Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

Marjan Walli-Attaei, Philip Joseph, Annika Rosengren, Clara K Chow, Sumathy Rangarajan, Scott A Lear, Khalid F AlHabib, Kairat Davletov, Antonio Dans, Fernando Lanas, Karen Yeates, Paul Poirier, Koon K Teo, Ahmad Bahonar, Felix Camilo, Jephat Chifamba, Rafael Diaz, Joanna A Didkowska, Vilma Irazola, Rosnah Ismail, Manmeet Kaur, Rasha Khatib, Xiaoyun Liu, Marta Mańczuk, J Jaime Miranda, Aytekin Oguz, Maritza Perez-Mayorga, Andrzej Szuba, Lungiswa P Tsolekile, Ravi Prasad Varma, Afzalhussein Yusufali, Rita Yusuf, Li Wei, Sonia S Anand, Salim Yusuf

Summary

Background Some studies, mainly from high-income countries (HICs), report that women receive less care (investigations and treatments) for cardiovascular disease than do men and might have a higher risk of death. However, very few studies systematically report risk factors, use of primary or secondary prevention medications, incidence of cardiovascular disease, or death in populations drawn from the community. Given that most cardiovascular disease occurs in low-income and middle-income countries (LMICs), there is a need for comprehensive information comparing treatments and outcomes between women and men in HICs, middle-income countries, and low-income countries from community-based population studies.

Methods In the Prospective Urban Rural Epidemiological study (PURE), individuals aged 35–70 years from urban and rural communities in 27 countries were considered for inclusion. We recorded information on participants' sociodemographic characteristics, risk factors, medication use, cardiac investigations, and interventions. 168 490 participants who enrolled in the first two of the three phases of PURE were followed up prospectively for incident cardiovascular disease and death.

Findings From Jan 6, 2005 to May 6, 2019, 202 072 individuals were recruited to the study. The mean age of women included in the study was 50·8 (SD 9·9) years compared with 51·7 (10) years for men. Participants were followed up for a median of 9·5 (IQR 8·5–10·9) years. Women had a lower cardiovascular disease risk factor burden using two different risk scores (INTERHEART and Framingham). Primary prevention strategies, such as adoption of several healthy lifestyle behaviours and use of proven medicines, were more frequent in women than men. Incidence of cardiovascular disease (4·1 [95% CI 4·0–4·2] for women *vs* 6·4 [6·2–6·6] for men per 1000 person-years; adjusted hazard ratio [aHR] 0·75 [95% CI 0·72–0·79]) and all-cause death (4·5 [95% CI 4·4–4·7] for women *vs* 7·4 [7·2–7·7] for men per 1000 person-years; aHR 0·62 [95% CI 0·60–0·65]) were also lower in women. By contrast, secondary prevention treatments, cardiac investigations, and coronary revascularisation were less frequent in women than men with coronary artery disease in all groups of countries. Despite this, women had lower risk of recurrent cardiovascular disease events (20·0 [95% CI 18·2–21·7] versus 27·7 [95% CI 25·6–29·8] per 1000 person-years in men, adjusted hazard ratio 0·73 [95% CI 0·64-0·83]) and women had lower 30-day mortality after a new cardiovascular disease event compared with men (22% in women versus 28% in men; p<0·0001). Differences between women and men in treatments and outcomes were more marked in LMICs with little differences in HICs in those with or without previous cardiovascular disease.

Interpretation Treatments for cardiovascular disease are more common in women than men in primary prevention, but the reverse is seen in secondary prevention. However, consistently better outcomes are observed in women than in men, both in those with and without previous cardiovascular disease. Improving cardiovascular disease prevention and treatment, especially in LMICs, should be vigorously pursued in both women and men.

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Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (M Walli-Attaei PhD, P Joseph MD, S Rangarajan MSc, Prof K K Teo PhD, Prof S S Anand MD, Prof S Yusuf DPhil); **Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof A Rosengren MD); **The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia** (Prof C K Chow PhD); **Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada** (Prof S A Lear PhD); **Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia** (K F AlHabib MBBS); **The Faculty of Medicine, Health Research Institute, Kazakh National University, Almaty, Kazakhstan** (Prof K Davletov PhD); **Department of Medicine, University of Philippines, Manila, Philippines** (Prof A Dans MD); **Department of Medicine, Universidad de La Frontera, Temuco, Chile**

Introduction

Over the past two decades, substantial efforts have been made to improve the cardiovascular health of women under the assumption that women with cardiovascular disease are managed less aggressively than men. Several campaigns, coalitions, and programmes[1,2] have been

(Prof F Lanas PhD); **Department of Medicine, Queen's University, Kingston, ON, Canada** (K Yeates MD); **Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec City, QC, Canada** (Prof P Poirier MD); **Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran** (A Bahonar PhD); **Facultad de Ciencias Medicas Eugenio Espejo, Universidad Universidad Tecnológica Equinoccial, Quito, Ecuador** (F Camilo MD); **Physiology Department, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe** (J Chifamba DPhil); **Estudios Clinicos Latinoamerica, Rosario, Argentina** (R Diaz MD); **Department of Epidemiology and Cancer Prevention, The Maria Sklodowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland** (Prof J A Didkowska PhD, M Mańczuk PhD); **Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina** (V Irazola MD); **South American Center of Excellence for Cardiovascular Health, Buenos Aires, Argentina** (V Irazola); **Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia, Medical Center, Kuala Lumpur, Malaysia** (R Ismail DrPh); **School of Public Health, Post Graduate Institute of Medical Education & Research, Chandigarh, India** (Prof M Kaur PhD); **Institute for Community and Public Health, Birzeit University, Birzeit, Palestine** (R Khatib PhD); **State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China** (X Liu PhD); **Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru** (J J Miranda PhD); **Department of Internal Medicine, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey** (A Oguz MD); **Facultad de Medicina, Universidad Nueva Granada and Clinica de Marly, Bogota, Colombia** (M Perez-Mayorga MD); **Wroclaw Medical University,**

Research in context

Evidence before this study

We searched the MEDLINE database, without language or publication date restrictions, for estimates of differences between women and men in cardiovascular disease risk factors, incidence, deaths, and use of treatments on Sept 15, 2019, and again on Nov 30, 2019. Our search terms were "gender" OR "sex" OR "women" AND "cardiovascular" OR "coronary heart disease" OR "coronary artery disease" OR "risk factor" OR "revascularization" OR "percutaneous coronary intervention" OR "coronary artery bypass grafting" OR "primary prevention" OR "statin" OR "secondary prevention".

Studies have emphasised that women are less likely to undergo revascularisation procedures and receive fewer guideline recommended therapies than men upon having a cardiovascular disease event. These findings, when viewed in isolation, have raised concerns that women are disadvantaged when it comes to cardiovascular disease care. However, much of the existing evidence was from North America and Europe, and most of the published literature are based on hospital registries, outpatient clinics, or administrative databases. We did not find any comprehensive report on differences between women and men in risk factors, management, and outcomes in those with and without a history of cardiovascular disease drawn from community-based populations.

Added value of this study

We systematically examine differences in risk factors, treatments, cardiovascular disease incidence, and mortality in a large population with and without previous cardiovascular disease between women and men from high-income, middle-income, and low-income countries. Our findings indicate that the cardiovascular disease risk factor burden is lower in women; this is consistent across countries at all economic levels and geographical regions. Moreover, primary prevention strategies are used more frequently in women than in men, and are accompanied by lower incidence of cardiovascular disease and mortality. By contrast, use of secondary prevention treatments, cardiac investigations, and coronary interventions, are less frequent in women than in men, but are not associated with a higher rate of recurrent cardiovascular disease or death in women over a median follow-up time of 9·5 (IQR 8·5–10·9) years. The differences in treatments and in outcomes in both women and men from low-income and middle-income countries compared with high-income countries are much larger than the differences between sexes globally or within groups of countries.

Implications of all the available evidence

Although there are contrasting patterns in the differences in treatment rates between women and men in those with and without previous cardiovascular disease, our data indicate that women do not have worse cardiovascular disease outcomes compared with men. The differences in cardiovascular disease incidence, death, and use of treatments in both women and men between high-income compared with low-income and middle-income countries, and North America and Europe versus other regions is much larger. Understanding and narrowing these gaps deserve greater attention.

initiated to improve awareness, advocacy, and research related to reducing the cardiovascular disease burden and to implement delivery care models and guidelines[3,4] that are specific to women. Despite these efforts, reported differences in the cardiovascular disease burden, management, and outcomes between women and men remain. Although some studies report that women have lower age-standardised cardiovascular disease incidence, prevalence, and death rates than men,[5,6] there are also reports that women with cardiovascular disease receive less care,[7–9] fewer investigations,[7–9] and have poorer outcomes[9,10] after a coronary event. These reports have led to renewed calls for intensified efforts to improve care for women.[1,2,11] To date, a comprehensive report of cardiovascular disease risk factor burden, management, and outcomes in women and men with and without a history of cardiovascular disease drawn from a community-based population sample is not available. Such community-based studies are crucial because hospital registries, data from outpatient clinics, and administrative databases do not provide information on primary prevention strategies nor do they include information regarding cardiovascular events and deaths before hospitalisation. Moreover, studies on cardiovascular disease differences between women and men are mainly from high-income countries (HICs)—largely from North America and western Europe—with little data from other regions or low-income and middle-income countries (LMICs). Because the majority of cardiovascular disease deaths now occur in LMICs,[12] it is important to examine the differences between women and men regarding disease prevention, treatment, incidence, and related deaths globally.

The aims of this Article are to describe differences between women and men from all countries and separately in those from HICs, middle-income countries (MICs), and low-income countries (LICs). Moreover, women and men will be compared by regions with regard to the burden of cardiovascular disease risk factors; the incidence of major cardiovascular disease (cardiovascular deaths, myocardial infarction, strokes, heart failure, and other major cardiovascular disease events) and all-cause death; case-fatality rates after an incident cardiovascular disease event; the use of preventive medicines, risk factor control, and healthy lifestyle behaviours in those with and without a history of cardiovascular disease; and differences in the rates of cardiac investigations, revascularisation procedures, and recurrent cardiovascular disease events in those with coronary artery disease over the 9·5 year follow-up.

Methods

Study design and participants

The Prospective Urban Rural Epidemiological (PURE) study is a large international prospective cohort study of 202 072 women and men aged 35–70 years from 1030 communities living in 27 HICs, MICs, and LICs, across six geographical regions: Asia, Africa, Europe, South America, North America, and the Middle East. The inclusion and exclusion criteria remained the same as previous PURE Articles.[13]

Details of the study design, sampling, and recruitment have been previously published and are also described in the appendix (pp 7–12).[13] Briefly, participants were enrolled in three phases, which began in 2003. In phase one, 157 705 participants were recruited from 17 countries, with 10 785 participants recruited in phase two from an additional four countries, and 9321 participants recruited in phase three from four more countries. Data from two ongoing cohorts from South America were also included (n=24 261) in phase three. The participating countries and communities were selected with the aim of obtaining a socioeconomically diverse study sample while also ensuring feasibility of long-term follow-up. Households within communities were selected to be broadly representative of the sociodemographic composition of the communities they live in. We have previously shown that the characteristics and death rates of the enrolled participants were similar to their national populations.[14]

The 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 protocol and all participants provided informed written consent.[13]

Procedures

Standardised methods were used to collect information on cardiovascular disease risk factors.[13] Blood samples were drawn from each participant at baseline data collection and centrally analysed using validated and standardised methods analysed at Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada. Medicines taken by the participant at least once per week in the month before enrolment onto the study were recorded by direct inspection of medicines or prescriptions.

Follow-up occurred at least every 3 years, during which information on clinical events (major cardiovascular disease, myocardial infarction, stroke, heart failure, and all-cause death) was obtained from participants or family members of deceased participants. Follow-up data are currently available for 168 490 participants from phase one and two, with ongoing follow-up in all other participants. Events were adjudicated in each country using standardised definitions, verbal autopsies,[15] and review of additional documents (eg, medical records, and hospital or physician reports).[13] In this Article, we report on follow-up event data available until July 5, 2019, and the median follow-up time was 9·5 (IQR 8·5–10·9) years.

We summarised the overall risk-factor burden using the previously validated non-laboratory based INTERHEART[16,17] and the Framingham[18] risk scores. We documented the use of antiplatelet drugs, β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, hypertension control, and adoption of healthy lifestyle behaviours (such as the consumption of a healthy diet, being physically active, and smoking cessation)

Department of Angiology, Diabetology and Hypertension, Wroclaw, Poland (Prof A Szuba PhD); **University of the Western Cape, School of Public Health, Cape Town, South Africa** (L P Tsolekile PhD); **Health Action by People, Thiruvananthapuram, India** (R Prasad Varma MD); **Achutha Menon Centre for Health Science Studies, Sree Chitra**

	Women (n=119 799)	Men (n=82 273)	p value
Age, distribution, and disease history			
Age	50·8 (9·9)	51·7 (10·0)	p<0·0001
Living in rural communities (%)	51 706 (43·2%)	36 387 (44·2%)	p<0·0001
Living in a high-income country (%)	9679 (8·1%)	8481 (10·3%)	p<0·0001
Living in a middle-income country (%)	86 379 (72·1%)	55 711 (67·7%)	p<0·0001
Living in a low-income country (%)	23 741 (19·8%)	18 081 (22·0%)	p<0·0001
Previous cardiovascular disease (%)	6348 (5·3%)	5310 (6·5%)	p<0·0001
Behavioural, psychosocial, and socioeconomic risk factors			
Current smokers	11 839/118 647 (10·0%)	29 410/81 500 (36·1%)	p<0·0001
High physical activity*	47 925/111 116(43·1%)	34 153/75 586 (45·2%)	p<0·0001
Healthy diet†	30 400/90 245 (33·7%)	21 678/65 016 (33·3%)	p=0·16
Ever consume alcohol	28 786/113 312 (25·4%)	39 191/77 716 (50·4%)	p<0·0001
Probable depression‡	16 351/112 540 (14·5%)	6111/76 644 (8·0%)	p<0·0001
Low education§	50 886/110 842 (45·9%)	28 779/77 627 (37·1%)	p<0·0001
Physical measures and blood pressure, mean (SD)			
Body-mass index, kg/m² (n=190 800)	26·6 (5·6)	25·7 (4·9)	p<0·0001
Waist circumference, cm (n=190 851)	84·3 (13·9)	89·0 (13·6)	p<0·0001
Waist:hip ratio (n=182 985)	0·85 (0·08)	0·92 (0·08)	p<0·0001
Systolic blood pressure, mm Hg (n=189 905)	129·9 (22·3)	133·5 (20·8)	p<0·0001
Diastolic blood pressure, mm Hg (n=189 946)	80·9 (12·1)	82·7 (12·3)	p<0·0001
Lipids and blood glucose, mean (SD)			
Total cholesterol, mmol/L (n=142 428)¶	5·5 (10·6)	5·2 (9·0)	p<0·0001
Triglycerides, mmol/L (n=140 193)¶	1·7 (5·3)	1·9 (4·6)	p<0·0001
LDL-cholesterol, mmol/L (n=138 307)¶	3·2 (1·0)	3·1 (1·0)	p<0·0001
HDL-cholesterol, mmol/L (n=139 631)¶	1·3 (0·4)	1·2 (0·3)	p<0·0001
non-HDL-cholesterol, mmol/L (n=139 625)¶	3·8 (1·1)	3·7 (1·1)	p<0·0001
ApoB, µmol/dL (n=20 940)	1·01 (0·3)	1·03 (0·3)	p<0·0001
ApoA1, mol/dL (n=20 978)	1·6 (0·4)	1·4 (0·3)	p<0·0001
ApoB:ApoA1 ratio (n=20 935)	0·68 (0·24)	0·75 (0·29)	p<0·0001
Total cholesterol:HDL-cholesterol ratio (n=139 625)¶	4·2 (7·0)	4·6 (7·6)	p<0·0001
Fasting blood glucose, mmol/L (n=141 250)	5·3 (1·8)	5·4 (1·9)	p<0·0001

Data are n (%), n/N (%), or mean (SD). *High physical activity was defined as more than 3000 metabolic equivalents × min per week. †Healthy diet was defined as having an alternative healthy eating index score of more than 31 (index scores range from 6 to 70). ‡Probable depression was defined as having five or more symptoms of depression; diagnosis was made on the basis of responses to Short-Form International Diagnostic Interview Schedule for Major Depressive Disorder. §Low education level was defined as no education, primary education only, or unknown education level. ¶Fasting blood samples used.

Table 1: **Participant baseline characteristics**

Tirunal Institute for Medical Sciences and Technology, Trivandrum, India (R Prasad Varma); **Department of Medicine, Dubai Medical University, Hatta Hospital, Dubai Health Authority, Dubai, United Arab Emirates** (A Yusufali MD); **School of Life Sciences, Independent University, Dhaka, Bangladesh** (R Yusuf PhD); **and National Centre for Cardiovascular Diseases, Cardiovascular Institute & Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, China** (Prof L Wei PhD)

Correspondence to: Dr Marjan Walli-Attaei, Population Health Research Institute, Hamilton, ON L8L 2X2, Canada
walliam@mcmaster.ca

See Online for appendix

separately in 11 658 participants with known cardiovascular disease (defined as those reporting a history of coronary heart disease including angina, myocardial infarction, coronary artery disease, and stroke) and those without (190 414 participants). Hypertension control was assessed in participants with elevated systolic and diastolic blood pressures (>140/90 mm Hg). Use of glucose lowering agents was documented in participants with self-reported diabetes. Smoking and its cessation, diet (using the modified Alternative Healthy Eating Index[19]), and physical activity (using the long-form International Physical Activity Questionnaire[20]) were documented at baseline data collection. Probable depression was defined as having five or more symptoms of depression, defined on the basis of responses to a Short-Form International Diagnostic Interview Schedule for Major Depressive Disorder. In participants with coronary artery disease, we recorded the proportion of participants who underwent percutaneous coronary intervention, coronary artery bypass grafting, and underwent cardiac diagnostic tests (echocardiograms, stress tests, and coronary angiograms).

Outcomes

There were two primary outcomes for this analysis. The first was major cardiovascular disease, a composite of cardiovascular deaths, myocardial infraction, stroke, heart failure, and other major cardiovascular events. The second primary outcome was all-cause death. Events from myocardial infarction, stroke, heart failure, and cardiovascular death are also reported as secondary outcomes. Detailed definitions of the events are available in the appendix (pp 13–22).

	Women (n=113 451)	Men (n=76 963)	p value
Overall	8·44 (8·43–8·46)	11·44 (11·41–11·46)	p<0·0001
Economic status			
High-income countries	11·44 (11·37–11·51)	14·38 (14·29–14·46)	p<0·0001
Middle-income countries	8·62 (8·59–8·66)	11·84 (11·79–11·89)	p<0·0001
Low-income countries	6·61 (6·57–6·64)	8·93 (8·88–8·97)	p<0·0001
Region			
North America and Europe	10·04 (10·00–10·09)	13·85 (13·78–13·92)	p<0·0001
South America	9·60 (9·56–9·64)	11·58 (11·53–11·64)	p<0·0001
Middle East	10·03 (9·96–10·10)	12·92 (12·83–13·01)	p<0·0001
China	7·27 (7·24–7·30)	11·47 (11·42–11·52)	p<0·0001
Southeast Asia	8·94 (8·89–8·99)	11·77 (11·69–11·84)	p<0·0001
South Asia	6·76 (6·73–6·80)	9·18 (9·14–9·23)	p<0·0001
Africa	8·02 (7·95–8·10)	8·73 (8·61–8·85)	p<0·0001
Russia and Central Asia	7·26 (7·18–7·34)	10·40 (10·23–10·56)	p<0·0001

All data are mean (95% CI). Participants with a history of cardiovascular diseases were excluded. Higher scores of the INTERHEART score indicate a higher risk factor burden. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity. The estimated 10-year cardiovascular disease risk based on the Framingham risk score indicates that 10·5% of women and 37·3% of men are at high risk (≥20%) of developing the disease (appendix p 25).

Table 2: **Mean non-laboratory INTERHEART risk score for women and men for the entire cohort and each economic and regional subgroup**

Statistical analysis

Continuous variables are presented as means with SDs. Categorical variables are presented as counts and proportions. We used direct standardisation, according to the age and sex distribution of the PURE cohort, to calculate the age-standardised incidence rates (per 1000 person-years) for cardiovascular events and deaths. We used multilevel Cox proportional hazard models to obtain the hazard ratios (HRs) for major cardiovascular disease, myocardial infarction, stroke, heart failure, and all-cause death. In the multilevel structure, we considered individual participants nested in centres and considered centres as a random intercept effect. We mutually adjusted HRs for age, sex, location, and education. In separate analyses, we adjusted HRs for the INTERHEART risk score to assess the effect of risk factors on the outcomes; age was removed from these models because it is included in the INTERHEART risk score. We included the interaction terms of sex and country economic status and sex and geographical region. The proportionality of hazards was evaluated by visual inspection of the log–log survival plots. For all events we considered the first occurrence of the event of interest. We calculated 30-day and 30-day to 1-year case fatality rates following myocardial infarction, stroke, or heart failure event after adjustment for age. We modelled the associations between sex and use of preventive medicines, risk factor control, healthy lifestyle behaviours, cardiac tests, and revascularisations using multilevel mixed effects logistic regressions, adjusted for age, sex, education, and clustering for centres. The associations between sex and use of preventive medicines was further examined by additionally adjusting the odds-ratios (OR) for the INTERHEART risk score to control for cardiovascular disease risk. Differences in proportions between women and men were compared using two-sided χ^2 tests and differences between means using two-sided t tests. Given the multiplicity of comparisons, p values should be interpreted cautiously, except when they are very small (eg, p<0·0001) or consistent across several different related analyses.

Role of the funding source

External 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. Three authors (MW-A, SR, and SY) had full access to the data and had final responsibility for the decision to submit for publication.

Results

Between Jan 6, 2005, and May 6, 2019, 202 072 participants (119 799 [59·3%] women and 82 273 [40·7%] men) aged 35–70 years were enrolled and followed up for measurement of risk factors associated with cardiovascular disease, incident cardiovascular disease and all-cause death. The median follow-up of the cohort was 9·5 (IQR 8·5–10·9) years. Table 1 presents baseline

characteristics of the study population. The mean age of women was 50·8 (SD 9·9) years compared with 51·7 (10) years for men. Less than half of the participants lived in a rural community (43·2% women and 44·2% men) and around 20% of both women and men included in the study were from a low-income country (table 1).

Fewer women were current smokers, had high levels of physical activity, or consumed alcohol, whereas probable depression and low education were more frequent in women than in men. Mean total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and ApoA1 concentrations were higher in women than men. By contrast, women had lower mean concentrations of triglycerides, ApoB, ratio of ApoB to ApoA1, and ratio of total cholesterol to HDL cholesterol. Waist circumference and waist:hip ratio were lower but mean BMI was higher in women than in men. Systolic and diastolic blood pressures and fasting blood glucose were also lower in women than in men. Fewer women reported a history of cardiovascular disease than men.

We assessed the risk factor burden in the subset of 190 414 participants who had not had a previous cardiovascular disease event (table 2). The mean INTERHEART risk score was lower in women than in men in the overall study (8·44 [95% CI 8·43–8·46] *vs* 11·44 [11·41–11·46]; p<0·0001) and also within all groups of countries categorised by economic status and by geographical regions. In both women and men, the risk factor burden was highest in high-income countries, especially North America and Europe, and lowest in low-income countries (table 2). The region with the lowest risk factor burden for men was Africa (8·73 [8·61–8·85]) and for women it was South Asia (6·76 [6·73–6·80]). Similar patterns were observed when examining the median INTERHEART risk score (appendix p 23).

The laboratory-based fasting cholesterol INTERHEART and the Framingham risk scores also showed similar patterns to the non-laboratory based INTERHEART risk factor analyses, with women having lower scores than men and a lower estimated 10-year risk of cardiovascular disease (appendix pp 24–25). A lower risk factor burden in women was also observed in participants with a history of cardiovascular disease, which remained even after the removal of smoking from the INTERHEART risk score

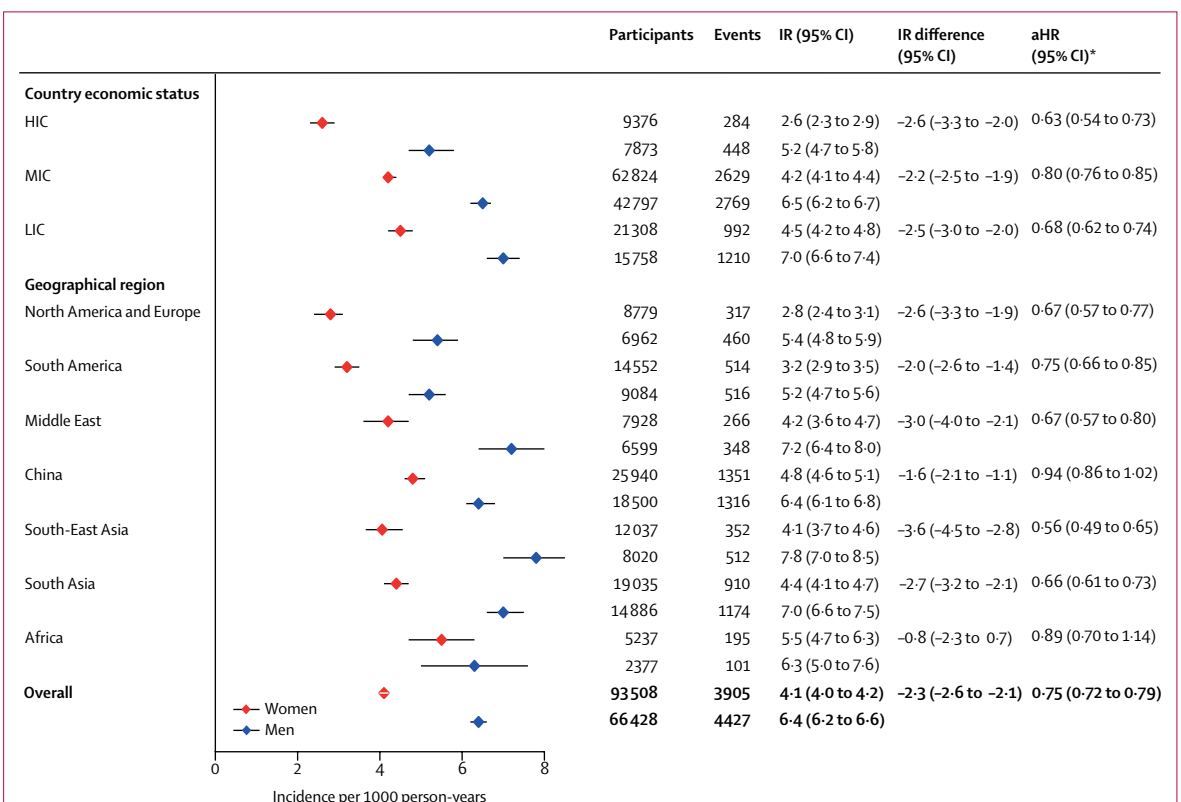
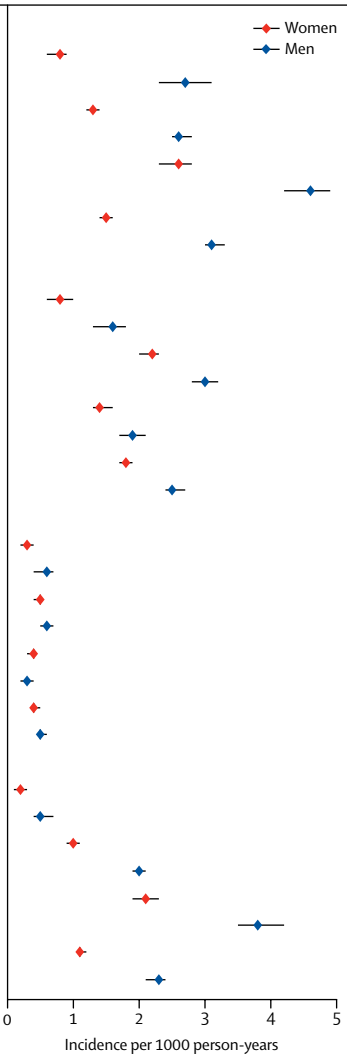


Figure 1: **Age-standardised incidence rates per 1000 person-years of major cardiovascular disease in those without a history of previous cardiovascular disease**
Major cardiovascular disease includes cardiovascular death, myocardial infarction, stroke, heart failure, and other major cardiovascular disease events. Errors bars represent 95% CIs. Participants with a history of cardiovascular diseases are excluded. Interaction between economic status and sex p<0·0001; interaction between geographic region and sex p<0·0001. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios are adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.



	Participants	Events	IR (95% CI)	IR difference (95% CI)	aHR (95% CI)*
Myocardial Infarction					
HIC	9376	92	0·8 (0·6 to 0·9)	−1·9 (−2·3 to −1·5)	0·45 (0·35 to 0·58)
	7873	215	2·7 (2·3 to 3·1)		
MIC	62825	802	1·3 (1·2 to 1·4)	−1·4 (−1·6 to −1·2)	0·61 (0·56 to 0·67)
	42797	1109	2·6 (2·5 to 2·8)		
LIC	21309	555	2·6 (2·3 to 2·8)	−2·0 (−2·4 to −1·6)	0·59 (0·52 to 0·66)
	15759	788	4·6 (4·2 to 4·9)		
Overall	**93510**	**1449**	**1·5 (1·4 to 1·6)**	**−1·6 (−1·8 to −1·4)**	**0·59 (0·55 to 0·63)**
	66429	**2112**	**3·1 (3·0 to 3·3)**		
Stroke					
HIC	9376	84	0·8 (0·6 to 1·0)	−0·8 (−1·1 to −0·4)	0·51 (0·39 to 0·67)
	7873	153	1·6 (1·3 to 1·8)		
MIC	62825	1357	2·2 (2·0 to 2·3)	−0·8 (−1·0 to −0·6)	0·91 (0·84 to 0·99)
	42797	1316	3·0 (2·8 to 3·2)		
LIC	21309	329	1·4 (1·3 to 1·6)	−0·5 (−0·7 to −0·2)	0·81 (0·69 to 0·96)
	15759	340	1·9 (1·7 to 2·1)		
Overall	**93510**	**1770**	**1·8 (1·7 to 1·9)**	**−0·7 (−0·9 to −0·6)**	**0·86 (0·80 to 0·92)**
	66429	**1809**	**2·5 (2·4 to 2·7)**		
Heart failure					
HIC	9376	39	0·3 (0·2 to 0·4)	−0·2 (−0·4 to 0·0)	0·69 (0·46 to 1·06)
	7873	63	0·6 (0·4 to 0·7)		
MIC	62825	300	0·5 (0·4 to 0·5)	−0·2 (−0·3 to −0·1)	0·87 (0·73 to 1·03)
	42797	286	0·6 (0·5 to 0·7)		
LIC	21309	81	0·4 (0·3 to 0·4)	0·0 (−0·1 to 0·1)	0·99 (0·69 to 1·42)
	15758	61	0·3 (0·2 to 0·4)		
Overall	**93510**	**420**	**0·4 (0·4 to 0·5)**	**−0·1 (−0·2 to −0·1)**	**0·86 (0·75 to 0·99)**
	66428	**410**	**0·5 (0·5 to 0·6)**		
Cardiovascular death					
HIC	9376	23	0·2 (0·1 to 0·3)	−0·4 (−0·5 to −0·2)	0·45 (0·27 to 0·75)
	7873	52	0·5 (0·4 to 0·7)		
MIC	62825	664	1·0 (0·9 to 1·1)	−1·0 (−1·2 to −0·9)	0·61 (0·55 to 0·68)
	42796	950	2·0 (1·9 to 2·1)		
LIC	21309	515	2·1 (1·9 to 2·3)	−1·7 (−2·1 to −1·3)	0·58 (0·52 to 0·66)
	15758	714	3·8 (3·5 to 4·2)		
Overall	**93510**	**1202**	**1·1 (1·1 to 1·2)**	**−1·1 (−1·3 to −1·0)**	**0·59 (0·55 to 0·64)**
	66427	**1716**	**2·3 (2·1 to 2·4)**		

Figure 2: **Age-standardised incidence rates per 1000 person-years of myocardial infarction, stroke, heart failure, and cardiovascular death in those without previous cardiovascular disease**

Errors bars represent 95% CIs. Of note, 385 other major cardiovascular events (261 in women and 124 in men) included in major cardiovascular are not presented above. Data are not presented by geographical region because the numbers of events of myocardial infarction, stroke, and heart failure are substantially reduced resulting in unstable estimates. Interaction between country economic status and sex p=0·0001 for myocardial infarction events; p=0·0001 for stroke events; p=0·3006 for heart failure events. Interaction between country economic status and sex p=0·0001 for cardiovascular deaths. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios are adjusted for location, education, INTERHEART risk score, and a random intercept for centre ID. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

(appendix pp 26–27). Women had a lower risk factor burden than men even after modifying the scoring system so that women and men were assigned the same number of points for age (appendix p 28).

8332 participants without history of cardiovascular disease had a major cardiovascular disease event during follow-up (3905 [47%] women and 4427 [53%] men), and 10 244 participants died from any cause (4570 [45%] women and 5674 [55%] men). Women had lower incidence of age-standardised major cardiovascular disease (4·1 [95% CI 4·0–4·2] per 1000 person-years) than did men (6·4 [6·2–6·6]). Lower incidence rates of major cardiovascular disease in women compared to men were observed across all economic and geographical regions, except Africa where there were relatively few events (figure 1). Overall, the risk of a major cardiovascular disease event was 38% lower in women without adjustment for the INTERHEART risk score (adjusted HR 0·62 [95% CI 0·60–0·65]), and this risk was only partly attenuated after further adjusting for the

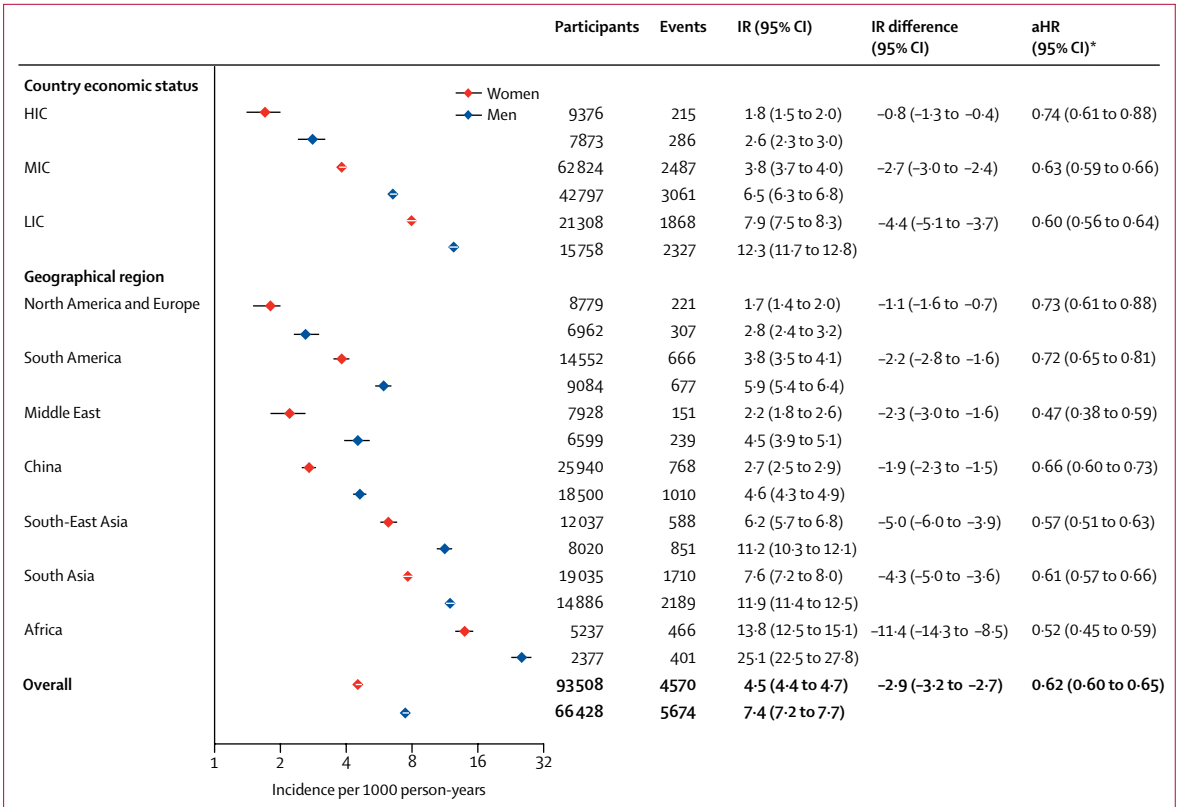


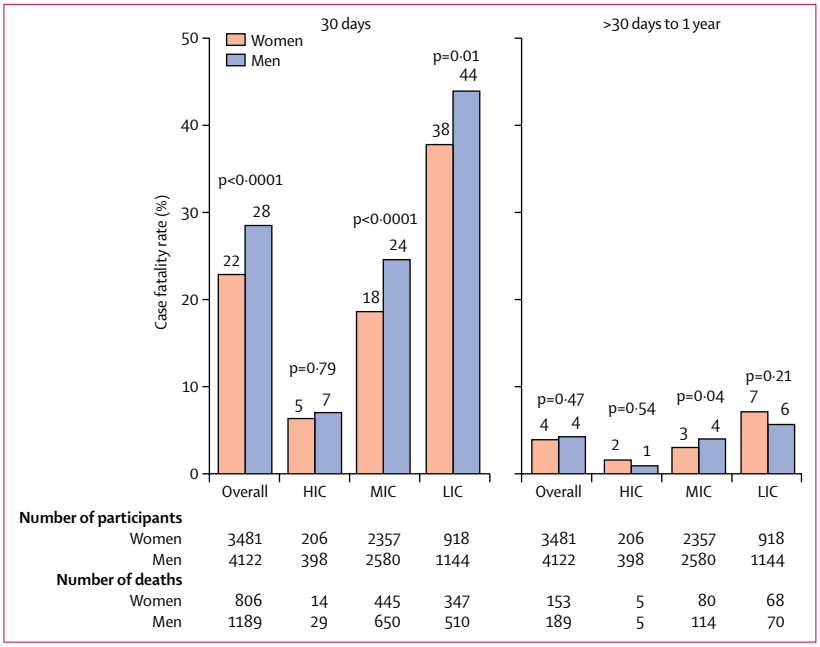
Figure 3: **Age-standardised incidence rates per 1000 person-years of all-cause death in those without previous cardiovascular disease**
Participants with a history of cardiovascular diseases are excluded. Interaction between sex and country economic status p<0·0001; Interaction between sex and geographic region p<0·0001. Errors bars represent 95% CIs. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

INTERHEART risk score (0·75 [0·72–0·79]). The risk of each component of major cardiovascular disease was also lower in women than men (figure 2). Overall, women had a 41% lower risk of myocardial infarction (0·59 [0·55–0·63]), a 14% lower risk of stroke (0·86 [95% CI 0·80–0·92]), a 14% lower risk of heart failure (0·86 [0·75–0·99]), and a 41% lower risk of cardiovascular death (0·59 [0·55–0·64]) compared with men.

Age-standardised all-cause deaths per 1000 person-years was also lower in women (4·5 [95% CI 4·4–4·7]) than in men (7·4 [7·2–7·7]). The smallest difference between all-cause death in men and women was in high-income countries (incidence rate difference 0·8) and the largest difference was reported in low-income countries (incidence rate difference 4·4), around five-times more than that seen in HICs (figure 3). Overall, the risk of all-cause death was 44% lower in women without adjustment for the INTERHEART risk score (adjusted HR 0·56 [95% CI 0·54–0·59]), and 38% lower after adjustment (0·62 [0·62–0·65]).

Overall, the 30-day case fatality rates after a myocardial infarction, stroke, or heart failure event were 22% for women and 28% in men (p<0·0001; figure 4). Similar 30-day case fatality rates were observed for women and men in high-income countries (5% in women and 7% in men; p=0·79). The difference in 30-day case fatality rates between women and men were more marked in middle-income countries (18% in women *vs* 24% in men; p<0·0001) and low-income countries (38% in women *vs* 44% in men; p=0·0058; figure 4). Examining the risk of cardiovascular death over the entire follow-up duration after a diagnosis of myocardial infarction, stroke, or heart failure did not alter our conclusions (appendix p 30). Lower 1-year case-fatality rates in women compared with men were also observed for each component of cardiovascular disease (ie, myocardial infarction, stroke, and heart failure), but these differences were not separately statistically significant (appendix p 31).

Of the 190414 participants without cardiovascular disease at baseline, use of antiplatelets, β blockers, ACE inhibitors or angiotensin receptor blockers, diuretics, calcium-channel blockers, statins, and glucose lowering agents was significantly higher in women after adjustment for the participants' sociodemographic characteristics and the INTERHEART risk score, but the differences in crude proportions were small (table 3). Women were also



	30 days				>30 days to 1 year			
Number of participants								
Women	3481	206	2357	918	3481	206	2357	918
Men	4122	398	2580	1144	4122	398	2580	1144
Number of deaths								
Women	806	14	445	347	153	5	80	68
Men	1189	29	650	510	189	5	114	70

Figure 4: **Case fatality rates after an incident myocardial infarction, stroke, or heart failure event in women and men by country economic status**
Case fatality rates adjusted for age. Participants with a history of cardiovascular diseases were excluded.

significantly more likely to have their hypertension controlled, and to quit smoking. However, the differences between women and men for consuming a healthy diet and physical activity was modest. By contrast, of the 11658 participants with previous cardiovascular disease women were significantly less likely to use antiplatelet drugs, ACE inhibitors or angiotensin receptor blockers, any blood-pressure lowering medicine, or statins, after adjustment for participants' sociodemographic characteristics and the INTERHEART risk score. However, women with a history of cardiovascular disease were more likely to use diuretics, calcium-channel blockers, and hypoglycaemic agents, and these participants were also more likely to have their hypertension controlled and be physically active (table 3).

Women were less likely to have echocardiograms, stress tests, coronary angiograms, or revascularisation procedures compared with men. These patterns were observed for countries at all economic levels (table 4). Despite the lower number of cardiac tests and revascularisation procedures in women, the risk of a subsequent major cardiovascular disease event was lower in women than men with a history of coronary disease (figure 5). This pattern was observed in low-income and middle-income countries but not in high-income countries, where the risk of subsequent cardiovascular disease was similar between women and men.

Discussion

Several key conclusions can be drawn from our study. First, overall burden of cardiovascular disease risk factors was lower in women than in men, in all groups of countries by economic status, in all geographical regions, and in participants with and without a history of cardiovascular disease. Second, women without a history of cardiovascular disease were more likely to use preventive medicines, have controlled hypertension, and to have quit smoking. However, the absolute differences in these crude proportions were small. Moreover, the risk of major cardiovascular disease and all-cause death in those without previous cardiovascular disease were also lower in women, even after adjustment for participants' risk factor burden. Third, in participants with previous cardiovascular disease, secondary prevention medicines, cardiac tests, and revascularisation procedures were less frequently used in women than men. Despite these findings, women with a history of cardiovascular disease had a lower risk of recurrent major cardiovascular disease event. The 30-day case fatality rates from an incident major cardiovascular disease event was also lower in women. Finally, although the differences in cardiovascular disease incidence and case-fatality rates between women and men were observed in countries at all economic levels, these differences were modest in high-income countries and considerably greater in other countries.

A lower risk factor burden in women than in men, which was observed with both the INTERHEART and Framingham scores, is consistent with previous studies. For instance, data from the UK Biobank in a sample of 471998 people without a history of cardiovascular disease reported that fewer women smoked and fewer had hypertension, diabetes, or obesity compared with men.[21] Data from the Framingham Offspring cohort reported that the 30-year risk of cardiovascular disease was substantially lower in women (7·6%) than men (18·3%).[22] A meta-analysis of 18 cohorts involving 250000 women and men from the USA reported lower calculated lifetime risk of death from cardiovascular disease in women than men.[23] PURE extends these observations to many countries in different regions of the world. The consistently lower risk factor burden in women compared with men in diverse settings suggests that women might be inherently at lower risk for cardiovascular disease than men. The reasons for this remain unclear, although, differences in oestrogen concentration are commonly thought to be the reason for women's cardioprotection. However, three large clinical trials of the effects oestrogens did not show benefit, and the role of oestrogens in protecting women from cardiovascular disease remains unproven.[24] Our data suggest that a higher prevalence of primary prevention strategies and healthy lifestyle behaviours observed in women is likely to contribute to their lower cardiovascular disease risk.

In participants without a history of cardiovascular disease, women had a lower risk of incident cardiovascular disease and all-cause deaths even after adjustment for the INTERHEART risk score. Adjusting for the individual

	Participants without a history of cardiovascular disease				Participants with a history of cardiovascular disease			
	Women, n/N (%)	Men, n/N (%)	Women *vs* men OR (95% CI)*	Women *vs* men OR (95% CI)†	Women, n/N (%)	Men, n/N (%)	Women *vs* men OR (95% CI)*	Women *vs* men OR (95% CI)†
Medication								
Antiplatelet drugs	3621/113 451 (3·2%)	2684/76 963 (3·5%)	0·96 (0·91–1·01)	1·34 (1·26–1·42)	1357/6348 (21·4%)	1660/5310 (31·3%)	0·67 (0·60–0·75)	0·65 (0·59–0·72)
β blockers	4410/113 451 (3·9%)	2070/76963 (2·7%)	1·53 (1·44–1·62)	2·34 (2·20–2·49)	1022/6348 (16·1%)	1020/5310 (19·2%)	0·73 (0·66–1·81)	0·93 (0·83–1·04)
ACE inhibitors or ARBs	7549/113 451 (6·7%)	4472/76963 (5·8%)	1·17 (1·12–1·22)	1·91 (1·82–2·00)	1280/6348 (20·2%)	1323/5310 (24·9%)	0·66 (0·59–0·73)	0·86 (0·77–0·96)
Diuretics	4669/113 451 (4·1%)	2345/76963 (3·0%)	1·47 (1·39–1·55)	2·20 (2·07–2·33)	896/6348 (14·1%)	579/5310 (10·9%)	1·27 (1·12–1·44)	1·56 (1·37–1·77)
Calcium-channel blockers	3495/113 451 (3·1%)	2123/76963 (2·8%)	1·25 (1·18–1·33)	1·80 (1·70–1·92)	755/6348 (11·9%)	629/5310 (11·8%)	1·04 (0·92–1·17)	1·28 (1·12–1·45)
Blood-pressure lowering medicines among those with known hypertension‡	13 932/21 878 (63·7%)	7584/12 285 (61·7%)	1·01 (0·96–1·06)	1·21 (1·15–1·28)	2308/3513 (65·7%)	1847/2703 (68·3%)	0·71 (0·63–0·80)	0·82 (0·72–0·92)
Statins	3952/113 451 (3·5%)	2509/ 76963 (3·3%)	1·08 (1·02–1·14)	1·60 (1·50–1·69)	951/6348 (15·0%)	1200/5310 (22·6%)	0·54 (0·48–0·60)	0·70 (0·62–0·79)
Use of glucose-lowering agents among those with known diabetes	4050/8090 (50·1%)	2977/5902 (50·4%)	1·02 (0·95–1·10)	1·19 (1·11–1·28)	668/1303 (51·3%)	572/1288 (44·4%)	1·03 (0·87–1·23)	1·31 (1·09–1·56)
Hypertension control and healthy lifestyle behaviours								
Hypertension controlled among those with known hypertension	6922/21 878 (31·6%)	3177/12 285 (25·9%)	1·34 (1·27–1·42)	NA	1205/3513 (34·3%)	860/2703 (31·8%)	1·11 (0·98–1·25)	NA
Quit smoking among ever smokers	9644/20 880 (46·2%)	14 606/42 541 (34·2%)	1·57 (1·51–1·63)	NA	770/1373 (56·1%)	1767/3242 (54·5%)	1·01 (0·87–1·18)	NA
Healthy eating	28 765/86 132 (33·4%)	20 284/61 182 (33·2%)	1·05 (1·03 to –1·07)	NA	1635/4113 (39·8%)	1394/3834 (36·4%)	1·21 (1·10–1·33)	NA
Physically active§	45 482/105 042 (43·3%)	32 259/70 546 (45·7%)	0·91 (0·89–0·93)	NA	2443/6074 (40·2%)	1894/5040 (37·6%)	1·21 (1·11–1·31)	NA

OR=odds ratio. ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. *OR adjusted for age, education, urban versus rural location. †OR adjusted for age, education, urban versus rural location, and INTERHEART risk score. ‡Blood-pressure lowering medicines include any of β blockers, ACE inhibitors, ARBs, diuretics, calcium-channel blockers, and alpha-antagonist. §High physical activity was defined as having performed more than 3000 metabolic equivalent × min per week.

Table 3: **Use of preventive medicines, risk factor control, and healthy lifestyle behaviours in participants without and with a history of cardiovascular disease**

	Cardiac tests									Revascularisation procedures (PCI or CABG)		
	Cardiac echocardiogram			Stress test			Coronary angiogram			Women, n/N (%)	Men, n/N (%)	Women *vs* Men OR* (95% CI)
	Women, n/N (%)	Men, n/N (%)	Women *vs* Men OR* (95% CI)	Women, n/N (%)	Men, n/N (%)	Women *vs* Men OR* (95% CI)	Women, n/N (%)	Men, n/N (%)	Women *vs* Men OR* (95% CI)			
Overall	1796/3930 (45·7%)	2155/3712 (58·1%)	0·77 (0·69–0·86)	829/3929 (21·1%)	1269/3706 (34·2%)	0·72 (0·62–0·85)	990/3935 (25·2%)	1538/3721 (41·3%)	0·62 (0·54–0·70)	477/3959 (12·1%)	1180/3759 (31·4%)	0·37 (0·32–0·42)
High-income countries	214/273 (78·4%)	499/600 (83·2%)	0·72 (0·49–1·04)	194/274 (70·8%)	494/604 (81·2%)	0·64 (0·40–1·02)	167/273 (61·2%)	444/605 (73·4%)	0·59 (0·42–0·82)	103/277 (37·2%)	424/623 (68·1%)	0·29 (0·22–0·40)
Middle-income countries	1408/3109 (45·3%)	1377/2580 (53·4%)	0·81 (0·71–0·93)	597/3107 (19·2%)	702/2570 (27·3%)	0·74 (0·62–0·88)	742/3113 (23·8%)	918/2582 (35·6%)	0·64 (0·55–0·74)	323/3129 (10·3%)	625/2592 (24·1%)	0·37 (0·31–0·44)
Low-income countries	174/548 (31·8%)	279/532 (52·4%)	0·63 (0·47–0·85)	38/548 (6·9%)	73/532 (13·7%)	0·72 (0·45–1·15)	81/549 (14·8%)	176/534 (33·0%)	0·54 (0·38–0·75)	51/553 (9·2%)	131/544 (24·1%)	0·50 (0·34–0·76)

PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. OR=odds ratio. *OR adjusted for age, education, urban versus rural location, and random intercept for centre.

Table 4: **Number of participants who received cardiac tests and coronary revascularisation procedures in women and men with coronary artery disease overall and by economic status**

components of the INTERHEART risk score instead of the overall INTERHEART risk score did not alter this conclusion (appendix pp 32–33). Although data that include large cohorts from low-income and middle-income countries are few in number, previous studies with predominantly North American and European populations have also reported lower cardiovascular disease incidence and deaths in women.[5,23]

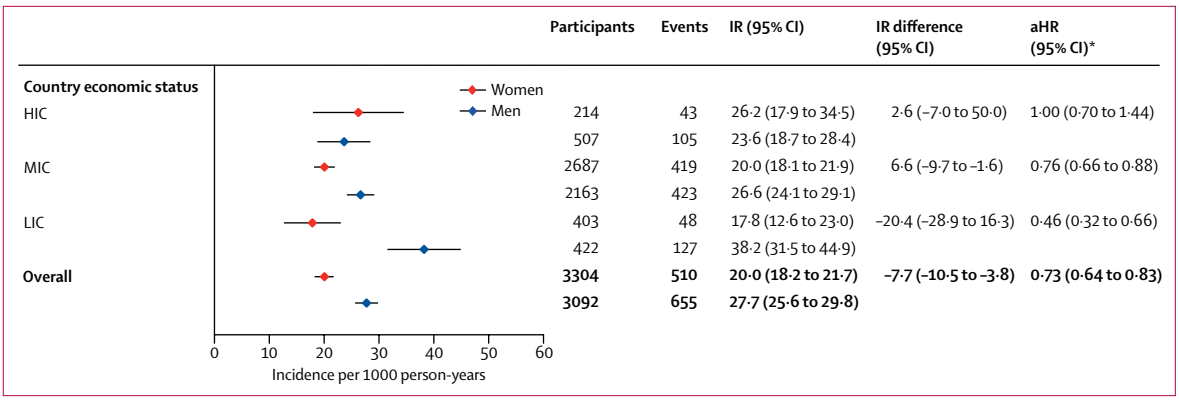


Figure 5: **Age-standardised incidence rates per 1000 person-year of major cardiovascular disease in those with a history of coronary artery disease**
Major cardiovascular disease includes cardiovascular death, myocardial infarction, stroke, heart failure, and other major cardiovascular disease events. Errors bars represent 95% CIs. Interaction between sex and country economic status p=0·0018. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

Unlike primary prevention, we observed that in participants with existing cardiovascular disease, secondary prevention drugs, diagnostic tests, and revascularisation procedures were less frequent in women than in men, which is consistent with previous studies.[10] Nevertheless, women had lower risks of recurrent cardiovascular disease events and 30-day deaths after a new cardiovascular disease event compared with men. Why women with established cardiovascular disease are treated less frequently while the opposite is seen in primary prevention is not clear. Participants with existing cardiovascular disease were approximately 7 years older than those without a history of cardiovascular disease (appendix pp 34–35), and it is possible that in those with cardiovascular disease, women are more likely to experience side-effects from antiplatelet drugs, thrombolytics, or statins and discontinue this medication compared with men.[25–27] Appropriate dosing of secondary prevention medicines might also vary for women and men. For example, Santema and colleagues[28] reported that women with heart failure with reduced ejection fraction required lower doses of guideline recommended therapies possibly because of their lower bodyweight and height compared with men.

Studies have also suggested that women more frequently present with atypical symptoms than do men,[29] which might contribute to delays in diagnosis and provision of subsequent care. However, reports of women presenting with atypical symptoms more frequently than men are highly variable largely because of the absence of standardised definitions and methods for collecting data on presenting symptoms. Following an acute event, women might also present to the health-care system later than men. The International Survey of Acute Coronary Syndromes in Transitional Countries registry reported that women with ST-elevation myocardial infarction had an approximately 30 min longer symptom onset to hospital presentation time than men.[30] However, there were no differences in door-to-balloon time or door-to-needle time between women and men. The lower number of revascularisation procedures observed in women with established coronary artery disease might partly be explained by a lower burden of atherosclerosis in women. Previous studies have reported that women are more likely than men to have non-obstructive coronary artery disease but, irrespective of age, men have significantly more obstructive coronary disease and multivessel disease than women across the spectrum of acute coronary syndrome.[31–35] Furthermore, data from previous studies show that although revascularisation is more common in men than in women with mild disease, sex differences in revascularisation are not observed in those with advanced disease.[31,34–36] We were unable to stratify revascularisation rate by disease severity at time of presentation, but women with previous cardiovascular disease had lower INTERHEART risk scores than did men with previous cardiovascular disease (appendix p 26). The lower INTERHEART risk scores might also contribute to less intensive investigation of women with previous cardiovascular disease. Given the older age at which women with coronary artery disease present compared with men, their perioperative risks from coronary artery bypass grafting surgery or percutaneous coronary intervention could be higher.[37] This might more often lead to a reluctance from physicians to perform some procedures in women than in men. Future research should therefore investigate whether women and men differ in their suitability and contraindications for certain treatments and procedures. Whether women and men differ in their priorities and preferences for secondary prevention medicines or revascularisation therapies is unknown.

The contrasting patterns in the differences between women and men in primary prevention compared

with secondary prevention are not readily explained. To date, most studies have acutely focused on treatment differences in women compared with men following a cardiovascular disease event and often conclude that some combination of implicit and explicit biases have resulted in women being undertreated.[38,39] However, both the lower incidence of cardiovascular disease and death in women than in men in those with and without a history of cardiovascular disease in our study suggests that the overall approaches to the prevention of cardiovascular disease do not lead to worse outcomes in women. Our data indicate that women with coronary artery disease have better prognosis despite less aggressive treatments. These findings suggest that there might be factors, other than a bias, that favour more vigorous management of cardiovascular disease in men.

Our data do not conflict with the literature. A systematic review of studies reporting sex differences in long-term prognosis after an acute myocardial infarction found that most studies reported similar or lower death rates for women compared with men, after adjustment for age and other characteristics.[40] Vaccarino and colleagues[41] came to a similar conclusion for early death (ie, in-hospital or during the first 4–6 weeks). In their review of studies published between 1966 and 1994, adjusting for age only resulted in no significant differences in deaths between women and men in nine of the 11 studies reviewed. In six studies that adjusted for age and other covariates, only one reported significantly more deaths in women than men. We also undertook a comprehensive review of the literature (appendix pp 34–35). A few studies suggested more deaths in women, particularly at younger ages in women with ST-elevation myocardial infarction,[42,43] but most large studies observed that cardiovascular disease outcomes were not higher in women compared with men. Interestingly, some of the studies reporting more deaths in young women with ST-elevation myocardial infarction found that the pattern persisted even in the subset of women receiving revascularisation procedures.[42,43]

Of note, for both women and men the incidence of a recurrent cardiovascular disease event and 30-day case fatality rates were greatest in low-income and middle-income countries, with little difference in high-income countries. A number of observational studies in low-income and middle-income countries have highlighted inadequate access to quality health-care services,[44] poor health literacy, and suboptimal use of medicines to control blood pressure,[45] cholesterol,[46] and glucose,[47] which might explain some of the excess burden of cardiovascular disease in these countries and support efforts to improve the management of cardiovascular disease for both women and men.

Our study has a few potential limitations. First, it is possible that the risk scores underestimate cardiovascular disease risk in women. The INTERHEART risk score does not include female-specific risk factors, such as gestational diabetes, history of pre-eclampsia, or pregnancy induced hypertension because information on these factors were not collected in PURE. The inclusion of these factors to improve cardiovascular disease risk prediction in women has not been previously evaluated.[48] Moreover, a systematic review of risk prediction models in women in the general population concluded that established sex independent cardiovascular disease risk predictors (ie, age, blood pressure, and smoking) made the greatest contribution to model performance.[48] Second, although we accounted for differences in risk factor burden when examining use of primary and secondary prevention medicines, we were unable to account for differences in eligibility for or contraindications to specific medicines. The remaining variations in treatment use could be due to unmeasured factors, such as differences in treatment preferences. Third, although our study is the first to explore differences between women and men in several geographical regions, the number of cardiovascular disease events in Africa was relatively low (ie, <400 people with incident cardiovascular disease); therefore, conclusions related to the burden of cardiovascular disease in women compared with men in Africa should be interpreted with caution. However, the incidence of cardiovascular disease and all-cause death were higher in men than in women in Africa, suggesting that the general pattern of higher cardiovascular disease death in men holds true for all regions of the world. Fourth, the detection of cardiovascular events in low-income and middle-income countries might be less complete if access to hospitals and diagnostic facilities were poorer for the participants in these countries. If this were the case, we would expect even higher rates of cardiovascular disease in both women and men in poorer countries, but this should not affect women and men differentially. Fifth, we are unable to discriminate between ST-elevation myocardial infarction from a non-ST-elevation myocardial infarction and outcomes in women compared with men could vary according to the type of acute coronary syndrome. The existing evidence is mixed; although many studies suggest no sex differences in deaths in both patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction,[33,49] some report worse outcomes in women with ST-elevation myocardial infarction compared with men, especially at younger ages.[42,43] Sixth, relatively few individuals developed incident heart failure (830 [0·5%] individuals). Therefore, conclusions related to differences between women and men in the incidence and case fatality rates of heart failure by country economic status should be interpreted with caution. Our findings, of lower incidence of heart failure in women than in men but similar death rates between the two groups as a result of heart failure, are generally consistent with previous studies.[50] With extended follow-up and a planned expansion of the PURE study, we expect to be able to

provide more robust results on heart failure in a few years. Similarly, case fatality rates beyond 30-days but less than 1-year and the 30-day case fatality rates in high-income countries were low. Therefore, conclusions related to the patterns by sex, especially during the 30-day to 1-year period, should be interpreted with caution.

In conclusion, treatments for cardiovascular disease were more common in women than men who do not have known cardiovascular disease (primary prevention); however, use of secondary prevention medications, diagnostic tests, and revascularisation procedures were less frequent in women. Despite these findings, consistently better outcomes were observed in women than in men in those without and in those with cardiovascular disease. Larger gaps were observed in disease management and worse outcomes in both women and men in poorer countries than in richer countries. Therefore, greater efforts to improve prevention and management of cardiovascular disease in both women and men worldwide, but especially in low-income and middle-income countries, are warranted.

Contributors

SY designed the study, obtained the funding, and oversaw its conduct since its inception 18 years ago. MW-A wrote the analysis plan and did all study analyses. MW-A and SY wrote the various drafts. SR coordinated the worldwide study. PJ, AR, CKC, SAL, and SSA reviewed and commented on the Article. All other authors coordinated the study in their countries and all commented on drafts of the paper.

Declaration of interests

We report no competing interests.

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