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CLINICAL RESEARCH
Epidemiology and prevention

Risk factors, cardiovascular disease, and mortality in South America: a PURE substudy

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Abstract

Aims In a multinational South American cohort, we examined variations in CVD incidence and mortality rates between subpopulations stratified by country, by sex and by urban or rural location. We also examined the contributions of 12 modifiable risk factors to CVD development and to death.

Methods and results This prospective cohort study included 24 718 participants from 51 urban and 49 rural communities in Argentina, Brazil, Chile, and Colombia. The mean follow-up was 10.3 years. The incidence of CVD and mortality rates were calculated for the overall cohort and in subpopulations. Hazard ratios and population attributable fractions (PAFs) for CVD and for death were examined for 12 common modifiable risk factors, grouped as metabolic (hypertension, diabetes, abdominal obesity, and high non-HDL cholesterol), behavioural (tobacco, alcohol, diet quality, and physical activity), and others (education, household air pollution, strength, and depression). Leading causes of death were CVD (31.1%), cancer (30.6%), and respiratory diseases (8.6%). The incidence of CVD (per 1000 person-years) only modestly varied between countries, with the highest incidence in Brazil (3.86) and the lowest in Argentina (3.07). There was a greater variation in mortality rates (per 1000 person-years) between countries, with the highest in Argentina (5.98) and the lowest in Chile (4.07). Men had a higher incidence of CVD (4.48 vs. 2.60 per 1000 person-years) and a higher mortality rate (6.33 vs. 3.96 per 1000 person-years) compared with women. Deaths were higher in rural compared to urban areas. Approximately 72% of the PAF for CVD and 69% of the PAF for deaths were attributable to 12 modifiable risk factors. For CVD, largest PAFs were due to hypertension (18.7%), abdominal obesity (15.4%), tobacco use (13.5%), low strength (5.6%), and diabetes (5.3%). For death, the largest PAFs were from tobacco use (14.4%), hypertension (12.0%), low education (10.5%), abdominal obesity (9.7%), and diabetes (5.5%).

Conclusions Cardiovascular disease, cancer, and respiratory diseases account for over two-thirds of deaths in South America. Men have consistently higher CVD and mortality rates than women. A large proportion of CVD and premature deaths could be averted by controlling metabolic risk factors and tobacco use, which are common leading risk factors for both outcomes in the region.

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Key questions

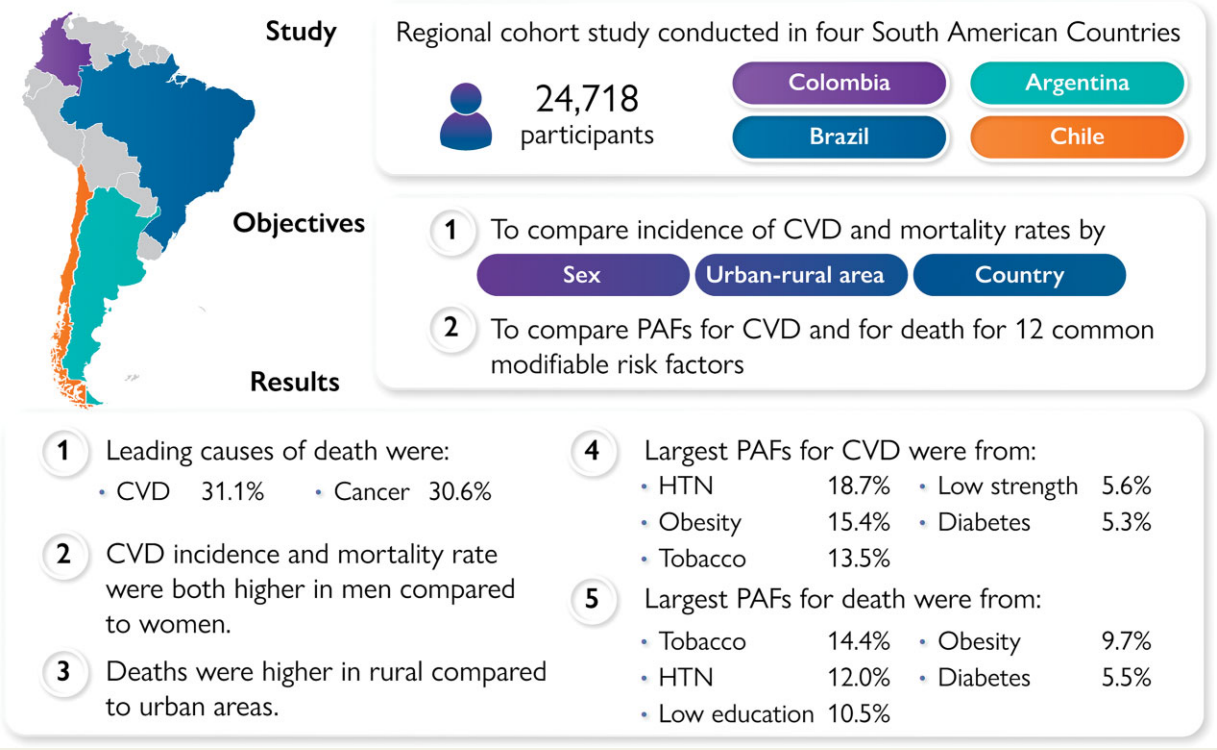
How do the rates of cardiovascular disease (CVD) and death vary within South America, and what are the predominant risk factors for each?

Key findings

Cardiovascular disease and death rates were both higher in men compared with women. Death rates were higher in rural compared with urban areas. Hypertension, obesity, diabetes, and tobacco use were leading risk factors for both CVD and death.

Take-home message

A large proportion of CVD and premature deaths in South America could be averted by policies aimed at controlling metabolic risk factors and tobacco use.



Structured Graphical Abstract Cardiovascular disease, deaths, and the largest risk factors for each outcome.

Keywords Cardiovascular disease • Mortality • South America

Introduction

In the past several decades, urbanization across South America has resulted in lifestyle changes, a higher burden of cardiometabolic risk factors in the population, and a larger contribution of non-communicable diseases to mortality and morbidity.[1–3] Cardiovascular disease (CVD) is the leading cause of death in South America, but further data are required to clarify the extent to which CVD and death rates differ in the region, as well as their contributing risk factors.[4] Studies examining fatal and non-fatal CVD in the region have mostly been conducted in single countries, have generally been small or moderate in size, and differed in methodology and sampling. Therefore, most of the available data do not permit direct comparisons across the region. Data to compare mortality rates across South America are more robust. However, the comparative impact of risk factors to CVD development and to deaths has only been studied in a limited scale within the region.[5–7] It is increasingly being recognized that the burden of CVD, of premature death, and their contributing determinants may differ in various countries at different levels of socioeconomic development, in men versus women, and in populations living in urban or rural communities. Therefore, health policies aimed at improving both CVD and premature mortality in South America would be better informed from additional contemporary data to understand how these two outcomes vary between countries, by sex, and by urban–rural location. Moreover, region-specific data are needed to understand the contributions of common modifiable risk factors to each outcome.[8]

Applying standardized methods for population sampling, data collection, and outcome assessment, the Prospective Urban Rural Epidemiology (PURE) study has collected extensive data on health

determinants for non-communicable diseases and clinical outcomes in ~24 000 participants from 100 communities in Argentina, Brazil, Chile, and Colombia, reflecting a geographically diverse population to study CVD, deaths, and their determinants. In this report, we examined the extent to which the incidence of CVD and mortality rates varied within the region. In participants without prior CVD, we examined the extent to which 12 common and modifiable risk factors contributed to each outcome.

Methods

Study design

PURE is an ongoing, prospective, population-based cohort study being conducted in 27 high-, middle-, or low-income countries. The study design has previously been reported.[9] Community-dwelling adults between 35 and 70 years of age were enrolled in the study. In South America, participants were included from 100 communities in four South American countries: Argentina, Brazil, Chile, and Colombia. These countries are classified as either upper-middle-income countries (Argentina, Brazil, and Chile) or lower-middle-income countries (Colombia) based on the World Bank classification system at the time of enrolment. Using prespecified guidelines, sites identified urban or rural communities from each country from which to recruit participants; and then a sample of households from each community with at least one member between 35 and 70 years of age (and intending to reside at the current home for at least 4 years) were invited to participate in the study. In Argentina, Brazil, and Chile, communities from 1 state/province were included, whereas in Colombia, communities from 10 states were included. Despite not being representative of all South American countries, the locations of communities are distributed widely across the region thereby providing more generalizable results than studies conducted in a single centre or single country (Supplementary material online, *Figure S1*). Prior analysis from PURE has demonstrated that the cohort broadly reflects the participating countries regarding population demographics and mortality rates.[10] Supplementary material online, Appendix provides a summary of the selection guidelines used to identify communities and households for the overall study, and within South America. The study was approved by local ethics committees in each study centre. Most of the recruitment occurred between 2006 and 2009. The PURE South America cohort has enrolled 24 749 of which 24 718 (99.9%) participants had at least one follow-up visit, and were included in this analysis (Supplementary material online, *Figure S2*).

Baseline data collection

At enrolment, data were collected using standardized questionnaires to document risk factors at the individual, household, and community levels. History of CVD at baseline was defined as a self-reported history of myocardial infarction (MI) or stroke. Based on their established association with both CVD and mortality shown in our global data, 12 risk factors collected at baseline were evaluated in this analysis.[8] These risk factors were metabolic risk factors (hypertension, diabetes, elevated non-high-density lipoprotein (HDL) cholesterol, and abdominal obesity); behavioural risk factors (tobacco use, alcohol use, diet quality, and physical activity); low education; household air pollution; low strength (based on grip strength); and depression. Hypertension was defined as a self-reported history of hypertension, baseline systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of blood pressure-lowering medications. Diabetes was defined as a baseline fasting glucose $\geq$126 mg/dL, self-reported history of diabetes, or treatment with a glucose-lowering agent. Waist and hip circumferences were measured using a standard protocol, and abdominal obesity was defined as a waist-to-hip ratio (WHR) >0.9 in men and >0.85 in women. Smoking and alcohol use were collected and quantified by self-report. We used a composite diet score for overall diet quality, which has been replicated in five independent cohorts (unpublished). Physical activity was measured using the International Physical Activity Questionnaire.[11] Education level was collected as part of the baseline assessment, and was chosen as the primary socioeconomic variable of interest because education was found to be a stronger socioeconomic predictor of CVD and mortality than wealth or income in a previous PURE analysis.[12] Grip strength was measured by JAMAR dynamometer. Household air pollution was collected at the household level, and defined as the use of kerosene or solid fuels as the primary fuel for cooking. Depression was defined as a score of at least five on an eight-symptom score of the Composite International Diagnostic Interview.[13] Fasting non-HDL cholesterol was chosen as the primary lipid value of interest because it had the strongest association with CVD in our global risk factor paper. Definitions for each risk factor are further summarized in Supplementary material online, *Table S1*. Categories of risk for each risk factor were based on those used in the PURE global risk factor paper.[8] This approach allows for consistent thresholds of risk to compare across different regions.

Follow-up and outcomes

Follow-up in the South America cohort was scheduled yearly by phone, and every 3 years in the home or health facility. A CVD event during follow-up was defined as the composite of cardiovascular death, stroke, MI, or heart failure. Non-fatal CVD events were self-reported, with additional supporting data requested if available. Cardiovascular disease events underwent adjudication within each country based on prespecified criteria (Supplementary material online, Appendix). Supporting documentation was also requested for deaths to assist with classification. A verbal autopsy questionnaire was completed by a household or family member if the cause of death was unknown. Deaths were also routinely reviewed centrally by a trained nosologist and classified using all available data. The cause of death was classified by the International Classification of Diseases (ICD)-10 code, or an alternative study code if not available through the ICD-10 framework (see Supplementary material online, Appendix).[14]

Statistical analysis

Age- and sex-standardized incidence rates for CVD and for death were calculated per 1000 person-years overall, by country, by sex, and by urban–rural location. Direct standardization to the overall South American cohort was applied to estimates in each subgroup. Leading causes of death are presented overall and by sex. Associations between individual risk factors, CVD, and mortality were examined in those without a prior history of CVD, using a single multivariable Cox frailty model, which was mutually adjusted for each risk factor in addition to age, sex, and urban or rural location. Each community was also included as a random intercept effect (i.e. frailty term) in the model. Estimates were calculated in individuals with complete data and presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The population-level risk associated with each risk factor (or group of risk factors) was estimated using average population attributable fractions (PAFs) based on the approach by Eide and Gefeller,[15] and using the 'averisk' package in R developed by Ferguson *et al.*[16] Using this approach, each risk factor was dichotomously categorized based on a pre-specified threshold level of risk (Supplementary material online, *Table S1*). Average PAF estimates were mutually adjusted for all risk factors, age, sex, and urban–rural location in a single multivariable model where risk factors were introduced

in all possible permutations, and resulting PAFs are the average estimates from all permutations. Using this approach, the cumulative risk attributable to risk factors is additive and does not exceed 100%. Further description of this method to calculate PAFs is summarized in Supplementary material online, Appendix. For groups of risk factors, the contribution of each was truncated at a lower limit of zero as this denotes the lowest theoretical level of risk that can be attributable to a risk factor. Exploratory analyses were conducted to examine risk factors with the largest PAFs by sex, by urban–rural area, and for the CVD outcomes of MI and stroke. Country-level PAFs were not calculated because of limited numbers of outcome events to perform such estimates when stratified at the country level. Analyses were conducted using R and SAS.

Results

Population characteristics

Baseline characteristics for the overall population, stratified by sex, and by country are summarized in *Table 1*. The mean age of the study population was 51.4 years and 61.4% were women. 57.4% of the population lived in urban areas, and 59.5% had a primary level education or less. History of tobacco use was reported in 43.4% and history of alcohol use was reported in 52.0%. The mean PURE diet score was 4.71 of a total score of 8, and 13.8% of the population reported low physical activity levels. Hypertension was present in 46.5%, and 9.4% had diabetes. The mean body mass index was 28.2 kg/m^2 (SD 5.5), and 65.9% met the definition of abdominal obesity based on WHR. The mean non-HDL cholesterol was 4.02 mmol/L (SD 1.1). The mean grip strength was 31.5 kg, and 11.4% were exposed to household air pollution through cooking.

Between countries, Argentina had the lowest education levels, and the highest use of tobacco and of alcohol. Brazil had the highest prevalence of hypertension and of depression. Chile had the lowest diet quality, physical activity levels, and grip strength; and the highest non-HDL cholesterol level, prevalence of abdominal obesity and diabetes, and exposure to household air pollution. In men, alcohol and tobacco use were both higher than in women, physical activity was lower, and diet quality was similar. Metabolic risk factors (abdominal obesity, blood pressure levels, hypertension, and diabetes) were more common in men. Grip strength was higher in men. Comparisons of risk factor levels in urban and rural areas are summarized in Supplementary material online, *Table S2*. More participants were female in urban (64.7%) compared with rural (56.8%) areas. Participants from rural areas had lower education levels and higher exposure to household air pollution. Depression, tobacco use, and low physical activity levels were more prevalent in urban areas. Diet quality, alcohol use, and cardiometabolic risk factor only modestly differed between urban and rural areas.

Incidence of cardiovascular disease

Over a mean follow-up of 10.3 years (mean centre follow-up ranging between 8.3 and 10.6 years), 1859 deaths and 1149 CVD events occurred. The overall age- and sex-standardized incidence of a CVD event in South America was 3.34 (95% CI 3.12–3.56) per 1000 person-years, ranging from 3.07 (95% CI 2.68–3.47) in Argentina to 3.86 (95% CI 3.34–4.38) per 1000 person-years in Brazil (*Figure 1* and Supplementary material online, *Table S3*). Cardiovascular disease incidence was higher in men (4.48, 95% CI 4.07–4.90) compared with women (2.60, 95% CI 2.34–2.85), which was consistent in all countries (*Figure 2*). Some countries had a higher incidence of CVD in urban areas, while in others, higher CVD rates were observed in rural areas (Supplementary material online, *Figure S3*).

Causes of death and mortality rate

Most deaths were attributable to CVD (31.1%), cancer (30.6%), or respiratory diseases (8.6%) (*Figure 3*). Cardiovascular disease was the most common cause of death in men, while cancer was the most common cause of death in women. The age- and sex-standardized mortality rate in the overall cohort was 4.90 (95% CI 4.64–5.17) per 1000 person-years. The mortality rate (per 1000 person-years) was highest in Argentina (5.98, 95% CI 5.45–6.51) and lowest in Chile (4.07, 95% CI 3.47–4.68) (*Figure 1*); higher in men (6.33, 95% CI 5.85–6.82) compared with women (3.96, 95% CI 3.65–4.26) (*Figure 2*); and in rural (5.49, 95% CI 5.06–5.92) compared with urban (4.60, 95% CI 4.26–4.95) areas (Supplementary material online, *Figure S3*).

Associations of risk factors with cardiovascular disease and death

A total of 23 608 participants did not have a history of CVD. Baseline characteristics were similar to that of the overall population (Supplementary material online, *Table S4*). Of these, 16 453 (70%) had data on all included risk factors (Supplementary material online, *Table S5*). Of the 12 individual or household modifiable risk factors examined for CVD, largest associations (i.e. HRs $>$ 2) were observed for current tobacco use; and moderate associations (i.e. HRs $>$ 1.5) were observed for hypertension, and diabetes (*Table 2*). Smaller associations (i.e. HRs $<$ 1.5) were observed for lower physical activity levels, low grip strength, and abdominal obesity. For death, the largest association was with current tobacco use. Moderate associations were observed for diabetes and lower physical activity levels; and smaller associations were observed for hypertension, abdominal obesity, low education, and the lowest quintile of strength.

Population attributable fractions for cardiovascular disease and for death

The 12 modifiable risk factors studied contributed to ∼72% of PAF for CVD in the cohort. Metabolic risk factors contributed to 41% of the PAF. The largest PAFs for CVD were related to hypertension (18.7%), abdominal obesity (15.4%), and tobacco use (13.5%); followed by low strength (5.6%), diabetes (5.3%), poor diet (3.4%), low education level (3.0%), and low physical activity (2.3%) (*Figure 4* and Supplementary material online, *Table S6*). High non-HDL cholesterol, depression, alcohol use, and household air pollution each contributed to 2% or less of the PAF for CVD.

Modifiable risk factors contributed to ∼69% of the PAF for death. Among individual risk factors, the largest PAFs for death were from tobacco use (14.4%), hypertension (12.0%), low education (10.5%), abdominal obesity (9.7%), diabetes (5.5%), low strength (5.1%), low physical activity (4.8%), and alcohol use (3.5%). Poor diet, depression, household air pollution, and non-HDL-cholesterol each

Table 1 Baseline characteristics of the study population overall, by country, and by sex

Factors	Overall	Country				Sex	
		Argentina	Brazil	Colombia	Chile	Men	Women
Number of participants	24 718	7239	5661	7253	3455	9553	15 165
Location, *n* (%)							
Urban	14 196 (57.4)	3457 (47.8)	3683 (65.1)	3614 (49.8)	2744 (79.4)	5008 (52.4)	9188 (60.6)
Rural	10 522 (42.6)	3782 (52.2)	1978 (34.9)	3639 (50.2)	711 (20.6)	4545 (47.6)	5977 (39.4)
Age, years, mean (SD)	51.4 (9.7)	50.86 (9.8)	51.69 (9.4)	50.55 (9.6)	51.66 (9.9)	51.6 (9.8)	51.2 (9.7)
Education, *n* (%)							
Primary or less	14 666 (59.5)	5211 (72.1)	2632 (46.5)	4806 (66.4)	1311 (38.5)	5739 (60.2)	8927 (59.0)
Secondary	5897 (23.9)	1665 (23.0)	1178 (20.8)	1419 (19.6)	1418 (41.6)	2136 (22.4)	3761 (24.9)
Trade/college/university	4085 (16.6)	355 (4.9)	1851 (32.7)	1016 (14.0)	677 (19.9)	1653 (17.3)	2432 (16.1)
Tobacco use, *n* (%)							
Current	5071 (20.6)	1919 (26.5)	1128 (19.9)	1009 (13.9)	829 (24.6)	2335 (24.6)	2736 (18.1)
Former	5600 (22.8)	1585 (21.9)	1500 (26.5)	1469 (20.3)	651 (19.3)	2995 (31.5)	2605 (17.2)
Never	13 935 (56.6)	3730 (51.6)	3032 (53.6)	4760 (65.8)	1886 (56.0)	4174 (43.9)	9761 (64.6)
Alcohol use, *n* (%)							
Current: low	7423 (30.4)	2746 (38.0)	1884 (33.3)	1204 (17.1)	1327 (39.2)	3393 (36.0)	4030 (26.9)
Current: moderate	1759 (7.2)	950 (13.2)	290 (5.1)	396 (5.6)	56 (1.7)	1350 (14.3)	409 (2.7)
Current: high	1213 (5.0)	810 (11.2)	96 (1.7)	255 (3.6)	9 (0.3)	923 (9.8)	290 (1.9)
Former	2289 (9.4)	402 (5.6)	455 (8.1)	1106 (15.7)	134 (4.0)	1313 (13.9)	976 (6.5)
Never	11 714 (48.0)	2314 (32.0)	2927 (51.8)	4075 (57.9)	1856 (54.9)	2456 (26.0)	9258 (61.9)
Diet score, mean (SD)	4.71 (1.7)	3.97 (1.3)	6.02 (1.3)	4.89 (1.5)	3.68 (1.6)	4.73 (1.7)	4.69 (1.6)
Physical activity, *n* (%)							
Low	3256 (13.8)	621 (8.8)	555 (10.4)	1199 (17.8)	686 (20.6)	1493 (16.8)	1763 (12.1)
Moderate	7562 (32.1)	1962 (27.9)	1656 (30.9)	2292 (34.0)	1275 (38.3)	2580 (28.9)	4982 (34.1)
High	12 718 (54.0)	4447 (63.3)	3151 (58.8)	3241 (48.1)	1368 (41.1)	4840 (54.3)	7878 (53.9)
BMI, kg/m^2, mean (SD)	28.2 (5.5)	29.45 (6.1)	27.78 (5.0)	26.25 (4.7)	29.77 (5.1)	27. 7 (4.9)	28.5 (5.8)
WHR >0.9 in men or >0.85 in women, *n* (%)	15 686 (65.9)	4301 (59.7)	3839 (73.9)	4186 (58.2)	2544 (81.0)	6911 (75.5)	8775 (60.0)
Lipid measures, mmol/L, mean (SD)							
Total cholesterol	5.21 (1.1)	5.22 (1.1)	5.12 (1.0)	5.20 (1.2)	5.41 (1.2)	5.16 (1.1)	5.24 (1.1)
LDL cholesterol	3.25 (0.9)	3.26 (0.9)	3.16 (0.8)	3.26 (0.9)	3.42 (0.9)	3.23 (0.9)	3.26 (0.9)
HDL cholesterol	1.19 (0.3)	1.24 (0.3)	1.21 (0.3)	1.11 (0.3)	1.16 (0.3)	1.11 (0.3)	1.24 (0.3)
Non-HDL cholesterol	4.02 (1.1)	3.98 (1.1)	3.91 (1.0)	4.09 (1.1)	4.25 (1.2)	4.05 (1.1)	4.01 (1.1)
Hypertension, *n* (%)	11 094 (46.5)	3575 (49.6)	2635 (50.7)	2666 (36.9)	1461 (46.2)	4634 (50.5)	6460 (44.0)
Diabetes, *n* (%)	2332 (9.4)	670 (9.3)	509 (9.0)	470 (6.5)	429 (12.4)	940 (9.8)	1392 (9.2)
Grip strength, kg, mean (SD)	31.5 (11.3)	33.13 (11.4)	35.51 (10.0)	29.47 (10.9)	25.95 (11.0)	40.7 (10.2)	25.7 (7.4)
Depression, *n* (%)	5257 (21.4)	1335 (18.5)	1414 (25.0)	1369 (18.9)	782 (23.0)	1227 (12.9)	4030 (26.7)
Household air pollution, *n* (%)	2494 (11.4)	82 (1.2)	233 (5.0)	1337 (20.2)	759 (26.6)	1037 (12.7)	1457 (10.7)

BMI, body mass index; SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; WHR, waist-to-hip ratio.

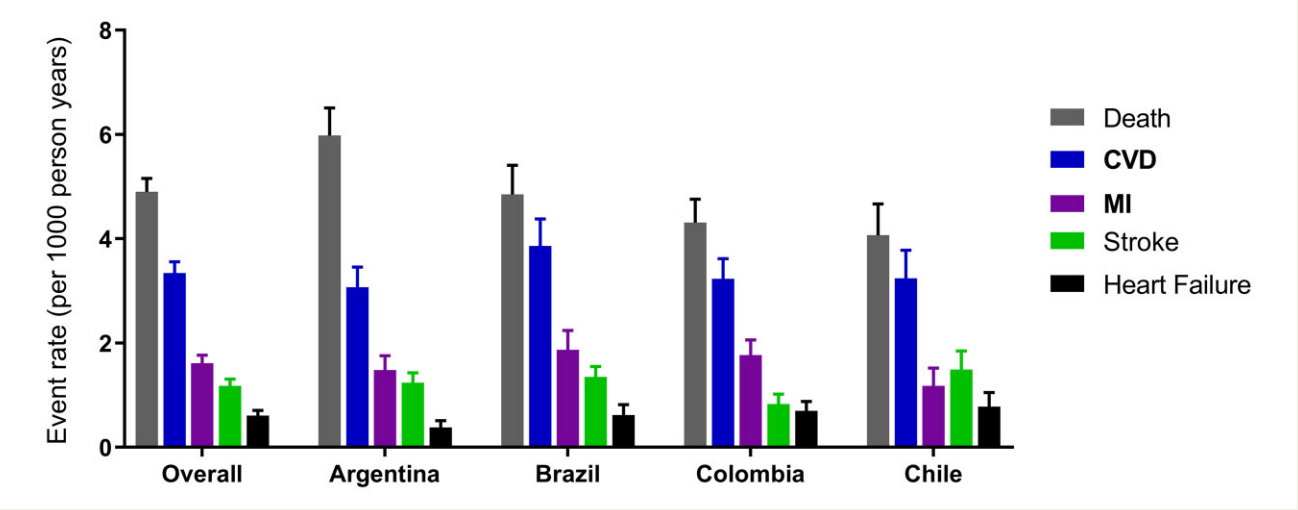


Figure 1 Age- and sex-standardized incidence of cardiovascular disease events and rates of death in Argentina, Brazil, Colombia, and Chile. CVD, cardiovascular disease; MI, myocardial infarction.

contributed to 2% or less of the PAF for death (*Figure 4* and Supplementary material online, *Table S6*).

Population attributable fractions for myocardial infarction and stroke

For MI, the five largest risk factors were abdominal obesity (PAF of 17.3%), tobacco use (13.4%), high non-HDL cholesterol (13.3%), hypertension (11.8%), and low strength (8.3%). The five largest risk factors for stroke were hypertension (PAF of 22.4%), tobacco use (15.9%), abdominal obesity (10.8%), poor diet (9.9%), and diabetes (5.2%).

Population attributable fractions for cardiovascular disease and for death by sex

In women, the five largest risk factors for CVD were hypertension (PAF of 17.4%), abdominal obesity (16.2%), tobacco use (10.4%), diabetes (5.3%), and poor diet (5.2%). In men, hypertension (20.2%), tobacco use (17.5%), abdominal obesity (12.3%), low strength (8.3%), and low education level (5.1%) were the largest risk factors. In women, the five largest risk factors for death were low education level (PAF of 13.0%), hypertension (12.2%), tobacco use (10.7%), abdominal obesity (10.1%), and diabetes (5.3%). In men, tobacco use (17.8%), hypertension (11.9%), low education level (8.6%), abdominal obesity (8.3%), and low strength (7.7%) were the largest risk factors.

Population attributable fractions for cardiovascular disease and for death in urban or rural areas

In urban areas, the five largest risk factors for CVD were hypertension (PAF of 20.7%), abdominal obesity (16.7%), tobacco use (12.3%), poor diet (7.7%), and low strength (5.8%). In rural areas, the five largest risk

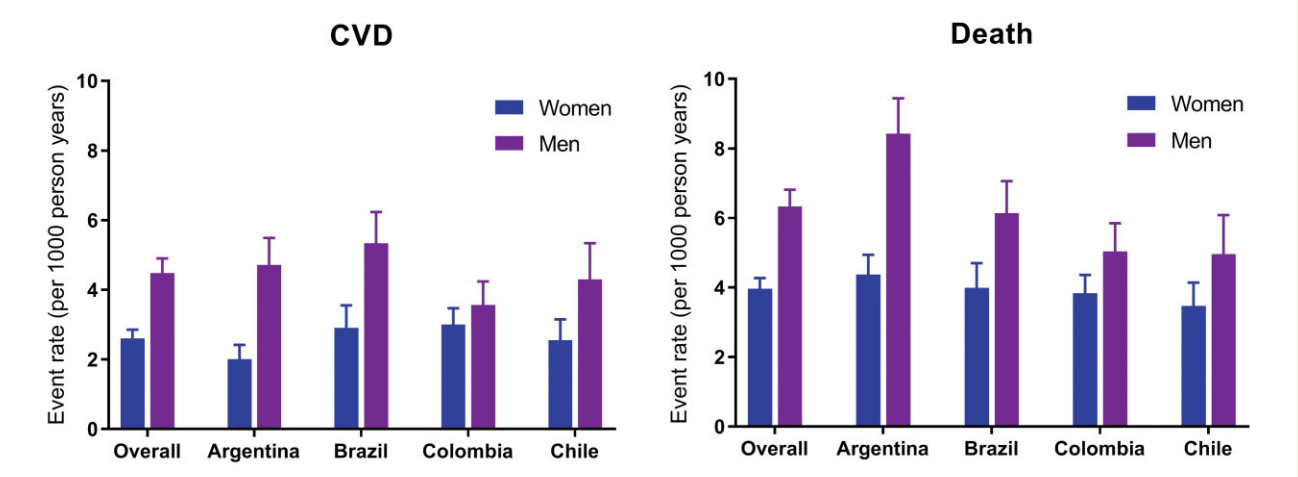


Figure 2 Age-standardized incidence of cardiovascular disease events and rates of death in men and women. CVD, cardiovascular disease; MI, myocardial infarction.

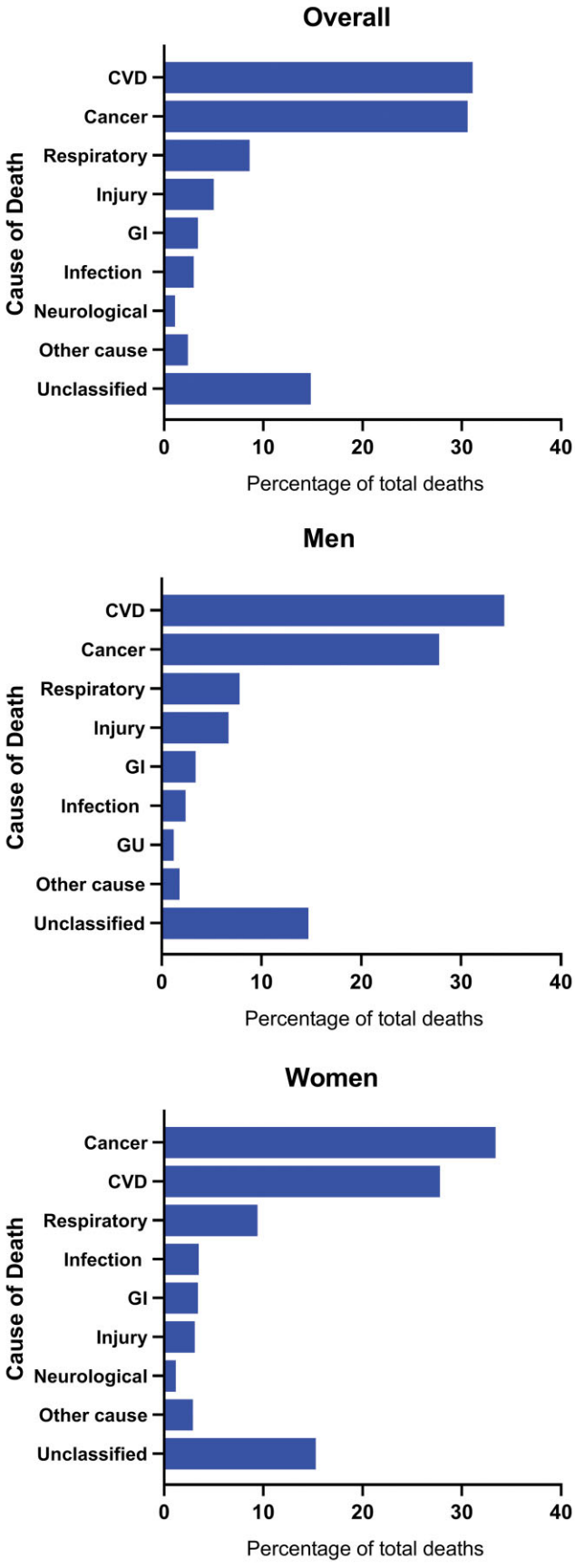


Figure 3 Leading causes of death overall, and by sex. CVD, cardiovascular disease; GI, gastrointestinal; GU, genitourinary.

Table 2 Associations between modifiable risk factors, cardiovascular disease, and deaths

Exposure	Death	CVD	MI	Stroke
Education				
Trade/college/university	Reference	Reference	Reference	Reference
Secondary	1.07 (0.85, 1.33)	0.92 (0.71, 1.19)	0.85 (0.58, 1.25)	1.15 (0.76, 1.74)
Primary or less	1.26 (1.03, 1.55)	1.05 (0.82, 1.33)	0.99 (0.70, 1.41)	1.08 (0.73, 1.60)
Tobacco use				
Never	Reference	Reference	Reference	Reference
Former	1.19 (1.02, 1.38)	1.40 (1.16, 1.69)	1.24 (0.93, 1.65)	1.55 (1.15, 2.10)
Current	2.16 (1.87, 2.49)	2.18 (1.81, 2.64)	2.46 (1.88, 3.21)	1.97 (1.43, 2.71)
Alcohol use				
Never	Reference	Reference	Reference	Reference
Former	1.32 (1.09, 1.61)	1.09 (0.85, 1.40)	1.01 (0.71, 1.44)	1.30 (0.87, 1.95)
Current: low	0.92 (0.79, 1.06)	0.75 (0.62, 0.91)	0.70 (0.53, 0.94)	0.89 (0.66, 1.21)
Current: moderate	0.82 (0.65, 1.04)	0.86 (0.64, 1.14)	0.80 (0.53, 1.20)	0.88 (0.53, 1.44)
Current: high	1.13 (0.89, 1.43)	0.73 (0.51, 1.04)	0.62 (0.37, 1.03)	1.06 (0.63, 1.80)
Diet score				
>4	Reference	Reference	Reference	Reference
3–4	1.00 (0.88, 1.14)	1.22 (1.03, 1.45)	1.08 (0.84, 1.38)	1.37 (1.04, 1.79)
≤2	1.07 (0.88, 1.31)	1.15 (0.88, 1.51)	0.97 (0.65, 1.44)	1.42 (0.94, 2.15)
Physical activity				
High	Reference	Reference	Reference	Reference
Moderate	1.27 (1.12, 1.45)	1.23 (1.04, 1.45)	1.19 (0.93, 1.53)	1.15 (0.88, 1.51)
Low	1.76 (1.50, 2.06)	1.37 (1.11, 1.70)	1.36 (1.00, 1.85)	1.13 (0.79, 1.62)
Hypertension	1.34 (1.18, 1.53)	1.77 (1.49, 2.10)	1.49 (1.16, 1.90)	1.85 (1.38, 2.46)
Diabetes	1.72 (1.49, 2.00)	1.85 (1.53, 2.23)	1.74 (1.32, 2.30)	2.13 (1.59, 2.85)
Non-HDL cholesterol (mmol/L)				
≤3.2	Reference	Reference	Reference	Reference
3.2–4.0	0.87 (0.74, 1.02)	0.89 (0.70, 1.12)	0.96 (0.66, 1.38)	0.90 (0.64, 1.27)
>4.0	0.81 (0.70, 0.94)	1.06 (0.86, 1.30)	1.48 (1.08, 2.04)	0.74 (0.54, 1.02)
Abdominal obesity	1.25 (1.08, 1.44)	1.44 (1.18, 1.75)	1.55 (1.16, 2.07)	1.27 (0.93, 1.73)
Grip strength				
Depression	1.05 (0.90, 1.22)	1.19 (0.98, 1.44)	1.42 (1.09, 1.85)	1.14 (0.83, 1.55)
Household air pollution	1.06 (0.87, 1.29)	0.87 (0.67, 1.13)	0.76 (0.52, 1.11)	0.81 (0.53, 1.25)
Quintile 5	Reference	Reference	Reference	Reference
Quintile 4	1.06 (0.88, 1.29)	1.15 (0.89, 1.48)	1.20 (0.83, 1.73)	1.15 (0.75, 1.78)
Quintile 3	1.06 (0.87, 1.28)	1.14 (0.89, 1.47)	1.11 (0.76, 1.61)	1.53 (1.02, 2.31)
Quintile 2	1.17 (0.96, 1.41)	1.28 (1.00, 1.64)	1.49 (1.04, 2.13)	1.43 (0.95, 2.17)
Quintile 1	1.36 (1.10, 1.67)	1.33 (1.01, 1.74)	1.48 (1.00, 2.21)	1.50 (0.96, 2.35)

All hazard ratios were mutually adjusted for age, sex, urban–rural location, and all 12 modifiable risk factors of interest.
CVD, cardiovascular disease; HDL, high density lipoprotein; MI, myocardial infarction.

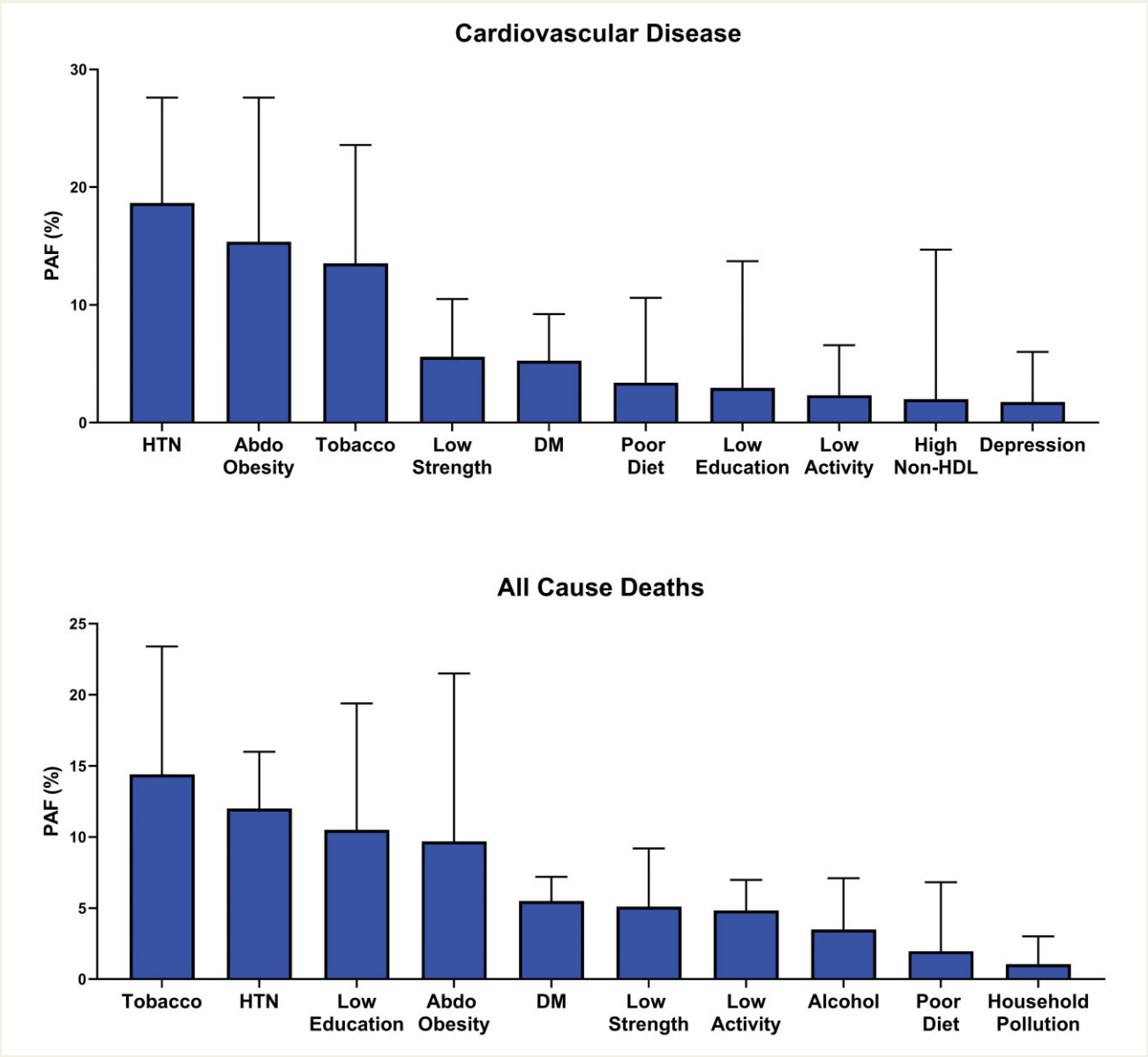


Figure 4 Population attributable fractions for cardiovascular disease events and death for the 10 largest modifiable risk factors for each outcome. PAF, population attributable fraction; DM, diabetes mellitus; HTN, hypertension.

factors for CVD were hypertension (16.2%), tobacco use (15.5%), low education (12.5%), abdominal obesity (11.1%), and low strength (5.4%). In urban areas, the largest risk factors for death were tobacco use (PAF of 16.5%), hypertension (11.8%), abdominal obesity (11.8%), low education (8.4%), and diabetes (6.0%). In rural areas, the largest risk factors were hypertension (12.3%), tobacco use (12.3%), low education (9.9%), abdominal obesity (7.5%), and low strength (5.4%)

Population attributable risk estimation using a sequential approach

The average PAF approach for our main analysis estimated the effect of a given risk factor using a mutually adjusted model. Sequential analysis of PAF using a model-based standardization approach could theoretically lead to larger estimates for upstream risk factors (e.g. education, behavioural risk factors). However, causal pathways have not been established for many risk factors we chose to study, limiting the applicability of this approach in our analysis. We performed an exploratory analysis using a model-based standardization approach, and the rank-order of risk factors was generally consistent with our main analysis, with the exception of low education, which was comparatively larger using a sequential approach (Supplementary material online, Appendix).

Discussion

To our knowledge, this is the largest prospective study to directly compare rates of CVD, death, and impact of multiple risk factors for both outcomes in South America. Over two-thirds of deaths in

the region were due to either CVD, cancer, or respiratory diseases. Deaths due to cancers were almost as common as those due to CVD, which may be due to a larger decline in CVD death rates compared with cancer death rates in the region over the past few decades.[5] In women, cancer surpassed CVD as the leading cause of death. Only modest variations in the incidence of CVD were observed between countries. Age- and sex-adjusted mortality rates varied to a larger extent between countries than that of CVD, with the highest rate of death in Argentina and lowest in Chile. In all countries, men experienced higher rates of CVD and deaths compared with women. Death was also consistently higher in rural areas in all countries (*Structured Graphical Abstract*).

Incident CVD was largely attributable to 12 modifiable risk factors, which together explained ~72% of its PAF in the region. As a group, metabolic risk factors were the predominant risk factors for CVD. The largest PAFs for CVD were from hypertension, smoking, and abdominal obesity, which collectively accounted for almost 50% of the population-level risk, and suggest that substantial reductions in CVD could be achieved by focusing on these three risk factors. While high non-HDL cholesterol only modestly contributed to the PAF for overall CVD, it was the third leading risk factor for MI. This is consistent with prior data suggesting that the risk associated with elevated cholesterol is larger for coronary artery disease compared with other CVD outcomes (such as stroke or heart failure), and therefore strategies to reduce cholesterol should remain an important health priority in the region.[8] Our finding that the largest population-level risk factors of MI were related to abdominal obesity, elevated lipids, and tobacco use is consistent with prior observations from the INTERHEART Latin American substudy where these three risk factors were also associated with the largest population-level risks.[17]

Hypertension, tobacco use, and obesity (in addition to low education level) were the leading risk factors for death in the region. Compared with our prior findings in PURE by country income level, and in other regions of the world, the similar contribution of metabolic risk factors and tobacco use to CVD and to death is what has been mainly observed in high-income countries rather than other middle-income countries, likely reflecting the epidemiological transition in South America to non-communicable diseases accounting for the vast majority of deaths.[8] The shared impact of these risk factors on both CVD and premature mortality also highlights that policies focused on their control would have a substantial impact on the health of the South American population. Key policies to reduce tobacco use have been generally well adopted in South America over the past 15 years, resulting in larger reductions in smoking prevalence compared with many other regions of the world.[18] Continued diligence to controlling tobacco use will have large benefits for preventing CVD and premature deaths in the population. Metabolic risk factor control remains a challenge. For example, while hypertension awareness and treatment are high in the South American countries that we studied, <40% of those treated achieve target blood pressure levels.[19] Improving metabolic risk factor control will require understanding context-specific barriers that limit care and system-level changes directed at overcoming these barriers.[20] In Colombia, we recently demonstrated the effectiveness of a community-level intervention that included treatment of CVD risk factors by non-physician health workers (NPHWs) using simplified management algorithms and counselling programmes; free antihypertensive and statin medications recommended by NPHWs supervised by physicians; and support from a family member or friend (treatment supporter) to improve adherence. This strategy increased hypertensive control from 11.5 to 68.9%, and could be widely applicable in the region.[21]

A consistent finding across all countries studied was that men experienced more CVD events and also died at a higher rate than women. This is in part due to the higher burden of metabolic risk factors and prevalence of tobacco use in men compared with women. Prior studies also report poorer control of cardiovascular risk factors in men.[22] Interestingly, we observed that many leading risk factors for CVD and death were shared among men and women. In both sexes, hypertension, abdominal obesity, and tobacco use were leading risk factors for CVD and for death, favouring the broad implementation of strategies aimed controlling these risk factors in both men and women. While women had lower rates of death compared with men, the adverse impact of low education was particularly striking in women, where it was the leading health determinant for death. Low education can impact survival through a broad range of downstream effects, including income inequality, occupation, community-level factors, and access to health care services; and further studies are needed to examine how these downstream effects potentially differ in men and women in the region.

Our study has some potential limitations. Since our data are based on four countries, results may not be generalizable to all South American countries. Moreover, within countries, the recruitment of participants was from a single province in Argentina, Brazil, and Chile, although in Colombia, participants were recruited from 10 provinces. The study also enrolled a higher proportion of women compared with the general population. However, data were collected from 100 communities with wide geographic spread, so our study likely mirrors the substantial diversity of the subcontinent's population. This differs from most studies that included individuals from only a single or at most few communities and almost always from a single country. Ideally, even larger studies in South America with representation from several states in each country as well as the involvement of additional countries are desirable. However, such large prospective studies are difficult to organize and fund and they are unlikely to be done in the foreseeable future. Although some misclassification of baseline risk factors is possible when self-reported, many risk factors were derived or supplemented with objective measures (e.g. blood pressure, plasma lipid concentration, grip strength, and anthropometry), or self-reported using validated instruments (e.g. physical activity and food frequency questionnaire) which would reduce this risk. We have not included information on ambient air pollution as this requires different approaches to analyses, and variation in this exposure is relatively small within a single region. It is likely that outdoor air pollution is an important risk factor for CVD as shown in several studies including the analysis of the global PURE study.[23]

In conclusion, CVD, cancer, and respiratory diseases account for more than two-thirds of deaths in the region. Although some variations in CVD and deaths occur between countries, men consistently experience worse outcomes than women across the region, and deaths are consistently higher in rural areas. A large proportion of CVD and deaths are attributable to a small number of modifiable risk factors. Strategies focused on reducing metabolic risk factors

and tobacco use are key to preventing both CVD and premature mortality in the region.

Authors' contributions

P.L.-J., P.J., and S.Y. contributed to the conception of the paper. S.I., P.L.-J., P.J., and S.Y. contributed to data analysis or interpretation. P.S., G.O., S.R., and A.O. conducted the study in different countries. P.L.-J., P.J., J.P.L.-L., F.L., A.A., and S.Y. significantly contributed to drafting the manuscript. F.L., S.R., and R.D. contributed to revising it critically for intellectual content.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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A full list of additional persons who have contributed to this PURE substudy is provided in Supplementary material online, Appendix, and we wish to acknowledge them for their contributions.

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Conflict of interest: The authors report research funding related to the PURE study, which is summarized in the Funding section. A.A. reports speaking fees and is an advisory board member for Novartis pharmaceuticals. No additional disclosures are reported by the authors.

Data availability

The PURE study is ongoing and data are not currently publicly available. Formal collaboration with other groups with similar data for expanded and pooled analyses will be considered.

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