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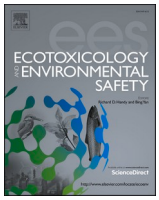

Potential causal associations of long-term exposure to $PM_{2.5}$ constituents and all-cause mortality: Evidence from the Pearl River Cohort study

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ABSTRACT

Evidence of the potential causal effect of $PM_{2.5}$ and its constituents on all-cause mortality based on large population cohort is still limited. Based on a large scale cohort of 341,098 participants in southern China, we developed a marginal structure Cox model based on inverse probability weighting, an established causal inference approach, to evaluate the potential causal associations between $PM_{2.5}$ constituents and all-cause mortality, taking into account time-varying covariates. Additionally, we further explored the modifying effects of demographic and lifestyle characteristics on these associations. For each IQR increase in black carbon and organic matter, the risk of all-cause mortality increased by 51 % (95 % *CI*: 40–62 %) and 52 % (95 % *CI*: 40–58 %), followed by ammonium, nitrate and sulfate (*HR* = 1.32, 1.38 and 1.39, respectively). Individuals < 65 years, unmarried, urban medical insured, not consuming alcohol, or not exercising were potentially more susceptible to the adverse effects for most $PM_{2.5}$ constituents (*P* for interaction < 0.10). The *HR* estimates for these subgroups ranged from 1.51 to 2.10 for black carbon, 1.40–1.71 for nitrate, 1.42–1.53 for sulfate, and 1.52–1.77 for organic matter. Various sensitivity analyses verified the robustness of our findings. This study presented compelling evidence of potential causal links between $PM_{2.5}$ constituents and all-cause mortality.

1. Introduction

Epidemiological research have demonstrated that atmospheric fine particulate matters (PM) exposure is related to a greater risk of diverse detrimental health results, such as cardiovascular diseases, respiratory diseases, tumors, and mutations (Mukherjee and Agrawal, 2018; Chen and Hoek, 2020; Orellano et al., 2020). Based on the Global Burden of Diseases (GBD) study (2019), over 4 million deaths globally could be resulted from PM exposure in that year, where 1.4 million of these deaths occurred in China (Collaborators, 2020). Potential mechanisms underlying the negative health effects of particulate matter exposure include intracellular oxidative stress, mutation and genotoxic reactions, and systemic inflammatory responses (Feng et al., 2016).

The risk of mortality attributed to $PM_{2.5}$ exposure was highly heterogeneous across regions, which might be due to the variation in its constituents (Liu et al., 2019). $PM_{2.5}$ is a composite mixture consisting of several chemical constituents, like black carbon, ammonium, nitrate, sulfate, and organic matter (Kang et al., 2023). Black carbon and organic matter primarily result from incomplete fuel combustion, which is more prevalent in areas with heavy traffic and industrial activities (Pateraki et al., 2020). Ammonium, nitrate, and sulfate are secondary pollutants formed through chemical reactions in the air involving sulfur dioxide and nitrogen oxides, originating from biomass and diesel combustion, and automobile exhaust emissions (Pateraki et al., 2020). The health

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effects of a specific constituent of $PM_{2.5}$ are diverse, while the overall toxicity of $PM_{2.5}$ largely depends on its composition (Wang et al., 2022; Shi et al., 2023; Liu et al., 2021). A prior study based on 16 cities in China showed that the toxicity of PM in the Pearl River Delta region was higher than that in other regions, which may be related to the heavy traffic emissions, weather patterns, and susceptibility of residents in the Pearl River Delta region (Chen et al., 2012). Although several studies have investigated the relationship between $PM_{2.5}$ constituents and mortality in other regions of China (Chen et al., 2021, 2018; Wang et al., 2019; Fu et al., 2023), there is still a dearth of solid evidence from the Pearl River Delta area, particularly based on large population cohorts.

Moreover, a large proportion of existing studies generally are supported by traditional methods of association assessment, the estimates from which are typically "conditional effects" obtained from regression models with covariates being directly incorporated (Dominici and Zigler, 2017; Janes et al., 2010). Given the variation in confounders across the individuals, the "conditional effect" often tends to be closer to the mean effect at the individual level (Wang et al., 2023). However, compared to these individual-level estimates, the population-level effect estimates generally have more policy implications, thus, are more preferred. Recent advances in causal inference approaches for the observational data enable the evaluation of the population-level effect estimates. By mimicking the randomized controlled trails, a pseudo-population would be created with confounders being homogenized across exposure groups. Effect estimates generated by comparing across the pseudo groups are considered having potential causal implications. Nevertheless, such evidence remains restricted in current studies.

This study adopted a causation inference method to explore the potential causal link between long-term $PM_{2.5}$ constituents exposure and all-cause mortality based on the Pearl River Cohort. We further assessed the potential modifying effects of demographic features and living habits.

2. Methods

2.1. Study population and outcome

The study utilized a large population cohort from the Major Science and Technology Projects of the 11th and 12th Five-Year Plans in China, which oriented to establish national demonstration areas for community-level collaborative innovation projects (Ruan et al., 2019; Wang et al., 2024a). And the participants in this cohort were selected on a community scale in southern China by stratified random cluster sampling. All enrolled subjects were required to undertake a comprehensive survey to obtain research information. Due to the accessibility of $PM_{2.5}$ constituents exposure concentrations, the study focused on a sub-cohort enrolled after January 1, 2013, consisting of 341,098 participants from Guangzhou and Zhongshan areas. Ethical approval was obtained by us from the Institutional Review Board at Sun Yat-sen University (L2017–030). All the individual participants in the study provided their informed consent.

The mortality data were obtained from the Centers for Disease Control and Prevention Death Registry in Guangzhou and Zhongshan. The length of the follow-up period was set as the time between registration and occurrence of death or the termination of the study on December 31, 2020.

2.2. Exposure and covariates

The main exposure in this study was $PM_{2.5}$ concentration and its constituents, namely black carbon, ammonium, nitrate, sulfate, and organic matter. The annual average concentrations of these pollutants, having a spatial resolution of 1 km × 1 km, were obtained from the ChinaHighAirPollutants (CHAP) datasets. The data collection and modeling process have been previously outlined in detail (Wei et al., 2023, 2021, 2020). The model estimation of these constituents' concentrations are well validated and widely used. In general, in relation to 126 ground monitoring stations distributed nationwide, the cross-validation R^2 values of each constituent ranged from 0.71 to 0.75 and the root-mean-square error (RMSE) was within the scope of 4.3–6.6 (Wei et al., 2023). Average annual exposure concentration for each pollutant was allocated to each participant in accordance with their residential address.

We utilized a directed acyclic graph (DAG) to detect confounding factors (Lipsky and Greenland, 2022). Mapping the DAG was informed by an extensive literature review and our prior research experience, as depicted in Fig. S2. Based on the insights from the DAG, the factors included sociodemographic factors (age, gender, education, marital status, ethnicity, and medical insurance) and lifestyle variables (smoking, alcohol consumption, and exercise). Information on participants' sociodemographic and lifestyle factors was gathered through direct-contact interviews with the assistance of well-trained nurses using computer-based questionnaires. These variables included age group (<65, ≥ 65), gender (male, female), education level (elementary, middle school, high school, and college), marital status (single, married, and widowed/divorced), ethnicity (Han or other), medical insurance (urban workers, non-working urban residents, new rural cooperative, or other), smoking habits (No or Yes), with Yes signifying at least one cigarette daily for a minimum duration of 6 months, alcohol consumption (No or Yes), with No signifying either no alcohol consumption or only a limited amount consumed within the past year, and exercise habits (No or Yes).

2.3. Statistical analysis

In this study we employed a marginal structure Cox model (MSM) utilizing inverse probability weighting (IPW) for assessing the potential causal relationship between each IQR increase in concentrations of $PM_{2.5}$ and its constituents and all-cause mortality. To account for the decreasing trend in the concentration of $PM_{2.5}$ and its constituents over time, we treated them as time-dependent variables (Zhang et al., 2018). The IPW approach utilized the concept of counterfactuals to simulate observational data in the form of a randomized controlled trial in order to create pseudo-populations and achieve the effect of balancing the observed confounding factors (Wu et al., 2020a; Cole and Hernan, 2008). The stabilized weights for the exposures were calculated as the ratio of the marginal probability of exposure to the generalized propensity score (GPS) (Robins et al., 2000). The GPS was obtained through regression of exposure variables against potential confounding factors. In order to address extreme weights, we capped the weights at 10 for those with a value exceeding 10 (Gruber et al., 2022). Moreover, we employed three different regression methods for calculating GPS: linear model (LM), generalized estimating equation (GEE), and gradient boosting machine learning (ML). The balance of covariates in the pseudo-population was assessed using the mean absolute correlation (AC), where AC values under 0.1 indicated the high quality of the simulated randomized controlled trial (Fig. S1) (Austin, 2019). Based on the results, we selected the GEE-IPWs method, which attained the best balance in covariates, as our main analysis model.

We adopted a sequential modeling strategy as follows:

Model 0: the crude time-dependent Cox model including either $PM_{2.5}$ or its constituents as the sole variable.

Model 1: model 0 with additional adjustment for age and gender.

Model 2: model 1 with further adjustment for education level, marital status, ethnicity, medical insurance, smoking habits, alcohol consumption and exercise habits.

Model 3: model 2 weighted by GPS using GEE.

We evaluated collinearity in the final model using the generalized variance inflation factor (GVIF), ensuring that GVIF values were below 5. Building upon Model 3, we carried out a stratified analysis according to sociodemographic and lifestyle variables to assess potential modification effects. Notably, upon applying the weights of Model 3 in the total

population to the stratified analyses, the balance of the covariates within subgroups was also achieved, as indicated by the AC values for the exposure against confounders in each subgroup (Table S1, all AC < 0.1). For imputing missing data, we employed the R multivariate imputation by chained equation (MICE) package (Zhang, 2016).

In order to guarantee the robustness of our results, several sensitivity analyses were performed. First, the final model was applied to the complete datasets without imputing missing values to assess the impact of data imputation. The characteristics of participants in the complete datasets are shown in Table S2. Second, we utilized IPW obtained through all three weighting methods in the final model. Third, a multi-constituent model analysis was conducted to evaluate the influence between constituents with low correlations ($r < 0.7$). In the multi-constituent model, all constituents with low correlations to the major constituent were adjusted as covariates based on the single-constituent model (Model 3) (Tao et al., 2023). Fourth, we also calculated the E-value to evaluate the implications of unmeasured confounding factors for the study results. A larger E-value indicated greater robustness of the results (Haneuse et al., 2019). The main outputs for these models were hazard ratio (*HR*) estimates for every IQR rise in $PM_{2.5}$ and its constituents. All the analysis work was performed using R version 4.1.3. Two-sided *P*-values < 0.05 were deemed statistically significant. We also evaluated *P*-values < 0.10 as the threshold for statistical interaction (Selvin, 2004).

3. Results

During the 8-year follow-up period, among the 341,098 participants, a total of 10,683 deaths occurred, representing a mortality rate of 3.13 % (Table 1). Male participants accounted for 49.9 % of the total sample. The mean age of the all-cause deaths group was 70.54 ± 14.58 years, while the survived group had an average age of 42.69 ± 16.07 years. The average exposure concentration of $PM_{2.5}$ among participants in 2013 was 52.14 ± 3.10 μg/m^3, gradually decreasing each year to 22.25 ± 1.77 μg/m^3 by 2020. The exposure concentration trend was similar for $PM_{2.5}$ constituents (Table 2).

Fig. 1 displays the *HR* estimates for the relationship between $PM_{2.5}$ constituents and all-cause mortality risk in both the marginal structure Cox model and the ordinary time-dependent Cox model. The *HR* estimate values in all Models indicated that $PM_{2.5}$ and each constituent were risk factors for all-cause death. In the final model (Model 3), the *HR* for risk of all-cause mortality was 1.45 (95 % *CI*: 1.35–1.56) for each IQR rise in $PM_{2.5}$ concentration. The *HR*s for black carbon, ammonium, nitrate, sulfate, and organic matter were 1.51 (95 % *CI*: 1.40–1.62), 1.32 (95 % *CI*: 1.26–1.38), 1.38 (95 % *CI*: 1.32–1.46), 1.39 (95 % *CI*: 1.31–1.45), and 1.52 (95 % *CI*: 1.40–1.58) for each IQR rise in the concentration, respectively. Comparatively, the ordinary time-dependent Cox model (Model 2) estimated the risk of all-cause mortality attributed to $PM_{2.5}$ and its constituents to be a little lower than the estimates obtained from the main model (Model 3). Table 3 presents the estimates for the remaining models.

In the subgroup analysis (Fig. 2), we observed significant modification effects for age (all *P* for interaction < 0.001), marital status (except for sulfate, the other *P* for interaction < 0.10), medical insurance (all *P* for interaction < 0.05), alcohol consumption (all *P* for interaction < 0.10) and exercise (all *P* for interaction < 0.001). Apart from ammonium, the impact on the risk for all-cause mortality was greater in the < 65 years old group (*HR* of <65 vs. ≥65, black carbon: 1.92 vs. 1.53, nitrate: 1.48 vs. 1.34, sulfate: 1.51 vs. 1.46, organic matter: 1.71 vs. 1.58). The risk of all-cause mortality related to $PM_{2.5}$ constituents was lowest among married individuals, with *HR* = 1.44 for black carbon, *HR* = 1.36 for nitrate, and *HR* = 1.46 for organic matter, followed by the *HR* estimates in the single group and the widowed & divorced group. Furthermore, participants with medical insurance for non-working urban residents showed the highest susceptibility to the effects of nitrates (*HR* = 1.50, 95 % *CI*, 1.34–1.64), sulfates (*HR* = 1.53, 95 % *CI*, 1.39–1.68), and organic matter (*HR* = 1.64, 95 % *CI*, 1.46–1.84), followed by the estimates in the urban workers medical insurance group and other groups. Residents with urban workers medical insurance were most vulnerable to black carbon (*HR* = 1.87, 95 % *CI*, 1.66–2.10), followed by the estimates in the medical insurance group for non-working urban residents (*HR* = 1.45, 95 % *CI*, 1.28–1.64), and in the others medical insurance group (*HR* = 1.34, 95 % *CI*, 1.11–1.60). In addition to the above factors, we did not find modification effect when the estimates were stratified by other demographic features, such as gender and education.

Similarly, when the results were stratified by lifestyle factors, residents who did not consume alcohol exhibited increased susceptibility to $PM_{2.5}$ constituents exposure (*HR* of No vs. Yes, black carbon: 1.51 vs. 1.29, ammonium: 1.34 vs. 1.13, nitrates: 1.40 vs. 1.18, sulfates: 1.42 vs. 1.01, organic matter: 1.52 vs. 1.04). Additionally, exercise showed a statistically significant interaction effect with each constituent. Individuals who did not exercise were more susceptible to black carbon (*HR* of No vs. Yes, 2.10 vs.1.41), sulfates (*HR* of No vs. Yes, 1.48 vs.1.36) and organic matter (*HR* of No vs. Yes, 1.77vs.1.40), while individuals who exercise were more susceptible to ammonium (*HR* of No vs. Yes, 1.27 vs.1.33) and nitrates (*HR* of No vs. Yes, 1.36vs.1.38). Effect modification regarding smoking was not observed.

The results obtained from the imputed data sets and complete data sets demonstrated the robustness of the findings (Table S3). Similarly, the results from the final model weighted by GPS using different methods (LM, ML, and GEE) were also consistent and reliable (Table S4).

Table 1
sociodemographic and lifestyle factors of all participants.

	Overall (N = 341,098) N (%)	Survived (n = 330,415) n (%)	All-cause death (n = 10,683) n (%)	*P*
Age (m±s)	43.57 ± 16.75	42.69 ± 16.07	70.54 ± 14.58	< 0.001
Age group				< 0.001
< 65	299,126 (87.7)	295,635 (89.5)	3491 (32.7)	
≥ 65	41,972 (12.3)	34,780 (10.5)	7192 (67.3)	
Gender				< 0.001
Male	170,243 (49.9)	164,011 (49.6)	6232 (58.3)	
Female	170,855 (50.1)	166,404 (50.4)	4451 (41.7)	
Education				< 0.001
Elementary	39,326 (11.5)	35,959 (10.9)	3367 (31.5)	
Middle	99,047 (29.0)	95,549 (28.9)	3498 (32.7)	
High	153,413 (45.0)	150,210 (45.5)	3203 (30.0)	
College	49,312 (14.5)	48,697 (14.7)	615 (5.8)	
Marital status				< 0.001
Single	78,385 (23.0)	77,648 (23.5)	737 (6.9)	
Married	254,997 (74.8)	246,225 (74.5)	8772 (82.1)	
Widowed & Divorced	7716 (2.3)	6542 (2.0)	1174 (11.0)	
Ethnic				< 0.001
Han	334,453 (98.1)	323,880 (98.0)	10,573 (99.0)	
Others	6645 (1.9)	6535 (2.0)	110 (1.0)	
Medical insurance				< 0.001
Urban workers	117,033 (34.3)	111,269 (33.7)	5764 (54.0)	
Non-working urban residents	72,394 (21.2)	69,331 (21.0)	3063 (28.7)	
New rural cooperative	34,616 (10.1)	34,181 (10.3)	435 (4.1)	
Others	117,055 (34.3)	115,634 (35.0)	1421 (13.3)	
Smoke				< 0.001
No	331,680 (97.2)	321,634 (97.3)	10,046 (94.0)	
Yes	9418 (2.8)	8781 (2.7)	637 (6.0)	
Alcohol				< 0.001
No	320,280 (93.9)	310,652 (94.0)	9628 (90.1)	
Yes	20,818 (6.1)	19,763 (6.0)	1055 (9.9)	
Exercise				< 0.001
No	98,193 (28.8)	93,642 (28.3)	4551 (42.6)	
Yes	242,905 (71.2)	236,773 (71.7)	6132 (57.4)	

Table 2
Annual exposure concentration of $PM_{2.5}$ and its constituents (mean ± sd).

	$PM_{2.5}$	Black carbon	Ammonium	Nitrate	Sulfate	Organic matter
2013	52.14 ± 3.10	4.25 ± 0.36	5.82 ± 0.18	9.24 ± 0.65	11.2 ± 0.60	19.8 ± 1.93
2014	45.11 ± 4.21	3.76 ± 0.39	5.16 ± 0.31	8.02 ± 0.87	9.91 ± 1.00	16.1 ± 2.59
2015	38.18 ± 2.51	3.44 ± 0.38	4.51 ± 0.20	6.54 ± 0.52	8.80 ± 0.70	13.1 ± 1.67
2016	34.55 ± 2.19	3.21 ± 0.33	4.06 ± 0.20	5.81 ± 0.51	7.89 ± 0.63	11.7 ± 1.55
2017	35.40 ± 1.46	3.22 ± 0.27	4.13 ± 0.22	6.34 ± 0.46	8.00 ± 0.35	12.1 ± 1.02
2018	33.05 ± 2.65	3.12 ± 0.36	3.93 ± 0.18	6.10 ± 0.65	7.45 ± 0.53	10.8 ± 1.85
2019	29.57 ± 1.62	2.96 ± 0.29	3.49 ± 0.16	5.33 ± 0.42	7.12 ± 0.42	9.18 ± 1.26
2020	22.25 ± 1.77	2.41 ± 0.29	2.65 ± 0.14	4.10 ± 0.36	5.62 ± 0.49	6.23 ± 1.18

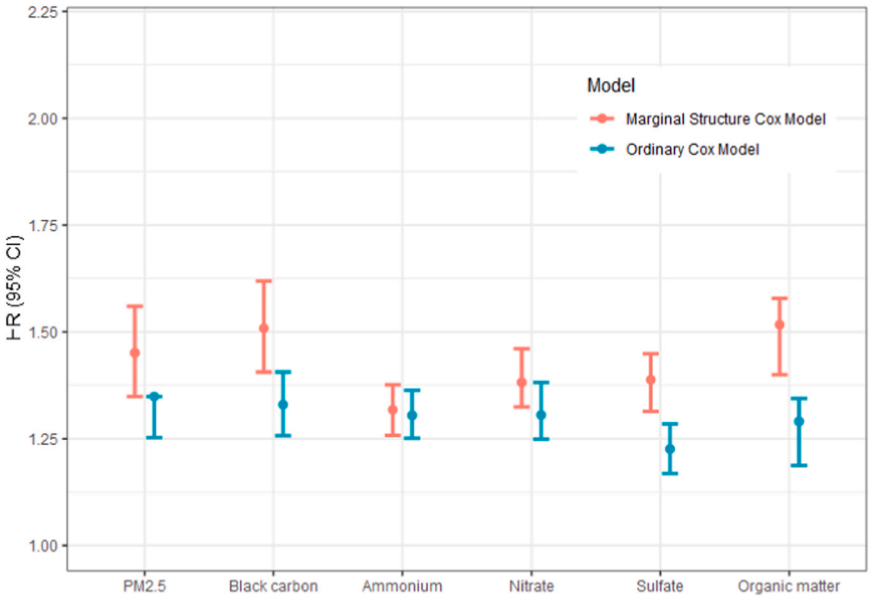

Fig. 1. *HR* and 95 % *CI* of $PM_{2.5}$ and its constituents to all-cause mortality in two different models.The red represents the marginal structure Cox model, which is weighted based on the ordinary Cox model using GPS obtained by GEE (Model 3). And the blue represents the time-dependent Cox model (Model 2).

Table 3
Hazard ratio (*HR*) of $PM_{2.5}$ and its constituents to all-cause death.

	Model 0		Model 1		Model 2		Model 3	
	HR	95 % *CI*	*HR*	95 % *CI*	*HR*	95 % *CI*	*HR*	95 % *CI*
$PM_{2.5}$	2.72^{***}	(2.54–2.90)	1.35^{***}	(1.35–1.45)	1.35^{***}	(1.25–1.35)	1.45^{***}	(1.35–1.56)
Black carbon	3.53^{***}	(3.38–3.69)	1.33^{***}	(1.27–1.39)	1.33^{***}	(1.26–1.41)	1.51^{***}	(1.40–1.62)
Ammonium	1.13^{***}	(1.07–1.18)	1.34^{***}	(1.28–1.40)	1.30^{***}	(1.25–1.36)	1.32^{***}	(1.26–1.38)
Nitrate	1.97^{***}	(1.88–2.08)	1.40^{***}	(1.34–1.46)	1.31^{***}	(1.25–1.38)	1.38^{***}	(1.32–1.46)
Sulfate	2.55^{***}	(2.47–2.66)	1.26^{***}	(1.20–1.30)	1.23^{***}	(1.17–1.28)	1.39^{***}	(1.31–1.45)
Organic matter	3.48^{***}	(3.37–3.60)	1.29^{***}	(1.24–1.40)	1.29^{***}	(1.19–1.34)	1.52^{***}	(1.40–1.58)

Model 0: ~one of $PM_{2.5}$ or its constituents.
Model 1: model 0 +age+gender.
Model 2: model1 +education+marital status+ethnic+medical insurance+smoke+alcohol+exercise.
Model 3: model 2 weighted by generalized estimating equation (GEE).
***: $P < 0.001$.

In the multi-constituent model, the *HR* of each main constituent remained significant, suggesting the results were robust compared with the single-constituent model (Table S5). Moreover, the E-values were all greater than 1, indicating that unmeasured confounding factors were unlikely to substantially change our observed findings (Table S6).

4. Discussion

In this large cohort study employing causal inference methods, we discovered a significant potential causal relationship between long-term $PM_{2.5}$ constituents exposure and an elevated risk of 32–52 % in all-cause mortality. Among $PM_{2.5}$ constituents, black carbon and organic matter had the highest health risk, followed by ammonium, nitrate and sulfate. Furthermore, our findings indicate potential modification effects of age, marital status, medical insurance, alcohol consumption, and exercise.

We observed significant associations between long-term exposure to $PM_{2.5}$ constituents and the increased mortality, which was consistent with previous findings (Hvidtfeldt et al., 2019; Goobie et al., 2022; He et al., 2024; Ostro et al., 2010). When the effect size of this study is converted to reflect a 1 $\mu g/m^3$ increase rather than an IQR increase in the exposure, it ranges from 1.10 to 1.83, also consistent with the range of estimates in existing studies. For instance, Ostro et al. (2010) reported

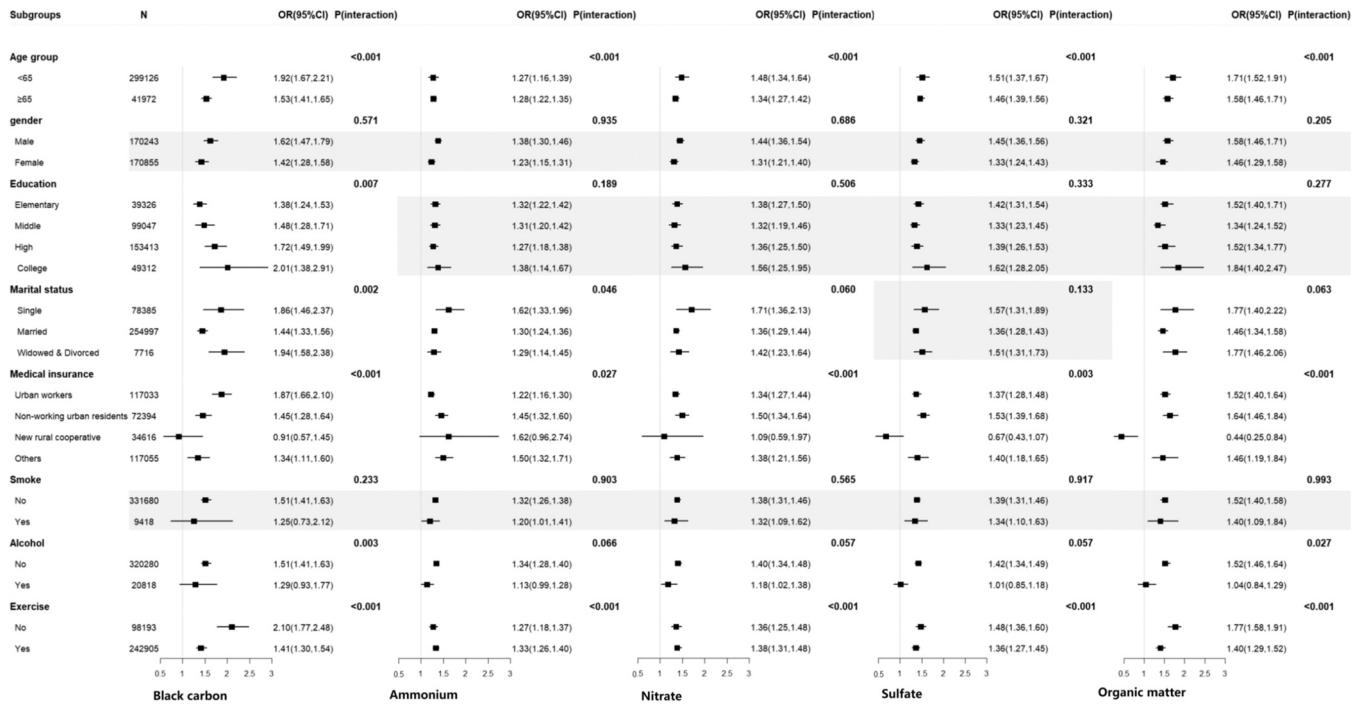

Fig. 2. The modification effects on the causal association between $PM_{2.5}$ constituents and all-cause mortality.

in a study in California that the *HRs* for all-cause mortality ranged from 1.06 to 1.93 following each 1 μg/m^3 increase in long-term exposure to $PM_{2.5}$ constituents. Similarly, a Danish study suggested *HRs* of mortality ranging from 1.07 to 4.66 per 1 μg/m^3 increment in the concentration of $PM_{2.5}$ constituents (Hvidtfeldt et al., 2019). Furthermore, several studies have reported on the health effects of long-term exposure to $PM_{2.5}$ constituents from the perspective of cause-specific mortality, and the estimates in these studies tended to be even greater than the estimates in this study. For example, a global multi-center study reported that each 1 μg/m^3 increase in the concentration of $PM_{2.5}$ and its constituents including sulfate, nitrate, and ammonium, was associated the *HRs* of mortality of 1.18, 8.02, 3.78, and 50.99, respectively, among patients with fibrotic interstitial lung disease (Goobie et al., 2022). Another cohort study focusing on Chinese children found that among all the components, black carbon had the greatest impact on mortality in childhood-onset lupus nephritis, with an *HR* of 2.14 for each 1 μg/m^3 increase in its concentration (He et al., 2024). These findings not only corroborated the connection between $PM_{2.5}$ constituents and mortality but also underscored the global heterogeneity in the risk of mortality (Chen et al., 2024). Consequently, our study furnished compelling evidence regarding the impact of exposure to $PM_{2.5}$ chemical constituents on all-cause mortality specifically within the Pearl River Delta region, contributing to the growing body of knowledge in this area.

We found that among the $PM_{2.5}$ constituents, black carbon and organic matter had the highest association with the risk of all-cause mortality, which was consistent with previous findings (Wang et al., 2019; He et al., 2024; Yang et al., 2019) and was supported by plausible biological mechanisms. Black carbon and organic matter, which are major constituents of $PM_{2.5}$, are directly released from the burning of fossil fuels and can adhere to ambient particulate matter (Liu et al., 2013). Black carbon has been linked to DNA methylation and oxidative stress (Niranjan and Thakur, 2017), which could contribute to cardiovascular damage and lung injury (Hvidtfeldt et al., 2019), thereby increasing the risk of suffering from cardiovascular diseases and the associated mortality (Yang et al., 2019). Similarly, organic matter has been associated with elevated blood pressure, raised heart rate variability, inflammation, and oxidative stress (Chen et al., 2021). These findings were consistent with epidemiological studies that suggested black carbon and organic matter increases risk of cardiovascular- and respiratory-related mortality (Yang et al., 2020). Ammonium, nitrate, and sulfate are the secondary pollutants formed through atmospheric reactions involving sulfur dioxide and nitrogen oxides (Pateraki et al., 2020). Nitrate could exert effect on the central nervous system by stimulating the hypothalamic-pituitary-adrenal (HPA) axis. This activation could either amplify or inhibit cardiometabolic responses. Consequently, nitrate demonstrated a more pronounced correlation with the onset of human cardiovascular diseases (Niu et al., 2018). Furthermore, research had indicated that nitrates were associated with lung inflammatory cells and respiratory tract damage (Zhang et al., 2021). Such associations could precipitate the onset and progression of respiratory diseases. Moreover, the acidity of nitrate and sulfate could directly induce airway hyper-reactivity and impair airway clearance, leading to lung injury and facilitating the uptake, conversion, and application of toxic substances (Yang et al., 2020). Notably, sulfate has been demonstrated to exhibit a positive correlation with biomarkers indicative of oxidative stress (Li et al., 2016). Cumulatively, these aspects constitute significant risk factors contributing to the development of cardiovascular disease (Yang et al., 2020). Ammonium, usually combined with nitrate and sulfate in the form of ammonium nitrate (NH_4NO_3) and ammonium sulfate($(NH_4)_2SO_4$), had uncertain biological mechanisms (Hao et al., 2023).

When results were stratified by demographic characteristics, we observed effect modification by age, marital status, and medical insurance. The subgroup analysis revealed that individuals under the age of 65 were more vulnerable to the detrimental health impacts of $PM_{2.5}$ constituents. Nevertheless, there remained a lack of unanimity regarding the influence of age on modifying the health risks associated with particulate matter exposure (Liu et al., 2021; Qi et al., 2024). For instance, in an analysis of the associations between $PM_{2.5}$ constituents and cardiovascular diseases in China, Liu et al. (2021) discovered that the elderly exhibited greater sensitivity to such effects. Conversely, another study in China, carried out by Qi et al. (2024) which explored the association between $PM_{2.5}$ constituents and cognitive function, indicated that young individuals demonstrated stronger susceptibility. These discrepant outcomes can be ascribed to factors such as

geographical location, pollution concentrations, differences in pollutant composition, along with other latent health factors relevant to the specific group of people (Mokoena et al., 2019). In particular, factors such as increased outdoor activities and varied lifestyle leading to higher exposure to $PM_{2.5}$ constituents among younger individuals (Zhou et al., 2022). As an illustration, in this study, we discovered that 72.55 % of young people and 61.71 % of older individuals engaged in regular exercise. The disparity between the two groups were statistically significant ($P < 0.001$). Moreover, given that elderly individuals have a diminished lung capacity, younger people might potentially inhale a greater quantity of environmental pollutants (Enright et al., 1994). This could also constitute a possible underlying reason. Additionally, we observed that married individuals demonstrated greater tolerance to the adverse health effects of black carbon, organic matter, and other $PM_{2.5}$ constituents. This could be ascribed to the presence of social support and a more structured lifestyle among married individuals, which might help reduce stress levels and promote positive overall health (Manvelian and Sbarra, 2020). Specifically, married couples typically pooled their economic resources, affording them enhanced living conditions and consequently facilitating access to facilities and amenities that served to alleviate the impact of environmental hazards (Cohen and Wills, 1985). Moreover, compared to their unmarried counterparts, married individuals generally possess more expansive social networks (Manvelian and Sbarra, 2020). When confronted with health problems related to $PM_{2.5}$ exposure, these supplementary connections can offer tangible forms of assistance. This might involve providing care and support during periods of illness or disseminating valuable information regarding preventive strategies (Tucker, 2002). The emotional sustenance derived from this broader social nexus further cushions the stress that accompanies potential health risks, bolstering the resilience of married individuals (Cohen and Wills, 1985). Moreover, our findings indicated that individuals with medical insurance for urban workers were more sensitive to the health hazards associated with black carbon. This could be linked to their higher exposure to road traffic pollution during daily commutes (Setton et al., 2008), as black carbon is a major constituent of vehicular emissions. Another potential rationale is that the distribution and sources of $PM_{2.5}$ constituents varied across urban and rural areas, with urban areas often experiencing higher levels of pollution compared to rural regions (Yang et al., 2019, 2020). Therefore, we suggested that cities should pay more attention to pollution emissions from transportation sources (Jiang et al., 2017), while rural areas may need to consider more pollution from the burning of crop residues (Wu et al., 2020b). Conversely, participants with medical insurance for non-working urban residents were more vulnerable to other $PM_{2.5}$ constituents. This might be attributed to individuals with medical insurance for non-working urban residents may encounter challenges in accessing adequate medical resources compared to those with insurance for urban workers (Li et al., 2018). Evidently, the current study revealed that the medical insurance for urban workers enjoyed a high level of financing and a diverse range of treatment options, whereas the comparatively lower-cost insurance for non-working urban residents and insurance for new rural cooperative offered more limited treatment (Wang et al., 2024b; Fan et al., 2021). Thus, the construction of more basic medical service facilities in rural areas and the optimization of medical services for non-employed people in cities should also be taken into account (Fan et al., 2021).

When results were stratified according to lifestyle indicators, we observed effect modification for alcohol consumption and exercise. Individuals who consumed alcohol exhibited greater tolerance to the risk of death associated with $PM_{2.5}$ constituents exposure, a result consistent with prior studies (Yao et al., 2022). We hypothesized that individuals with poorer health conditions might tend to abstain from alcohol, and therefore, non-alcohol consumption might serve as a marker of poor health conditions and a higher risk of mortality, rather than being a causal factor for vulnerability to $PM_{2.5}$ constituents exposure. While this finding may be the result of selection bias, additional studies are needed to support our hypothesis. Additionally, the modification effect of exercise observed in this study was complex, as exercise could lead to increased inhalation of $PM_{2.5}$, resulting in higher health risks. However, exercise also provides overall health benefits (Tainio et al., 2021). Additional research is needed to have a more profound comprehension of the connection between exercise and the effects of $PM_{2.5}$ constituents on health.

This study has several notable strengths. First, this is the initial study, to our knowledge, to explore the potential causal association between $PM_{2.5}$ constituents and all-cause mortality using causal inference methods. This approach provides valuable insights into the potential causal links between these factors. Second, the large population size of the community survey ensured high statistical power and thereby greater generalizability of findings for similar populations.

Some limitations should be noted. First, the assumption of no unmeasured confounding factors, a prerequisite for causal inference, is challenging to meet in practice. Nonetheless, the sensitivity analysis conducted in this study, particularly the E-value analysis, indicated that the results remained robust even when considering potential unmeasured confounders. Second, the exposure assessment of $PM_{2.5}$ constituents was based on residential addresses rather than individual-level data. This approach introduced the possibility of exposure misclassification, as individuals living in the same street were allocated the same exposure values. However, in reality, even when people are close geographically, their actual exposures vary due to their unique activity patterns. This type of error, known as a combination of Berkson error and classical error, might result in bias towards the null and an underestimation of the true effect (Bateson et al., 2007; Zeger et al., 2000). Finally, the pollutants concentrations in this study did not conform to a normal distribution, even after transformations, but we still used Gaussian distribution as the link function in propensity score. Gaussian distribution is still the optimal option based on the existing statistical theory and the limited number of link functions available. In this context, we have developed multiple models for estimating the generalized propensity score including a machine learning algorithm (XGboost) which does not depend on the distribution of pollutant concentrations. Moreover, based on the AC values, the generalized propensity score in this study can effectively balance the covariates, even when the pollutant concentrations did not follow a normal distribution. The same framework of methodology has been commonly used in previous studies (Wang et al., 2023; Robins et al., 2000; Zhang et al., 2024).

5. Conclusion

In conclusion, this large population-based cohort study in southern China established an independent potential causal relationship between each $PM_{2.5}$ constituents and all-cause mortality. The findings highlighted the diverse health risks associated with different constituents, owing to variations in their sources and distribution patterns. Furthermore, the study demonstrated that individuals under 65 years old, unmarried, urban medical insured, not consuming alcohol, or not exercising exhibited a more pronounced relationship between $PM_{2.5}$ constituents and all-cause mortality. Therefore, it is recommended that pollution control policies better shift their focus from $PM_{2.5}$ mass to chemical composition, recognizing the importance of specific constituents. Furthermore, environmental health policies should prioritize the needs of vulnerable populations.

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Huanle Cai: Conceptualisation, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing—original draft, Writing–review and editing. **Yuqin Zhang:** Conceptualisation, Data curation, Methodology, Validation, Writing–review and editing. **Jing Wei:** Data curation, Methodology, Resources, Validation. **Wayne R. Lawrence:** Writing–review and editing. **Shirui Chen:** Conceptualisation, Data curation, Methodology. **Huanhuan Cheng:** Writing—review and editing. **Hui Tang:** Writing—review and editing. **Dan Chen:** Writing—review and editing. **Ying Wang:** Writing—review and editing. **Jing Gu:** Conceptualisation, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing—review and editing. **Wangjian Zhang:** Conceptualisation, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing—review and editing. **Yuantao Hao:** Conceptualisation, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing—review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.117897.

Data availability

Data will be made available on request.

References

Austin, P.C., 2019. Assessing covariate balance when using the generalized propensity score with quantitative or continuous exposures. Stat. Methods Med. Res. 28 (5), 1365–1377. https://doi.org/10.1177/0962280218756159.

Bateson, T.F., Coull, B.A., Hubbell, B., Ito, K., Jerrett, M., Lumley, T., Thomas, D., Vedal, S., Ross, M., 2007. Panel discussion review: session three-issues involved in interpretation of epidemiologic analyses–statistical modeling. J. Expo. Sci. Environ. Epidemiol. 17 (2), S90–S96. https://doi.org/10.1038/sj.jes.7500631.

Chen, Y., Chen, R., Chen, Y., Dong, X., Zhu, J., Liu, C., van Donkelaar, A., Martin, R.V., Li, H., Kan, H., Jiang, Q., Fu, C., 2021. The prospective effects of long-term exposure to ambient $PM_{2.5}$ and constituents on mortality in rural east china. Chemosphere 280, 130740. https://doi.org/10.1016/j.chemosphere.2021.130740.

Chen, J., Hoek, G., 2020. Long-term exposure to pm and all-cause and cause-specific mortality: a systematic review and meta-analysis. Environ. Int. 143, 105974. https://doi.org/10.1016/j.envint.2020.105974.

Chen, R., Kan, H., Chen, B., Huang, W., Bai, Z., Song, G., Pan, G., 2012. Association of particulate air pollution with daily mortality: the china air pollution and health effects study. Am. J. Epidemiol. 175 (11), 1173–1181. https://doi.org/10.1093/aje/kwr425.

Chen, S., Liu, D., Huang, L., Guo, C., Gao, X., Xu, Z., Yang, Z., Chen, Y., Li, M., Yang, J., 2024. Global associations between long-term exposure to $PM_{2.5}$ constituents and health: a systematic review and meta-analysis of cohort studies. J. Hazard. Mater. 474, 134715. https://doi.org/10.1016/j.jhazmat.2024.134715.

Chen, C., Xu, D., He, M.Z., Wang, Y., Du, Z., Du, Y., Qian, Y., Ji, D., Li, T., 2018. Fine particle constituents and mortality: a time-series study in beijing, china. Environ. Sci. Technol. 52 (19), 11378–11386. https://doi.org/10.1021/acs.est.8b00424.

Cohen, S., Wills, T.A., 1985. Stress, social support, and the buffering hypothesis. Psychol. Bull. 98 (2), 310–357.

Cole, S.R., Hernan, M.A., 2008. Constructing inverse probability weights for marginal structural models. Am. J. Epidemiol. 168 (6), 656–664. https://doi.org/10.1093/aje/kwn164.

Collaborators, G.R.F., 2020. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. Lancet 396 (10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2.

Dominici, F., Zigler, C., 2017. Best practices for gauging evidence of causality in air pollution epidemiology. Am. J. Epidemiol. 186 (12), 1303–1309. https://doi.org/10.1093/aje/kwx307.

Enright, P.L., Kronmal, R.A., Manolio, T.A., Schenker, M.B., Hyatt, R.E., 1994. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular health study research group. Am. J. Respir. Crit. Care Med. 149 (2 Pt 1), 430–438. https://doi.org/10.1164/ajrccm.149.2.8306041.

Fan, X., Su, M., Si, Y., Zhao, Y., Zhou, Z., 2021. The benefits of an integrated social medical insurance for health services utilization in rural china: evidence from the china health and retirement longitudinal study. Int. J. Equity Health 20 (1), 126. https://doi.org/10.1186/s12939-021-01457-8.

Feng, S., Gao, D., Liao, F., Zhou, F., Wang, X., 2016. The health effects of ambient $PM_{2.5}$ and potential mechanisms. Ecotoxicol. Environ. Saf. 128, 67–74. https://doi.org/10.1016/j.ecoenv.2016.01.030.

Fu, J., Fei, F., Wang, S., Zhao, Q., Yang, X., Zhong, J., Hu, K., 2023. Short-term effects of fine particulate matter constituents on mortality considering the mortality displacement in zhejiang province, china. J. Hazard. Mater. 457, 131723. https://doi.org/10.1016/j.jhazmat.2023.131723.

Goobie, G.C., Carlsten, C., Johannson, K.A., Khalil, N., Marcoux, V., Assayag, D., Manganas, H., Fisher, J.H., Kolb, M., Lindell, K.O., Fabisiak, J.P., Chen, X., Gibson, K.F., Zhang, Y., Kass, D.J., Ryerson, C.J., Nouraie, S.M., 2022. Association of particulate matter exposure with lung function and mortality among patients with fibrotic interstitial lung disease. JAMA Intern. Med. 182 (12), 1248–1259. https://doi.org/10.1001/jamainternmed.2022.4696.

Gruber, S., Phillips, R.V., Lee, H., van der Laan, M.J., 2022. Data-adaptive selection of the propensity score truncation level for inverse-probability-weighted and targeted maximum likelihood estimators of marginal point treatment effects. Am. J. Epidemiol. 191 (9), 1640–1651. https://doi.org/10.1093/aje/kwac087.

Haneuse, S., Vanderweele, T.J., Arterburn, D., 2019. Using the e-value to assess the potential effect of unmeasured confounding in observational studies. JAMA 321 (6), 602–603. https://doi.org/10.1001/jama.2018.21554.

Hao, H., Wang, Y., Zhu, Q., Zhang, H., Rosenberg, A., Schwartz, J., Amini, H., van Donkelaar, A., Martin, R., Liu, P., Weber, R., Russel, A., Yitshak-Sade, M., Chang, H., Shi, L., 2023. National cohort study of long-term exposure to $PM_{2.5}$ components and mortality in medicare american older adults. Environ. Sci. Technol. 57 (17), 6835–6843. https://doi.org/10.1021/acs.est.2c07064.

He, G., Wang, Y., Cheng, C., Guo, J., Lin, Z., Liang, Z., Jin, B., Tao, L., Rong, L., Chen, L., Lin, T., Hua, Y., Park, S., Mo, Y., Li, J., Jiang, X., 2024. $PM_{2.5}$ constituents associated with mortality and kidney failure in childhood-onset lupus nephritis: a 19-year cohort study. Sci. Total Environ. 949, 175333. https://doi.org/10.1016/j.scitotenv.2024.175333.

Hvidtfeldt, U.A., Geels, C., Sorensen, M., Ketzel, M., Khan, J., Tjonneland, A., Christensen, J.H., Brandt, J., Raaschou-Nielsen, O., 2019. Long-term residential exposure to pm(2.5) constituents and mortality in a danish cohort. Environ. Int. 133 (Pt B), 105268. https://doi.org/10.1016/j.envint.2019.105268.

Janes, H., Dominici, F., Zeger, S., 2010. On quantifying the magnitude of confounding. Biostatistics 11 (3), 572–582. https://doi.org/10.1093/biostatistics/kxq007.

Jiang, B., Liang, S., Peng, Z.R., Cong, H., Levy, M., Cheng, Q., Wang, T., Remais, J.V., 2017. Transport and public health in china: the road to a healthy future. Lancet 390 (10104), 1781–1791. https://doi.org/10.1016/S0140-6736(17)31958-X.

Kang, N., Wu, R., Liao, W., Zhang, C., Liu, X., Mao, Z., Huo, W., Hou, J., Zhang, K., Tian, H., Lin, H., Wang, C., 2023. Association of long-term exposure to $PM_{2.5}$ constituents with glucose metabolism in chinese rural population. Sci. Total Environ. 859 (Pt 2), 160364. https://doi.org/10.1016/j.scitotenv.2022.160364.

Li, W., Wilker, E.H., Dorans, K.S., Rice, M.B., Schwartz, J., Coull, B.A., Koutrakis, P., Gold, D.R., Keaney, J.J., Lin, H., Vasan, R.S., Benjamin, E.J., Mittleman, M.A., 2016. Short-term exposure to air pollution and biomarkers of oxidative stress: the framingham heart study. J. Am. Heart Assoc. 5 (5). https://doi.org/10.1161/JAHA.115.002742.

Li, T., Zhang, Y., Wang, J., Xu, D., Yin, Z., Chen, H., Lv, Y., Luo, J., Zeng, Y., Liu, Y., Kinney, P.L., Shi, X., 2018. All-cause mortality risk associated with long-term exposure to ambient $PM_{2.5}$ in china: a cohort study. Lancet Public Health 3 (10), e470–e477. https://doi.org/10.1016/S2468-2667(18)30144-0.

Lipsky, A.M., Greenland, S., 2022. Causal directed acyclic graphs. JAMA 327 (11), 1083–1084. https://doi.org/10.1001/jama.2022.1816.

Liu, C., Chen, R., Sera, F., Vicedo-Cabrera, A.M., Guo, Y., Tong, S., Coelho, M., Saldiva, P., Lavigne, E., Matus, P., Valdes, O.N., Osorio, G.S., Pascal, M., Stafoggia, M., Scortichini, M., Hashizume, M., Honda, Y., Hurtado-Diaz, M., Cruz, J., Nunes, B., Teixeira, J.P., Kim, H., Tobias, A., Iniguez, C., Forsberg, B., Astrom, C., Ragettli, M.S., Guo, Y.L., Chen, B.Y., Bell, M.L., Wright, C.Y., Scovronick, N., Garland, R.M., Milojevic, A., Kysely, J., Urban, A., Orru, H., Indermitte, E., Jaakkola, J., Ryti, N., Katsouyanni, K., Analitis, A., Zanobetti, A., Schwartz, J., Chen, J., Wu, T., Cohen, A., Gasparrini, A., Kan, H., 2019. Ambient particulate air pollution and daily mortality in 652 cities. N. Engl. J. Med. 381 (8), 705–715. https://doi.org/10.1056/NEJMoa1817364.

Liu, D., Li, J., Zhang, Y., Xu, Y., Liu, X., Ding, P., Shen, C., Chen, Y., Tian, C., Zhang, G., 2013. The use of levoglucosan and radiocarbon for source apportionment of $PM_{2.5}$ carbonaceous aerosols at a background site in east china. Environ. Sci. Technol. 47 (18), 10454–10461. https://doi.org/10.1021/es401250k.

Liu, L., Zhang, Y., Yang, Z., Luo, S., Zhang, Y., 2021. Long-term exposure to fine particulate constituents and cardiovascular diseases in chinese adults. J. Hazard. Mater. 416, 126051. https://doi.org/10.1016/j.jhazmat.2021.126051.

Manvelian, A., Sbarra, D.A., 2020. Marital status, close relationships, and all-cause mortality: results from a 10-year study of nationally representative older adults. Psychosom. Med. 82 (4), 384–392. https://doi.org/10.1097/PSY.0000000000000798.

Mokoena, K.K., Ethan, C.J., Yu, Y., Shale, K., Liu, F., 2019. Ambient air pollution and respiratory mortality in xi'an, china: a time-series analysis. Respir. Res. 20 (1), 139. https://doi.org/10.1186/s12931-019-1117-8.

Mukherjee, A., Agrawal, M., 2018. A global perspective of fine particulate matter pollution and its health effects. Rev. Environ. Contam. Toxicol. 244, 5–51. https://doi.org/10.1007/398_2017_3.

Niranjan, R., Thakur, A.K., 2017. The toxicological mechanisms of environmental soot (black carbon) and carbon black: focus on oxidative stress and inflammatory pathways. Front. Immunol. 8, 763. https://doi.org/10.3389/fimmu.2017.00763.

Niu, Y., Chen, R., Xia, Y., Cai, J., Ying, Z., Lin, Z., Liu, C., Chen, C., Peng, L., Zhao, Z., Zhou, W., Chen, J., Wang, D., Huo, J., Wang, X., Fu, Q., Kan, H., 2018. Fine particulate matter constituents and stress hormones in the hypothalamus-pituitary-adrenal axis. Environ. Int. 119, 186–192. https://doi.org/10.1016/j.envint.2018.06.027.

Orellano, P., Reynoso, J., Quaranta, N., Bardach, A., Ciapponi, A., 2020. Short-term exposure to particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and all-cause and cause-specific mortality: systematic review and meta-analysis. Environ. Int. 142, 105876. https://doi.org/10.1016/j.envint.2020.105876.

Ostro, B., Lipsett, M., Reynolds, P., Goldberg, D., Hertz, A., Garcia, C., Henderson, K.D., Bernstein, L., 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the california teachers study. Environ. Health Perspect. 118 (3), 363–369. https://doi.org/10.1289/ehp.0901181.

Pateraki, S., Asimakopoulos, D.N., Maggos, T., Assimakopoulos, V.D., Bougiatioti, A., Bairachtari, K., Vasilakos, C., Mihalopoulos, N., 2020. Chemical characterization, sources and potential health risk of $PM_{2.5}$ and PM_1 pollution across the greater athens area. Chemosphere 241, 125026. https://doi.org/10.1016/j.chemosphere.2019.125026.

Qi, J., Zhao, N., Liu, M., Guo, Y., Fu, J., Zhang, Y., Wang, W., Su, Z., Zeng, Y., Yao, Y., Hu, K., 2024. Long-term exposure to fine particulate matter constituents and cognitive impairment among older adults: an 18-year chinese nationwide cohort study. J. Hazard. Mater. 468, 133785. https://doi.org/10.1016/j.jhazmat.2024.133785.

Robins, J.M., Hernan, M.A., Brumback, B., 2000. Marginal structural models and causal inference in epidemiology. Epidemiology 11 (5), 550–560. https://doi.org/10.1097/00001648-200009000-00011.

Ruan, B., Yu, Z., Yang, S., Xu, K., Ren, J., Yao, J., Wu, N., Yu, C., Deng, M., Xie, T., Chen, P., Wang, C., Li, Y., Zhao, Y., Sheng, J., Hou, Y., Wu, Z., Jin, S., Chen, Y., Li, M., Zhu, F., Tang, H., Hao, Y., Pang, X., Lu, L., Yang, W., Yuan, Z., Xu, A., Li, Z., Ni, M., Yan, Y., Zhong, Q., Zhou, L., Li, G., Meng, Q., Hu, J., Zhou, H., Zhang, G., Li, D., Jiang, W., Li, Q., Wu, P., Xing, R., Gu, J., Gao, D., Li, L., 2019. Establishment and development of national community-based collaborative innovation demonstration areas to achieve the control target of hepatitis b in china. BMC Infect. Dis. 19 (1), 617. https://doi.org/10.1186/s12879-019-4150-9.

S. Selvin, {Statistical analysis of epidemiologic data}, Oxford University Press, 2004.

Setton, E.M., Keller, C.P., Cloutier-Fisher, D., Hystad, P.W., 2008. Spatial variations in estimated chronic exposure to traffic-related air pollution in working populations: a simulation. Int. J. Health Geogr. 7, 39. https://doi.org/10.1186/1476-072X-7-39.

Shi, L., Zhu, Q., Wang, Y., Hao, H., Zhang, H., Schwartz, J., Amini, H., van Donkelaar, A., Martin, R.V., Steenland, K., Sarnat, J.A., Caudle, W.M., Ma, T., Li, H., Chang, H.H., Liu, J.Z., Wingo, T., Mao, X., Russell, A.G., Weber, R.J., Liu, P., 2023. Incident dementia and long-term exposure to constituents of fine particle air pollution: a national cohort study in the united states. Proc. Natl. Acad. Sci. USA 120 (1), e2083685177. https://doi.org/10.1073/pnas.2211282119.

Tainio, M., Jovanovic, A.Z., Nieuwenhuijsen, M.J., Hu, L., de Nazelle, A., An, R., Garcia, L., Goenka, S., Zapata-Diomedi, B., Bull, F., 2021. T.H. Sa, Air pollution, physical activity and health: a mapping review of the evidence. Environ. Int. 147, 105954. https://doi.org/10.1016/j.envint.2020.105954.

Tao, B., Li, Z., Wang, Y., Wu, J., Shi, X., Shi, J., Liu, Q., Wang, J., 2023. Environment pollutants exposure affects the endogenous activation of within-host mycobacterium tuberculosis. Environ. Res. 227, 115695. https://doi.org/10.1016/j.envres.2023.115695.

Tucker, J.S., 2002. Health-related social control within older adults' relationships. J. Gerontol. Ser. B-Psychol. Sci. Soc. Sci. 57 (5), P387–P395. https://doi.org/10.1093/geronb/57.5.p387.

Wang, Y., Du, Z., Zhang, W., Wang, X., Lin, X., Liu, Y., Deng, Y., Zhang, D., Gu, J., Xu, L., Hao, Y., 2024a. Cohort profile: the pearl river cohort study. Int. J. Epidemiol. 53 (5). https://doi.org/10.1093/ije/dyae112.

Wang, X., Guo, Y., Cai, M., Qian, Z.M., Zhang, S., Zhang, Z., Yang, Y., Vaughn, M.G., Aaron, H.E., Wu, F., Zhang, Y., Lin, H., 2022. Constituents of fine particulate matter and asthma in 6 low- and middle-income countries. J. Allergy Clin. Immunol. 150 (1), 214–222. https://doi.org/10.1016/j.jaci.2021.12.779.

Wang, Y., Shi, Z., Shen, F., Sun, J., Huang, L., Zhang, H., Chen, C., Li, T., Hu, J., 2019. Associations of daily mortality with short-term exposure to $PM_{2.5}$ and its constituents in shanghai, china. Chemosphere 233, 879–887. https://doi.org/10.1016/j.chemosphere.2019.05.249.

Wang, Y., Wei, J., Zhang, Y., Guo, T., Chen, S., Wu, W., Chen, S., Li, Z., Qu, Y., Xiao, J., Deng, X., Liu, Y., Du, Z., Zhang, W., Hao, Y., 2023. Estimating causal links of long-term exposure to particulate matters with all-cause mortality in south china. Environ. Int. 171, 107726. https://doi.org/10.1016/j.envint.2022.107726.

Wang, E., Zhu, M., Lin, Y., Xi, X., 2024b. Multilevel medical insurance mitigate health cost inequality due to air pollution: evidence from china. Int. J. Equity Health 23 (1), 153. https://doi.org/10.1186/s12939-024-02238-9.

Wei, J., Li, Z., Chen, X., Li, C., Sun, Y., Wang, J., Lyapustin, A., Brasseur, G.P., Jiang, M., Sun, L., Wang, T., Jung, C.H., Qiu, B., Fang, C., Liu, X., Hao, J., Wang, Y., Zhan, M., Song, X., Liu, Y., 2023. Separating daily 1 km $PM_{2.5}$ inorganic chemical composition in china since 2000 via deep learning integrating ground, satellite, and model data. Environ. Sci. Technol. https://doi.org/10.1021/acs.est.3c00272.

Wei, J., Li, Z., Cribb, M., Huang, W., Xue, W., Sun, L., Guo, J., Peng, Y., Li, J., Lyapustin, A., Liu, L., Wu, H., Song, Y., 2020. Improved 1km resolution $PM_{2.5}$ estimates across china using enhanced space–time extremely randomized trees. Atmos. Chem. Phys. 20 (6), 3273–3289. https://doi.org/10.5194/acp-20-3273-2020.

Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., Su, T., Cribb, M., 2021. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in china: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136. https://doi.org/10.1016/j.rse.2020.112136.

Wu, X., Braun, D., Schwartz, J., Kioumourtzoglou, M.A., Dominici, F., 2020a. Evaluating the impact of long-term exposure to fine particulate matter on mortality among the elderly. Sci. Adv. 6 (29), eaba5692. https://doi.org/10.1126/sciadv.aba5692.

Wu, J., Kong, S., Wu, F., Cheng, Y., Zheng, S., Qin, S., Liu, X., Yan, Q., Zheng, H., Zheng, M., Yan, Y., Liu, D., Ding, S., Zhao, D., Shen, G., Zhao, T., Qi, S., 2020b. The moving of high emission for biomass burning in china: view from multi-year emission estimation and human-driven forces. Environ. Int. 142, 105812. https://doi.org/10.1016/j.envint.2020.105812.

Yang, Y., Ruan, Z., Wang, X., Yang, Y., Mason, T.G., Lin, H., Tian, L., 2019. Short-term and long-term exposures to fine particulate matter constituents and health: a systematic review and meta-analysis. Environ. Pollut. 247, 874–882. https://doi.org/10.1016/j.envpol.2018.12.060.

Yang, J., Zhou, M., Li, M., Yin, P., Hu, J., Zhang, C., Wang, H., Liu, Q., Wang, B., 2020. Fine particulate matter constituents and cause-specific mortality in china: a nationwide modelling study. Environ. Int. 143, 105927. https://doi.org/10.1016/j.envint.2020.105927.

Yao, Y., Lu, T., Liu, Y., Qin, Q., Jiang, J., Xiang, H., 2022. Association of depressive symptoms with ambient pm(2.5) in middle-aged and elderly chinese adults: a cross-sectional study from the china health and retirement longitudinal study wave 4. Environ. Res. 203, 111889. https://doi.org/10.1016/j.envres.2021.111889.

Zeger, S.L., Thomas, D., Dominici, F., Samet, J.M., Schwartz, J., Dockery, D., Cohen, A., 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108 (5), 419–426. https://doi.org/10.1289/ehp.00108419.

Zhang, Z., 2016. Multiple imputation with multivariate imputation by chained equation (mice) package. Ann. Transl. Med. 4 (2), 30. https://doi.org/10.3978/j.issn.2305-5839.2015.12.63.

Zhang, Y., Chen, S., Wei, J., Jiang, J., Lin, X., Wang, Y., Hao, C., Wu, W., Yuan, Z., Sun, J., Wang, H., Du, Z., Zhang, W., Hao, Y., 2024. Long-term PM_1 exposure and hypertension hospitalization: a causal inference study on a large community-based cohort in south china. Sci. Bull. 69 (9), 1313–1322. https://doi.org/10.1016/j.scib.2024.03.028.

Zhang, J., Cheng, H., Wang, D., Zhu, Y., Yang, C., Shen, Y., Yu, J., Li, Y., Xu, S., Zhang, S., Song, X., Zhou, Y., Chen, J., Jiang, J., Fan, L., Wang, C., Hao, K., 2021. Chronic exposure to $PM_{2.5}$ nitrate, sulfate, and ammonium causes respiratory system impairments in mice. Environ. Sci. Technol. 55 (5), 3081–3090. https://doi.org/10.1021/acs.est.0c05814.

Zhang, Z., Reinikainen, J., Adeleke, K.A., Pieterse, M.E., Groothuis-Oudshoorn, C., 2018. Time-varying covariates and coefficients in cox regression models. Ann. Transl. Med. 6 (7), 121. https://doi.org/10.21037/atm.2018.02.12.

Zhou, P., Hu, J., Yu, C., Bao, J., Luo, S., Shi, Z., Yuan, Y., Mo, S., Yin, Z., Zhang, Y., 2022. Short-term exposure to fine particulate matter constituents and mortality: case-crossover evidence from 32 counties in china. Sci. China Life Sci. 65 (12), 2527–2538. https://doi.org/10.1007/s11427-021-2098-7.