ARTICLE

Long term exposure to $PM_{2.5}$ chemical components associated with prevalence of cardiovascular diseases in China

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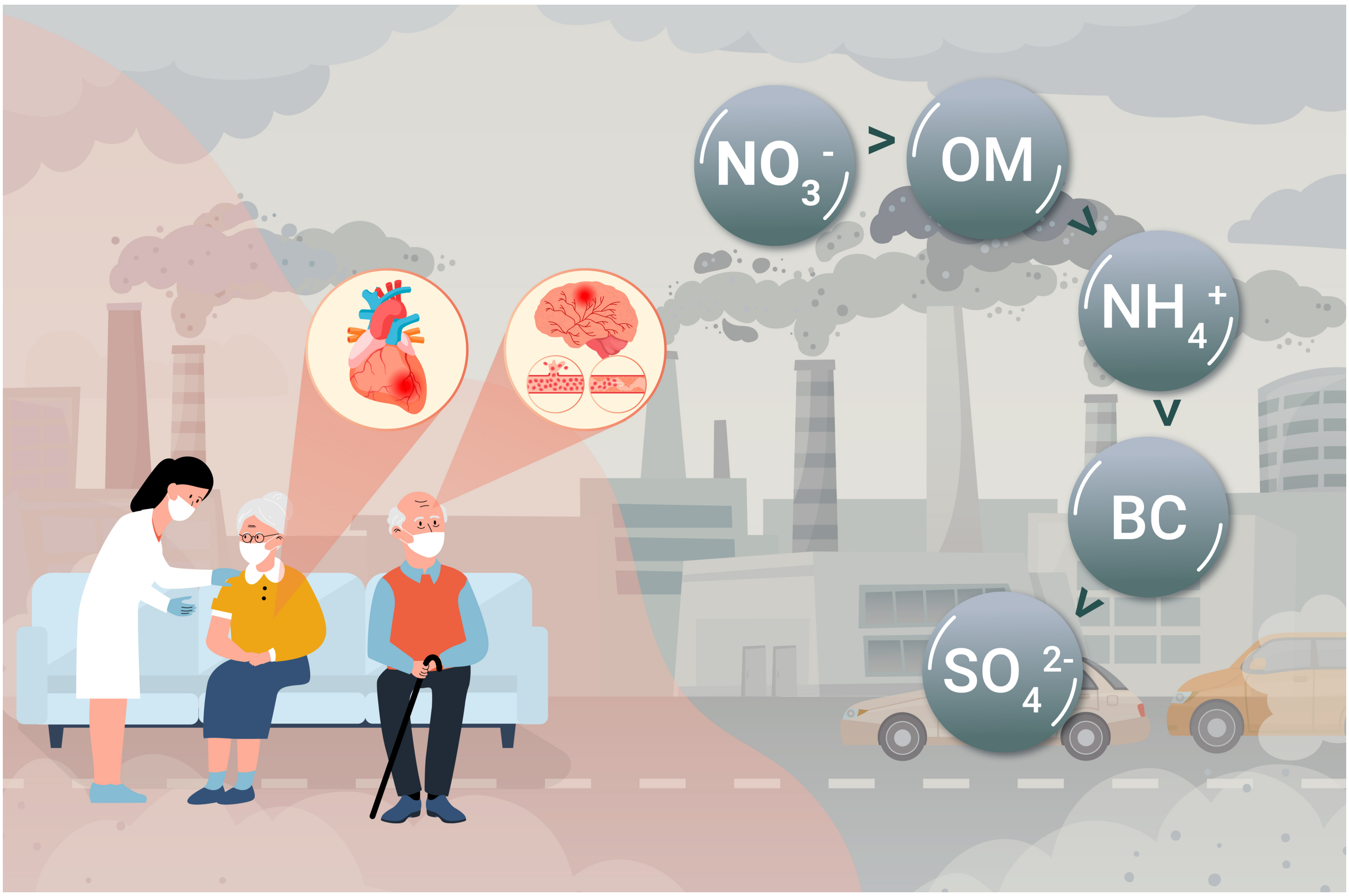
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Nitrate, organic matter, ammonium, black carbon, and sulphate top air pollution's cardiovascular burden.
- Targeting traffic and fossil fuel sources of pollution may reduce China's cardiovascular disease burden.
- Northern and Central China face higher cardiovascular burden from air pollution, mainly from organic matter.

ARTICLE

Long term exposure to $PM_{2.5}$ chemical components associated with prevalence of cardiovascular diseases in China

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Introduction:Ambient fine particulate matter pollution ($PM_{2.5}$) has been widely associated with cardiovascular disease (CVD). However, less is known about the contribution of different chemical components of $PM_{2.5}$ to CVD using a nationally representative sample in China. Methods:A nationally representative sample of older adults was recruited from 31 provinces, municipalities, or autonomous regions of China by the fourth national Urban and Rural Elderly Population Survey in 2015. We estimated the annual average concentrations of $PM_{2.5}$ and its five dust-free chemical components (black carbon [BC], organic matter [OM], sulphate [SO_4^{2-}], nitrate [NO_3^-], and ammonium [NH_4^+]) at geocoded residential addresses with the spatial resolution of 10×10 km using bilinear interpolation. Logistic regression models were constructed to estimate the associations between $PM_{2.5}$ chemical components and prevalence of self-reported CVD, and potential reducible fractions were further estimated using counterfactual analyses. Results:A total of 220,425 participants with a mean age of 69.73 years, 52.24% females, and 6.08% minor ethnicity were included in the study, of which 55,837 (25.3%) reported having CVD. An interquartile range (IQR) increment in annual $PM_{2.5}$ chemical components was associated with significantly elevated risk of CVD prevalence. The odds ratios were 1.254 (95% CI: 1.235-1.275, IQR: 7.11 μg/m^3) for NO_3^-, 1.197 (95% CI: 1.178-1.216, IQR: 4.35 μg/m^3) for NH_4^+, 1.187 (95% CI: 1.173-1.202, IQR: 5.34 μg/m^3) for OM, 1.122 (95% CI: 1.107-1.137, IQR: 0.97 μg/m^3) for BC, and 1.106 (95% CI: 1.089-1.123, IQR: 4.67 μg/m^3) for SO_4^{2-}. The associations were significantly stronger in those older than 70 years. Conclusions: Our study suggests that long-term exposure to $PM_{2.5}$ chemical components could increase the risk of CVD prevalence. Future air pollution guidelines target reducing specific $PM_{2.5}$ chemical components may help alleviate the burden of CVD.

INTRODUCTION

Cardiovascular diseases (CVDs), primarily consisting of ischemic heart disease and stroke, are the leading cause of mortality, accounting for approximately one-third of deaths worldwide in 2019.[1] China experienced the greatest burden of CVD in 2019, with an estimated 120.3 million prevalent CVD cases and 4.6 million CVD deaths, as reported by the Global Burden of Diseases Study.[2,3] The prevalence of CVD is driven by a constellation of clinical, environmental, behavioral, and social risk factors.[4] To prevent CVD, targeted policies aimed at controlling modifiable risk factors are needed, and these policies should be informed by high-quality and representative evidence.[5]

Air pollution is the most important environmental risk factor to CVD, and globally, approximately 20% of CVD deaths can be attributable to air pollution.[6] Fine particulate matter ($PM_{2.5}$) is the most thoroughly studied air pollutant that is linked to CVD incidence, mortality, and hospitalization in China and across the globe.[7-14] Recent studies also indicate that air pollution originating from different sources may influence human health differently due to the difference in chemical components and toxic metal content.[15-17] However, much of the existing evidence has investigated ambient $PM_{2.5}$ as a single exposure, failing to account for the differences in the chemical components of $PM_{2.5}$. Ambient $PM_{2.5}$ has a complex chemical composition that varies spatiotemporally, which may show different toxicity on human health.[18] Characterizing the relationship between $PM_{2.5}$ chemical components and CVD can assist prioritizing policy efforts to curb the emission of the most hazardous components of $PM_{2.5}$ and protect the high-risk populations.[19]

China has the largest older population globally and the older population is one of the most susceptible groups to the adverse CVD outcomes from ambient air pollution.[20,21] However, the relationship between $PM_{2.5}$ chemical components and CVD among older adults in China has not been well characterized with a large and nationally representative sample. In this study, we leveraged data on over 200,000 participants from the fourth national Urban and Rural Elderly Population (UREP) survey conducted in 2015, and we aim to disentangle the associations of long-term exposure to $PM_{2.5}$ chemical components with the prevalence of CVD among the older population in China.

MATERIALS AND METHODS

Data source

UREP is a nationally representative survey designed to understand the chronic disease, healthcare needs, livelihood, and socioeconomic status of older residents (≥60 years) in mainland China.[22,23] The survey, which has been conducted every five years since 2000, is administered by the National Committee on Aging, an organization established and managed by the State Council of China. Data used in this study were taken from the fourth survey of UREP conducted in 2015.

UREP obtained a nationwide sample of people over 60 years using a multistage sampling strategy. The UREP survey investigated over 200,000 residents aged 60 year or older from 7488 communities or villages across 31 mainland China provinces, autonomous regions, and municipalities (not including Hong Kong, Macao, or Taiwan). A flowchart that demonstrates the three-stage sampling process is shown in Figure S1. Only older adults aged 60 years and above were included and the participants with missing covariates were excluded, yielding a final analytic sample of 220,425 individuals (98.1% of the investigated sample, Figure 1). Since the UREP used a sampling approach of probability proportional to population, it is a self-weighted survey with each participant having the same weight and no further weights are needed in statistical analyses. Since all the participants were older adults with the age of at least 60 years and less likely to move actively across areas, the sample participants were assumed to be long-term residents of their addresses.

The data collection process of UREP was approved by the institutional review board of the Chinese National Bureau of Statistics. The National Committee on Aging granted permission for data analyses in this study. Informed consent was obtained from each participant prior to the interview.

Exposure measurement

We obtained daily concentrations of $PM_{2.5}$ total mass and its five dust-free chemical components (black carbon [BC], organic matter [OM], sulphate

[SO_4^{2-}], nitrate [NO_3^-], and ammonium [NH_4^+]) at 10×10 km spatial resolution from the Tracking Air Pollution (TAP) database in China (http://tapdata.org.cn/).[24,25] The TAP provides a timely and fully covered gridded raster data set on $PM_{2.5}$ chemical components in China since 2000. It fuses multiple data sources including ground-based situ observations, bottom-up emission inventory, as well as satellite-based aerosol optical depth estimates, and derived the daily gridded data on $PM_{2.5}$ and its chemical components using Weather Research and Forecasting-Community Multiscale Air Quality modeling system. The TAP daily $PM_{2.5}$ chemical components data have good consistency with ground-based observations, and the average out-of-bag correlation coefficients for $PM_{2.5}$ chemical components ranged from 0.67 to 0.80.[25]

We estimated the annual concentrations (365-day average) of $PM_{2.5}$ mass and its chemical components prior to the date of the investigation (from August 2015 to December 2015) at the participant's residential address. The residential addresses were converted into longitudes and latitudes using the application programming interface of Amap (Gaode map). To enhance the spatial resolution of air pollution data, we applied a bilinear interpolation algorithm, which utilized inverse distance weights to determine the concentration of air pollutants at each residential address.[26] The bilinear interpolation algorithm to enhance the spatial resolution of environmental variables is presented in Figure S2.[27-29] Figure S2a shows the nearest four gridded raster data (typically retrieved from satellite remote sensing) for environmental variables at patient's residential address P. The environmental variables at location P (denoted as Y(P)) can be estimated as a weighted average of the concentrations of the nearest four grids surrounding P using the following formula:

$$Y(\mathrm{P}) = Y_{11}\omega_{11} + Y_{12}\omega_{12} + Y_{21}\omega_{21} + Y_{22}\omega_{22}$$

$$\omega_{11} = \frac{(x_2 - x_P)(y_2 - y_P)}{(x_2 - x_1)(y_2 - y_1)}$$

$$\omega_{12} = \frac{(x_2 - x_P)(y_P - y_1)}{(x_2 - x_1)(y_2 - y_1)}$$

$$\omega_{21} = \frac{(x_P - x_1)(y_2 - y_P)}{(x_2 - x_1)(y_2 - y_1)}$$

$$\omega_{22} = \frac{(x_P - x_1)(y_P - y_1)}{(x_2 - x_1)(y_2 - y_1)}$$

Where Y_{11}, Y_{12}, Y_{21}, and Y_{22} are the concentrations of environmental variables in the nearest four grids around location P, and $\omega_{11}, \omega_{12}, \omega_{21}$, and ω_{22} are the associated weights (Figure S2a). The weights can be computed from the distance between the residential address (x_P and y_P) to the grids of air pollutants (x_1 and y_1, x_2 and y_2, x_3 and y_3, x_4 and y_4), and the grids closer to patient's address P will be assigned larger weights. The estimated concentrations of environmental variables using bilinear interpolation method are presented in Figure S2b. Bilinear interpolation enhances spatial resolution by transforming the spatially discrete environmental grids data into spatially smoothed and continuous estimates of environmental variables.

Outcome

The primary outcome of this study was the prevalence of CVD as self-reported by the respondent at the time of the investigation (from August 2015 to December 2015). CVD in this study included coronary heart disease, angina, stroke, and other major cardiovascular disorders. These outcomes were collected using structured questionnaire and face-to-face interviews by centrally trained staff following a standardized protocol.[22,23]

Covariates

We selected a set of covariates based on availability of data and potential confounding relationships. Self-reported age, sex, and ethnicity were included as demographic variables. Ethnicity was categorized as Han Chinese and non-Han Chinese, in which the small-frequency minority ethnicities were lumped into one to enhance model stability and maximize the statistical power. Education included illiterate, primary school, middle school, and ≥high school. Marital status was categorized as married, widowed, divorced, and unmarried.[30] Physical activity was a self-reported question asking the number of physical exercises per week (never, less than one, 1 to 2, 3 to 5, and ≥6 times). Financial status was a five-point Likert scale categorical variable (very bad, bad, neutral, good, and very good). Rurality was a binary variable that was ascertained based on the participant's residential address (rural or urban).[31] Daily data on ambient temperature and relative humidity with the spatial resolution of 9*9 km grids were retrieved from the fifth generation of European ReAnalysis (ERA5)-Land data set.[32] We calculated 14-day averages of temperature and relative humidity prior to the date of investigation at participant's residential address using bilinear interpolation as proxy of meteorologic variables.

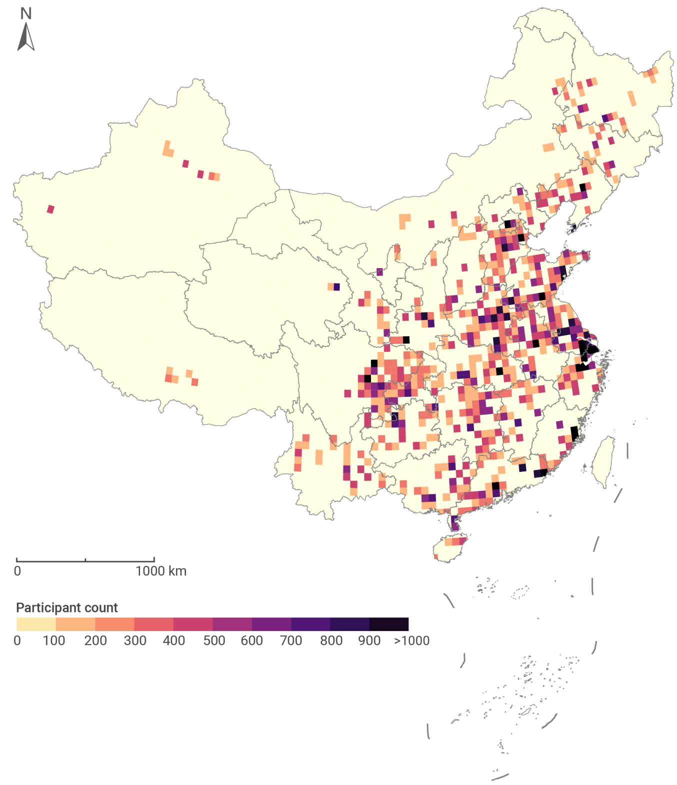

Figure 1. A map of the spatial distribution of study participants.

Statistical analyses

Overall participant characteristics and by the prevalence of CVD were reported as mean (standard deviation, SD) for numeric variable and frequency (percent) for categorical variables. Logistic regression models were constructed to estimate the associations (odds ratio [ORs] and 95% confidence intervals [CI]) between per interquartile range increment in $PM_{2.5}$ and its chemical components with the prevalence of CVD. We further constructed natural cubic splines to demonstrate the exposure-response curves, and we specified the knots at quartiles. We then conducted formal interaction analyses of $PM_{2.5}$ and its chemical components with CVD by age groups, sex, ethnicity, rurality, education, marital status, and financial status as a way of identifying potentially vulnerable populations. The statistical significance of the interaction was determined by the p-value of the interaction term in logistic regression models. Continuous age was categorized into smaller than 70 and greater or equal to 70 years.

To estimate the potential reducible fractions for CVD, we first constructed logistic regression models that estimate the quantitative relationship between a specified air pollutant (A) and the outcome (Y) while account for the covariate set (W), and we note this model as $E[Y|A, W]$. We then estimated two scenarios based on the logistic regression models:[10-12,33] (1) the estimated outcome when the air pollutant was set to the observed level for each participant: $\widehat{E}[Y|A_{\mathrm{observed}}, W]$; and (2) the estimated outcome when the air pollutant

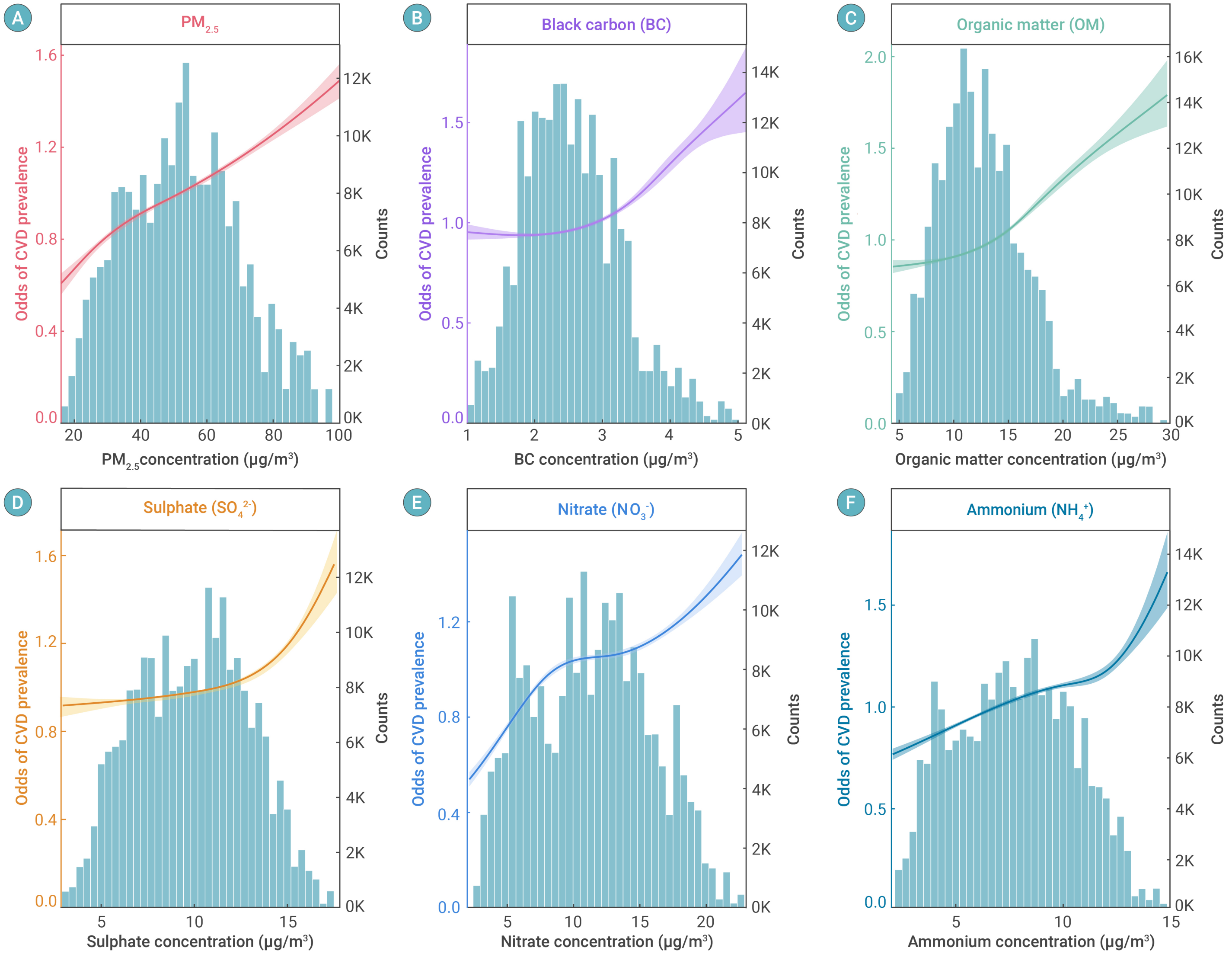

Figure 2. Exposure-response relationships of annual concentrations of ambient $PM_{2.5}$ and its chemical components [black carbon (BC), organic matter (OM), sulphate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+)] with CVD.

was set to the counterfactual level for each participant: $\widehat{E}[Y|A_{\text{counterfactual}}, W]$, where the counterfactual scenario was defined as the lowest 5th percentile of each $PM_{2.5}$ chemical component in our sample. If the levels of $PM_{2.5}$ and its chemical components in the sample were lower than the counterfactual levels, they were kept unchanged in the counterfactual scenario. The potential reducible numbers were estimated by taking the differences between the observed and predicted number of CVD cases: $\widehat{E}[Y|A_{\text{observed}}, W] - \widehat{E}[Y|A_{\text{counterfactual}}, W]$. The potential reducible fractions were then calculated as the division of the reducible number of CVD cases by the observed total number of CVD cases:

$$\text{potential reducible fraction} = \frac{\widehat{E}[Y|A_{\text{observed}}, W] - \widehat{E}[Y|A_{\text{counterfactual}}, W]}{\widehat{E}[Y|A_{\text{observed}}, W]}$$

The corresponding 95% confidence intervals were estimated using a bootstrap method, with 1000 replicate samples generated for each model.[34]

No imputation was conducted as the analyses were based on a complete data set. All statistical tests were two-sided, and a p-value ≤0.05 or a 95% CI of an OR not including one was considered statistically significant. All the data cleaning, statistical modeling, and data visualization were performed using statistical computing environment R 4.2.2.[35] The results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Sensitivity analyses

Several sensitivity analyses were performed to check the robustness of our findings. (1) To check the consistency of model results at different exposure windows, we estimated the concentrations of $PM_{2.5}$ and its chemical components at different lag years. (2) To examine the robustness of results to residual confounding caused by smoking, we included smoking status as a covariate in a subsample of 21,925 participants (9.9% of the entire sample) who reported their smoking status. (3) To further examine the potential bias caused by unmeasured variables, we computed the E-values for each fully-adjusted ORs and their 95% CIs. E-value shows the minimum strength of the association between a confounder and an exposure or outcome that is necessary to nullify the observed significant association.[36-38] A larger E-value indicates a stronger likelihood of a causal relationship, with the minimum value being one. (4) We estimated logistic regression models using subsamples excluding those with hypertension, with diabetes, and with hypertension or diabetes to examine the impact of excluding individuals with chronic diseases. (5) Instead of the logistic regression models in our primary approach, we fitted Poisson regression models using the same set of covariates to test the robustness of our findings to the specification of statistical models.

RESULTS

Among the 220,425 participants (mean age: 69.73 years, 52.24% female,

Table 1. Ambient $PM_{2.5}$ and it chemical components, participant characteristics in overall sample and by CVD

Variables	Overall (n=220,425)	CVD=No 164,588 (74.7%)	CVD=Yes 55,837 (25.3%)	p
Annual average concentrations of air pollution				
$PM_{2.5}$, median [IQR], μg/m^3	52.52 [38.98, 64.52]	51.91 [37.99, 64.07]	53.65 [41.66, 66.47]	<0.001
BC, median [IQR], μg/m^3	2.49 [2.03, 3.01]	2.47 [2.02, 2.98]	2.54 [2.07, 3.09]	<0.001
OM, median [IQR], μg/m^3	12.40 [9.94, 15.28]	12.24 [9.82, 15.04]	12.83 [10.24, 15.80]	<0.001
SO_4^{2-}, median [IQR], μg/m^3	9.99 [7.46, 12.13]	9.91 [7.37, 12.11]	10.05 [7.68, 12.26]	<0.001
NO_3^-, median [IQR], μg/m^3	11.26 [7.40, 14.51]	11.10 [7.25, 14.40]	11.63 [8.34, 14.83]	<0.001
NH_4^+, median [IQR], μg/m^3	7.74 [5.47, 9.82]	7.68 [5.35, 9.75]	7.92 [5.91, 9.94]	<0.001
Participant characteristics				
Age, median [IQR], years	68 [63, 75]	67 [63, 75]	70 [64, 77]	<0.001
Sex				<0.001
Female	115,142 (52.24)	83,079 (50.48)	32,063 (57.42)	
Male	105,283 (47.76)	81,509 (49.52)	23,774 (42.58)	
Ethnicity				<0.001
Han	207,016 (93.92)	154,042 (93.59)	52,974 (94.87)	
Non-han	13,409 (6.08)	10,546 (6.41)	2,863 (5.13)	
Education				<0.001
≥High school	22,518 (10.22)	16,230 (9.86)	6,288 (11.26)	
Middle school	41,501 (18.83)	30,818 (18.72)	10,683 (19.13)	
Primary school	91,035 (41.30)	69,023 (41.94)	22,012 (39.42)	
Illiterate	65,371 (29.66)	48,517 (29.48)	16,854 (30.18)	
Marital status				<0.001
Married	159,876 (72.53)	120,677 (73.32)	39,199 (70.20)	
Widowed	55,511 (25.18)	39,826 (24.20)	15,685 (28.09)	
Divorced	1,838 (0.83)	1,370 (0.83)	468 (0.84)	
Unmarried	3,200 (1.45)	2,715 (1.65)	485 (0.87)	
Physical activity				<0.001
Never	108,961 (49.43)	81,770 (49.68)	27,191 (48.70)	
<1	9,665 (4.38)	7,275 (4.42)	2,390 (4.28)	
1 to 2	27,041 (12.27)	20,406 (12.40)	6,635 (11.88)	
3 to 5	27,018 (12.26)	20,096 (12.21)	6,922 (12.40)	
≥6	47,740 (21.66)	35,041 (21.29)	12,699 (22.74)	
Financial status				<0.001
Very good	2,802 (1.27)	2,311 (1.40)	491 (0.88)	
Good	32,606 (14.79)	26,034 (15.82)	6,572 (11.77)	
Neutral	129,718 (58.85)	98,845 (60.06)	30,873 (55.29)	
Bad	46,284 (21)	31,941 (19.41)	14,343 (25.69)	
Very bad	9,015 (4.09)	5,457 (3.32)	3,558 (6.37)	
Rurality				<0.001
Urban	114,926 (52.14)	83,953 (51.01)	30,973 (55.47)	
Rural	105,499 (47.86)	80,635 (48.99)	24,864 (44.53)	
Annual concentrations of meteorologic variables				
Temperature, median [IQR], °C	15.51 [13.48, 17.43]	15.64 [13.77, 17.62]	15.01 [11.92, 16.68]	<0.001
Relative humidity, median [IQR], %	72.37 [59.85, 76.13]	73.49 [61.53, 76.33]	67.16 [56.09, 75.41]	<0.001

Abbreviations: BC=black carbon; NH_4^+ = ammonium; NO_3^- = nitrate; OM=organic matter; OR: odds ratio; $PM_{2.5}$: particulate matter <2.5 μm in aerodynamic diameter; IQR: interquartile range; SO_4^{2-} =sulphate.

Table 2. Associations of interquartile range increment in annual average concentrations of ambient $PM_{2.5}$ and its chemical components with the prevalence of CVD

Air pollutant	IQR ($\mu g/m^3$)	OR (95% CI)	
		Unadjusted model	Fully-adjusted model†
$PM_{2.5}$	25.55	1.234 (1.217-1.250)	1.248 (1.230-1.265)
NO_3^-	7.11	1.217 (1.198-1.235)	1.254 (1.235-1.275)
NH_4^+	4.35	1.159 (1.142-1.177)	1.197 (1.178-1.216)
OM	5.34	1.192 (1.178-1.206)	1.187 (1.173-1.202)
BC	0.97	1.132 (1.118-1.147)	1.122 (1.107-1.137)
SO_4^{2-}	4.67	1.092 (1.076-1.109)	1.106 (1.089-1.123)

Abbreviations: BC=black carbon; CI: confidence interval; IQR: interquartile range; NH_4^+ = ammonium; NO_3^- = nitrate; OM=organic matter; OR: odds ratio; $PM_{2.5}$: particulate matter <2.5 μm in aerodynamic diameter; SO_4^{2-} =sulphate.

† Fully-adjusted model accounts for age, sex, ethnicity, education, marital status, physical activity, financial status, rurality, splines of temperature and relative humidity (five degrees of freedom), and province.

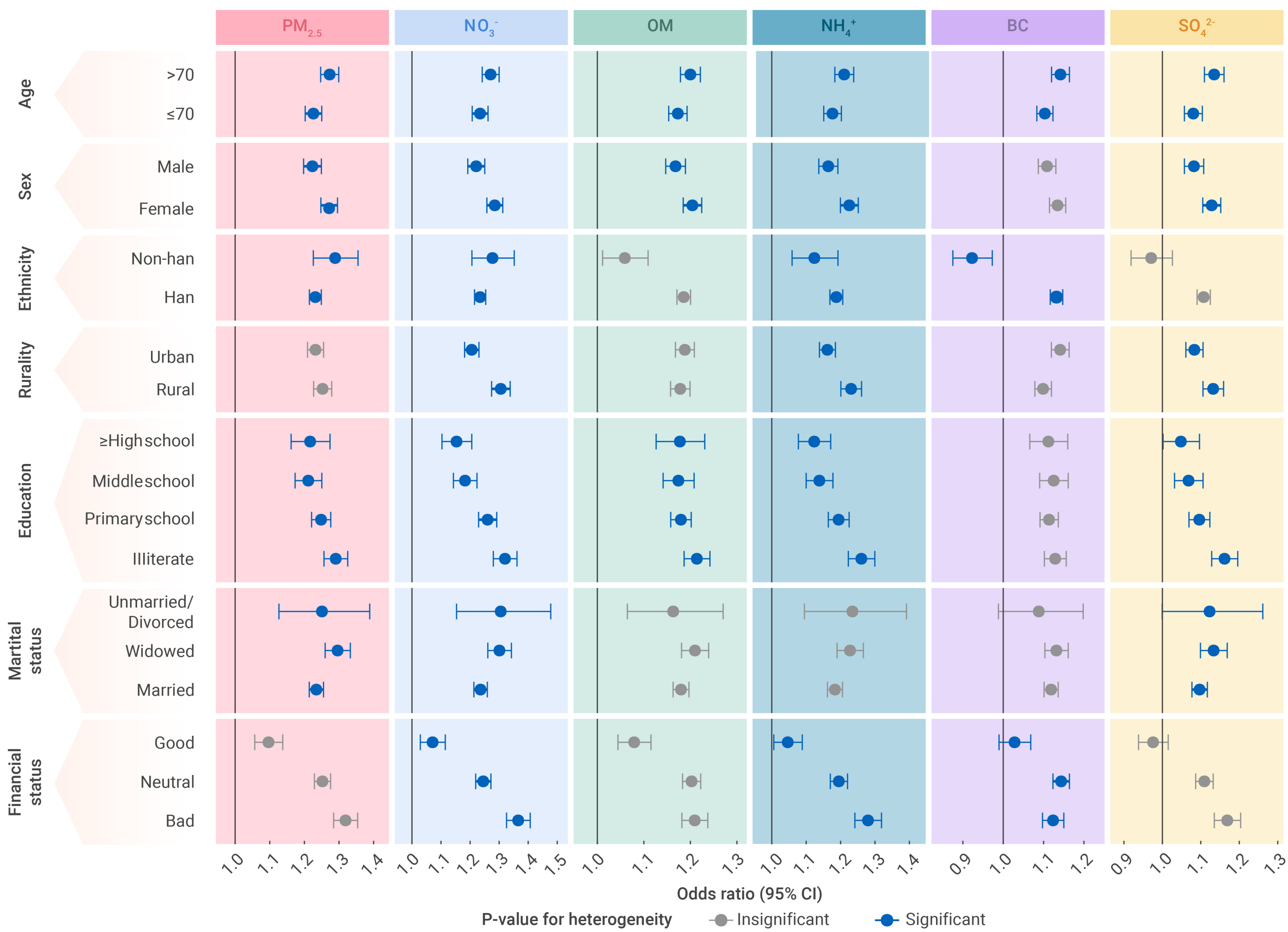

Figure 3. Associations of ambient $PM_{2.5}$ and its chemical components [black carbon (BC), organic matter (OM), sulphate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+)] with CVD by age, sex, occupation, region, economic status, and rurality.

and 6.08% minor ethnicity) who responded to the survey, 55,837 (25.3%) reported to have CVD. Compared to participants who did not have CVD, those with CVD were older, had a higher percentage of female and Han Chinese, received more education, were more likely to be widowed, had worse financial status and a higher percent of urban residents (Table 1). Participants who reported to have CVD were exposed to significantly higher levels of $PM_{2.5}$ and its all five chemical components including BC, OM, SO_4^{2-}, NO_3^-, and NH_4^+ (Table 1).

Associations of $PM_{2.5}$ and its chemical components with CVD

Table 2 shows the unadjusted and fully adjusted estimates for the associations between $PM_{2.5}$ chemical components and CVD prevalence. Each

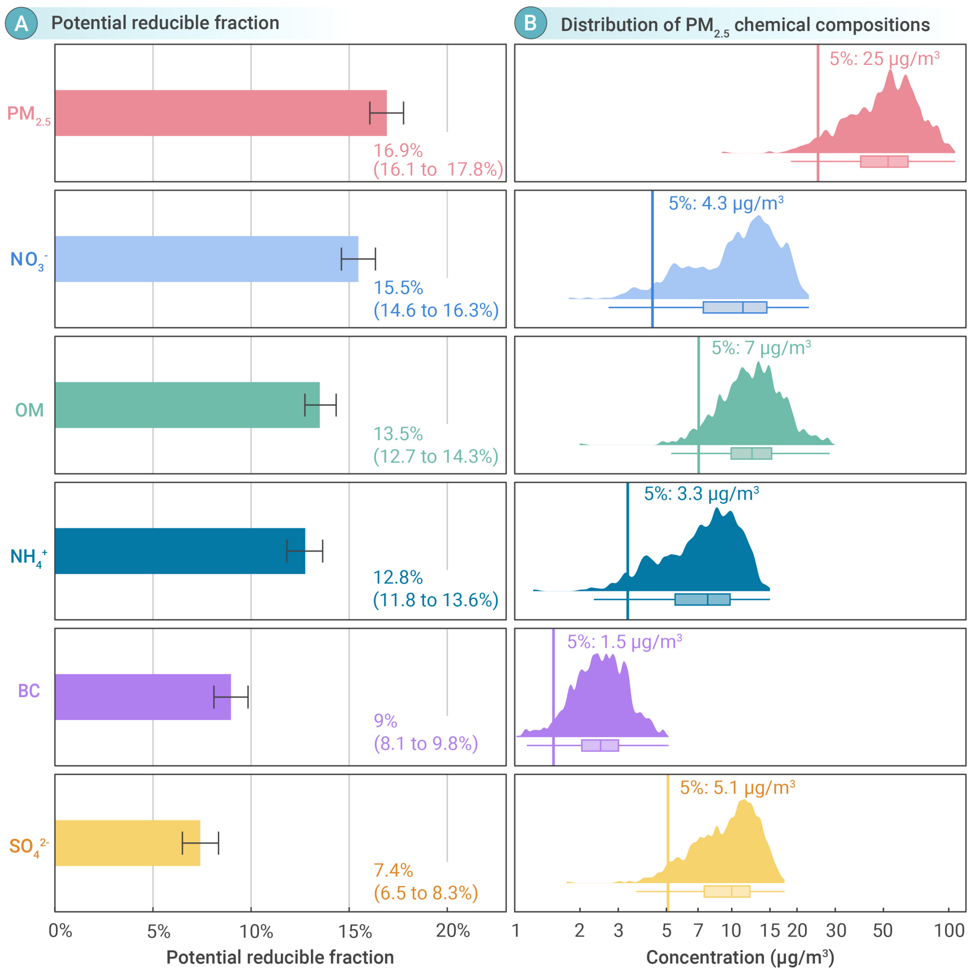

Figure 4. Potential reducible fraction of CVD attributable to ambient $PM_{2.5}$ and its chemical components [black carbon (BC), organic matter (OM), sulphate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+)].

interquartile range (IQR) increment in annual average concentrations of $PM_{2.5}$ chemical components were associated with significantly elevated risk of CVD prevalence, and the fully adjusted ORs and associated 95% CIs were 1.254 (95% CI: 1.235-1.275, IQR: 7.11 μg/m^3) for NO_3^-, 1.197 (95% CI: 1.178-1.216, IQR: 4.35 μg/m^3) for NH_4^+, 1.187 (95% CI: 1.173-1.202, IQR: 5.34 μg/m^3) for OM, 1.122 (95% CI: 1.107-1.137, IQR: 0.97 μg/m^3) for BC, and 1.106 (95% CI: 1.089-1.123, IQR: 4.67 μg/m^3) for SO_4^{2-}. The OR and the corresponding 95% CI were 1.248 (95% CI: 1.230-1.265) for $PM_{2.5}$ mass per IQR increment (25.55 μg/m^3). The trend of OR effect sizes was similar and consistent in unadjusted models.

In Figure 2, we presented the exposure-response curves between $PM_{2.5}$ chemical components with the risk of CVD prevalence using spline analyses. The exposure-response curves for the five $PM_{2.5}$ chemical components exhibited a close-to-linear trend at lower pollutant concentrations, but they showed an upward trend with increasing gradient at higher pollutant concentrations. The exposure-response curve between $PM_{2.5}$ mass and CVD prevalence appeared approximately linear, with a slight decreasing gradient at around 40 μg/m^3.

Subgroup analyses by age, sex, ethnicity, region, economic status, and rurality

Figure 3 demonstrates the forest plot of ORs and 95% CIs for the associations between $PM_{2.5}$ chemical components and CVD prevalence by different subgroups, with the colors showing the statistical significance for heterogeneity across subgroups. We found that the effect sizes were consistently larger among participants who were older than 70 years for all five chemical components. Additionally, the positive associations were significantly stronger among participants who were female or had lower levels of education for four chemical components except for BC.

Potential reducible numbers/fractions

The potential reducible numbers/fractions were estimated using counterfactual analyses to represent the percentage reduction in CVD prevalence that would occur if the concentrations of ambient $PM_{2.5}$ and its chemical constituents were reduced to the 5th percentiles in their statistical distributions. Figure 4 presents the potential reducible fractions of CVD prevalence attributable to long-term exposure to $PM_{2.5}$ and its five major chemical components, as well as the statistical distributions and 5th percentiles of the air pollutants. The results revealed that the potential reducible fractions were the highest for NO_3^- (15.5%; 95% CI: 14.6% to 16.3%), followed by OM (13.5%; 95% CI: 12.7% to 14.3%), NH_4^+ (12.8%; 95% CI: 11.8% to 13.6%), BC (9%; 95% CI: 8.1% to 9.8%), and SO_4^{2-} (7.4%; 95% CI: 6.5% to 8.3%). The relationship between $PM_{2.5}$ chemical components and CVD prevalence as demonstrated by the potential reducible fractions agreed with the pattern of ORs estimated in logistic regression models.

Figure 5 and Table S1 present a breakdown of the potential reducible fractions of CVD prevalence attributable to $PM_{2.5}$ chemical components decomposed to provinces, municipalities, or autonomous regions. The analysis revealed that Northern and Central China had the highest burden of CVD prevalence attributable to $PM_{2.5}$, particularly in Tianjin (29.6%), Hebei (28.8%), Beijing (26.7%), Shandong (25.9%), and Henan (24.3%). Moreover, our results showed that OM exceeded NO_3^- as the largest contributor to CVD prevalence in these heavily polluted provinces or municipalities, such as Tianjin (potential reducible fraction: 8.4% for OM versus 6.7% for NO_3^-), Hebei (potential reducible fraction: 8.1% for OM versus 6.8% for NO_3^-), and Beijing (potential reducible fraction: 8.1% for OM versus 6.4% for NO_3^-).

Sensitivity analyses

When the air pollution exposure was measured at different lag years, the effect sizes of associations between $PM_{2.5}$ chemical components and CVD prevalence remained consistently significant, but were smaller at longer lag years (Table S2). In a subsample of 21,925 participants, further adjusting for smoking status resulted in similarly significant OR estimates, but wither wider 95% CIs, and the effect sizes of the point estimates were slightly larger (Table S3). We further computed the E-values for our univariate and multivariable logistic regression models and evaluated the overall evidence for causality (Table S4); the E-values for $PM_{2.5}$ chemical components varied from 1.26 to 1.48, suggesting that the observed associations were unlikely to be distorted by a substantial unmeasured confounder, and providing support for plausible causal relationships. In subsamples of participants excluding those with hypertension, with diabetes, and with hypertension or diabetes, the relative rankings of $PM_{2.5}$ and its chemical components with the prevalence of CVD were consistent with the main results (Table S5). When alternating the logistic regression models in our main approach to Poisson models, the pattern of incidence rate ratios and 95% CIs was similarly consistent (Table S6).

DISCUSSION

In this study, we analyzed a nationally representative sample of 220,425 older adults recruited from 31 provinces, municipalities, or autonomous regions by the UREP survey. Our findings revealed that all five major $PM_{2.5}$

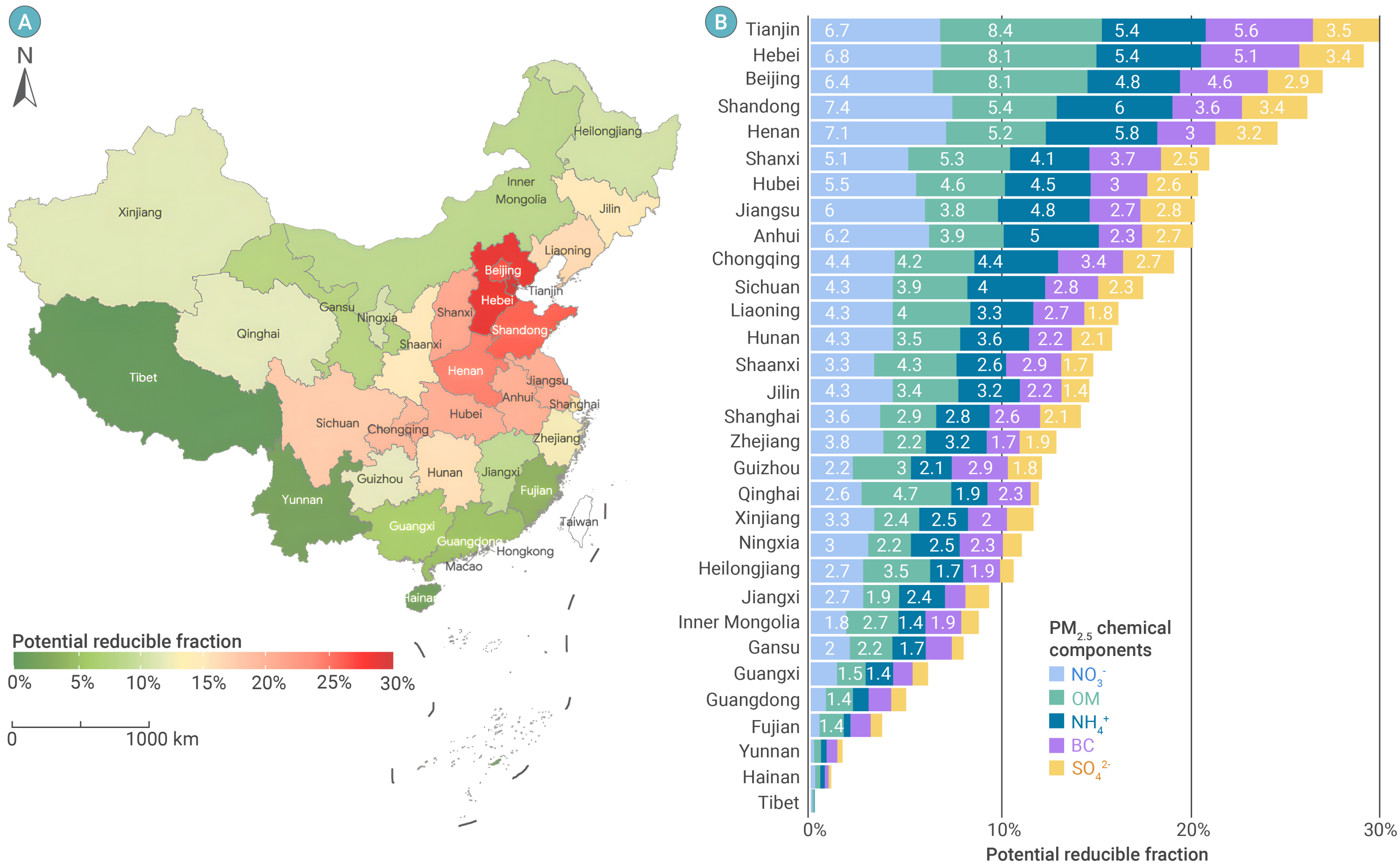

Figure 5. Potential reducible fraction of CVD attributable to ambient $PM_{2.5}$ chemical components [black carbon (BC), organic matter (OM), sulphate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+)] by provinces in China.

chemical components were associated with an increased risk of CVD prevalence. Counterfactual analyses further reveal that the chemical components that contributed to the largest burden of CVD prevalence were NO_3^-, OM, NH_4^+, BC, and SO_4^{2-}. Moreover, we found that the associations were significantly and consistently stronger in participants who were older than 70 years.

Despite the well-established association between ambient air pollution and human health since the landmark Harvard Six Cities Study in 1993,[39] current guidelines treat $PM_{2.5}$ mass as a whole, ignoring the heterogeneity across $PM_{2.5}$ chemical components.[40] To address this knowledge gap, several organizations, including the World Health Organization, the United States National Academy of Sciences, and the Health Effects Institute, have long been seeking for decisive evidence on the relative toxicity of individual $PM_{2.5}$ chemical components.[41] Our study fills in this knowledge gap and highlights the importance of a targeted control for $PM_{2.5}$ chemical components, prioritized in the order of NO_3^-, OM, NH_4^+, BC, and SO_4^{2-}, to effectively reduce the burden of CVD prevalence.

BC and OM are primary particles generated by anthropogenic fossil fuel combustion,[42,43] while NO_3^-, NH_4^+, and SO_4^{2-} are the secondary constituents formed from gaseous precursors attached to the particles. In China, haze events have become increasingly characterized by a higher prevalence of NO_3^- as the primary constituent of $PM_{2.5}$ chemical components in recent years,[44] likely explained by the rapidly growing domestic vehicle population, increasingly emitted NH_3 sources, and weaker deposition.[45,46] OM is another important component of $PM_{2.5}$ generated by combustion-related emissions and secondary reactions. OM contains highly toxic components such as polycyclic aromatic hydrocarbons and polychlorinated biphenyls that impose substantial risk to human health. Previous air pollution source attribution studies suggested that decreasing NO_3^- air pollution by reducing NO_x was much less effective than reducing NH_3 emissions.[46] Therefore, our study has the public health implications that the government should enforce more targeted regulations and control on NH_3 emissions via limiting the application of agricultural fertilizers and introducing green-energy vehicles with higher fossil fuel combustion efficiency.

The findings of this study align with a few prior studies. A province-level study in China conducted from 2005 to 2018 reported that NO_3^- was associated with a higher population mortality burden compared to $PM_{2.5}$ mass.[47] Another four-year time-series study in Southern China reported that short-term exposure to ambient NH_4^+, elemental carbon, SO_4^{2-}, NO_3^-, and organic carbon were associated with significantly elevated risk of cardiovascular mortality.[48] A nationwide cohort study of over 90,000 Chinese adults followed for eight years similarly found that BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} were associated with increased cardiovascular mortality, but not for soil dust.[49] All these studies supported the validity of our findings and collectively call for regulatory actions on limiting NH_3 emissions and fossil fuel combustion to combat the global epidemic of CVD.

The biological mechanisms that support the associations between $PM_{2.5}$ chemical components and CVD prevalence are complex, and several hypotheses have been proposed to explain the observed associations. The pivotal mechanisms are chronic oxidative stress and systemic inflammation as $PM_{2.5}$ chemical constituents are inhaled and deposited in the airways and the lung.[15] Small-particle components may penetrate the alveolar space or blood–brain-barrier and subsequently enter the bloodstream circulation, causing an adverse impact on distant organs including heart and brain.[50] Despite these well-known mechanisms, further toxicological studies are needed to better understand the effect of $PM_{2.5}$ chemical constituents on the progression of CVD.

Our study has several strengths. This is a nationally representative survey of Chinese older residents, and the large sample size yielded strong statistical power to characterize the relationship between $PM_{2.5}$ chemical constituents and CVD prevalence; we were also able to calculate the potential reducible fractions of CVD attributable to $PM_{2.5}$ chemical constituents by province, municipalities, or autonomous regions. The combination of data on residential addresses and high temporal resolution (daily) exposure data enables us to precisely evaluate air pollution at the individual level. This study takes place in a rapidly developing country with a high burden of CVD prevalence and elevated levels of air pollution, and the evidence can enlighten environmental policies in countries with rapidly expanding economies and significant air pollution issues.

Nonetheless, our study has several limitations. The cross-sectional study design inherently limits the strength of evidence and impedes the ability to draw causal conclusions. The spatial resolution of the exposure data, which was 10*10 km, was restricted by the scarcity of monitoring stations and insufficient computing power of the existing method. The definition of the outcome was self-reported and may be subject to outcome misclassification. Since the UREP did not collect full data on lifestyle (such as smoking status) and other environmental variables (such as green and blue space), we were not able to account for these variables in the current study. The analyses of secondary data may be vulnerable to missing data on confounders, but our sensitivity analyses, which included E-values and a subsample with more complete covariate data, confirmed that the evidence is robust and unlikely to be influenced by significant unobserved confounders. Our statistical models added each $PM_{2.5}$ chemical component in the models separately and are essentially single-pollutant models given the high correlation between the components, and this strategy limits the interpretability of the individual effect of each component on the outcome. We assumed that the participants were long-term residents in the area of their addresses, but a small proportion of them may not be living in their address and lead to exposure misclassification. Although this study was designed to be a nationally representative study, the three-stage multistage sampling may lead to less representative results due to inherent limitations of undercoverage and selection biases because large sections of the population were not selected as sampling units. Due to limited access to area-level data, we were not able to account for area-level socioeconomic status as covariates in our models.

CONCLUSION

Long-term exposure to $PM_{2.5}$ chemical components was associated with a significantly elevated risk of CVD prevalence in Chinese older adults, with stronger associations seen in NO_3^-, OM, NH_4^+, BC, and SO_4^{2-}. Our findings imply that more targeted control on chemical components of $PM_{2.5}$, primarily traffic- and fossil fuel combustion-related sources, may help alleviate the burden of CVD in China.

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AUTHOR CONTRIBUTIONS

MC and BS contributed to the development of the study concept and design. MC, BS, and GH cleaned the data, conducted statistical analyses, and wrote the first draft of the study. All authors provided critical revision of the manuscript. YT and HL provided administrative and technical support, as well as supervision.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

The data collection process of UREP was approved by the institutional review board of the Chinese National Bureau of Statistics. The National Committee on Aging granted permission for data analyses in this study. Informed consent was obtained from each participant prior to the interview.

DATA AND CODE AVAILABILITY

See the materials and methods section for details. The data in this study are available from the lead contact upon reasonable request.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2024.100077

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