Associations of outdoor fine particulate air pollution and cardiovascular disease in 157 436 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

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Summary

Background Most studies of long-term exposure to outdoor fine particulate matter ($PM_{2·5}$) and cardiovascular disease are from high-income countries with relatively low $PM_{2·5}$ concentrations. It is unclear whether risks are similar in low-income and middle-income countries (LMICs) and how outdoor $PM_{2·5}$ contributes to the global burden of cardiovascular disease. In our analysis of the Prospective Urban and Rural Epidemiology (PURE) study, we aimed to investigate the association between long-term exposure to $PM_{2·5}$ concentrations and cardiovascular disease in a large cohort of adults from 21 high-income, middle-income, and low-income countries.

Methods In this multinational, prospective cohort study, we studied 157 436 adults aged 35–70 years who were enrolled in the PURE study in countries with ambient $PM_{2·5}$ estimates, for whom follow-up data were available. Cox proportional hazard frailty models were used to estimate the associations between long-term mean community outdoor $PM_{2·5}$ concentrations and cardiovascular disease events (fatal and non-fatal), cardiovascular disease mortality, and other non-accidental mortality.

Findings Between Jan 1, 2003, and July 14, 2018, 157 436 adults from 747 communities in 21 high-income, middle-income, and low-income countries were enrolled and followed up, of whom 140 020 participants resided in LMICs. During a median follow-up period of 9·3 years (IQR 7·8–10·8; corresponding to 1·4 million person-years), we documented 9996 non-accidental deaths, of which 3219 were attributed to cardiovascular disease. 9152 (5·8%) of 157 436 participants had cardiovascular disease events (fatal and non-fatal incident cardiovascular disease), including 4083 myocardial infarctions and 4139 strokes. Mean 3-year $PM_{2·5}$ at cohort baseline was 47·5 μg/m³ (range 6–140). In models adjusted for individual, household, and geographical factors, a 10 μg/m³ increase in $PM_{2·5}$ was associated with increased risk for cardiovascular disease events (hazard ratio 1·05 [95% CI 1·03–1·07]), myocardial infarction (1·03 [1·00–1·05]), stroke (1·07 [1·04–1·10]), and cardiovascular disease mortality (1·03 [1·00–1·05]). Results were similar for LMICs and communities with high $PM_{2·5}$ concentrations (>35 μg/m³). The population attributable fraction for $PM_{2·5}$ in the PURE cohort was 13·9% (95% CI 8·8–18·6) for cardiovascular disease events, 8·4% (0·0–15·4) for myocardial infarction, 19·6% (13·0–25·8) for stroke, and 8·3% (0·0–15·2) for cardiovascular disease mortality. We identified no consistent associations between $PM_{2·5}$ and risk for non-cardiovascular disease deaths.

Interpretation Long-term outdoor $PM_{2·5}$ concentrations were associated with increased risks of cardiovascular disease in adults aged 35–70 years. Air pollution is an important global risk factor for cardiovascular disease and a need exists to reduce air pollution concentrations, especially in LMICs, where air pollution levels are highest.

Funding Full funding sources are listed at the end of the paper (see Acknowledgments).

Introduction

Outdoor fine particulate matter ($PM_{2·5}$) air pollution is an important global risk factor for cardiovascular disease.[1,2] The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017[3] estimated that long-term exposure to ambient $PM_{2·5}$ contributed to 2·9 million deaths (5·2% of all global deaths).Nearly 50% of these deaths were attributable to ischaemic heart disease and stroke, which occur primarily in low-income and middle-income countries (LMICs) where outdoor $PM_{2·5}$ concentrations are especially high.[4]

Direct epidemiological evidence for an association between long-term $PM_{2·5}$ exposure and cardiovascular disease risk is mostly based on studies from high-income

Lancet Planet Health 2020; 4: 235–45

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countries.[5–7] Compared with LMICs, exposure to air pollution is substantially lower in high-income countries and the distribution of cardiovascular disease incidence and risk factors also differ, limiting direct extrapolation of relative and absolute risks from high-income countries to LMICs.[8] Although studies from LMICs have found an association between cardiovascular disease mortality and short-term increases in $PM_{2·5}$ air pollution,[9] few studies of long-term $PM_{2·5}$ effects have been done in these countries.[10–14] For example, the global exposure mortality model for long-term $PM_{2·5}$ exposure and mortality[15] is based on pooled results from 41 cohort studies in 16 countries, of which only one was conducted in an LMIC (China). Another study of all-cause mortality in China was published in 2018, which reported a hazard ratio (HR) of 1·08 (95% CI 1·06–1·09) per 10 μg/m³ $PM_{2·5}$ increase.[11] Furthermore, evidence on specific cardiovascular disease outcomes from LMICs is scarce. An important study in China found large associations between high $PM_{2·5}$ concentrations and stroke incidence (HR 1·13 [95% CI 1·09–1·17] per 10 μg/m³ $PM_{2·5}$ increase).[13] Future studies are needed to replicate these findings and to investigate all types of cardiovascular disease in settings with high $PM_{2·5}$ concentrations in other LMICs.

In our analysis of the Prospective Urban and Rural Epidemiology (PURE) cohort study, we aimed to investigate the association between long-term exposure to $PM_{2·5}$ concentrations and cardiovascular disease in a large cohort of adults from 21 high-income, middle-income, and low-income countries.

Research in context

Evidence before this study

A growing body of evidence indicates an association between cardiovascular disease and ambient fine particulate matter ($PM_{2·5}$) air pollution. However, few prospective studies of $PM_{2·5}$ and cardiovascular disease have been undertaken in developing countries, where 80% of the burden of cardiovascular disease occurs, or in populations exposed to high $PM_{2·5}$ concentrations (eg, above the WHO interim health guideline of >35 μg/m³). To date, only five studies of long-term exposure and cardiovascular disease have been done in populations exposed to high $PM_{2·5}$ concentrations, all of which were done in China. Furthermore, in many large studies, individual-level data were not available for other cardiovascular disease risk factors that might confound associations between $PM_{2·5}$ and cardiovascular disease. The paucity of data on the impact of long-term exposure to air pollution on cardiovascular disease in most low-income and middle-income countries (LMICs), where levels of exposure are high, leads to substantial uncertainty in disease burden assessments.

Added value of this study

We prospectively studied 157 436 adults aged 35–70 years at enrolment from 21 low-income, middle-income, and high-income countries within the Prospective Urban and Rural Epidemiology (PURE) study. We compared long-term outdoor $PM_{2·5}$ concentrations for 747 urban and rural communities with a mean 3-year baseline $PM_{2·5}$ concentration of 47·5 μg/m³ (range 6–140), thereby covering the majority of the global distribution of $PM_{2·5}$ concentrations. We assessed associations between $PM_{2·5}$ concentration and all cardiovascular disease events (fatal and non-fatal) and cardiovascular disease mortality, while adjusting for a comprehensive set of individual, household, and geographical covariates that were collected using a standardised protocol. We observed consistent increases in cardiovascular disease events and mortality across all $PM_{2·5}$ concentrations and in LMICs. The strongest association was identified between stroke and $PM_{2·5}$. No consistent associations were observed for non-cardiovascular disease deaths. By capturing a diverse global population exposed to a wide range of $PM_{2·5}$ concentrations and including standardised objective measures of cardiovascular disease risk factors, this study adds to our understanding of the global impacts of $PM_{2·5}$ air pollution on cardiovascular disease burden.

Implications of all the available evidence

$PM_{2·5}$ is an important global risk factor for cardiovascular disease, especially stroke. A need exists to reduce air pollution concentrations, especially in LMICs, where air pollution levels are highest.

Methods

Study design and participants

The design and methods of the PURE study have been described previously[16–18] and are summarised in the appendix (p 2). Our analysis included individuals aged 35–70 years from 747 urban and rural communities from 21 low-income, middle-income, and high-income countries.[16]

The study was designed to include countries that represented a wide range of socioeconomic levels, on the basis of 2006 World Bank classifications at study entry. We included four high-income countries (Canada, Saudi Arabia, Sweden, United Arab Emirates), seven upper-middle-income countries (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, Turkey), five LMICs (China, Colombia, Iran, Palestine, the Philippines), and five low-income countries (Bangladesh, India, Pakistan, Tanzania, Zimbabwe). We sampled communities, which comprised of urban neighbourhoods or rural villages, and several communities were identified within each centre to represent distinct geographical areas in each country. The study was coordinated by the Population Health Research Institute (Hamilton Health Sciences, Hamilton, ON, Canada) and approved by the Hamilton Health Sciences Research Ethics Board and local ethics committees at each centre.

This analysis included 157 436 adults for whom follow-up data were available, from countries with ambient $PM_{2·5}$ estimates.

Procedures

Data on a comprehensive set of individual and household cardiovascular disease risk factors were collected at study enrolment via standardised protocols. Individual variables were age, sex, smoking status, physical activity (assessed using the International Physical Activity Questionnaire),[19] a healthy eating index (the PURE diet score), baseline cardiovascular disease and other chronic conditions, cardiovascular disease medication use at baseline, arterial hypertension, waist-to-hip ratio, INTERHEART risk score (a composite index of individual risk measures for future cardiovascular disease),[20] level of education, and occupational class. Household variables were household wealth index (asset inventory)[21] and primary use of dirty fuels (ie, solid fuels and kerosene) for cooking as a proxy for household air pollution.[22] Geographical covariates at the community, regional, and national level were location (urban or rural) for each community, country-level gross domestic product (GDP) per capita (standardised to US$), Night Light Development Index score (a global proxy of population density and economic activity),[23] and a measure of health-care access and quality (regional level for China and India; national level for other countries).[24] All individual, household, and geographical variables are described in the appendix (p 3).

We contacted participants at least every 3 years to ascertain the occurrence of clinical events and vital status. Up to three attempts were made to interview all households, supplemented with administrative health record information when available.[8,17] Data contains mortality for 98·4% and non-fatal cardiovascular disease for 94·1% of participants. All cardiovascular disease events were adjudicated by an expert committee in each country, and to ensure standard classification of events across all countries and over time, a selection of cases was also adjudicated centrally. Event definitions are described in the appendix (p 4).

Assessment of outdoor $PM_{2·5}$ air pollution exposure

Our primary outdoor $PM_{2·5}$ estimates were derived using a Bayesian hierarchical model that integrates $PM_{2·5}$ ground monitor measurements, satellite retrievals of aerosol optical depth, and chemical transport models.[25] This model had high prediction of existing ground based monitors (R^2=0·91; root mean square error 10·7 μg/m³) and was used to estimate global exposures to $PM_{2·5}$ for GBD 2017.[3] 3-year rolling mean $PM_{2·5}$ estimates were available for 2000, 2005, 2010, and 2011–16 at an approximate spatial resolution of 11×11 km. We assigned predicted $PM_{2·5}$ concentrations to global positioning system coordinates for the centre of each PURE community at baseline using data for the nearest available proceding year (eg, 2016 baseline years were assigned 2015 estimates, 2008 baseline years were assigned 2005 estimates). We also did sensitivity analyses to investigate exposures on the basis of an approximate 5-year mean $PM_{2·5}$ concentration before baseline and the mean $PM_{2·5}$ concentration for the entire study period (2001–18). We also did additional sensitivity analyses using a separate widely accepted model of global $PM_{2·5}$ concentrations (appendix p 12).[26]

Outcomes

Outcomes for this analysis were cardiovascular disease events (fatal and non-fatal cardiovascular disease), myocardial infarctions (fatal and non-fatal), strokes (fatal and non-fatal), cardiovascular disease deaths (death from myocardial infarction, stroke, heart failure, and unexpected death without other causes), all non-accidental deaths, and all non-cardiovascular disease deaths.

Statistical analysis

We modelled associations between community $PM_{2·5}$ concentrations and each event definition using Cox proportional hazards frailty models. Person-years of follow-up were calculated from study enrolment to the date of a non-fatal cardiovascular disease event, death, or most recent follow-up. The proportional hazards assumption was assessed using stratified Kaplan-Meier curves with weighted Schoenfeld residuals. The community was included as a random intercept to account for within-community clustering of individuals and the fact that $PM_{2·5}$ was assessed at the community level. For missing individual and household categorical variables, we included a missing data category in analyses. We present HRs and 95% CIs per 10 μg/m³ increase in $PM_{2·5}$.

We present incremental models adjusted for a comprehensive set of individual, household, and community factors. Model 1 included age, sex, baseline year, and a community random intercept. Model 2 included additional individual and household cardiovascular disease risk factors determined a priori (smoking status, physical activity, the PURE diet index, baseline cardiovascular disease and chronic conditions, cardiovascular disease medication use, hypertension, INTERHEART risk score, education, occupational class, household wealth index, and dirty fuel use for cooking). Model 3 was our a priori preferred model adjusted for geographical covariates (urban or rural location, country baseline GDP per capita, Night Light Development Index score, and a Healthcare Access and Quality Index score). For Model 3, we assessed the shape of the concentration–response curve using risk functions that capture a variety of potentially non-linear associations,[27] an approach used previously to estimate the global exposure–response association for $PM_{2·5}$ and mortality.[15] We also repeated models 1–3 with categorical $PM_{2·5}$ quintiles, whereby the lowest $PM_{2·5}$ quintile was the reference group. We ran models for all PURE participants (n=157 436) and participants residing in LMICs (n=140 020).

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See **Online** for appendix

The PURE cohort is distributed across diverse urban and rural communities, with unique local and regional contexts that can influence both $PM_{2·5}$ concentrations and cardiovascular disease. We created two additional models to assess unmeasured community and centre confounding. Model 4 included all variables in model 3 with a nested random intercept for communities by centre and subdivided by urban and rural areas (n=89), to control for the PURE urban–rural sampling method. Model 5 included all variables in model 3 plus centre-specific urban–rural indicators, to control for unmeasured differences between centres and urban–rural areas.

We did subgroup analyses to assess potential differences in the associations between $PM_{2·5}$ and cardiovascular disease using model 3. We stratified by subgroups of sex, age, smoking status, household wealth index, education, cooking fuel, urban–rural community context, country income status (high-income countries or upper-middle-income countries *vs* LMICs or low-income countries), and $PM_{2·5}$ concentrations relative to the WHO interim target (<35 μg/m³ or ≥35 μg/m³). Statistically significant differences (p<0·05) between strata were tested using interaction terms between subgroup variables and $PM_{2·5}$.

We also did five additional types of sensitivity analyses to assess the robustness of our results. First, we ran models with different $PM_{2·5}$ exposure periods including 5-year means at baseline and mean $PM_{2·5}$ concentration between 2001 and 2018. Second, we assessed results using a separate global $PM_{2·5}$ exposure model, which included $PM_{2·5}$ estimates from all sources and with dust and salt removed.[26] Third, we restricted models on the basis of community size to evaluate potential differences in $PM_{2·5}$ exposure measurement error. Fourth, we examined the influence of community temperature, green space, and traffic related air pollution on $PM_{2·5}$ model results (appendix p 4). Fifth, we examined incremental models by removing each covariate in model 3 to examine model sensitivity to individual covariates.

We calculated population-attributable fractions[28] using HRs from model 3 and PURE community $PM_{2·5}$ baseline estimates with a $PM_{2·5}$ counterfactual of 10 μg/m³ (ie, the current WHO air quality guideline).

All analyses were done using SAS (version 9.4) and R (version 3.4.2) statistical software.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2003, and July 14, 2018, 157 436 adults from 21 high-income, middle-income, and low-income countries were enrolled and followed up, of whom 140 020 participants resided in LMICs. The mean age of participants at enrolment was 50·2 years (SD 9·7) and 58% of participants were women. During a median follow-up period of 9·3 years (IQR 7·8–10·8; corresponding to 1·4 million person-years), we documented 9996 non-accidental deaths, of which 3219 were attributed to cardiovascular disease. Other common causes of classified death included cancers (19%), respiratory diseases (6%), infections (5%), renal disease (2%), and endocrine or metabolic diseases (2%). 9152 (5·8%) of 157 436 participants had cardiovascular disease events (fatal and non-fatal incident cardiovascular disease), including 4083 myocardial infarctions and 4139 strokes.

The mean 3-year $PM_{2·5}$ concentration at baseline was 47·5 μg/m³ (SD 32·6), ranging from 6 μg/m³ in Vancouver (BC, Canada) to 140 μg/m³ in Jaipur (India; figure 1). $PM_{2·5}$ exposure quintiles were: quintile 1 (<17·3 μg/m³); quintile 2 (>17·3–27·1 μg/m³); quintile 3 (>27·1–47·3 μg/m³); quintile 4 (>47·3–77·9 μg/m³); and quintile 5 (>77·9 μg/m³). Correlations between $PM_{2·5}$ concentrations for 3-year

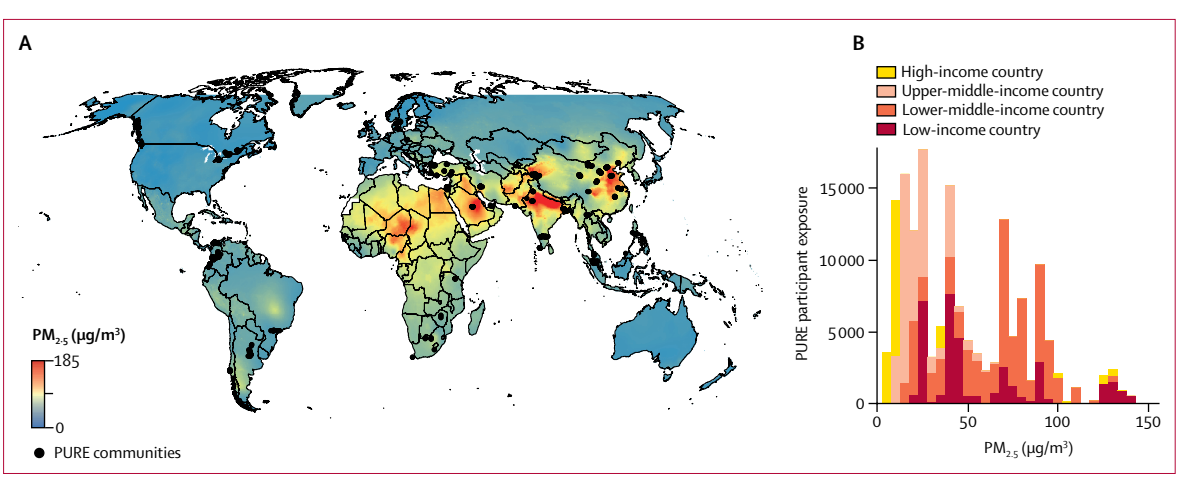

Figure 1: **Location of PURE communities and 2009–11 mean $PM_{2·5}$ concentrations**
(A) Map of PURE communities. (B) Histogram of 3-year mean $PM_{2·5}$ concentrations at baseline for 157 436 PURE participants.

	Overall (n=157 436)	Quintile 1 (n=31 283)	Quintile 2 (n=30 776)	Quintile 3 (n=31 512)	Quintile 4 (n=31 687)	Quintile 5 (n=32 178)
Ambient $PM_{2·5}$ air pollution (μg/m³)	47·5 (32·5)	12·2 (3·7)	22·0 (2·9)	38·5 (4·9)	65·2 (8·9)	97·6 (17·7)
Total follow-up, person-years	1 410 528	281 059	263 513	299 450	275 899	290 607
Communities	747	139	113	180	147	168
Age, years	50·2 (9·7)	52·4 (9·4)	50·9 (9·6)	49·0 (9·7)	50·1 (9·5)	50·6 (10·3)
Sex						
Women	91 243 (58·0%)	17 671 (56·5%)	18 943 (61·6%)	17 894 (56·8%)	18 534 (58·5%)	18 201 (56·6%)
Men	66 193 (42·0%)	13 612 (43·5%)	11 833 (38·4%)	13 618 (43·2%)	13 153 (41·5%)	13 977 (43·4%)
Smoking status*						
Current	32 936 (20·9%)	5865 (18·8%)	4976 (16·2%)	7912 (25·1%)	7713 (24·3%)	6470 (20·1%)
Former	17 382 (11·0%)	7801 (24·9%)	4079 (13·3%)	2543 (8·1%)	1496 (4·7%)	1463 (4·6%)
Never	105 571 (67·1%)	17 454 (55·8%)	21 467 (69·8%)	20 842 (66·1%)	21 953 (69·3%)	23 855 (74·1%)
Physical activity*						
Low	26 732 (17·0%)	3924 (12·5%)	5103 (16·6%)	5829 (18·5%)	5369 (16·9%)	6507 (20·2%)
Moderate	54 797 (34·8%)	9240 (29·5%)	9554 (31·0%)	10 879 (34·5%)	13 436 (42·4%)	11 688 (36·3%)
High	64 359 (40·9%)	15 826 (50·6%)	12 681 (41·2%)	12 353 (39·2%)	11 353 (35·8%)	12 146 (37·8%)
PURE diet score	4·0 (1·9)	4·9 (1·8)	4·3 (1·8)	3·6 (2·1)	3·4 (1·8)	3·7 (1·9)
Abdominal obesity†	74 917 (47·6%)	17 299 (55·3%)	14 841 (48·2%)	13 103 (41·6%)	14 509 (45·8%)	15 165 (47·1%)
INTERHEART risk score‡	10·2 (5·8)	12·9 (6·2)	10·5 (5·9)	9·1 (5·6)	9·4 (5·3)	9·2 (5·3)
Chronic condition§	29 674 (18·8%)	6867 (22·0%)	6765 (21·9%)	5983 (19·0%)	4746 (15·0%)	5313 (16·5%)
Cardiovascular disease at baseline	11 812 (7·5%)	2460 (7·9%)	2289 (7·4%)	2089 (6·6%)	2456 (7·8%)	2518 (7·8%)
Medications for cardiovascular disease (%)	26 089 (16·6%)	7973 (25·5%)	5315 (17·3%)	4719 (15·0%)	3929 (12·4%)	4153 (12·9%)
Hypertension	59 932 (38·1%)	13 425 (42·9%)	12 191 (39·6%)	9560 (30·3%)	11 699 (36·9%)	13 057 (40·6%)
Solid fuel use for cooking	40 227 (25·6%)	1174 (3·8%)	7192 (23·4%)	11 100 (35·2%)	12 536 (39·6%)	8225 (25·6%)
Education*						
Primary school or less	67 255 (42·7%)	12 765 (40·9%)	11 696 (38·0%)	17 105 (54·3%)	14 660 (46·3%)	11 029 (34·3%)
Secondary school	59 564 (37·8%)	8544 (40·8%)	12 762 (41·5%)	10 152 (32·2%)	13 982 (44·1%)	14 124 (43·9%)
Post-secondary school	30 145 (19·2%)	9913 (31·7%)	6262 (20·4%)	4055 (12·9%)	2951 (9·3%)	6964 (21·6%)
Household wealth index*						
Tertile 1	49 471 (31·4%)	11 439 (36·6%)	7489 (24·3%)	11 978 (38·0%)	10 713 (33·8%)	7852 (24·4%)
Tertile 2	51 213 (32·5%)	10 294 (32·9%)	10 959 (35·6%)	9363 (29·7%)	11 384 (35·9%)	9213 (28·6%)
Tertile 3	52 903 (33·6%)	9421 (30·1%)	12 018 (39·1%)	9588 (30·4%)	8446 (26·7%)	13 430 (41·7%)
Unskilled worker	32 045 (20·4%)	4406 (14·1%)	4221 (13·7%)	6339 (20·1%)	8581 (27·1%)	8498 (26·4%)
Area of residence						
Urban	83 887 (53·3%)	16 310 (52·1%)	17 062 (55·4%)	17 042 (54·1%)	11 459 (36·2%)	22 014 (68·4%)
Rural	73 549 (46·7%)	14 973 (47·9%)	13 714 (44·6%)	14 470 (45·9%)	20 228 (63·8%)	10 164 (31·6%)
Country GDP per capita, $US	8488 (13 399)	25 622 (19 956)	5506 (3635)	5891 (9374)	2696 (1880)	2932 (4958)
Night Light Development Index score¶	29·3 (39·4)	18·9 (20·5)	37·5 (47·2)	19·1 (24·2)	22·6 (35·6)	48·1 (50·6)
Healthcare Access and Quality Index score‖	65·1 (16·3)	77·4 (14·8)	58·8 (11·5)	55·6 (13·5)	68·2 (15·8)	65·6 (16·1)
Country income category**						
High-income country	17 417 (11·1%)	14 410 (46·1%)	0	1489 (4·7%)	0	1518 (4·7%)
Upper-middle-income country	41 647 (26·5%)	15 714 (50·2%)	15 985 (51·9%)	8593 (27·3%)	1355 (4·3%)	0
Lower-middle-income country	63 712 (40·5%)	1159 (3·7%)	6928 (22·5%)	8793 (27·9%)	24 366 (76·9%)	22 466 (69·8%)
Low-income country	34 660 (22·0%)	0	7863 (25·6%)	12 637 (40·1%)	5966 (18·8%)	8194 (25·5%)

Data are mean (SD), n, or n (%). $PM_{2·5}$ exposure quintiles were: quintile 1 (<17·3 μg/m³); quintile 2 (>17·3–27·1 μg/m³); quintile 3 (>27·1–47·3 μg/m³); quintile 4 (>47·3–77·9 μg/m³); and quintile 5 (>77·9 μg/m³). GDP=gross domestic product. *Data were missing for these variables, thus values in columns do not sum to the overall column totals. †Defined as a waist-to-hip ratio of ≥0·9 for men and ≥0·85 for women. ‡Composite index of individual risk measures, whereby a higher index score equates to higher cardiovascular disease risk. §Baseline chronic conditions included cardiovascular disease, cancers, diabetes, chronic obstructive pulmonary disease, asthma, tuberculosis, and HIV/AIDS. ¶Proxy measure of local population density and economic activity, whereby a higher index score represents a larger population and higher economic activity. ‖Measure based on causes of death that should not occur in the presence of effective health care (higher index scores equate to better healthcare). **Defined according to 2006 World Bank classification at time of study entry.

Table 1: **Population characteristics of the study population overall and by $PM_{2·5}$ concentration quintile**

	Events, n	Main models			Models controlling for unmeasured contextual factors	
		Model 1	Model 2	Model 3	Model 4	Model 5
All countries (n=157 436)*						
Major cardiovascular disease†	9152	1·09 (1·07–1·11)	1·08 (1·06–1·09)	1·05 (1·03–1·07)	1·05 (1·02–1·08)	1·08 (1·01–1·16)
Myocardial infarction	4083	1·07 (1·05–1·10)	1·06 (1·03–1·08)	1·03 (1·00–1·06)	1·04 (0·99–1·09)	1·11 (1·02–1·21)
Stroke	4139	1·13 (1·10–1·15)	1·12 (1·09–1·14)	1·07 (1·05–1·10)	1·07 (1·03–1·11)	1·11 (1·00–1·22)
Cardiovascular disease mortality	3219	1·07 (1·04–1·10)	1·04 (1·02–1·07)	1·03 (1·00–1·06)	1·05 (1·01–1·09)	1·12 (1·02–1·23)
Non-accidental mortality‡	9996	1·01 (0·99–1·03)	0·99 (0·97–1·00)	0·98 (0·96–0·99)	0·98 (0·95–1·01)	1·08 (1·01–1·15)
Non-cardiovascular disease mortality	6777	0·96 (0·94–0·99)	0·94 (0·92–0·96)	0·94 (0·93–0·96)	0·94 (0·92–0·97)	1·05 (0·98–1·13)
LMICs (n=140 020)§						
Major cardiovascular disease†	8374	1·09 (1·07–1·11)	1·10 (1·08–1·12)	1·05 (1·03–1·08)	1·05 (1·02–1·08)	1·09 (1·02–1·17)
Myocardial infarction	3699	1·07 (1·04–1·10)	1·08 (1·05–1·11)	1·02 (0·99–1·05)	1·04 (0·99–1·10)	1·11 (1·02–1·22)
Stroke	3849	1·14 (1·11–1·17)	1·15 (1·12–1·18)	1·09 (1·06–1·12)	1·07 (1·02–1·12)	1·12 (1·01–1·25)
Cardiovascular disease mortality	3108	1·02 (0·99–1·05)	1·03 (1·00–1·06)	1·03 (1·00–1·06)	1·05 (1·00–1·09)	1·12 (1·02–1·24)
Non-accidental mortality‡	9451	0·97 (0·95–1·00)	0·97 (0·95–0·99)	0·98 (0·96–1·00)	1·00 (0·97–1·03)	1·08 (1·00–1·15)
Non-cardiovascular disease mortality	6343	0·93 (0·91–0·95)	0·93 (0·91–0·95)	0·95 (0·93–0·97)	0·96 (0·93–1·00)	1·06 (0·98–1·14)

Data are hazard ratios per 10 μg/m³ $PM_{2·5}$ increase (95% CI). Model 1 included age, sex, baseline year, and community random effect. Model 2 included the same risk factors as model 1 with the addition of smoking status, physical activity, PURE diet index score, waist-to hip ratio, INTERHEART risk score, use of solid fuels for cooking, education level, household wealth index, occupational class, baseline cardiovascular disease and chronic conditions, cardiovascular disease medication use, and hypertension (determined a priori). Model 3 included all the variables in model 2, with the addition of geographical covariates (urban or rural location, baseline country gross domestic product per capita, Night Light Development Index score, and a national or regional Healthcare Access and Quality Index). Model 4 included all the variables in model 3 with the addition of a nested random intercept for each community by centre (subdivided by urban and rural areas). Model 5 included all the variables in model 3, with the addition of an indicator variable for each centre urban–rural area. LMICs=low-income and middle-income countries. *Argentina, Bangladesh, Brazil, Canada, Colombia, Chile, China, India, Iran, Malaysia, Palestine, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe. †Death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure; each subcategory includes fatal and non-fatal events. ‡All deaths excluding injuries. §Argentina, Bangladesh, Brazil, Colombia, Chile, China, India, Iran, Malaysia, Palestine, Pakistan, Philippines, Poland, Saudi Arabia, South Africa, Tanzania, Turkey, and Zimbabwe.

***Table 2*: Associations between 3-year mean outdoor $PM_{2·5}$ concentration at baseline and cardiovascular disease events and mortality**

baseline, 5-year baseline, study period mean, and 3-year means for 2005, 2010, and 2015 were high (r=0·98) and consistent across regions (appendix p 13). We therefore present results utilising our a priori main exposure measure, 3-year $PM_{2·5}$ averages preceding cohort entry.

Individual, household, and geographical characteristics varied significantly across $PM_{2·5}$ quintiles (table 1). Measures associated with poverty were more prevalent at higher $PM_{2·5}$ concentrations than lower $PM_{2·5}$ concentrations, which was expected since 22 466 (69·8%) of 32 178 individuals in the highest $PM_{2·5}$ quartiles were from lower-middle-income countries and 8194 (25·5%) of 32 178 individuals were from low-income countries. Mean INTERHEART risk scores (12·9 [SD 6·2] *vs* 9·2 [5·3]), the number of participants who were ever smokers (13 666 [43·7%] *vs* 7933 [24·7%]), and the number of individuals on cardiovascular disease medication at baseline (7973 [25·5%] *vs* 4152 [12·9%]) were higher in the lowest $PM_{2·5}$ quintile than the highest $PM_{2·5}$ quintile.

In the entire PURE cohort (n=157 436), in model 3, a 10 μg/m³ increase in $PM_{2·5}$ was associated with an HR of 1·05 (95% CI 1·03–1·07) for major cardiovascular disease events and 1·03 (1·00–1·06) for cardiovascular disease deaths (table 2). The largest association was observed for stroke (HR 1·07 [95% CI 1·05–1·10]). The findings for the LMIC models were similar to the analyses of the overall PURE cohort, with a slightly larger risk for stroke (HR 1·09 [95% CI 1·06–1·12]). No consistent associations were observed for $PM_{2·5}$ and non-accidental mortality and non-cardiovascular disease mortality in overall and LMIC models.

Model 4 incorporated a nested random effect of communities within centres and yielded generally similar results to model 3. In model 5, we included centre urban–rural areas (n=89) as indicator variables in the model to control for unmeasured differences between urban and rural areas within centres, as well as differences between centres. In all models, the risk for cardiovascular disease mortality (1·12 [95% CI 1·02–1·25]), non-accidental mortality (1·08 [1·01–1·15]), and non-cardiovascular disease mortality (1·05 [0·98–1·13]) increased per 10 μg/m³ increase in $PM_{2·5}$. The risk for cardiovascular disease events also increased slightly (HR 1·08 [95% CI 1·01–1·16]). HR estimates were almost identical in the LMIC cohort. 20 centre urban or rural clusters had no variation in $PM_{2·5}$ across communities, and thus were not included in model 5 (13 692 individuals from seven countries). The mean within-centre urban and rural $PM_{2·5}$ range was 7 μg/m³.

In model 3, linear and non-linear HR slopes for cardiovascular disease events, stroke, and myocardial infarction were similar, with increased risk observed

across the entire range of $PM_{2·5}$ (figure 2). For cardiovascular disease mortality, the non-linear HR followed an exponential distribution, with a small HR slope below 80 μg/m³ followed by increases between 80 and 140 μg/m³. Repeating models 1–3 with $PM_{2·5}$ quintiles as categorical exposures provided additional insight with regard to non-linear associations between $PM_{2·5}$ and cardiovascular disease (appendix p 15). In model 2, HRs for cardiovascular disease mortality, major cardiovascular disease events, myocardial infarction, and stroke all had concentration–response relationships. However, the concentration–response was only present for stroke and major cardiovascular disease events after accounting for geographical variables. The HR for stroke, using quintile 1 as the reference, was 0·83 (95% CI 0·64-1·07) for quintile 2, 1·25 (0·98–1·58) for quintile 3, 1·41 (1·09–1·84) for quintile 4, and 1·75 (1·31–2·32) for quintile 5 (appendix p 15).

Subgroup analyses of cardiovascular disease events showed risk was consistent when stratified by individual, household, and geographical characteristics (table 3). The risk for cardiovascular disease, myocardial infarction, stroke, and cardiovascular disease mortality, was fairly similar for women and men, ever and never smokers, and across levels of education and wealth. At baseline, 11812 (7·5%) of 157436 participants had cardiovascular disease. The risk for cardiovascular disease events was slightly higher for individuals without cardiovascular disease at baseline (1·05 [95% CI 1·03–1·08]) than individuals with cardiovascular disease at baseline (1·03 [1·01–1·06]). Although mean $PM_{2·5}$ was slightly higher in urban communities (49·3 μg/m³ [SD 35·0]) compared with rural communities (45·4 μg/m³ [29·3]), larger associations between mean $PM_{2·5}$ concentration and stroke were observed in rural communities (HR 1·13 [95% CI 1·09–1·18]) than urban communities (1·05 [1·01–1·09]). The risk for cardiovascular disease events was greater for high-income countries or upper-middle-income countries (HR 1·14 [95% CI 1·07–1·21]) than LMICs or low-income countries (1·05 [1·02–1·07]) or middle-income countries alone (1·07 [1·04–1·11]). When stratified by the WHO interim target of 35 μg/m³, the risk for cardiovascular disease events was higher in areas with $PM_{2·5}$ concentrations of less than 35 μg/m³ (HR 1·15 [95% CI 1·02–1·29]) than areas with $PM_{2·5}$ concentrations of 35 μg/m³ or higher (1·05 [1·02–1·08]).

Sensitivity analyses demonstrate the robustness of our results (appendix p 17). The correlations between different $PM_{2·5}$ exposure periods (r>0·98) and an independent $PM_{2·5}$ prediction model (r>0·85) were high and consistently show increased cardiovascular disease risk with different $PM_{2·5}$ metrics in models 3 and 5. The addition of environmental exposure variables (community temperature, green space, and traffic related air pollution) to model 3 did not change HRs for cardiovascular disease events but increased the risk for cardiovascular disease mortality (HR 1·07 [95% CI 1·04–1·10]). Removing the largest communities and missing data categories did not change model results. When the community random intercept was removed from model 3, the risk for cardiovascular disease events was reduced (HR 1·03 [95% CI 1·03–1·04]), but was increased in model 5. Incrementally removing variables from model 3 showed that our results are not sensitive to specific individual variables, but removal of geographical variables, especially country GDP, increased the risk for cardiovascular disease (appendix p 19). We calculated population-attributable fractions separately for fatal and non-fatal cardiovascular disease events, myocardial infarction, stroke, and cardiovascular disease mortality on the basis of the HRs from model 3 (appendix p 21). Using the WHO reference exposure concentration of 10 μg/m³, the $PM_{2·5}$ population-attributable fractions for the PURE cohort were 13·9% (95% CI 8·8–18·6) for cardiovascular disease events, 8·4% (0·0–15·4) for myocardial infarction, 19·6% (13·0–25·8) for stroke, and 8·3% (0·0–15·2) for cardiovascular disease mortality.

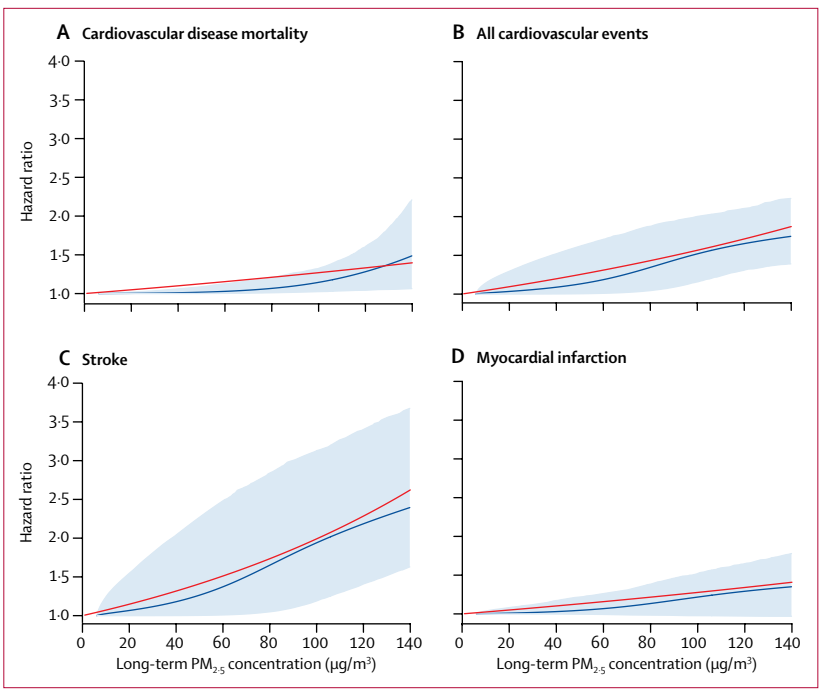

Figure 2: **Non-linear exposure–response functions for cardiovascular disease mortality (A), all cardiovascular disease events (B), stroke (C), and myocardial infarction (D) based on model 3**
Cardiovascular disease events included fatal and non-fatal events. Red lines show linear hazard ratio estimates and blue lines show non-linear hazard ratio estimates. Shaded areas represent 95% CIs for the non-linear models.

Discussion

In this prospective cohort study, long-term outdoor $PM_{2·5}$ was consistently associated with increased risk for cardiovascular disease. Models for deaths were sensitive to adjustment for geographical factors and no consistent association was observed for non-cardiovascular disease deaths. Our study included a diverse population residing in LMICs, and thus our results

	Participants (n=157 436)	Cardiovascular disease	Myocardial infarction	Stroke	Cardiovascular disease mortality
Overall (model 3)	157 436 (100%)	1·05 (1·03–1·07)	1·03 (1·00–1·06)	1·07 (1·05–1·10)	1·03 (1·00–1·06)
Sex					
Women	91 243 (58%)	1·07 (1·04–1·10)*	1·05 (1·01–1·09)*	1·08 (1·05–1·12)	1·04 (1·00–1·07)*
Men	66 193 (42%)	1·03 (1·01–1·05)*	1·00 (0·97–1·03)*	1·06 (1·03–1·09)	1·01 (0·98–1·03)*
Age, years					
≤60	128 171 (81%)	1·03 (1·01–1·06)*	1·01 (0·98–1·04)	1·07 (1·04–1·10)	1·02 (0·98–1·05)
>60	29 266 (19%)	1·06 (1·03–1·08)*	1·03 (1·00–1·07)	1·06 (1·03–1·10)	1·02 (0·99–1·06)
Baseline cardiovascular disease					
Yes	11 812 (8%)	1·03 (1·00–1·06)*	1·00 (0·97–1·05)	1·04 (0·98–1·08)*	1·03 (0·98–1·07)
No	145 624 (92%)	1·05 (1·03–1·08)*	1·03 (1·00–1·06)	1·08 (1·05–1·11)*	1·02 (1·00–1·05)
Smoking status					
Never smoker	105 571 (68%)	1·06 (1·04–1·09)*	1·04 (1·00–1·07)*	1·09 (1·06–1·12)*	1·06 (1·02–1·09)*
Ever smoker	50 318 (32%)	1·03 (1·00–1·05)*	0·99 (0·96–1·02)*	1·06 (1·02–1·09)*	0·98 (0·95–1·01)*
Household Wealth Index					
Lowest	49 471 (32%)	1·08 (1·05–1·11)	1·06 (1·02–1·11)	1·08 (1·04–1·12)	1·04 (1·00–1·08)
Middle	51 213 (33%)	1·03 (1·01–1·06)	1·00 (0·96–1·04)	1·07 (1·03–1·11)	0·99 (0·96–1·03)
Highest	52 903 (34%)	1·03 (1·00–1·06)	1·01 (0·98–1·05)	1·06 (1·02–1·10)	1·02 (0·98–1·06)
Education					
Primary or less	67 255 (43%)	1·07 (1·04–1·09)*	1·05 (1·01–1·08)*	1·08 (1·05–1·12)	1·02 (1·00–1·06)
Secondary school or higher	89 706 (57%)	1·02 (1·00–1·05)*	0·98 (0·96–1·01)*	1·05 (1·02–1·09)	1·00 (0·97–1·04)
Household air pollution					
Clean fuel	109 305 (74%)	1·04 (1·02–1·06)	1·01 (0·98–1·04)	1·06 (1·02–1·09)	1·00 (0·97–1·04)
Dirty fuel	40 227 (26%)	1·06 (1·03–1·09)	1·03 (0·99–1·07)	1·10 (1·05–1·14)	1·03 (1·00–1·07)
Community location					
Urban	83 887 (53%)	1·03 (1·01–1·06)*	1·02 (0·99–1·05)	1·05 (1·01–1·09)*	1·02 (0·98–1·05)
Rural	73 549 (47%)	1·09 (1·05–1·12)*	1·04 (0·99–1·09)	1·13 (1·09–1·18)*	1·05 (1·01–1·09)
Country income category					
High income or UMIC	59 064 (38%)	1·14 (1·07–1·21)*	1·11 (1·03–1·21)*	1·08 (1·00–1·18)*	0·91 (0·82–1·01)*
LMIC or low income	98 372 (62%)	1·05 (1·02–1·07)*	1·01 (0·98–1·05)*	1·10 (1·06–1·13)*	1·03 (1·00–1·07)*
WHO interim health target†					
<35 μg/m³	69 862 (44%)	1·15 (1·02–1·29)	0·98 (0·84–1·17)	1·36 (1·16–1·58)	1·09 (0·93–1·29)
≥35 μg/m³	87 574 (56%)	1·05 (1·02–1·08)	1·04 (1·00–1·08)	1·05 (1·01–1·10)	1·09 (1·04–1·13)

Data are n (%) or hazard ratio per 10 μg/m³ $PM_{2.5}$ increase (95% CI). Model 3 included the following variables: age, sex, baseline year, smoking status, physical activity, PURE diet index score, waist-to-hip ratio, INTERHEART risk score, use of solid fuels for cooking, education level, household wealth index, occupational class, baseline cardiovascular disease and chronic conditions, cardiovascular disease medication use, hypertension, and geographical covariates (urban or rural location, baseline country gross domestic product per capita, Night Light Development Index score, and a national or regional Healthcare Access and Quality Index. UMIC=upper-middle-income country. LMIC=low-income and middle-income country. *Statistically significant differences (p<0·05) between strata were tested using interaction terms between subgroup variables and $PM_{2.5}$. †Models restricted to $PM_{2.5}$ concentrations above and below the WHO interim health target of 35 μg/m³.

Table 3: **Subgroup analyses for the associations of $PM_{2.5}$ with cardiovascular disease, myocardial infarction, stroke, and cardiovascular disease mortality**

provide new information about associations between ambient $PM_{2.5}$ and cardiovascular disease across a much wider range of $PM_{2.5}$ concentrations (6–140 μg/m³) than reported previously.

Our results suggest cardiovascular disease risk increases across the global range of $PM_{2.5}$. A 2018 meta-analysis identified 53 studies of long-term $PM_{2.5}$ and cardiovascular disease mortality, of which only six studies were done outside North America or Europe.[29] Mean $PM_{2.5}$ concentration in all studies was 15·7 μg/m³, lower than the mean of 47·5 μg/m³ in PURE.[29] The meta-regression estimate for a 10% increase in $PM_{2.5}$ at a mean exposure of 10 μg/m³ was a 14·6% (95% CI 12·5–16·7%) increase in cardiovascular disease mortality. This meta-analysis also identified that at higher $PM_{2.5}$ concentrations the risks were reduced, but few studies were available for $PM_{2.5}$ concentrations higher than 35 μg/m³. Only one mortality study from LMICs was included (n=189793 men from 45 areas in China), where an HR of 1·09 (95% CI 1·08–1·09) for cardiovascular disease mortality per 10 μg/m³ increase in $PM_{2.5}$ was observed.[10] Our study addresses this important data gap by suggesting that the risk for cardiovascular disease events (including both fatal and non-fatal events) and cardiovascular disease deaths increase at high $PM_{2.5}$ concentrations. We observed positive associations with cardiovascular disease events

(HR 1·05 [95% CI 1·03–1·07]) and cardiovascular disease mortality (1·03 [1·00–1·05]) per 10 μg/m³ increase in $PM_{2·5}$. After controlling for unmeasured contextual factors, the HR for all cardiovascular disease events increased to 1·08 (95% CI 1·01–1·16). These estimates are smaller than previous estimates and might be associated with differences in $PM_{2·5}$ exposure ranges assessed; the distribution of cause-specific mortality in PURE compared with studies done in North America and Europe; a greater extent of covariate adjustment in our study compared with the previous studies; and exposure measurement error associated with the diverse range of communities included in the PURE study, which could attenuate results. However, across the full range of $PM_{2·5}$ concentrations, we observed consistently increased risks for models restricted to LMICs, for populations exposed to long-term $PM_{2·5}$ concentrations of 35 μg/m³ or higher (the WHO interim target), and in models restricted to within-locality comparisons.

Stroke was most strongly associated with $PM_{2·5}$ in our study (HR 1·07 per 10 μg/m³ increase in $PM_{2·5}$ [95% CI 1·05–1·10]). These finding contribute to a growing body of literature that identifies stroke as a potentially important outcome affected by $PM_{2·5}$, especially at high $PM_{2·5}$ concentrations. A study of stroke mortality within the China-PAR project[13] reported an HR of 1·13 (95% CI 1·09–1·17) for all incident strokes per 10 μg/m³ increase in $PM_{2·5}$ (n=17 575 individuals in 15 provinces), and increased risks for ischaemic stroke and haemorrhagic stroke separately. A separate study in Hong Kong found an increased risk for ischaemic strokes (HR 1·21 [95% CI 1·04–1·41]), but no association with haemorrhagic stroke.[14] Although we were unable to assess stroke subtypes in PURE, in combination with studies from high-income countries,[30,31] our study results strengthen the evidence of increased stroke risk with high $PM_{2·5}$ concentrations.

We found no consistent associations between $PM_{2·5}$ concentrations and non-accidental mortality or non-cardiovascular disease mortality. We observe increased risks in models with locality indicators, suggesting that unmeasured contextual factors influence mortality. For example, the risk for non-cardiovascular disease deaths was lower in model 3 (HR 0·94 [95% CI 0·93–0·96]) than model 5 (1·05 [0·98–1·13]). Although consistent associations with non-accidental and non-cardiovascular disease mortality have been reported,[15,29] this might be associated with differences in the distribution of mortality causes in high-income countries compared with that of the LMIC populations included in the PURE cohort. Of the 9996 non-accidental deaths recorded during follow-up, approximately 32% were attributed to cardiovascular disease. Other common causes of classified death included cancers (19%), respiratory diseases (6%), infections (5%), renal disease (2%), and endocrine or metabolic diseases (2%). Associations between $PM_{2·5}$ and specific non-cardiovascular disease mortality will be investigated in future studies, as additional events (including non-fatal events) accrue during follow-up.

Our estimated population-attributable fraction for $PM_{2·5}$ and cardiovascular disease within the PURE population suggests substantial contributions to disease burden: 8·3% (95% CI 0·0–15·2) for cardiovascular disease mortality; 13·9% (8·8–18·6) for cardiovascular disease events; 8·4% (0·0–15·4) for myocardial infarction; and 19·6% (13·0–25·8) for stroke using a reference of 10 μg/m³ (the current WHO $PM_{2·5}$ air quality guideline). These population-attributable fraction estimates have large confidence intervals and thus should be interpreted with caution. Our estimates are generally comparable to the GBD 2017 for cardiovascular disease deaths (8%), cardiovascular disease disability-adjusted life-years (9%), ischaemic heart disease (13%), and stroke (8%), which used a counterfactual distribution of $PM_{2·5}$ of 2·5–5·9 μg/m³.[32] However, we did not observe consistent associations with non-cardiovascular disease deaths, which constitute over 50% of the estimated attributable deaths to outdoor $PM_{2·5}$ in the GBD estimates.[4] Comprehensive analyses of different population-attributable fractions for modifiable cardiovascular disease risk factors within the PURE study (eg, behavioural, metabolic, and socioeconomic risk factors) provide relative comparisons for our $PM_{2·5}$ population-attributable fraction estimates.[33] Although PURE is not representative of the global population (and therefore should not be interpreted as representing the global population-attributable fraction from $PM_{2·5}$ air pollution), our results suggest that long-term outdoor $PM_{2·5}$ is an important contributor to cardiovascular disease globally.

The strengths of this study include the diverse population included, which enabled investigation of a wide range of $PM_{2·5}$ concentrations across 21 countries spanning from low-income countries to high-income countries; uniform assessment of long-term $PM_{2·5}$ using state-of-the art exposure estimation methods; objective measurement of a comprehensive suite of individual cardiovascular disease risk factors and standardised data collection for household and community characteristics; and prospective recording of fatal and non-fatal events that were adjudicated using standard definitions. However, our study also had limitations. First, we were unable to control for the daily or seasonal variations in $PM_{2·5}$ exposures, and we did not have annual estimates before 2010. However, $PM_{2·5}$ concentrations for PURE communities were highly correlated (r=0·98) for these different time periods and sensitivity analyses using another $PM_{2·5}$ prediction model with annual estimates revealed similar results. Second, we assigned $PM_{2·5}$ by study community (eg, urban neighbourhoods and rural villages). Although outdoor $PM_{2·5}$ concentrations are not likely to vary substantially, exposure misclassification might be present and our analyses are driven by between-community $PM_{2·5}$ differences. Third, we were only able to examine $PM_{2·5}$ mass, but the composition of $PM_{2·5}$ is likely to vary substantially across PURE communities. In

sensitivity analyses examining $PM_{2.5}$ mass estimates with salt and dust removed, we observed larger associations with cardiovascular disease events and stroke, but no associations with myocardial infarction or cardiovascular death. We controlled for household air pollution using a survey-based indicator of cooking with dirty fuels. Quantitative assessment of $PM_{2.5}$ concentrations from household air pollution has been incorporated into a subset of the PURE cohort,[34] and will be incorporated into future analyses with extended follow-up. Fourth, models were also sensitive to geographical adjustments. We have previously shown how diseases and deaths vary by economic status in the PURE study,[8] and $PM_{2.5}$ concentrations are also associated with economic status. However, models that further controlled for unmeasured geographical factors resulted in slightly larger HRs for cardiovascular disease events and considerably higher HRs for non-accidental and non-cardiovascular disease mortality. Our results from model 3 might therefore be a conservative estimate of the association between long-term $PM_{2.5}$ and cardiovascular disease.

Long-term ambient $PM_{2.5}$ was positively associated with cardiovascular disease events, especially stroke, in this large and diverse prospective cohort study. Our results provide new information about the associations between ambient $PM_{2.5}$ and cardiovascular disease across a much wider range of $PM_{2.5}$ concentrations (6–140 μg/m³) than reported previously, and within a diverse population residing in LMICs, while adjusting for an extensive set of individual, household, and community cardiovascular disease risk factors. These findings reinforce the need to reduce air pollution in all countries, especially in LMICs where air pollution levels are highest.

Contributors

PH and MB led the PURE-AIR pollution study. SY designed the PURE study, obtained funding, and has overseen study conduct since inception 18 years ago. PH, MB, AL, RB, and SY drafted this manuscript. SR coordinated the worldwide study. All other authors coordinated the study in their respective countries and contributed to the drafts of the manuscript.

Declaration of interests

SY, SR, MB, and KYe report grants from the Canadian Institutes of Health Research and the Ontario Ministry of Health and Long-Term Care during the conduct of the study. PH reports a grant from the Canadian Institutes of Health Research and the National Institutes of Health Sciences, during the conduct of the study. SY reports a grant from the Marion W Burke Endowed Chair of the Heart and Stroke Foundation of Canada. All other authors declare no competing interests.

Data sharing

Data from PURE are not available for public use.

Acknowledgments

The PURE study is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute, the Canadian Institutes of Health Research (including through the Strategy for Patient-Oriented Research via the Ontario SPOR Support Unit), the Heart and Stroke Foundation (ON, Canada), and the Ontario Ministry of Health and Long-Term Care. The PURE-AIR study is funded by the Canadian Institutes for Health Research (grant 136893) and by the Office of the Director, National Institutes of Health (award DP5OD019850). It is also funded by unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier Laboratories, and GlaxoSmithKline, and additional contributions from Novartis, King Pharma, and from several national and local organisations in participating countries. Further details on the funding and participating countries and institutions, and on collaborating staff, are shown in the appendix (p 21).

References

1 Brook RD, Newby DE, Rajagopalan S. The global threat of outdoor ambient air pollution to cardiovascular health: time for intervention. *JAMA Cardiol* 2017; **2:** 353–54.

2 Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2018; **72:** 2054–70.

3 Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1923–94.

4 Brauer M, Freedman G, Frostad J, et al. Ambient air pollution exposure estimation for the Global Burden of Disease 2013. *Environ Sci Technol* 2016; **50:** 79–88.

5 Crouse DL, Peters PA, van Donkelaar A, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect* 2012; **120:** 708–14.

6 Di Q, Wang Y, Zanobetti A, et al. Air pollution and mortality in the Medicare population. *N Engl J Med* 2017; **376:** 2513–22.

7 Hayes RB, Lim C, Zhang Y, et al. $PM_{2.5}$ air pollution and cause-specific cardiovascular disease mortality. *Int J Epidemiol* 2020; **49:** 25–35.

8 Dagenais GR, Leong DP, Rangarajan S, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* 2020; **395:** 785–94.

9 Liu C, Chen R, Sera F, et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019; **381:** 705–15.

10 Yin P, Brauer M, Cohen A, et al. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. *Environ Health Perspect* 2017; **125:** 117002.

11 Li T, Zhang Y, Wang J, et al. All-cause mortality risk associated with long-term exposure to ambient $PM_{2.5}$ in China: a cohort study. *Lancet Public Health* 2018; **3:** e470–77.

12 Yang Y, Tang R, Qiu H, et al. Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. *Environ Int* 2018; **117:** 99–106.

13 Huang K, Liang F, Yang X, et al. Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project. *BMJ* 2019; **367:** l6720.

14 Qiu H, Sun S, Tsang H, et al. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. *Neurology* 2017; **88:** 1709–17.

15 Burnett R, Chen H, Szyszkowicz M, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci USA* 2018; **115:** 9592–97.

16 Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J* 2013; **166:** 636–46.

17 Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J* 2009; **158:** 1–7.

18 Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; **371:** 818–27.

19 Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; **35:** 1381–95.

20 Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364:** 937–52.

21 Gupta R, Kaur M, Islam S, et al. Association of household wealth index, educational status, and social capital with hypertension awareness, treatment, and control in south Asia. *Am J Hypertens* 2017; **30:** 373–81.

22 Hystad P, Duong M, Brauer M, et al. Health effects of household solid fuel use: findings from 11 countries within the Prospective Urban and Rural Epidemiology study. *Environ Health Perspect* 2019; **127:** 57003.

23 Keola S, Andersson M, Hall O. Monitoring economic development from space: using nighttime light and land cover data to measure economic growth. *World Dev* 2015; **66:** 322–34.

24 Fullman N, Yearwood J, Abay SM, et al. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. *Lancet* 2018; **391:** 2236–71.

25 Shaddick G, Thomas ML, Amini H, et al. Data integration for the assessment of population exposure to ambient air pollution for Global Burden of Disease assessment. *Environ Sci Technol* 2018; **52:** 9069–78.

26 van Donkelaar A, Martin RV, Brauer M, et al. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. *Environ Sci Technol* 2016; **50:** 3762–72.

27 Nasari MM, Szyszkowicz M, Chen H, et al. A class of non-linear exposure-response models suitable for health impact assessment applicable to large cohort studies of ambient air pollution. *Air Qual Atmos Health* 2016; **9:** 961–72.

28 Hoorn SV, Ezzati M, Rodgers A, Lopez AD, Murray CJL. Estimating attributable burden of disease from exposure and hazard data. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks: global and regional burden of diseases attributable to selected major risk factors, vol 2. Geneva: World Health Organization, 2004: 2129–40.

29 Vodonos A, Awad YA, Schwartz J. The concentration-response between long-term $PM_{2.5}$ exposure and mortality; a meta-regression approach. *Environ Res* 2018; **166:** 677–89.

30 Stafoggia M, Cesaroni G, Peters A, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect* 2014; **122:** 919–25.

31 Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; **356:** 447–58.

32 Institute for Health Metrics and Evaluation. GBD compare. Seattle, WA: Institute for Health Metrics and Evaluation, University of Washington. http://vizhub.healthdata.org/gbd-compare/ (accessed Nov 6, 2015).

33 Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020; **395:** 795–808.

34 Arku RE, Birch A, Shupler M, Yusuf S, Hystad P, Brauer M. Characterizing exposure to household air pollution within the Prospective Urban Rural Epidemiology (PURE) study. *Environ Int* 2018; **114:** 307–17.