Associations of long-term fine particulate matter exposure with all-cause and cause-specific mortality: results from the ChinaHEART project

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Summary

Background The chronic effects of fine particulate matter ($PM_{2.5}$) at high concentrations remains uncertain. We aimed to examine the relationship of long-term $PM_{2.5}$ exposure with all-cause and the top three causes of death (cardiovascular disease [CVD], cancer, and respiratory disease), and to analyze their concentration-response functions over a wide range of concentrations.

Methods We enrolled community residents aged 35–75 years from 2014 to 2017 from all 31 provinces of the Chinese Mainland, and followed them up until 2021. We used a long-term estimation dataset for both $PM_{2.5}$ and O_3 concentrations with a high spatiotemporal resolution to assess the individual exposure, and used Cox proportional hazards models to estimate the associations between $PM_{2.5}$ and mortalities.

Findings We included 1,910,923 participants, whose mean age was 55.6 ± 9.8 years and 59.4% were female. A 10 μg/m^3 increment in $PM_{2.5}$ exposure was associated with increased risk for all-cause death (hazard ratio 1.02 [95% confidence interval 1.012–1.028]), CVD death (1.024 [1.011–1.037]), cancer death (1.037 [1.023–1.052]), and respiratory disease death (1.083 [1.049–1.117]), respectively. Long-term $PM_{2.5}$ exposure nonlinearly related with all-cause, CVD, and cancer mortalities, while linearly related with respiratory disease mortality.

Interpretation The overall effects of long-term $PM_{2.5}$ exposure on mortality in the high concentration settings are weaker than previous reports from settings of $PM_{2.5}$ concentrations < 35 μg/m^3. The distinct concentration-response relationships of CVD, cancer, and respiratory disease mortalities could facilitate targeted public health efforts to prevent death caused by air pollution.

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Keywords: Air pollution; PM2.5; All-cause mortality; Cause-specific mortality; Concentrationresponse functions

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Research in context

Evidence before this study

We searched PubMed up to October 31, 2022, without language restrictions. The search terms included "air pollution", "fine particulate matter", "$PM_{2.5}$", "mortality", "death", "long-term", and "chronic". A few epidemiological studies had investigated the associations between long-term $PM_{2.5}$ exposure and mortality in the settings of $PM_{2.5}$ above 35 μg/m^3. However, these studies reported controversial results, which could be due to the limitations in methodology. The concentration-response (C-R) functions between long-term $PM_{2.5}$ exposure and all-cause and cardiovascular disease (CVD) mortality (the primary cause of mortality) appeared different from those of the areas with low concentrations. Besides this, knowledge remains scarce regarding the C-R functions between long-term $PM_{2.5}$ exposure and the other two (following CVD mortality) of the top three cause-specific mortalities, i.e., cancer and respiratory diseases.

Added value of this study

To the best of our knowledge, this is the largest nationwide cohort study to investigate the relationship of long-term $PM_{2.5}$ exposure with all-cause and cause-specific mortality in the high concentration settings. In this study of 1.9 million adults aged 35–75 years, we found that the long-term $PM_{2.5}$ exposure sub-linearly related to all-cause mortality across a broad range of $PM_{2.5}$ concentrations from 17 to 102 μg/m^3, with a 6% increased risk per 10 μg/m^3 increase of $PM_{2.5}$ at the level of ≥50.4 μg/m^3. However, no significant association existed below 50.4 μg/m^3. The risk of all-cause death in this study was weaker than those observed in the settings of $PM_{2.5}$ concentrations < 35 μg/m^3, and the effects in this study resulted mainly from the combined distinct C-R functions of the top three cause-specific mortalities. The C-R functions of CVD and cancer mortalities were nonlinear with the inflection points at about 50 μg/m^3. While respiratory disease mortality was linearly associated with long-term $PM_{2.5}$ exposure.

Implications of all the available evidence

The mortalities associated with long-term $PM_{2.5}$ exposure in China may be overestimated in previous studies, particularly in the areas of $PM_{2.5}$ concentration < 50 μg/m^3. The distinct concentration-response relationships of CVD, cancer, and respiratory disease mortalities could help refine the estimation of disease burden and preventable death number due to improved air quality in the settings of $PM_{2.5}$ above 35 μg/m^3, and provide evidence for facilitating public health policy making to reduce extra mortality caused by $PM_{2.5}$.

Introduction

Air pollution is one of the top environmental threats to public health, associated with 6.7 million excess deaths globally in 2019, of which 4.1 million were attributed to ambient fine particulate matter (airborne particles ≤2.5 μm in aerodynamic diameter, $PM_{2.5}$).[1,2] The main burden of disease associated with $PM_{2.5}$ were from the areas of high concentrations (≥35 μg/m^3), where half of the world's population lives.[3]

However, the chronic effects of $PM_{2.5}$ at high concentrations remain uncertain. The concentration-response (C-R) functions between long-term $PM_{2.5}$ exposure and all-cause and cardiovascular disease (CVD) mortality (the primary cause of mortality) appear different from those in low concentrations,[4–8] with linear associations of about a 7–15% increased risk of all-cause death and a 9–26% increased risk of CVD death by each 10 μg/m^3 increase in $PM_{2.5}$ exposure.[9–12] A few studies from the high exposure settings reported controversial results, which could be due to the limitations in methodology. A main problem is the poor simulation accuracy of $PM_{2.5}$ concentrations in historical period without ground monitoring data.[5–7,13] Some studies did not collect information on individual addresses or use high spatial resolution simulations, which further reduced the accuracy of individual $PM_{2.5}$ exposure.[4,7,13] Other studies included mostly the rural residents,[6,8] or only the elderly population,[5,14] or only men,[7] whose response may differ from the general population. Moreover, previous studies mainly focused on lung cancer,[7] we know little about the C-R functions between long-term $PM_{2.5}$ exposure and the other two (following CVD mortality) of the top three cause-specific mortalities, i.e., cancer and respiratory diseases.

Therefore, we aimed to examine the associations between long-term $PM_{2.5}$ exposure and the risk of all-cause death, CVD death, cancer death, and respiratory disease death in China, where the $PM_{2.5}$ level distributes in a wide range and averages much higher than 35 μg/m^3, and further analyze the C-R functions of these associations. Our analysis included 1.9 million community residents, estimated $PM_{2.5}$ exposure based on high spatiotemporal resolution data with ground monitoring, and further adjusted another main pollutant, O_3.

Methods

Study participants

We included participants of the Health Evaluation And risk Reduction through nationwide Teamwork (China-HEART) who were enrolled from November 2014 to December 2017, the design of ChinaHEART project (formerly named China PEACE MPP) has been detailed previously.[15–17] This project recruited community residents aged 35–75 years who had lived in the region for at least 6 of the preceding 12 months from 143 counties (87 rural counties, 56 urban districts) in all 31 provinces of the Chinese Mainland. The study sites were select to

provide diversity in geographical distribution, economic development, and population structure.[16] Study site selection also took into account population size, population stability, and local capacity to support the project, see Appendix p 3 for detailed information on sampling design. The central ethics committee at the China National Center for Cardiovascular Diseases approved this project. All enrolled participants provided written informed consent.

Data collection

We collected the information on sociodemographic status, lifestyle information, medical history, and medication by standardized in-person interviews at baseline. Sociodemographic status included age, sex, occupation (farmer, worker, retire, or other), and education levels (primary school or less, middle, or above high school). Lifestyle information covered tobacco smoking (current smoker or non-smoker) and alcohol use (current drinker or non-drinker). The classification of urbanicity (rural or urban) and geographic region (Central, East, North, Northeast, Northwest, South, and Southwest) were defined based on the participants' residential addresses. We also collected the information of indoor fuels in the urban and rural areas of each province through the seventh National Census. Fuel types were divided into solid fuels (coal and wood) and clean fuels (gas and electricity).[18] In addition, we collected information on province-level Gross Domestic Product (GDP) and the number of hospital beds per thousand people through the China Statistical Yearbook 2022.

Trained personnel performed height, weight, and blood pressure measurements for the participants. When measuring weight and height, participants were required to wear light clothes and had their shoes and headgears removed. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared (kg/m^2). Blood pressure was measured twice after a 5-min rest, using a standardized electronic blood pressure monitor (Omron HEM-7430, Omron Corporation, Japan). A third measurement was performed if the difference between the two blood pressure measurements was greater than 10 mmHg, and the average of the last two measurements was recorded. Hypertension was defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, or taking blood pressure medications. Diabetes was defined by prior diagnosis or current treatment with anti-diabetes medication. CVD included myocardial infarction, stroke, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG).

Exposure assessment

We used the long-term estimation dataset for both $PM_{2.5}$ and O_3 concentrations with high temporal (day) and spatial resolution (1 km × 1 km), which is the only one available in China.[19] The daily average $PM_{2.5}$ concentrations and O_3 daily maximum of 8 h average concentrations (O_3 - 8 h max) for 2013–2017 were obtained based on a random forest model, which exhibited excellent accuracy.[20] In this model, ground measurements, meteorological variables, satellite data, chemical transport model output, geographic variables and socioeconomic variables were collected. The estimations of $PM_{2.5}$ and O_3 concentrations were highly consistent with the air pollution monitoring stations, and the test-R^2 values of the estimated yearly concentrations were 0.90 for $PM_{2.5}$, and 0.69 for O_3.[19]

At baseline, we collected the information of residential address for each participant. Then we matched 1-km grid-cell $PM_{2.5}$ and O_3 exposure to each participant by linking the residential address to the grid that residential address fall in. In this study, long-term exposure to $PM_{2.5}$ and O_3 were averaged over baseline and the previous year. For example, if a participant was enrolled in 2015, then long-term exposure is the average concentrations of 2014 and 2015.

Outcomes

We obtained the information on death and the underlying cause of death from follow-up and the National Cause-of-death Surveillance System up to 31 December 2021.[21] The outcomes included all-cause and cause-specific deaths. We used the International Classification of Diseases, 10th Revision (ICD-10), to identify death from CVD (I00–I99), ischemic heart disease (IHD, I20–I25), ischemic stroke (I63–I69), hemorrhagic stroke (I60–I62), cancer (C00–C99), lung cancer (C33–C34), other cancers (C00–C32, C35–C99), and respiratory diseases (J00-J99).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and compared by t test, and categorical variables were summarized by frequencies with percentages and compared by chi-square test. We used mean ± SD, median (interquartile), minimum, and maximum to describe the central tendency and dispersion for $PM_{2.5}$ and O_3. Spearman's correlation was used to examine the correlations between $PM_{2.5}$ and O_3.

We used Cox proportional hazards models to assess the associations between long-term $PM_{2.5}$ exposure and mortality, with the time-scale setting as duration from baseline to the date of death or censored at the year of the follow-up in 2021. For each cause-specific mortality, deaths due to other reasons were considered as competing events.[22] The proportional hazards assumption for each variable was verified using stratified Kaplan–Meier curves with weighted Schoenfeld residuals (all $P > 0.05$) (Appendix pp 6–7). We fitted the single-pollutant models and two-pollutant models. Covariates in the single-pollutant models included age, sex, smoking status, drinking status, urbanicity, geographic region, occupation, education and BMI. In the

two-pollutant models, long-term O_3 exposure was further adjusted. Hazard ratios (HRs) and confidence intervals (CIs) were presented for a 10 μg/m^3 increment in the $PM_{2.5}$ concentrations. We investigated the C-R functions between long-term $PM_{2.5}$ exposure and mortality by fitting restricted cubic splines with 3 knots, which was determined by Akaike information criterion (AIC) and Bayesian information criterion (BIC) values (Appendix p 7).[23]

We also plotted the C-R functions by geographical region. We conducted stratified analyses by $PM_{2.5}$ concentrations (<50.4 μg/m^3 vs ≥ 50.4 μg/m^3). We chose 50.4 μg/m^3 as the cut-off point, because it was the median $PM_{2.5}$ concentrations, and the inflection points of the C-R functions were all around this value. We conducted subgroup analyses to assess the potential effect modifiers, including age, sex, BMI, smoking status, drinking status, and urbanicity. Considering that hypertension, diabetes and CVD might be intermediate factors in the causal chain of air pollution and mortality, we did not include medical history in the Cox model, but we conducted subgroup analyses according to hypertension, diabetes and CVD. Statistically significant differences were tested using the interaction of stratified variables and $PM_{2.5}$.

We also performed several sensitivity analyses to examine the robustness of the main findings. (1) We redefined long-term $PM_{2.5}$ exposure as the annual average $PM_{2.5}$ concentrations at baseline. (2) We redefined long-term $PM_{2.5}$ exposure as the 5-year average $PM_{2.5}$ concentrations for the period including the baseline and the 4 years before. (3) We further adjusted for the indoor fuel types in the single-pollutant and two-pollutant models. (4) We further adjusted for province-level GDP and the number of hospital beds per thousand people in models. (5) We excluded the accidental death. (6) We excluded participants with $PM_{2.5}$ exposure < 35 μg/m^3. (7) We used Frailty model to assess the associations between long-term $PM_{2.5}$ exposure and mortality, in which the counties were controlled as clusters.[24] (8) We used time-varying exposure on a 1-year time scale to assess the associations between long-term $PM_{2.5}$ exposure and mortality.

All analyses were performed using SAS (version 9.4) and R (version 3.5.1). A two-sided P-value < 0.05 was considered statistically significant.

Role of the funding source

The funder 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

Baseline characteristics and long-term pollutants exposure

We included 1,910,923 participants in this study, whose mean age was 55.6 ± 9.8 years and 59.4% were female. Among the participants, 19.4% were current smokers and 10.6% current drinkers; 60.8% lived in the rural areas (Table 1). The baseline $PM_{2.5}$ exposure ranged from 16.9 μg/m^3 to 101.8 μg/m^3, with a median (interquartile) of 50.4 (41.0–59.1) μg/m^3. The $PM_{2.5}$ exposures of 86% (1,638,838/1,910,923) of participants were ≥35 μg/m^3. The baseline O_3 exposure ranged from 55.3 μg/m^3 to 111.3 μg/m^3, with a median (interquartile) of 87.0 (80.7–93.9) μg/m^3. The average $PM_{2.5}$ exposure varied greatly across geographic regions, with the highest level in Central and the lowest in Southwest (Fig. 1). The concentration of $PM_{2.5}$ gradually decreased from 2013 (Appendix p 8). The Spearman coefficients between $PM_{2.5}$ and O_3 exposures were positive ranging from 0.295 to 0.401, with statistical significance (all P < 0.001) (Appendix p 8).

People exposed to $PM_{2.5}$ ≥ 50.4 μg/m^3 were more likely to live in the urban and Central, and have hypertension, diabetes, or CVD than those exposed to $PM_{2.5}$ < 50.4 μg/m^3 (Table 1). Male and female were similarly distributed in age, urbanicity, and geography subgroups (Appendix p 9).

Outcomes

In total, 60,356 all-cause deaths occurred during a median follow-up period of 5.5 years, including 24,334 due to CVD (9007 IHD, 6239 ischemic stroke, 5151 hemorrhagic stroke, and 3937 other CVDs), 20,895 cancer (6174 lung cancer, 14,721 other cancers), and 3839 respiratory disease.

Associations between $PM_{2.5}$ exposure and outcomes, and the C-R functions

The associations between long-term $PM_{2.5}$ exposure and mortality are shown in Table 2. In the two-pollutant models, a 10 μg/m^3 increment in $PM_{2.5}$ exposure was associated with increased risk for all-cause death (HR 1.02 [95% CI 1.012–1.028]), CVD death (1.024 [1.011–1.037]), IHD death (1.074 [1.051–1.097]), ischemic stroke death (1.037 [1.01–1.065]), cancer death (1.037 [1.023–1.052]), lung cancer death (1.084 [1.057–1.112]), other cancers death (1.018 [1.001–1.035]), and respiratory disease death (1.083 [1.049–1.117]), respectively. Associations were similar in the single-pollutant models. Sensitivity analyses 1–5 showed that the results remained consistent after redefining long-term $PM_{2.5}$ exposure, further adjusting for fuel types, further adjusting for province-level GDP and the number of hospital beds per thousand people, or excluding the accidental death (Appendix pp 11–15). Sensitivity analysis 6 showed that when limiting the analysis only to people with $PM_{2.5}$ exposure higher than 35 μg/m^3, the HRs of CVD and respiratory disease mortality were larger than the results of main analysis, and those of cancer mortality were similar (Appendix p 16). Sensitivity analysis 7 showed that when using the frailty model, the HRs were smaller than the results of main

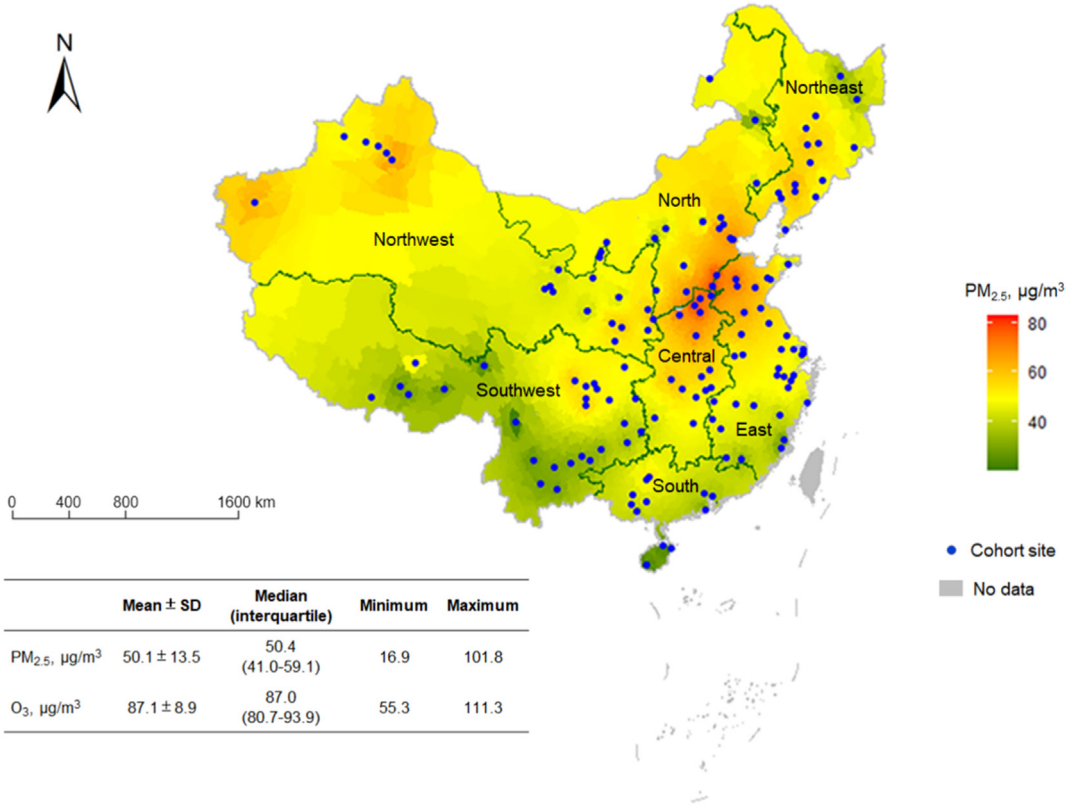
	Total	$PM_{2.5}$ < 50.4 μg/m^3	$PM_{2.5}$ ≥ 50.4 μg/m^3	P
N	1,910,923	951,554 (49.8)	959,369 (50.2)	
Age (years)	55.6 ± 9.8	55.4 ± 9.9	55.8 ± 9.7	<0.001
35–39	87,744 (4.6)	48,793 (5.1)	38,951 (4.1)	<0.001
40–49	486,209 (25.4)	248,480 (26.1)	237,729 (24.8)	
50–59	603,935 (31.6)	296,169 (31.1)	307,766 (32.1)	
60–69	570,660 (29.9)	277,668 (29.2)	292,992 (30.5)	
70–75	162,375 (8.5)	80,444 (8.5)	81,931 (8.5)	
Sex				
Male	776,609 (40.6)	391,051 (41.1)	385,558 (40.2)	<0.001
Female	1,134,314 (59.4)	560,503 (58.9)	573,811 (59.8)	
Occupation				
Farmer	930,065 (48.7)	528,105 (55.5)	401,960 (41.9)	<0.001
Worker	153,802 (8.1)	68,742 (7.2)	85,060 (8.9)	
Retire	319,672 (16.7)	124,152 (13.1)	195,520 (20.4)	
Other	507,384 (26.5)	230,555 (24.2)	276,829 (28.9)	
Education				
Primary school or less	845,499 (44.2)	484,627 (50.9)	360,872 (37.6)	<0.001
Middle	612,871 (32.1)	266,308 (28.0)	346,563 (36.1)	
Above high school	423,932 (22.2)	182,006 (19.1)	241,926 (25.2)	
Unknown	28,621 (1.5)	18,613 (2.0)	10,008 (1.0)	
Smoking				
Current smoker	370,795 (19.4)	196,768 (20.7)	174,027 (18.1)	<0.001
Non-smoker	1,540,128 (80.6)	754,786 (79.3)	785,342 (81.9)	
Drinking				
Current drinker	203,179 (10.6)	101,168 (10.6)	102,011 (10.6)	0.977
Non-drinker	1,707,744 (89.4)	850,386 (89.4)	857,358 (89.4)	
BMI (kg/m^2)	24.6 ± 3.4	24.3 ± 3.4	24.9 ± 3.4	<0.001
<24	866,360 (45.3)	466,970 (49.1)	399,390 (41.6)	<0.001
24–27.9	750,486 (39.3)	353,515 (37.1)	396,971 (41.4)	
≥28	294,077 (15.4)	131,069 (13.8)	163,008 (17.0)	
Hypertension	874,900 (45.8)	425,838 (44.8)	449,062 (46.8)	<0.001
Diabetes	118,243 (6.2)	52,337 (5.5)	65,906 (6.8)	<0.001
CVD	64,532 (3.4)	25,171 (2.7)	39,361 (4.1)	<0.001
Primary fuel type				
Clean fuels	1,625,061 (85.0)	757,413 (79.6)	867,648 (90.4)	<0.001
Solid fuels	285,862 (15.0)	194,141 (20.4)	91,721 (9.6)	
Urbanicity				
Rural	1,161,816 (60.8)	662,104 (69.6)	499,712 (52.1)	<0.001
Urban	749,107 (39.2)	289,450 (30.4)	459,657 (47.9)	
Geographic region				
Central	200,041 (10.5)	28,850 (3.0)	171,191 (17.8)	<0.001
East	489,677 (25.6)	268,463 (28.2)	221,214 (23.1)	
North	205,137 (10.7)	94,727 (10.0)	110,410 (11.5)	
Northeast	310,639 (16.3)	99,399 (10.4)	211,240 (22.0)	
Northwest	205,455 (10.7)	73,306 (7.7)	132,149 (13.8)	
South	191,034 (10.0)	151,948 (16.0)	39,086 (4.1)	
Southwest	308,940 (16.2)	234,861 (24.7)	74,079 (7.7)	

Data are mean ± standard deviation (SD) or frequencies with percentages. $PM_{2.5}$: fine particulate matter; BMI: body mass index; CVD: cardiovascular disease.

Table 1: **Baseline characteristics stratified by the median of baseline 2-year $PM_{2.5}$ exposure.**

analysis, but still significant (Appendix p 17). Sensitivity analysis 8 showed that when using time-varying exposure, the results remained consistent with the main analysis (Appendix p 17).

The shapes of the C-R functions varied by the causes of death. The C-R function between long-term $PM_{2.5}$ exposure and all-cause mortality was nonlinear, with a steeper slope at higher concentrations at inflection point



	Mean ± SD	Median (interquartile)	Minimum	Maximum
$PM_{2.5}$, μg/m³	50.1 ± 13.5	50.4 (41.0-59.1)	16.9	101.8
O_3, μg/m³	87.1 ± 8.9	87.0 (80.7-93.9)	55.3	111.3

Fig. 1: Map of average baseline 2-year $PM_{2.5}$ exposure. $PM_{2.5}$: fine particulate matter.

of 44.8 μg/m³ (P for nonlinearity < 0.001). The C-R functions of CVD mortality was J curve, with a small HR slope of decreased risk at <49.3 μg/m³ and a large HR slope of increased risk ≥49.3 μg/m³ (P for nonlinearity < 0.001); and participants with $PM_{2.5}$ exposure levels of 46–51 μg/m³ had the strongest negative association (Appendix p 18). Similar patterns were observed in IHD and ischemic stroke mortality. While for cancer mortality, the slope became flattened at ≥50.3 μg/m³ (P for nonlinearity < 0.001). Lung cancer and other cancers had this similar pattern, although the effects were weaker in other cancers. The C-R function between $PM_{2.5}$ and respiratory disease mortality was linear (P for nonlinearity = 0.124) (Fig. 2). In addition, the shapes of

	Event, n (%)	Unadjusted	Single-pollutant model	Two-pollutant model
		HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause	60,356 (3.16)	0.999 (0.993, 1.005)	1.022 (1.014, 1.030)	1.020 (1.012, 1.028)
CVD	24,334 (1.27)	1.008 (0.998, 1.018)	1.022 (1.010, 1.035)	1.024 (1.011, 1.037)
IHD	9007 (0.47)	1.095 (1.078, 1.113)	1.081 (1.059, 1.104)	1.074 (1.051, 1.097)
Ischemic stroke	6239 (0.33)	1.006 (0.987, 1.025)	1.019 (0.994, 1.045)	1.037 (1.010, 1.065)
Hemorrhagic stroke	5151 (0.27)	0.927 (0.908, 0.947)	0.978 (0.953, 1.004)	0.980 (0.954, 1.007)
Cancer	20,895 (1.09)	1.028 (1.018, 1.038)	1.034 (1.020, 1.047)	1.037 (1.023, 1.052)
Lung cancer	6174 (0.32)	1.071 (1.053, 1.090)	1.084 (1.059, 1.110)	1.084 (1.057, 1.112)
Other cancers	14,721 (0.77)	1.010 (0.998, 1.022)	1.013 (0.998, 1.029)	1.018 (1.001, 1.035)
Respiratory disease	3839 (0.20)	0.940 (0.917, 0.964)	1.093 (1.060, 1.127)	1.083 (1.049, 1.117)

P value, HR, 95% CIs from Cox regression. Single-pollutant analysis adjusted for age, sex, smoking status, drinking status, urbanicity, geographic region, occupation, education, and body mass index. Two-pollutant analysis adjusted for age, sex, smoking status, drinking status, urbanicity, geographic region, occupation, education, body mass index, and annual average O_3 concentrations. HR: hazard ratio; 95% CI: 95% confidence intervals; $PM_{2.5}$: fine particulate matter; CVD: cardiovascular disease; IHD: ischemic heart disease.

Table 2: **HRs and 95% CIs for the associations between long-term $PM_{2.5}$ exposure and all-cause and cause-specific mortality.**

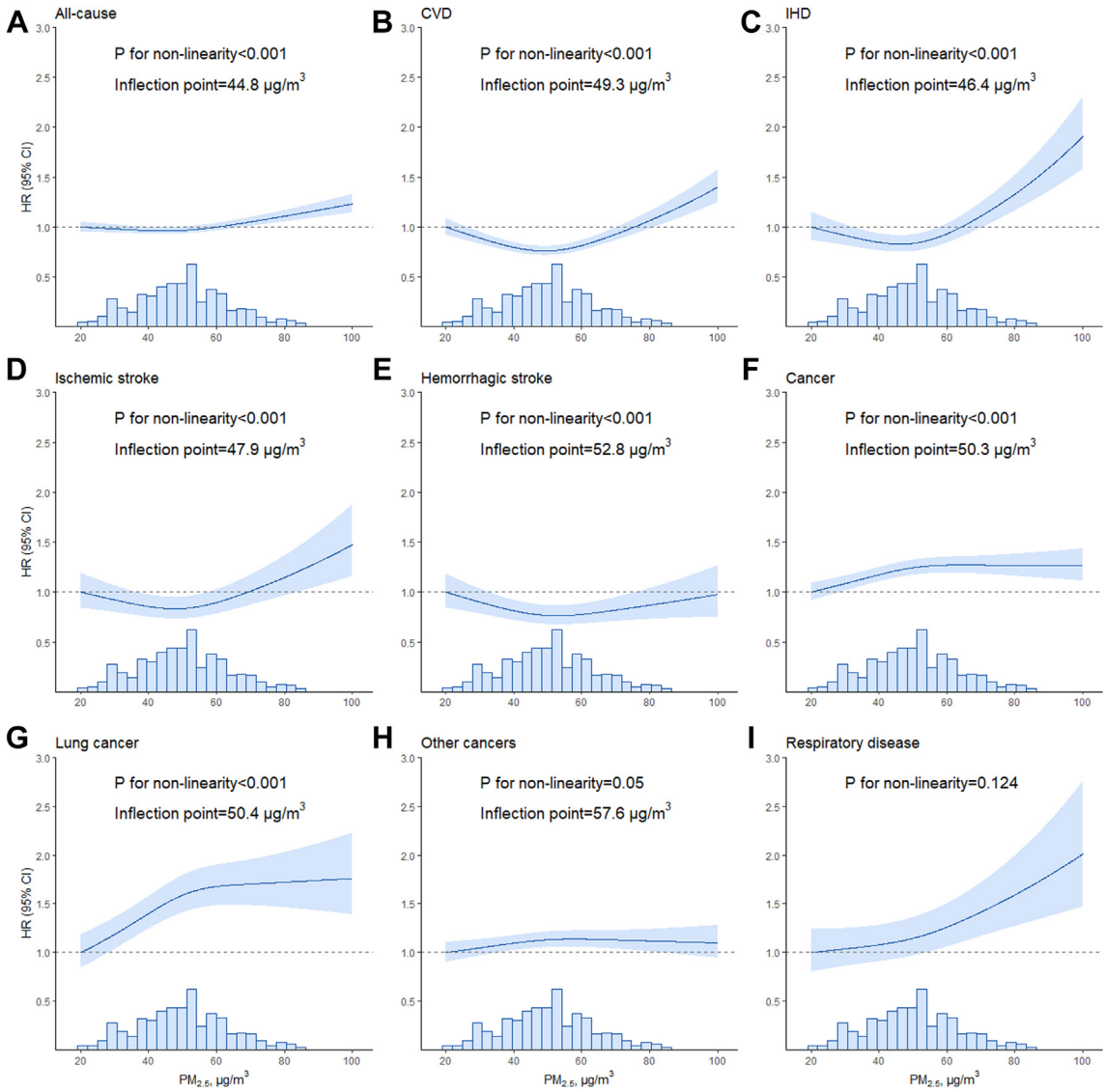


Fig. 2: The concentration-response (C-R) functions between long-term $PM_{2.5}$ exposure and mortality. A: All-cause mortality; B: CVD mortality; C: IHD mortality; D: Ischemic stroke mortality; E: Hemorrhagic stroke mortality; F: Cancer mortality; G: Lung cancer mortality; H: Other cancers mortality; I: Respiratory disease mortality. All analyses were conducted by Cox proportional hazards models adjusted for age, sex, smoking status, drinking status, urbanicity, geographic region, occupation, education, body mass index, and annual average O_3 concentrations. HRs are based on comparisons to HRs for 16.9 μg/m^3.

C-R functions also varied by geographical region (Appendix pp 20–22).

Stratified and subgroup analyses

The stratified analyses of $PM_{2.5}$ concentrations showed significant interactions in all-cause, CVD, and cancer mortalities (Fig. 3). Long-term $PM_{2.5}$ exposure was associated with an increased risk of all-cause mortality in those exposed to $PM_{2.5} \geq 50.4$ μg/m^3 (HR 1.058, 95% CI 1.042–1.075). The association was not significant in those exposed to $PM_{2.5} < 50.4$ μg/m^3 (HR 0.983, 95% CI 0.966–1.002) (P for interaction < 0.001). Long-term $PM_{2.5}$ exposure was associated with an increased risk of CVD mortality in those exposed to $PM_{2.5} \geq 50.4$ μg/m^3 (HR 1.153, 95% CI 1.125–1.182), but a decreased risk in those exposed to $PM_{2.5} < 50.4$ μg/m^3 (HR 0.962, 95% CI 0.935–0.989) (P for interaction < 0.001). There was no significant heterogeneity in the associations between $PM_{2.5}$ and respiratory disease mortality at different levels of $PM_{2.5}$ concentrations (P for interaction = 0.146). The subgroup analyses of age, BMI, drinking status, and urbanicity also showed significant interactions (Appendix pp 23–26).

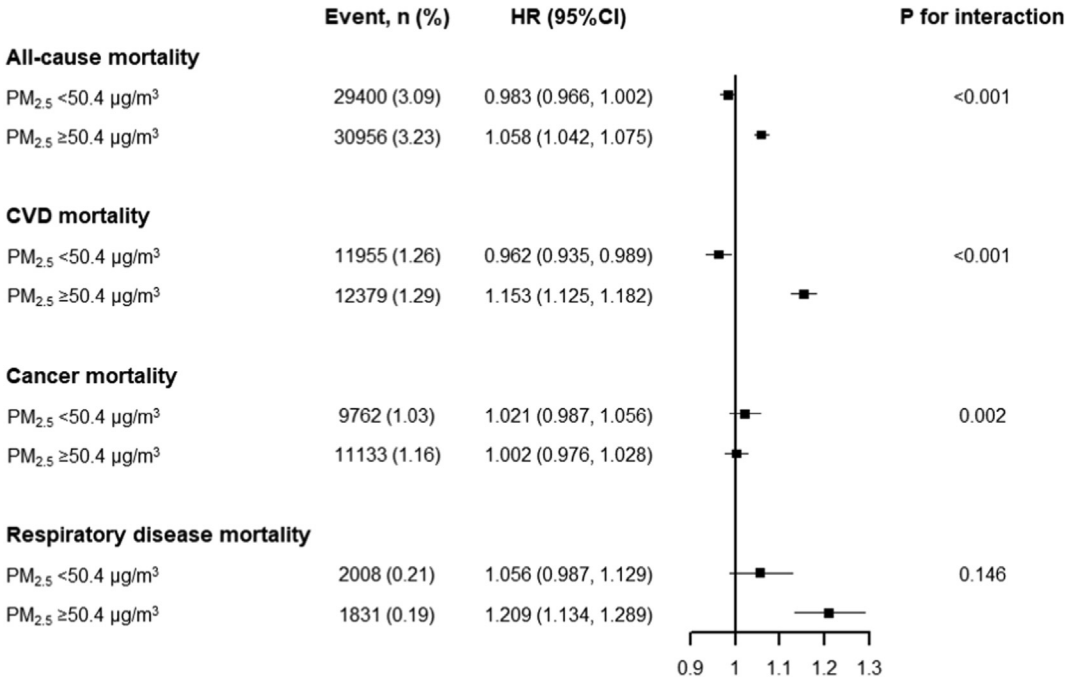


Fig. 3: Stratified analyses of HRs and 95% CIs for the associations between long-term $PM_{2.5}$ exposure and mortality. HR: hazard ratio; 95% CI: 95% confidence intervals; $PM_{2.5}$: fine particulate matter; CVD: cardiovascular disease. P value, HR, 95% CIs from Cox proportional hazards models adjusted for age, sex, smoking status, drinking status, urbanicity, geographic region, occupation, education, body mass index, and annual average O_3 concentrations.

Discussion

This study found that the long-term $PM_{2.5}$ exposure sublinearly related to all-cause mortality across a broad range of $PM_{2.5}$ concentrations from 17 to 102 μg/m^3, with a 6% increase risk per 10 μg/m^3 increase of $PM_{2.5}$ at the level of ≥50.4 μg/m^3. But no significant association existed below 50.4 μg/m^3. The risk of all-cause death in this study was weaker than the results of studies in the settings of $PM_{2.5}$ concentrations < 35 μg/m^3,[10–12] and the effects in this study resulted mainly from the combined distinct C-R functions of the top three cause-specific mortalities. The C-R functions of CVD and cancer mortalities were nonlinear with the inflection points at about 50 μg/m^3. While respiratory disease mortality was linearly associated with long-term $PM_{2.5}$ exposure. These findings could help refine the estimation of the disease burden and preventable death number due to the improved air quality in the settings of $PM_{2.5}$ above 35 μg/m^3, thus facilitate public policy making for these regions home to half of the global population.

In this study, we found a 2–8% increased risk of death by each 10 μg/m^3 increase in $PM_{2.5}$ exposure, which is similar to the effects observed in high exposure areas (3% in the Prospective Urban and Rural Epidemiology [PURE] study, 2% in the China Chronic Disease and Risk Factors Surveillance [CCDRFS]),[13,25] but weaker than the effects observed in low exposure settings.[10–12,26] The main reason for the different effects between high and low exposure settings would be the difference in the sources and compositions of $PM_{2.5}$,[27] as studies have shown that the toxicity of particulate matter is driven by a complex interaction of particle size range, geographic location, and source category.[28] In addition, differences in population characteristics and exposure assessment methodology may also contribute to different effects between high and low exposure settings.

In the settings with annual mean $PM_{2.5}$ concentrations higher than 35 μg/m^3, we reported a completely novel pattern of nonlinear association between $PM_{2.5}$ and all-cause mortality, which differs from the supralinear association in low-exposure countries.[29,30] In higher exposure settings, the Chinese Longitudinal Healthy Longevity Survey (CLHLS) found that the C-R function between $PM_{2.5}$ and all-cause mortality was steeper at concentrations below 60.9 μg/m^3.[5] While the China Family Panel Studies (CFPS) found that the function was piecewise linear, with a near-linear increase in the risk at concentrations below 30 μg/m^3 and above 60 μg/m^3, but null effects in between.[4] The nationwide regulatory $PM_{2.5}$ monitoring network in China was established in 2013, all of these studies had a period without ground monitoring data, during which

the $PM_{2.5}$ concentrations were simulated with poor accuracy. The CFPS merely assigned individual exposures at county level due to a lack of specific address information. And all the participants in the CLHLS only came from the elderly population. These differences in exposure and population age structure may partially explain the inconsistency of C-R function in these studies.

The patterns of C-R function between $PM_{2.5}$ exposure and CVD mortality observed in this study are different from those in the settings of $PM_{2.5}$ < 35 μg/m^3, which generally show linear relationships down to very low concentrations or somewhat steeper curves at low than at higher concentrations, with no evidence of a threshold.[29,31–33] The C-R curve of cardiovascular mortality was a J shape, with a small HR slope of decreased risk at the low $PM_{2.5}$ level (<50 μg/m^3) and a large HR slope of increased risk at the high level (≥50 μg/m^3). This association is somehow similar with that in the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) study which included 103 thousand rural adults and 14 thousand urban adults in China and showed a stronger association at $PM_{2.5}$ concentrations above 60 μg/m^3.[6] The PURE study included 157 thousand adults from 21 countries and showed an exponential distribution with a small HR slop below 80 μg/m^3, followed by an increase above 80 μg/m^3.[13] While another two studies in China showed stronger associations at $PM_{2.5}$ between 35 and 75 μg/m^3, and then observed attenuation at higher levels.[7,25] Possible reason for the negative association below 50 μg/m^3 in this study may be that most areas of low $PM_{2.5}$ exposure were the least developed in China, and usually had the most limited medical resources and worst traffic facilities, which may impede the emergent medical care.[34] The accessibility and quality of emergent medical care mainly affect CVD death rather than cancer death. Although we adjusted for geographic region, province-level GDP, and the number of hospital beds per thousand people, the effects of suboptimal emergent medical care could not be completely eliminated.

We also noted that participants with $PM_{2.5}$ exposure levels of 46–51 μg/m^3 had the strongest negative association between $PM_{2.5}$ exposure and CVD mortality. Among these participants, the proportion of indoor solid fuel consumption was almost twice that of the total population (28% vs. 15%), and nearly half were from northern regions (43%). The C-R functions by geographical region also showed that there was no significant association between $PM_{2.5}$ exposure and CVD mortality in Northeast China and Northwest China. Because of the cold climate in northern China, residents spend most of their time indoors in winter, and they use a higher proportion of solid fuels indoors. Therefore, although outdoor $PM_{2.5}$ concentrations are highest in winter,[19] the health effects from air pollution on these populations may come mainly from indoor air pollutants, thus weakening the impact of outdoor air pollutants.

To the best of our knowledge, it is the first time that we reported the C-R functions of long-term $PM_{2.5}$ exposure with cancer and respiratory disease mortalities in the settings with an average $PM_{2.5}$ concentration above 35 μg/m^3. Cancer mortality was supra-linearly associated with long-term $PM_{2.5}$ exposure; the risk of cancer death increased with the increasing of $PM_{2.5}$ exposure in the settings of low concentrations (<50 μg/m^3), rather than high $PM_{2.5}$ concentrations (≥50 μg/m^3). It is well known that lung cancer is supra-linearly associated with long-term $PM_{2.5}$ exposure in the settings of $PM_{2.5}$ below 35 μg/m^3.[9,31,35] The only study investigating the C-R function between $PM_{2.5}$ and lung cancer mortality in the settings with an average $PM_{2.5}$ concentration above 35 μg/m^3 was based on a Chinese male cohort, and indicated uncertainty due to a small events number.[7] We found similar patterns of C-R functions in lung cancer and other cancers, although the effect in the later was weaker. While the risk of death due to respiratory disease increased linearly as the $PM_{2.5}$ exposure increased, which is similar with those from the settings of $PM_{2.5}$ below 35 μg/m^3.[9,36]

In this study, we found that the C-R functions differed by cause of death. The possible explanation is that within the $PM_{2.5}$ concentration range from 17 to 102 μg/m^3, the physical and chemical composition of the atmosphere may change, resulting in different distribution of $PM_{2.5}$ components responsible for health effects across the exposure range. Previous studies have shown that the health effects caused by $PM_{2.5}$ are related to its chemical components. For example, components such as organic carbon, elemental carbon, and chloride ions are associated with blood pressure; components such as zinc, cobalt, and manganese are associated with cardiovascular biomarkers.[37,38] Therefore, due to the spatial variation in $PM_{2.5}$ components, a single-shape C-R function is unlikely to be applicable to deaths from different causes. More studies are needed to clarify the health effects of specific components, so as to obtain a more comprehensive understanding of the C-R functions between $PM_{2.5}$ and cause-specific mortality.

Our subgroup analyses showed that age, BMI, drinking status, and urbanicity could modify the associations between long-term $PM_{2.5}$ exposure and mortality. Previous studies have shown that age and BMI could modify the associations between long-term exposure to $PM_{2.5}$ and mortality, but the effects of modification were inconsistent due to difference in population characteristics and exposure assessment.[26,39,40] Recent study showed that light and moderate drinkers had healthier lifestyle behaviors than non-drinkers, such as lower rates of smoking, lower BMI, and higher vegetable intake.[41] In a similar air pollution environment, these healthy lifestyle behaviors may partially offset the

harmful effects of long-term exposure to $PM_{2.5}$, which may help explain the lower risk in drinkers. Differences in health effects of $PM_{2.5}$ exposure between urban and rural areas may be due to differences in sources and compositions of particulate matter, and access to medical care. In rural areas, the main sources of $PM_{2.5}$ are biomass burning. These different effect estimates in subgroups might be the main reason for the previous controversial results, as previous studies included mostly the rural residents, or only the elderly population, or only men.

It should be cautious to interpret our findings with the following considerations. First, we did not collect the data on indoor $PM_{2.5}$ exposure. The use of solid fuels is an important contributor to indoor air pollution and the basis for global burden of disease (GBD) to estimate the exposure level of indoor air pollution.[42] In this study, we collected the information on indoor fuels through census data, and the results were consistent after adjusting for fuel types. Second, other pollutants, such as O_3, nitrogen dioxide, and black carbon, could confound the chronic effects of $PM_{2.5}$ on mortality.[29] Due to data unavailability, we only included O_3 in the two-pollutant models, and the results changed slightly after adjusting for annual average O_3 concentrations. Future studies should consider the potential confounding effects of other pollutants. Finally, we did not use a random sampling design, so it may not represent the entire Chinese population. We compared the characteristics of study population with the national census and showed that the proportion of participants with high school education and above in the cohort is slightly higher than that in the general Chinese population,[15] These highly educated participants were more health-conscious, and therefore may have better outcome than the general population when suffer a disease, which may potentially lead to underestimate the effects of $PM_{2.5}$.

In conclusion, we found weaker chronic effects of $PM_{2.5}$ on mortality across a broad range of $PM_{2.5}$ concentrations from 17 to 102 $\mu g/m^3$, compared to those reported in the settings of $PM_{2.5}$ concentrations < 35 $\mu g/m^3$. The mortalities associated with long-term $PM_{2.5}$ exposure in China may be overestimated in previous studies, particularly in the areas of $PM_{2.5}$ concentration < 50 $\mu g/m^3$. We demonstrated distinct concentration-response relationships of CVD, cancer, and respiratory disease mortalities, which could help refine the estimation of disease burden and preventable death number due to improved air quality in the settings of $PM_{2.5}$ above 35 $\mu g/m^3$. Our findings provide evidence for facilitating public health policy making to reduce extra mortality caused by $PM_{2.5}$.

Contributors

WL did the statistical analysis and drafted the manuscript, with further contributions from BC, RJ, JG, XS, BP and LL. LS, WX, YZ, WH, and HY collected the health data; RM, QW, and JB developed exposure prediction models; all authors accessed and verified the underlying data. AT, YS, and XL revised the manuscript critically. TL and JL designed the study and gave final approval of the version to be published. TL and JL had final responsibility for the decision to submit for publication.

Data sharing statement

The data are not publicly available. The ChinaHEART project (formerly named China PEACE MPP) only provides conditional data access for qualified researchers with legitimate requests; a formal application and research proposal is required. Please contact cvd-project@nccd.org.cn to seek approval for data access.

Editor note

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Declaration of interests

The authors declared no relevant conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100908.

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