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Associations of long-term exposure to $PM_{2.5}$ constituents with serum uric acid and hyperuricemia in Chinese adults

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Abstract

Objective Little is known about the magnitude of the relation of ambient fine particulate matter ($PM_{2.5}$) constituents with hyperuricemia and serum uric acid (SUA) levels. Therefore, we aimed to assess the associations and to identify the most hazardous constituent.

Methods This study included 72,840 participants from the China Multi-Ethnic Cohort. Annual average concentrations of $PM_{2.5}$ mass and its major 7 constituents were matched to individuals by residential address. SUA levels exceeding 7.0 mg/dL (417 μmol/L) for men and 6.0 mg/dL (357 μmol/L) for women were considered to be hyperuricemia. Multiple logistic and linear regressions were performed on the association of single exposure to $PM_{2.5}$ constituents with hyperuricemia and SUA, separately. The weighted quantile sum method was applied to examine the joint effect of $PM_{2.5}$ constituents on hyperuricemia/SUA.

Results Significant positive associations were discovered between $PM_{2.5}$ constituents and SUA/hyperuricemia. For example, the odds ratio (95% confidence interval) of hyperuricemia for per standard deviation increase of $PM_{2.5}$ mass, black carbon, organic matter, ammonium, and nitrate concentrations were 1.22 (1.12–1.32), 1.17 (1.08–1.27), 1.20 (1.10–1.31), 1.21 (1.11–1.31), and 1.28 (1.18–1.40), respectively. The joint exposure to $PM_{2.5}$ constituents was significantly positively correlated with hyperuricemia (1.09, 1.05–1.14) and SUA (1.05, 1.03–1.06). And the weight of nitrate was the largest (0.668 for hyperuricemia, 0.586 for SUA).

Conclusions Our findings suggest that long-term exposure to $PM_{2.5}$ constituents is associated with increased SUA levels and a higher risk of hyperuricemia. In particular, nitrate seems to be the main contributor. This study may help prevent hyperuricemia by promoting the introduction of precise preventive measures.

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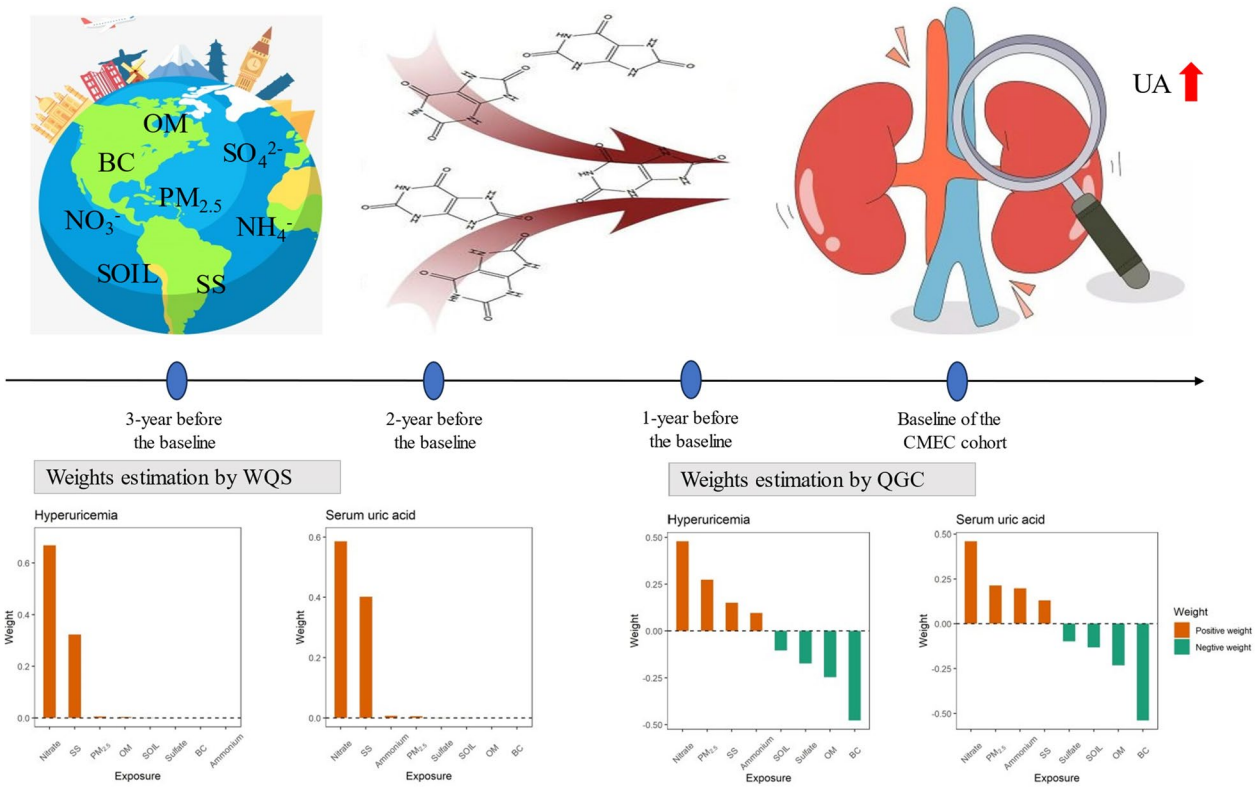
Highlights

- Considering the constituents of $PM_{2.5}$ in assessing its toxicity and health effects.
- Exposure to $PM_{2.5}$ constituents was related with serum uric acid and hyperuricemia.
- Nitrate contributed most to serum uric acid levels and hyperuricemia.
- The results of joint effects were verified by two different statistical methods.
- A large-scale sample of nearly 100,000 subjects from diverse ethnic backgrounds.

Keywords $PM_{2.5}$ constituents, Serum uric acid, Hyperuricemia, Mixture effect, Weighted quantile sum regression, Quantile g-computation

Graphical Abstract



Introduction

Hyperuricemia, caused by an aberrant elevation in serum uric acid (SUA) level, has progressively emerged as the second most common metabolic disease after type 2 diabetes [1, 2]. It is an independent risk factor for multiple adverse health conditions, such as gout, diabetes, and cardiovascular disease which accounts for more than 40% of deaths in China [1, 3–5]. In recent decades, hyperuricemia has become increasingly pervasive throughout the world [6, 7]. Many epidemiological studies showed that the prevalence of hyperuricemia in China has reached nearly 13.3% with more than 180 million patients, whose number of patients is much higher than others [8–10]. By this token, hyperuricemia, elevated SUA level, and its complications have become great public health concerns.

Ambient particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) represents a significant concern as it ranks sixth in terms of disability-adjusted life-years, indicating its substantial impact on public health [11]. As a typical and intricate mixture, the toxicity of $PM_{2.5}$ was largely determined by its chemical constituents, mainly

including black carbon (BC), organic matter (OM), ammonium, nitrate, sulfate, soil particles (SOIL), and sea salt (SS) [12, 13]. These constituents may exert different effects on SUA/hyperuricemia through oxidative stress, systemic inflammation or others [14]. To my knowledge, just three environmental epidemiological surveys have analyzed the health effects of $PM_{2.5}$ constituents on SUA levels, with none on hyperuricemia [14–16]. Nevertheless, the focus of these studies was on specific population, such as pregnant women, and short-term exposure effects, two of which only considered single exposure effect [14–16]. Therefore, further investigation in adults is warranted to comprehensively understand the cumulative impact of $PM_{2.5}$ constituents on uric acid and to identify the main contributors, which could help integrated disease prevention and management. However, to date, no large population-based epidemiological evidence links long-term exposure to $PM_{2.5}$ constituents with SUA and hyperuricemia in adults.

Accordingly, based on the China Multi-Ethnic Cohort (CMEC), we aimed to examine the single and joint effects of long-term exposure to $PM_{2.5}$ constituents and hyperuricemia/SUA. In addition, we also aimed to identify which constituent of $PM_{2.5}$ was the most harmful. The current study would provide further insight into the mechanisms of $PM_{2.5}$ constituents on uric acid to promote precise regulatory and public health strategies to reduce air pollution damage.

Materials and methods

Participants

The current study used data from the baseline of the CMEC study, which has been described in detail previously [17]. In brief, the CMEC study recruited a total of 99,556 participants aged 30 to 79 from 5 provinces (Sichuan, Chongqing, Yunnan, Guizhou, and Tibet) of Southwest China using a multistage, stratified cluster sampling method. The baseline study was conducted between May 2018 and September 2019 and collected questionnaire data, a thorough physical examination, and clinical laboratory testing. The design of this study is shown in Additional file 1: Fig. S1. Written informed permission was acquired from each subject. Ethical approval was received from the Sichuan University Medical Ethical Review Board (K2016038, K2020022).

The inclusion criteria for this study population are shown in Additional file 1: Fig. S2. Among those individuals, we excluded participants: (1) who did not provide an incomplete address or lived at the present address for less than 3 years; (2) who were in Aba because they lived a nomadic life, having no fixed residence; (3) who were in Tibet because they had different genetic backgrounds and lived at high altitudes and thus were less comparable to people living at low and middle altitudes; (4) who self-reported gout; (5) who were not within 30–79 years; and (6) who were with unavailable information on any outcome, exposure, or covariates. Ultimately, 72,840 participants were included.

Assessment of exposure data

Exposure data of $PM_{2.5}$ constituents from 2001 to 2017 were from the Global Burden of Disease (GBD) Study [18]. The data were a combination of ground measurements, satellite retrievals, and chemical transport models (CTM). Seven different algorithms were used to estimate satellite aerosol optical depth (AOD) measurements inversely weighted by their errors against the Aerosol Robotic Network based on 10 km × 10 km resolution satellite imagery. Next, converting the satellite-based $PM_{2.5}$ estimates to near-surface $PM_{2.5}$ by the geoscience-based approach, which is an effective method relating satellite AOD retrievals to $PM_{2.5}$ using the GEOS-Chem CTM in combination with a statistical fusion to ground-based observations. Data selection and estimation methods for $PM_{2.5}$ and its constituents have been described in detail in previous studies [19, 20].

In this study, the average monthly concentration of $PM_{2.5}$ mass and its constituents were matched to each individual based on geocoded residential addresses. Then, each participant's 3-year average exposure concentrations prior to the baseline survey were calculated to represent long-term exposure.

Assessment of outcome

Participants' venous blood samples were collected after overnight fasting (at least 8 h), and SUA levels were measured by an AU5800 Automated Chemistry Analyzer (Beckman Coulter Commercial Enterprise, Shanghai, China) at the baseline of CMEC. The instrument was calibrated before testing. All the preceding operations were performed by trained professionals. Hyperuricemia was defined as SUA > 7.0 mg/dL (417 μmol/L) in men and > 6.0 mg/dL (357 μmol/L) in women [21].

Covariates

In this study, we included the following covariates in the main analyses: age (< 65, ≥ 65, years), sex (male or female), ethnicity (Han, minority), marital status (did not cohabit, cohabited), education (illiteracy, primary school, junior high school, high school, junior college, college or above), occupation (agriculture and related, factory worker, clerk, self-employed, unemployed, other), province (Guizhou, Sichuan, Yunnan,

Chongqing), annual family income (CNY; < 12,000, 12,000–19,999, 20,000–59,999, 60,000–99,999, 100,000–199,999, and ≥ 200,000), rural/urban (rural or urban), BMI ([0, 28) and [28, Inf], kg/m^2), physical activity (METs, MET-h/day), smoking status (never smoke, smoke or quit), passive smoking status (yes or no), alcohol consumption (never drinking, drinking), Mediterranean diet (MED) score, indoor air pollution (light, moderate, heavy). Details about covariates are placed in Supplementary text.

Statistical analysis

Single exposure analyses

Multiple logistic regression and linear regression were used to assess the association of $PM_{2.5}$ mass/constituents with hyperuricemia and SUA, respectively. Our analysis started with no covariates (crude model) and then gradually expanded by adding additional covariates. Model 1 was adjusted for age, sex, ethnicity, marital status, education, occupation, province, annual family income, rural/urban, and BMI. Based on model 1, model 2 was further adjusted for physical activity, smoking status, passive smoking status, alcohol consumption, MED score, and indoor air pollution. The variables adjusted in subsequent analyses were the same as the covariates in Model 2.

Joint exposure analyses

We applied the Weighted Quantile Sum (WQS) regression to study the joint effect of $PM_{2.5}$ constituents. The WQS method was consistent with two stages [22, 23]. In the first stage, all constituents were converted into quantiles and weighted the sum to construct the WQS index. In the second stage, the WQS index was included in a regression model with covariates which were the same as model 2 to estimate the combined effect of $PM_{2.5}$ constituents on hyperuricemia and SUA. Weight estimates (importance) for each constituent and mixed exposure effects associated with per unit increase of WQS index were reported. Additional details for WQS regression are represented in Supplementary text.

Subgroup analyses

The stratified variables were age (< 65, ≥ 65, years), sex (male, female), education (below high school, high school and above), physical activity (less than the mean, greater than or equal to the mean), and MED score (less than the mean, greater than or equal to the mean). We added an interaction term between the pollutant and the stratified variable to examine whether the difference between the groups was statistically significant.

Sensitivity analyses

First, we changed the exposure window to 2-, 4- and 5-year averages of the $PM_{2.5}$ constituents' concentrations to represent the long-term exposure. Second, we included the self-reported gout participants at baseline. Third, based on model 2, we further adjusted environmental factors (temperature and relative humidity). Fourth, based on model 2, further adjusting the gaseous pollutants: nitrogen dioxide (NO_2) and ozone (O_3). Fifth, we used the quantile g-computation (QGC) regression [24], another method for analyzing joint effects, to verify the results of WQS. Details about the data source (temperature, relative humidity, NO_2 and O_3) and the QGC method are represented in Supplementary text. Finally, we limited the cubic spline transformation of exposure variables to investigate whether there was a linear relationship between exposure and outcome.

We reported the odds ratio (OR) and changes in μmol/L with the 95% confidence interval (CI) corresponding to an SD increase in exposures for hyperuricemia and SUA levels, respectively. All the analyses were conducted using R software (Version 4.1.2). *P*-values < 0.05 in two-sided testing were regarded as statistically significant.

Results

Descriptive statistics

Table 1 summarizes the basic characteristics of 72,840 individuals. Those participants had 13,488 cases of hyperuricemia, with an incidence rate of 18.5%. In addition, we observed that 16% of the research population was ≥ 65 years old, and 28,683 (39.4%) were male participants. The average SUA concentration was 317.88 μmol/L for the total population, 287.66 μmol/L for participants without hyperuricemia, and 450.86 μmol/L for hyperuricemia participants.

The summary distributions of $PM_{2.5}$ constituents during the 3 years before the baseline of the CMEC cohort are outlined in Table 2. The 3-year mean (SD) concentrations were 37.88 (21.59) μg/m^3 for $PM_{2.5}$ mass, 1.95 (1.14) μg/m^3 for BC, 8.57 (5.00) μg/m^3 for OM, 6.01 (3.46) μg/m^3 for ammonium, 7.67 (5.57) μg/m^3 for nitrate, 10.13 (5.03) μg/m^3 for sulfate, etc. The distribution levels of $PM_{2.5}$ mass and its constituents were slightly higher in hyperuricemia participants (Additional file 1: Table S1). Spatial distributions of $PM_{2.5}$ mass and its constituents are shown in Additional file 1: Fig. S3. Additional file 1: Table S2 provides information on the specific sources of the $PM_{2.5}$ constituents.

Associations of $PM_{2.5}$ mass and its constituents with hyperuricemia/SUA

The estimated odds ratio (95%CI) of hyperuricemia and change in μmol/L (95%CI) of SUA concentrations

Table 1 Basic characteristics of the participants ($n = 72,840$)

Variables	Total ($n = 72,840$)	Non-hyperuricemia ($n = 59,352$)	Hyperuricemia ($n = 13,488$)	*P* value
Age (%), years				< 0.001
< 65	61,166 (84.0)	50,340 (84.8)	10,826 (80.3)	
≥ 65	11,674 (16.0)	9012 (15.2)	2662 (19.7)	
Sex (%)				< 0.001
Male	28,683 (39.4)	21,056 (35.5)	7627 (56.5)	
Female	44,157 (60.6)	38,296 (64.5)	5861 (43.5)	
Ethnicity (%)				0.180
Han	46,713 (64.1)	38,131 (64.2)	8582 (63.6)	
Minority	26,127 (35.9)	21,221 (35.8)	4906 (36.4)	
Marital status (%)				< 0.001
Did not cohabit	7864 (10.8)	6246 (10.5)	1618 (12.0)	
Cohabited	64,976 (89.2)	53,106 (89.5)	11,870 (88.0)	
Education (%)				< 0.001
Illiteracy	16,828 (23.1)	13,941 (23.5)	2887 (21.4)	
Primary school	18,639 (25.5)	15,536 (26.2)	3103 (23.0)	
Junior high school	19,961 (27.4)	16,275 (27.4)	3686 (27.3)	
High school	8997 (12.4)	7083 (12.0)	1914 (14.2)	
Junior college	5230 (7.2)	4117 (6.9)	1113 (8.3)	
College or above	3185 (4.4)	2400 (4.0)	785 (5.8)	
Rural/urban (%)				< 0.001
Urban	38,096 (52.3)	30,465 (51.3)	7631 (56.6)	
Rural	34,744 (47.7)	28,887 (48.7)	5857 (43.4)	
Province (%)				< 0.001
Guizhou	15,279 (21.0)	11,580 (19.6)	3699 (27.5)	
Sichuan	18,249 (25.1)	14,324 (24.1)	3925 (29.1)	
Yunnan	20,306 (27.8)	17,292 (29.1)	3014 (22.3)	
Chongqing	19,006 (26.1)	16,156 (27.2)	2850 (21.1)	
Occupation (%)				< 0.001
Agriculture and related	25,880 (35.5)	21,881 (37.0)	3999 (29.6)	
Unemployed	21,132 (29.0)	16,818 (28.3)	4314 (32.0)	
Factory worker	5523 (7.6)	4476 (7.5)	1047 (7.8)	
Clerk	11,592 (15.9)	9219 (15.5)	2373 (17.6)	
Self-employed	4660 (6.4)	3725 (6.3)	935 (6.9)	
Other	4053 (5.6)	3233 (5.4)	820 (6.1)	
Mediterranean diet score [mean (SD)]	24.87 (4.43)	24.93 (4.42)	24.64 (4.46)	< 0.001
Annual family income (%), CNY [a]				< 0.001
< 12,000	12,700 (17.4)	10,375 (17.5)	2325 (17.2)	
12,000–19,999	12,505 (17.2)	10,434 (17.6)	2071 (15.4)	
20,000–59,999	26,395 (36.2)	21,761 (36.6)	4634 (34.4)	
60,000–99,999	11,155 (15.3)	8938 (15.1)	2217 (16.4)	
100,000–199,999	8070 (11.1)	6309 (10.6)	1761 (13.1)	
≥ 200,000	2015 (2.8)	1535 (2.6)	480 (3.5)	
Smoking status (%)				< 0.001
Never smoke	54,100 (74.3)	45,496 (76.7)	8604 (63.8)	
Smoke or quit	18,740 (25.7)	13,856 (23.3)	4884 (36.2)	
Passive smoking status (%)				0.154
No	35,193 (48.3)	28,601 (48.2)	6592 (48.9)	
Yes	37,647 (51.7)	30,751 (51.8)	6896 (51.1)	

Table 1 (continued)

Variables	Total ($n=72,840$)	Non-hyperuricemia ($n=59,352$)	Hyperuricemia ($n=13,488$)	*P* value
Alcohol consumption (%)				< 0.001
Never drinking	40,579 (55.7)	34,355 (57.9)	6224 (46.1)	
Drinking	32,261 (44.3)	24,997 (42.1)	7264 (53.9)	
Indoor air pollution (%)				< 0.001
Light	11,492 (15.8)	8893 (15.0)	2599 (19.3)	
Moderate	57,681 (79.2)	47,394 (79.8)	10,287 (76.3)	
Heavy	3667 (5.0)	3065 (5.2)	602 (4.4)	
BMI (%), kg/m^2				< 0.001
[0, 28)	64,114 (88.0)	53,696 (90.5)	10,418 (77.2)	
[28, Inf]	8726 (12.0)	5656 (9.5)	3070 (22.8)	
Physical activity [mean (SD)], MET-h/day	26.76 (18.34)	27.36 (18.44)	24.12 (17.68)	< 0.001
SUA levels [mean (SD)], μmol/L	317.88 (88.05)	287.66 (59.79)	450.86 (66.61)	< 0.001

[a] CNY denotes China Yuan; BMI, body mass index; MET, metabolic equivalent; SUA, serum uric acid

Table 2 Summary distributions of $PM_{2.5}$ mass, and its constituents in the 3-year exposure window before the baseline of the CMEC study

Exposure	Mean	SD	Min	Percentile			Max
				25%	50%	75%	
$PM_{2.5}$, μg/m^3	37.88	21.59	6.77	12.72	40.66	56.61	70.76
BC, μg/m^3	1.95	1.14	0.31	0.65	2.06	2.96	3.73
Ammonium, μg/m^3	6.01	3.46	0.90	1.89	6.58	9.06	11.11
Nitrate, μg/m^3	7.67	5.57	0.33	1.34	7.15	12.60	16.22
OM, μg/m^3	8.57	5.00	1.36	2.85	8.88	12.81	16.82
Sulfate, μg/m^3	10.13	5.03	2.16	4.03	10.81	14.34	17.14
SOIL, μg/m^3	2.99	1.83	0.43	1.04	2.97	4.58	6.45
SS, μg/m^3	0.03	0.03	0.00	0.01	0.02	0.03	0.11

SD, standard deviation; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; BC, black carbon; OM, organic matter; SOIL, soil particles; SS, sea salt

contributed by each SD increase of $PM_{2.5}$ mass and its constituents are shown in Table 3 and Additional file 1: Fig. S4. Significant positive associations were observed in the main model (model 2). The ORs of hyperuricemia for per SD increase of $PM_{2.5}$ mass, BC, OM, ammonium, nitrate, sulfate, SOIL, and SS were 1.22 (1.12–1.32), 1.17 (1.08–1.27), 1.20 (1.10–1.31), 1.21 (1.11–1.31), 1.28 (1.18–1.40), 1.14 (1.06–1.23), 1.19 (1.11–1.28), and 1.13 (1.08–1.19), respectively. The changes in μmol/L (95%CI) of SUA concentrations were 9.02 (6.73–11.32) for $PM_{2.5}$ mass, 7.58 (5.39–9.77) for BC, 8.15 (5.78–10.53) for OM, 8.94 (6.70–11.17) for ammonium, 10.11 (7.80–12.42) for nitrate, 7.19 (5.11–9.27) for sulfate, 7.62 (5.57–9.68) for SOIL, and 5.52 (4.05–6.98) for SS.

Figure 1 displays the relative weight estimation of $PM_{2.5}$ constituents for hyperuricemia and SUA concentration in the mixture exposure analyses. WQS represented the mixture effect of the eight exposures (per unit increase in WQS index) was positively associated with hyperuricemia (1.09, 1.05–1.14) and elevated SUA (1.05, 1.03–1.06) (Additional file 1: Table S3). The top estimated weight was nitrate; the remaining seven exposures' weights were smaller or near zero.

Subgroup analyses

Education, physical activity, and MED score modified the associations between $PM_{2.5}$ constituents and hyperuricemia or SUA (Figs. 2, 3). Education-specific analyses revealed that exposure to $PM_{2.5}$ mass, BC, OM, ammonium, nitrate, sulfate, and SOIL was associated with a higher risk of hyperuricemia in people with lower education levels. The change of SUA level was 12.43 (9.64–15.21) μmol/L for per SD increase in $PM_{2.5}$ mass, for instance, in the lower education level population, which is larger than people with higher education levels (5.69, 1.36–10.02). Besides, the populations with high physical activity levels and low MED scores were more susceptible

Table 3 Association of long-term exposure to $PM_{2.5}$ mass and its constituents (per SD increase, μg/m^3) with hyperuricemia and SUA concentrations

Air pollutant	Crude[a]		Model 1[b]		Model 2[c]	
Hyperuricemia, OR (95%CI), *P* value						
$PM_{2.5}$	1.09 (1.07–1.11)	< 0.001	1.22 (1.12–1.32)	< 0.001	1.22 (1.12–1.32)	< 0.001
BC	1.08 (1.06–1.10)	< 0.001	1.17 (1.08–1.27)	< 0.001	1.17 (1.08–1.27)	< 0.001
Ammonium	1.10 (1.07–1.12)	< 0.001	1.21 (1.12–1.31)	< 0.001	1.21 (1.11–1.31)	< 0.001
Nitrate	1.07 (1.05–1.09)	< 0.001	1.28 (1.17–1.39)	< 0.001	1.28 (1.18–1.40)	< 0.001
OM	1.07 (1.05–1.09)	< 0.001	1.20 (1.10–1.31)	< 0.001	1.20 (1.10–1.31)	< 0.001
Sulfate	1.11 (1.09–1.13)	< 0.001	1.15 (1.06–1.24)	< 0.001	1.14 (1.06–1.23)	< 0.001
SOIL	1.09 (1.07–1.12)	< 0.001	1.19 (1.11–1.29)	< 0.001	1.19 (1.11–1.28)	< 0.001
SS	1.16 (1.14–1.18)	< 0.001	1.14 (1.08–1.20)	< 0.001	1.13 (1.08–1.19)	< 0.001
SUA, changes in μmol/L (95%CI), *P* value						
$PM_{2.5}$	7.98 (7.34–8.62)	< 0.001	8.92 (6.62–11.23)	< 0.001	9.02 (6.73–11.32)	< 0.001
BC	7.77 (7.14–8.41)	< 0.001	7.53 (5.33–9.72)	< 0.001	7.58 (5.39–9.77)	< 0.001
Ammonium	8.25 (7.61–8.88)	< 0.001	8.94 (6.70–11.18)	< 0.001	8.94 (6.70–11.17)	< 0.001
Nitrate	7.47 (6.83–8.10)	< 0.001	9.87 (7.55–12.19)	< 0.001	10.11 (7.80–12.42)	< 0.001
OM	7.50 (6.86–8.13)	< 0.001	7.87 (5.49–10.24)	< 0.001	8.15 (5.78–10.53)	< 0.001
Sulfate	8.76 (8.12–9.39)	< 0.001	7.35 (5.27–9.44)	< 0.001	7.19 (5.11–9.27)	< 0.001
SOIL	8.12 (7.48–8.75)	< 0.001	7.41 (5.35–9.46)	< 0.001	7.62 (5.57–9.68)	< 0.001
SS	3.55 (2.91–4.18)	< 0.001	5.71 (4.24–7.17)	< 0.001	5.52 (4.05–6.98)	< 0.001

BMI, body mass index; $PM_{2.5}$, particulate matter with aerodynamic diameters of ≤ 2.5 μm; BC, black carbon; OM, organic matter; SOIL, soil particles; SS, sea salt; SD, standard error; OR, odds ratio; CI, confidence interval; SUA, serum uric acid

[a] Crude model adjusted for nothing

[b] Model 1 adjusted for age, gender, ethnicity, marital status, education, occupation, province, annual family income, rural/urban, BMI

[c] Model 2 adjusted for age, gender, ethnicity, marital status, education, occupation, province, annual family income, rural/urban, BMI, physical activity, smoking status, passive smoking status, alcohol consumption, Mediterranean diet score, indoor air pollution

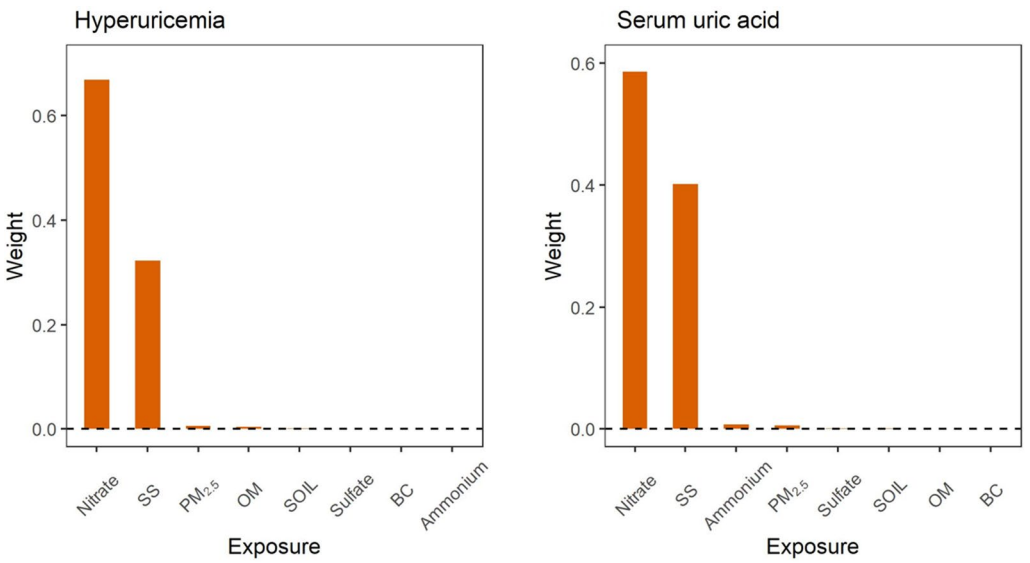


Fig. 1 Weights estimation of $PM_{2.5}$ mass and its constituents by WQS method. The result was adjusted for age, sex, ethnicity, marital status, education, occupation, province, annual family income, rural/urban, BMI, physical activity, smoking status, passive smoking status, alcohol consumption, Mediterranean diet score, indoor air pollution. *Abbreviations*: $PM_{2.5}$, particulate matter with aerodynamic diameters of ≤ 2.5 μm; SOIL, soil particles; SS, sea salt; BC, black carbon; OM, organic matter; WQS, weighted quantile sum; SUA, serum uric acid

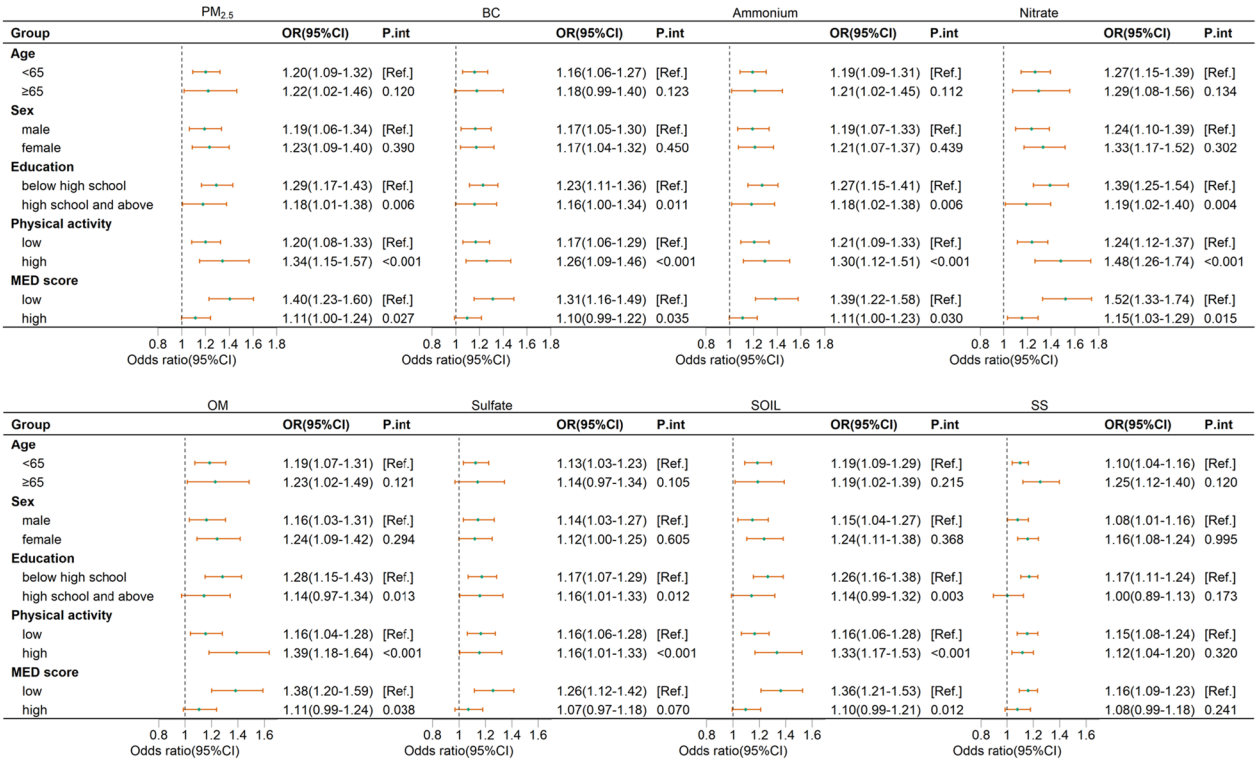


Fig. 2 Subgroup analyses of odds ratio for hyperuricemia, associated with per SD increase in exposure to $PM_{2.5}$ mass and its constituents. *Abbreviations*: SD, standard error; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm. BC, black carbon; OM, organic matter; SOIL, soil particles; SS, sea salt; P. int, p for interaction

to the negative effects of $PM_{2.5}$ mass, BC, OM, ammonium, nitrate, and SOIL.

Sensitivity analyses

The sensitivity analyses showed robust associations between $PM_{2.5}$ mass/its constituents and hyperuricemia and SUA level. When using the 2-, 4-, and 5-year mean annual concentrations in analyses, the result became slightly higher in the 4-year and 5-year exposure while slightly lower in the 2-year exposure window analysis (Additional file 1: Table S4). Specifically, the analysis, including self-reported gout participants, presented highly similar estimates of OR for hyperuricemia and change in μmol/L for SUA (Additional file 1: Table S5). Moreover, $PM_{2.5}$ mass and its constituents continued to have a significant association with hyperuricemia and SUA in the model, further adjusting temperature and relative humidity (Additional file 1: Table S5). Additionally, in the model further adjusted for gaseous contaminants (NO_2 and O_3), highly comparable associations were observed (Additional file 1: Table S5), except that the associations between BC/OM and hyperuricemia became statistically insignificant. The mixture effect estimated by the QGC method was nearly consistent with the value estimated by WQS (Additional file 1: Table S3), with nitrate having the highest positive weight (0.479 for hyperuricemia, 0.460 for SUA) (Additional file 1: Fig. S5 and Table S6). The dose–response relationships between the 3-year average pollutant exposure and hyperuricemia/SUA are presented in Additional file 1: Figs. S6 and S7. All the relationships are approximately linear.

Discussion

This study explored the correlation of long-term exposure to $PM_{2.5}$ constituents with hyperuricemia and SUA levels. Utilizing the baseline data from 78,240 subjects of the CMEC cohort study, a few notable findings stand out. Significant associations were observed between single and joint long-term exposure to $PM_{2.5}$ mass, BC, OM, ammonium, nitrate, sulfate, SOIL, SS and hyperuricemia/SUA. Nitrate might be the most responsible constituent. Furthermore, subgroup analyses represented a higher risk of hyperuricemia and more significantly increased levels of SUA among less well-educated, higher physical activity, and lower MED scores populations. To the best

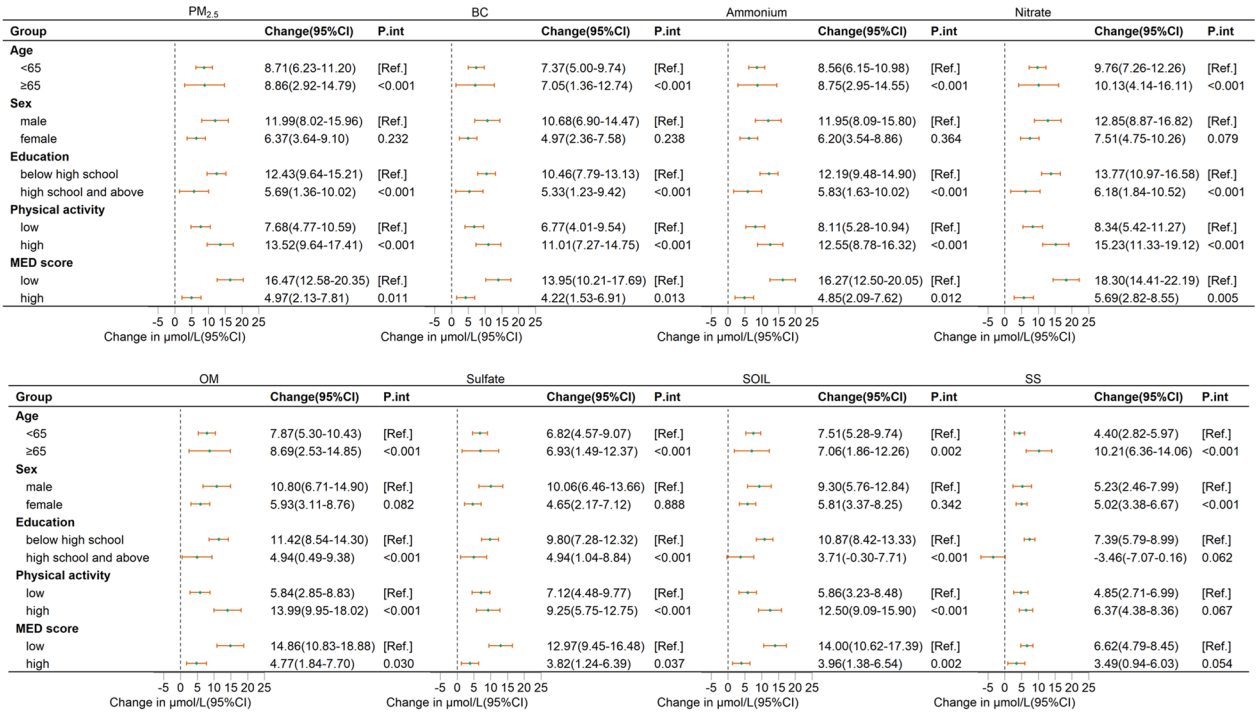


Fig. 3 Subgroup analyses of change in μmol/L of SUA concentrations, associated with per SD increase in exposure to $PM_{2.5}$ mass and its constituents. *Abbreviations*: SD, standard error; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm. BC, black carbon; OM, organic matter; SOIL, soil particles; SS, sea salt; SUA, serum uric acid; P. int, p for interaction

of our knowledge, this is the first large-scale epidemiologic study conducted in adults to study the association.

Comparison with other studies

Limited studies have examined the effects of $PM_{2.5}$ constituents on uric acid. For instance, one research based on a total of 808 older adults from the Veterans Affairs Normative Aging Study analyzed the associations of single and combined short-term exposure to BC, V, Ni, and other $PM_{2.5}$ constituents with SUA [15], ignoring that air pollution probably acts cumulatively. Nevertheless, it observed a positive relationship between BC and SUA, which was in agreement with our study. And the significant positive relationship of $PM_{2.5}$ mixture with SUA was revealed as well. Another longitudinal panel study in Wuhan conducted among college students also probed associations between $PM_{2.5}$ constituents and SUA [16]. However, the results of this study did not yield a significant relationship between the variables. Possible explanations for this lack of significance could be attributed to variations in the reported $PM_{2.5}$ constituents, differences in study regions, or disparities among the populations under investigation. In addition, a population-based study carried out in China found that exposure to $PM_{2.5}$ mass and its constituents of OM, BC, nitrate, and ammonium was positively associated with SUA [14]. Interestingly, these four constituents were also part of the constituents examined in our study, which we still found positive associations. Nevertheless, it is important to note that the aforementioned study focused specifically on pregnant women and solely conducted single exposure analyses.

Compared with the above studies, our study aimed to investigate the associations between single and joint long-term exposure to $PM_{2.5}$ constituents and SUA level and hyperuricemia in adults. Additionally, we used two different methods (WQS and QGC) to estimate the joint exposure effect and agreed that nitrate was the most influential constituent. In short, the available environmental epidemiological evidence was generally consistent regarding the deleterious health effects of $PM_{2.5}$ constituents on uric acid, providing guidance for policymakers to develop accurate strategies to control disease burden.

Potential mechanism

Several potential biological mechanisms have been proposed, including systemic inflammation, interfering with lipid metabolism that can lead to glomerulus damage, oxidative stress, insulin resistance, and changes in cardiac autonomic function [25–30]. It is well known that the toxic effects of $PM_{2.5}$ are determined to a large extent by its chemical constituents [13], which may have

distinct effect on uric acid at certain stages. However, the biological deleterious reactions caused by different constituents are still poorly understood. In this study, nitrate was the most significantly associated constituent of $PM_{2.5}$ with hyperuricemia and SUA. It was formed by the conversion of gas from NOx products in automobile exhaust into particles [31, 32]. Liu et al. [33] discovered that nitrate was strongly associated with markers of inflammation (fibrinogen, C-reactive protein, etc.), which may play crucial roles in inducing systematic inflammation and coagulation. A repeated measurement study of healthy adults in Beijing, China, supported the association between nitrate and oxidative stress [34]. It reported that nitrate could increase circulating levels of two antioxidant enzymes: extracellular superoxide dismutase (EC-SOD) and glutathione peroxidase 1 (GPX1), which were essential in the body's antioxidant system. Ammonium and sulfate, the main water-soluble inorganic ions (WSIs), are similarly conducted from vehicle emission or through photochemical oxidations and heterogeneous reactions [35]. Studies also found ammonium and sulfate were related to oxidative stress, fibrinogen and C-reactive protein [32, 33]. Sea salt is emitted from the sea surface through bubble-bursting processes. In evaporation from seawater, sea salt can form nitrate and sulfate with nitrogen dioxide and sulfur dioxide in the air, thus adversely affecting health [36].

As a common constituent of $PM_{2.5}$, BC is mainly derived from gasoline and diesel vehicle exhaust combustion [37]. One review has shown that exposure to BC may cause inflammation and oxidative stress [38]. In addition, a panel study revealed that black carbon was significantly associated with worsening insulin resistance [39]. Similarly to black carbon, OM is a mixture of polycyclic aromatic hydrocarbons (PAHs), alkylated PAHs, and so on [40]. In cell experiments, it was suggested that OM in diesel exhaust particles could induce inflammatory genes and increase the secretion of chemokines CXLC8/interleukin-8 and matrix metalloproteinase 1 [41].

Usually, as the carrier of harmful elements, soil dust (SOIL) causes serious harm to human health. It contains many metallic elements such as Co, Pb, Cd, Ga, etc. [42] Metal exposure could cause tubulointerstitial nephropathy and toxic effects on blood nucleoproteins, altering purine metabolism and thereby leading to hyperuricemia [43, 44].

In the result of the WQS method, nitrate and sea salt weighted much higher than other constituents, which deserved our attention. Based on our understanding, first, since nitrate particles are formed by the oxidation of nitrogen oxides emitted from vehicles, people may have a higher chance of being exposed to this pollutant in daily life [31, 32]. Second, nitrate concentrations in southwest China are also high. Third, nitrate can be more pathogenic as it could affect serum uric acid by a variety of mechanisms mentioned above [33, 34], including systematic inflammation, coagulation and oxidative stress, etc. Thus, nitrate could be the most harmful component. Finally, sea salt provides multiple pathways to affect uric acid by forming nitrates and sulfates [36]. This may result in it being given a higher weight than others. Additional research is needed in the future to clarify the mechanisms between $PM_{2.5}$ constituents and elevated SUA levels and to mechanistically explain the reasons for the large differences in weights.

The explanation for the subgroup analyses results

The education-specific analyses demonstrated an evidently increased risk of hyperuricemia and SUA elevation among individuals with less than a high school education. One possible reason is that limited access to quality healthcare and preventive services and a lack of health knowledge can contribute to the higher prevalence of hyperuricemia within this subpopulation [2, 45]. Referring to physical activity-specific analyses, we found that people with a high level of physical activity may have a stronger association. It has been shown that the volume of inhalation load and the total number of particles deposited during exercise is higher than at rest [46]. Physically active individuals often engage in outdoor exercises, leading to heavily exposed to air pollutants, thus the cumulative effect of air pollutants may increase the probability of hyperuricemia [47]. Moreover, our findings indicated that adherence to the Mediterranean diet could mitigate the risk of hyperuricemia and increasing of SUA levels resulting from $PM_{2.5}$ constituents. Dietary patterns are closely related to the development of hyperuricemia and increasing of SUA through the indirect effect of intestinal flora or the direct influence of host purine metabolism [48]. In this context, the Mediterranean diet helps to reduce SUA concentration, thereby preventing hyperuricemia.

Implications

Exploring the link between $PM_{2.5}$ constituents and uric acid levels aids in the identification of individuals at an elevated risk of developing hyperuricemia and associated conditions. This knowledge enables healthcare providers to target interventions and preventive measures to those individuals, including lifestyle modifications, early detection, and appropriate management strategies. In addition, this study helps us better understand the effects of air pollution on metabolic health. Uric acid is an important biomarker for conditions like gout and hyperuricemia, while $PM_{2.5}$ mass and its constituents are common air pollutants. By studying their relationship, we can uncover

the contributions of air pollution to metabolic disorders, providing new insights for the prevention and treatment of related diseases. What is more, this study still possesses vital public health implications. By identifying high-risk populations, encouraging targeted measures, and promoting precise prevention strategies, we can effectively reduce the harm on uric acid caused by $PM_{2.5}$ constituents at a population level. For example, controlling vehicle exhaust emissions which is the main source of nitrate, promoting electric vehicles or upgrading new energy could be an effective strategy. This research highlights the importance of comprehensive public health approaches and collaborative efforts to safeguard the well-being of individuals and communities in the face of air pollution challenges.

Limitations and strengths

It is important to acknowledge the limitations of this study. One of the limitations is the estimation of pollutant exposure levels based on participants' residential addresses, which may introduce inaccuracies due to individual differences. Therefore, there is a possibility of misclassification in the estimation of exposure. Besides, the cross-sectional nature of this study restricts the exploration of a causal link between $PM_{2.5}$ constituents and hyperuricemia/SUA. But we implemented several measures to remedy this deficiency. The self-reported gout participants at baseline were excluded from this study. Moreover, individuals' SUA level and hyperuricemia were decided at baseline. Meanwhile, we used 3-year average exposure data prior to the baseline survey and excluded those who lived at their current address for less than 3 years. These rigorous steps were taken to minimize the potential for causal inversion and enhance the validity of our findings.

Despite these limitations, this study also possesses several notable strengths. First, this is the pioneering epidemiological study to date to investigate the relationship between long-term exposure to $PM_{2.5}$ constituents and hyperuricemia/SUA in Chinese adults, which provides essential insights into the health effects of air pollution and can help shape air quality policy. Second, the data we used are from a large population-based study. A standardized whole-process quality control system ensures the quality of data [17]. Third, the exposure data used in our study are the same source used for CBD, which has been proven accurate [20]. Meanwhile, the large sample size ensures the universality and generalization of our results. Fourth, we incorporate a comprehensive set of covariates, which minimizes confounding biases and lends greater credibility to the observed associations. Finally, we employ two widely accepted methods, namely WQS and QGC, to investigate the joint exposure of $PM_{2.5}$ constituents and hyperuricemia/SUA. The utilization of these robust statistical approaches strengthens the validity and reliability of our findings. Notably, both methods concur on identifying the most influential constituent, enhancing the consistency and confidence of our results.

Conclusions

This study revealed that long-term exposure to ambient $PM_{2.5}$ mass, BC, OM, ammonium, nitrate, sulfate, SOIL, and SS, were significantly associated with hyperuricemia and elevated SUA levels. Besides, we further found nitrate was the most harmful constituent. Furthermore, individuals with lower education levels, higher levels of physical activity, and lower adherence to the Mediterranean diet (MED) exhibit increased vulnerability to the adverse effects of $PM_{2.5}$ constituents. These findings may significantly help us understand the toxicity of $PM_{2.5}$ constituents, which may shed new light on mitigating the burden of $PM_{2.5}$-related uric acid and allow policymakers to achieve precise prevention.

Abbreviations

AOD	Aerosol optical depth
BC	Black carbon
BMI	Body mass index
CI	Confidence interval
CMEC	China Multi-Ethnic Cohort
GBD	Global Burden of Disease
GEOS-Chem	Chemical transport model
METs	Metabolic equivalent tasks
OM	Organic matter
OR	Odds ratio
$PM_{2.5}$	Particulate matter with aerodynamic diameter $\leq$ 2.5 μm
QGC	Quantile g-computation
SD	Standard deviation
SOIL	Soil particles
SS	Sea salt
SUA	Serum uric acid
WQS	Weighted quantile sum

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-023-00809-1.

Additional file 1. Supplementary material.

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Author contributions

CK and YJ wrote the original draft and supplementary material. CK, DY and TX conducted statistical analyses. JY, XH, and LH revised the manuscript. LJ, YT, YJ, LX, DJ, and ZJ collected the baseline data and reviewed relevant literature. LH provided the particulate matter constituent data and wrote the corresponding text. GB, XL, and ZX guided this work. As the supervisor of this work, GB

and XL have complete access to all the data in this study and are responsible for ensuring the accuracy of the data analysis.

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Availability of data and materials
The dataset is from the China Multi-Ethnic Cohort (CMEC) study which is not publicly available, as per the requirements in the data contribution agreements. Consult the corresponding author if you need.

Declarations

Ethics approval and consent to participate
Written informed permission was acquired by each subject. Ethical approval was received from the Sichuan University Medical Ethical Review Board (K2016038, K2020022).

Consent for publication
Written informed permission was acquired by each subject.

Competing interests
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.

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