contain personal health information. Requests for access to informationa can be sent to the PURE Publications Committee and the PHRI study project office (phri.contracts@phri.ca).

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