Long-term exposure to ambient PM2.5 and its constituents is associated with MAFLD

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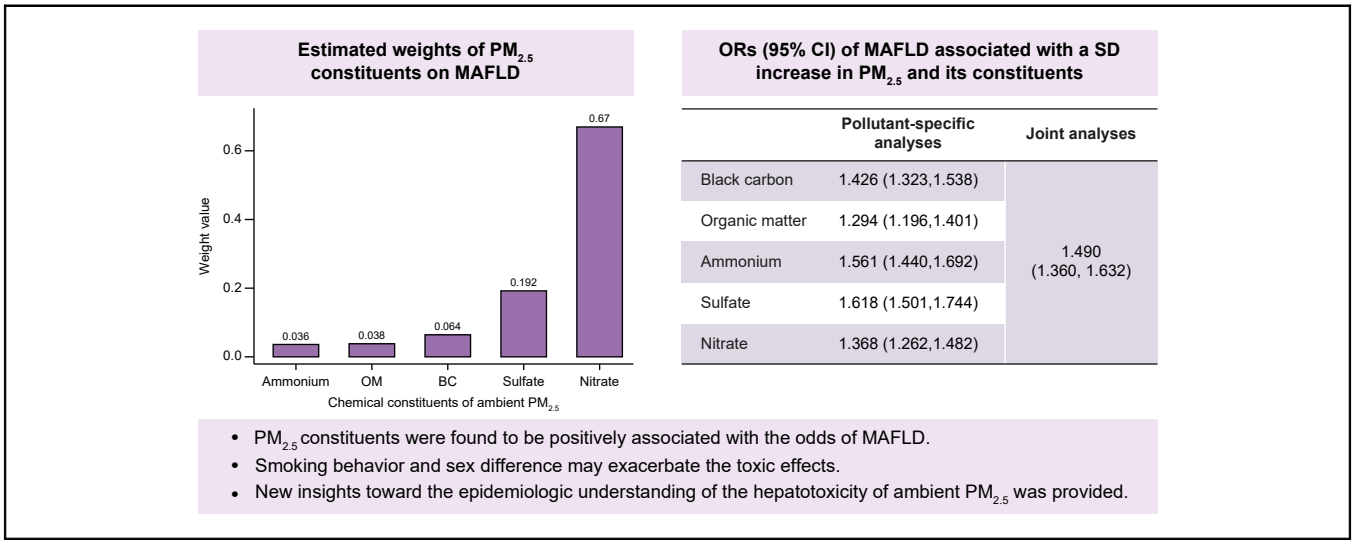
Graphical abstract



Highlights

- Ambient $PM_{2.5}$ constituents are positively associated with the risk of MAFLD.
- Nitrate is the most heavily weighted particle in the joint effect on MAFLD.
- Smoking and male sex may exacerbate the toxic effects of $PM_{2.5}$.
- We provide novel insights into the hepatotoxicity of ambient $PM_{2.5}$.

Impact and implications

This large-scale epidemiologic study explored the associations between constituents of fine particulate pollution ($PM_{2.5}$) and metabolic dysfunction-associated fatty liver disease (MAFLD), and further revealed which constituents play a more important role in increasing the risk of MAFLD. In contrast to previous studies that examined the effects of $PM_{2.5}$ as a whole substance, this study carefully explored the health effects of the individual constituents of $PM_{2.5}$. These findings could (1) help researchers to identify the specific particles responsible for hepatotoxicity, and (2) indicate possible directions for policymakers to efficiently control ambient air pollution, such as targeting the sources of nitrate pollution.

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Research article

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Long-term exposure to ambient PM2.5 and its constituents is associated with MAFLD

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Background & Aims: Existing evidence suggests that long-term exposure to ambient fine particulate pollution ($PM_{2.5}$) may increase metabolic dysfunction-associated fatty liver disease (MAFLD) risk. However, there is still limited evidence on the association of $PM_{2.5}$ constituents with MAFLD. Therefore, this study explores the associations between the five main chemical constituents of $PM_{2.5}$ and MAFLD to provide more explicit information on the liver exposome.

Methods: A total of 76,727 participants derived from the China Multi-Ethnic Cohort, a large-scale epidemic survey in southwest China, were included in this study. Multiple linear regression models were used to estimate the pollutant-specific association with MAFLD. Weighted quantile sum regression was used to evaluate the joint effect of the pollutant-mixture on MAFLD and identify which constituents contribute most to it.

Results: Three-year exposure to $PM_{2.5}$ constituents was associated with a higher MAFLD risk and more severe liver fibrosis. Odds ratios for MAFLD were 1.480, 1.426, 1.294, 1.561, 1.618, and 1.368 per standard deviation increase in $PM_{2.5}$, black carbon, organic matter, ammonium, sulfate, and nitrate, respectively. Joint exposure to the five major chemical constituents was also positively associated with MAFLD (odds ratio 1.490, 95% CI 1.360–1.632). Nitrate contributed most to the joint effect of the pollutant-mixture. Further stratified analyses indicate that males, current smokers, and individuals with a high-fat diet might be more susceptible to ambient $PM_{2.5}$ exposure than others.

Conclusions: Long-term exposure to $PM_{2.5}$ and its five major chemical constituents may increase the risk of MAFLD. Nitrate might contribute most to MAFLD, which may provide new clues for liver health. Males, current smokers, and participants with high-fat diets were more susceptible to these associations.

Impact and implications: This large-scale epidemiologic study explored the associations between constituents of fine particulate pollution ($PM_{2.5}$) and metabolic dysfunction-associated fatty liver disease (MAFLD), and further revealed which constituents play a more important role in increasing the risk of MAFLD. In contrast to previous studies that examined the effects of $PM_{2.5}$ as a whole substance, this study carefully explored the health effects of the individual constituents of $PM_{2.5}$. These findings could (1) help researchers to identify the specific particles responsible for hepatotoxicity, and (2) indicate possible directions for policymakers to efficiently control ambient air pollution, such as targeting the sources of nitrate pollution.

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is estimated to exist in about 40% of adults worldwide.[1–3] There is no curative treatment for MAFLD, so the search for modifiable risk and protective factors remains a clinical and public health priority.[3,4]

Emerging epidemiologic evidence consistently showed that ambient air pollution may be a risk factor for MAFLD.[5–7] Specifically, particulate matter 2.5 μm or less in diameter ($PM_{2.5}$) can reach the pulmonary alveoli, enter the blood circulation, and finally reach the liver, where it is catabolized. Toxicologic studies

Keywords: Metabolic dysfunction-related fatty liver disease; ambient fine particulate matter constituents; hepatotoxicity; joint exposure analysis.

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found that $PM_{2.5}$ can cause damage to the liver and also lead to metabolic dysfunction in the liver.[8,9] These new findings may provide further clues to guide the prevention and clinical treatment of MAFLD.[10]

Notably, ambient $PM_{2.5}$ originates from the complex interaction of multiple emissions and chemical reactions; it is a mixture of various chemical constituents, such as elemental carbon, organic carbon, sulfate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+). These $PM_{2.5}$ constituents have different toxicological profiles, which may lead to different effects on liver health; simultaneously, they can further reflect specific emission sources to inform mitigation strategies. Therefore, understanding the constituent-specific effect on liver health may provide a clearer perspective on $PM_{2.5}$ hepatotoxicity, which will help establish a more specific source-oriented $PM_{2.5}$ control strategy. A few studies investigated the effect of chemical constituents of $PM_{2.5}$ on metabolic disorders or diseases.[11–14] For instance, black carbon and organic matter were found to be mainly associated with glucose levels,[12] particle sulfate mainly associated with metabolic syndrome (MetS),[13] and organic carbon matter mainly associated with subclinical atherosclerosis.[14] However, evidence on the associations between $PM_{2.5}$ constituents and MAFLD is limited.

This epidemiologic study aims to assess whether long-term exposure to ambient $PM_{2.5}$ and five major constituents were associated with the odds of MAFLD and to explore the constituents that contribute most to the joint effect on MAFLD. This study was conducted on the basis of the China Multi-Ethnic Cohort (CMEC), a large-scale cohort composed of several ethnic groups in southwest China.[15]

Materials and methods

Study design and data collection

We used baseline data from the China Multi-Ethnic Cohort (CMEC) to conduct a cross-sectional, observational study to assess the relationship between $PM_{2.5}$ constituents and MAFLD. The CMEC recruited 99,556 participants, aged 30-79, from the general population in five southwestern provinces of China between May 2018 and September 2019.[15] Participants answered a questionnaire through a face-to-face interview, had physical measurements taken, and provided biological samples. The entire process was guided by uniformly trained investigators and qualified physicians. The study design, survey methods, quality control strategies, and limitations of CMEC have been reported elsewhere.[15,16] The CMEC received ethical approval (K2016038 and K2020022) from the Sichuan University Medical Ethical Review Board, and all participants provided written informed consent.

Assessment of $PM_{2.5}$ and its constituents

Estimates of the monthly total mass of $PM_{2.5}$ and its five major constituents (black carbon [BC], organic matter [OM], sulfate, nitrate, and ammonium) were obtained from the V4.CH.02 product developed by the Dalhousie University Atmospheric Composition Analysis Group.[17] The V4.CH.02 product methodology for datasets used in this study was described before. Briefly, the monthly total mass of $PM_{2.5}$ at 10 km × 10 km resolution was simulated by the Goddard Earth Observing System chemical transport model, which incorporated the aerosol optical depth retrievals from several satellite instruments and then calibrated with ground-based observations from China meteorological monitoring stations.[17] Further, concentrations of five major $PM_{2.5}$ chemical constituents were estimated through simulated relative contributions of each constituent against the total mass of $PM_{2.5}$.

For this study, the total mass of $PM_{2.5}$ and the annual concentrations of its five chemical constituents' before the baseline survey of each CMEC participant was estimated according to the geocoded residential address information. In line with existing studies, we used a 3-year average of total mass $PM_{2.5}$ and its five chemical constituents before the baseline survey as the individual exposures.

Ascertainment of MAFLD cases

According to the definition for MAFLD proposed by an international expert consensus statement, participants were identified as MAFLD cases if they had hepatic steatosis and met at least one of the following three criteria: overweight or obese, type 2 diabetes mellitus (T2DM) or if they were normal weight with evidence of metabolic dysregulation.[18] Hepatic steatosis was detected by abdominal ultrasonography. The presence of overweight or obesity was assessed as body mass index (BMI) ≥23 kg/m^2 (Asian-specific cut-off), where BMI was calculated as weight (kg) divided by height squared (m^2). T2DM was identified as fasting plasma glucose ≥7.0 mmol/L or hemoglobin A1c ≥6.5%. The presence of metabolic dysregulation was assessed as the presence of two or more of the following conditions: 1) a waist circumference ≥90/80 cm in men/women (the cut-off for Asians), 2) blood pressure ≥130/85 mmHg or related drug treatment, 3) triglycerides ≥1.70 mmol/L or related drug treatment, 4) HDL-C <1.0 mmol/L for males and <1.3 mmol/L for females, 5) prediabetes (*i.e.*, fasting glucose levels from 5.6 to 6.9 mmol/L or hemoglobin A1c from 5.7% to 6.4%), 6) homeostasis model assessment of insulin resistance score ≥ 2.5, and 7) plasma high-sensitivity C-reactive protein level >2 mg/L. Considering related variables collected by the CMEC, this study utilized the first five conditions to diagnose patients in the actual diagnosis process based on the accessibility of data.

Potential confounders and model adjustments

Potential confounders were recognized based on known and suspected MAFLD risk factors associated with $PM_{2.5}$ exposure and were summarized in a causal-directed acyclic graph (Fig. S1). Potential confounders included individual demographic, socioeconomic, health behavior variables, and environmental factors. Based on the directed acyclic graph, we adjusted our model for age, sex, highest education level attained, annual household income, ethnicity and admission sites, urban area, smoking status, alcohol consumption, unhealthy diets, physical activity, secondhand smoking exposure, biomass fuel exposure, 3-year average temperature, and 3-year average relative humidity. Detailed definitions of these variables are provided in the supplementary text.

Statistical analysis

We used pollutant-specific logistic regression models to estimate the associations between each $PM_{2.5}$ constituent and MAFLD and calculated the prevalence odds ratio of MAFLD per standard deviation (SD) increase in pollutant concentration to measure the associations. We initially explored the crude association between $PM_{2.5}$ constituents and MAFLD (model 0), then adjusted for baseline factors (age, sex, education level, household income, ethnicity and admission sites, and urban area) in model 1, and

further adjusted for health behaviors (smoking status, alcohol consumption, unhealthy diet, physical activity, second-hand smoking exposure, and biomass fuel exposure) and environmental factors (3-year average temperature and 3-year average relative humidity) in model 2.

We applied a generalized weighted quantile sum (WQS) regression with a logit link function to estimate the association between the $PM_{2.5}$ constituent mixture and MAFLD.[19] The WQS approach simultaneously estimated the weights of each constituent and the coefficient of the $PM_{2.5}$ mixture. The weights reflected the contribution of each constituent to the association and were used to calculate the weighted sum of constituents, often called the WQS index. The coefficient represents the log odds ratio (OR) per 1-unit increase in the WQS index. We adjusted for the same confounders as those in the final pollutant-specific logistic regression models. As suggested by an anonymous reviewer, we also performed a sensitivity analysis with additional adjustments for central obesity and diabetes mellitus.

To explore whether potential factors would modify the associations, we conducted subgroup analyses by sex (male and female), age group (categorized as ≥65 *vs.* <65 years), smoking status (never, current smoker, and previous smoker), alcohol consumption (never, low/moderate, and high), the presence of high-fat diet, the presence of central obesity, and the presence of diabetes mellitus. We carried out sensitivity analyses to test the robustness of the findings to different exposure windows (2- and 4-year average concentration), different target populations (additionally excluding participants with self-reported pregnancy, cancer, or tuberculosis and those in Lhasa, Tibet because of low variability of ambient air pollutant owing to high altitude – approximately 3,650 m) and alternative model adjustment (further adjusted for family history of hypertension and diabetes). To evaluate the effects of $PM_{2.5}$ and its constituents on the severity of MAFLD, we fitted generalized linear regression models with the same confounders as in model 2 in the context of the degree of liver fibrosis and the degree of metabolic disorders, respectively. The degree of liver fibrosis was evaluated by non-invasive test indices (*i.e.*, APRI [aspartate aminotransferase-to-platelet ratio], FIB-4 [fibrosis-4], and Forns index); the severity of metabolic disorders was assessed according to the number of major metabolic disorders (0 to 6). Detailed definitions were described in the supplementary text.

Further, the observations with missing data were excluded if the missing ratio was less than 5% or imputed by the multivariate imputation method if the missing ratio was between 5% and 10%. The results from model 2 with imputed data were compared with the complete case analyses in the supplementary file.

All analyses were performed on complete case data using R version 4.1.0. This study has been reported per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline and the corresponding checklist is shown in Table S1.[20]

Results

We included 80,201 participants from the CMEC who had the same fixed available address for more than 3 years and for whom MAFLD had been reliably diagnosed or ruled out. Of these, 4.29% of the eligible population were excluded (31 with cirrhosis and 3,443 with data missing on key covariates and potential modifiers), leaving 76,727 participants for analysis. The general characteristics of the participants for analysis are shown in Table 1. Of the 76,727 participants used for analysis, 46,296 (60%) were women; the mean (SD) age was 51.97 (11.53) years. There were 15,216 (19.8%) cases of MAFLD, of which 12,767 (83.9%) had central obesity and 3,689 (24.2%) had diabetes. The distributions of $PM_{2.5}$ and its constituents are shown in Fig. 1. Based on the participants' residential addresses, the mean (SD) 3-year concentrations of $PM_{2.5}$, BC, ammonium, nitrate, OM, and sulfate were 36.39 (21.79), 1.88 (1.14), 5.75 (3.52), 7.23 (5.66), 8.20 (5.05) and 9.78 (5.10) $\mu g/m^3$, respectively.

The pollutant-specific logistic regression models showed that $PM_{2.5}$ mass and its constituents are both associated with MAFLD (Table 2). Higher concentrations of both $PM_{2.5}$ and its constituents were associated with a statistically significantly higher prevalence of MAFLD. For the fully adjusted model, a per-SD increase in the 3-year average $PM_{2.5}$ mass concentration was positively associated with MAFLD (OR 1.480; 95% CI 1.366-1.605), and per-SD increases in the 3-year average BC (1.426, 1.323-1.538), OM (1.294, 1.196-1.401), ammonium (1.561, 1.440-1.692), sulfate (1.618, 1.501-1.744) and nitrate (1.368, 1.262-1.482) concentrations were also positively associated with MAFLD.

The WQS logistic regression models showed that the WQS index of the mixed constituents was positively associated with MAFLD risk (OR 1.490, 95% CI 1.360- 1.632). In the pollutant-mixture, nitrate, sulfate, BC, OM, and ammonium weight estimations were 0.670, 0.192, 0.064, 0.038, and 0.036, respectively (Fig. 2).

Subgroup analyses showed consistent positive associations of $PM_{2.5}$ and its constituents with MAFLD across different subgroups (Fig. 3). Certain subgroups of people are more susceptible to $PM_{2.5}$ and its constituents, including males, older adults (≥65 years-old), current smokers, and those who consume a high-fat diet. For example, the ORs of nitrate (1.506, 1.344-1.688), sulfate (1.897, 1.700-2.116), ammonium (1.794, 1.598-2.015), BC (1.632, 1.464-1.818) and OM (1.389, 1.242-1.555) were higher in males (Tables S2–S6).

Sensitivity analyses further validated the reliability of the primary findings. After additionally adjusting for central obesity and diabetes mellitus, the OR of MAFLD associated with joint exposure to $PM_{2.5}$ constituents was 1.780 (1.614–1.963) (Table S7). Sensitivity analyses suggested similar results of estimated ORs of MAFLD for $PM_{2.5}$ and its constituents when changing the exposure-window to 2-year or 4-year concentrations (Table S8). Little change in results occurs when additionally excluding participants with self-reported pregnancy, cancer, or tuberculosis and those from Lhasa (Tables S9–S11). The ORs for $PM_{2.5}$ and its constituents are slightly lower when additionally adjusted for a family history of hypertension and diabetes mellitus (Table S12). The concentration-response relationships of the 3-year average pollutant and MAFLD suggest that these relationships are approximately linear (Fig. S2). As for the association of $PM_{2.5}$ constituents and the severity of MAFLD, we observed significant positive associations of most $PM_{2.5}$ constituents with the severity of liver fibrosis (Table S13) and slightly positive (but not significant) associations with the number of metabolic disorders (Table S14). This lack of significance could be explained by the fact that fewer people had more severe metabolic disorders (Table S15), so the sample size was insufficient to explore this association.

Table 1. Characteristics of the participants according to the presence of MAFLD.

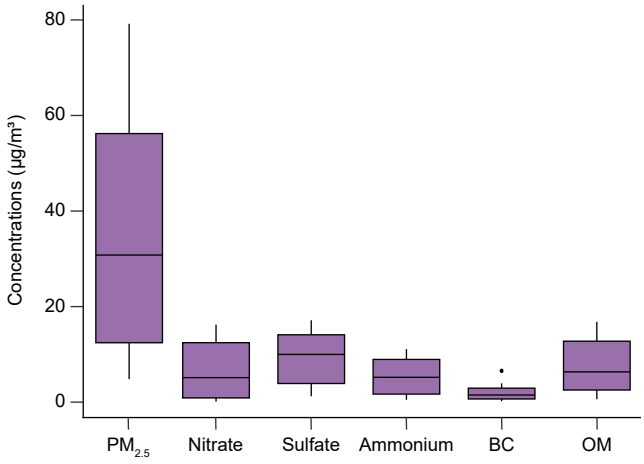
Variable[a]	Overall (N = 76,727)	MAFLD	
		No, n = 61,511	Yes, n = 15,216
Demographics			
Age, years	51.97±11.53	51.79±11.69	52.69±10.79
Sex			
Male	30,431 (39.7%)	23,292 (37.9%)	7,139 (46.9%)
Female	46,296 (60.3%)	38,219 (62.1%)	8,077 (53.1%)
BMI, kg/m^2	24.10±3.42	23.35±3.07	27.11±3.06
Waist-to-hip ratio	0.88±0.07	0.87±0.07	0.93±0.06
Han ethnicity	46,212 (60.2%)	36,368 (59.1%)	9,844 (64.7%)
Urban area			
Urban	38,478 (50.1%)	29,662 (48.2%)	8,816 (57.9%)
Rural	38,249 (49.9%)	31,849 (51.8%)	6,400 (42.1%)
Education level			
Elementary school or below	38,816 (50.6%)	31,472 (51.2%)	7,344 (48.3%)
Middle or high school	29,315 (38.2%)	23,269 (37.8%)	6,046 (39.7%)
College or above	8,596 (11.2%)	6,770 (11.0%)	1,826 (12.0%)
Annual household income, ¥			
<2,0000	27,255 (35.5%)	22,303 (36.3%)	4,952 (32.5%)
2,0000-199,999	39,094 (51.0%)	31,265 (50.8%)	7,829 (51.5%)
≧200,000	10,378 (13.5%)	7,943 (12.9%)	2,435 (16.0%)
Lifestyle behaviors			
Smoking Status			
Never smoker	56,928 (74.2%)	46,234 (75.2%)	10,694 (70.3%)
Current smoker	15,896 (20.7%)	12,374 (20.1%)	3,522 (23.1%)
Previous smoker	3,903 (5.1%)	2,903 (4.7%)	1,000 (6.6%)
Second-hand smoking exposure	38,510 (50.2%)	30,870 (50.2%)	7,640 (50.2%)
Alcohol consumption			
Never	43,209 (56.3%)	35,055 (57.0%)	8,154 (53.6%)
Low or Moderate[b]	25,703 (33.5%)	20,342 (33.1%)	5,361 (35.2%)
High[b]	7,815 (10.2%)	6,114 (9.9%)	1,701 (11.2%)
Total energy intake, kcal/day	1,644.38±607.05	1,630.78±602.38	1,699.32±622.58
High-fat diet[c]	42,512 (55.4%)	33,828 (55.0%)	8,684 (57.1%)
Low fruit or vegetable intake[d]	26,992 (35.2%)	21,612 (35.1%)	5,380 (35.4%)
Physical activity			
Low	46,453 (60.5%)	37,784 (61.4%)	8,669 (57.0%)
Moderate	4,798 (6.3%)	3,788 (6.2%)	1,010 (6.6%)
High	25,476 (33.2%)	19,939 (32.4%)	5,537 (36.4%)
Biomass fuel exposure			
Light	12,104 (15.8%)	9,680 (15.7%)	2,424 (15.9%)
Moderate	60,676 (79.1%)	48,480 (78.8%)	12,196 (80.2%)
Heavy	3,947 (5.1%)	3,351 (5.4%)	596 (3.9%)
Clinical characteristics			
Central obesity[e]	44,483 (58.0%)	31,716 (51.6%)	12,767 (83.9%)
Diabetes mellitus	8,575 (11.2%)	4,886 (7.9%)	3,689 (24.2%)
Family history of hypertension	24,480 (31.9%)	18,969 (30.8%)	5,511 (36.2%)
Family history of diabetes mellitus	8,294 (10.8%)	5,942 (9.7%)	2,352 (15.5%)

MAFLD, metabolic dysfunction-associated fatty liver disease; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter.
[a] Mean ± SD or n (%) were used to present descriptive analysis of the data for continuous and categorical variables, respectively; differences between MAFLD and non-MAFLD participants were examined with *t* test (for continuous variables) and Chi-squared test (for categorical variables).
[b] Low/moderate alcohol consumption was defined as consuming ≤20 g/day of alcohol for women or ≤30 g/day for men; high alcohol consumption was defined as consuming >20 g/day of alcohol for women or >30 g/day for men.
[c] High-fat diet was defined as consuming fat ≥75 g/day.
[d] Low fruit or vegetable intake was defined daily fruit and vegetable intake <500 g.
[e] Central obesity was defined as a waist-to-hip ratio of 0.85 or higher for women and 0.9 or higher for men.

Discussion

As previously mentioned, ambient $PM_{2.5}$ is a mixture of various chemical constituents. Identifying the toxic agents in $PM_{2.5}$ and quantifying each constituent's effect on the health outcome of interest would be valuable.[11] Although a few studies have reported the associations between $PM_{2.5}$ mass and the risk of liver diseases,[5,21–23] it is unclear which constituent of $PM_{2.5}$ contributes the most to MAFLD. Based on a large-scale multi-ethnic epidemiological survey in southwest China, this study of 80,201 individuals investigated the association between MAFLD and long-term exposure to $PM_{2.5}$ chemical constituents (BC, OM, sulfate, nitrate, and ammonium).

We found that increased concentrations of nitrate, sulfate, and possibly BC, were associated with an increased risk of MAFLD using either the pollutant-specific or joint analyses strategies. Our findings were robust when adjusting for an extended set of covariates. Our findings suggested that males were more susceptible to associations between MAFLD and its major chemical constituents, and nitrate may play the most considerable role in increasing MAFLD risk. These robust findings



	$PM_{2.5}$	Nitrate	Sulfate	Ammonium	BC	OM
Min	4.817	0.117	1.236	0.494	0.203	0.603
Max	79.194	16.219	17.136	11.106	6.553	16.817
Mean	36.389	7.229	9.782	5.753	1.885	8.203
IQR	43.786	11.561	10.203	7.261	2.267	10.222

Fig. 1. Distribution of the 3-year average concentrations of $PM_{2.5}$ mass and its major chemical constituents at the residences of CMEC participants. BC, black carbon; OM, organic matter; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter.

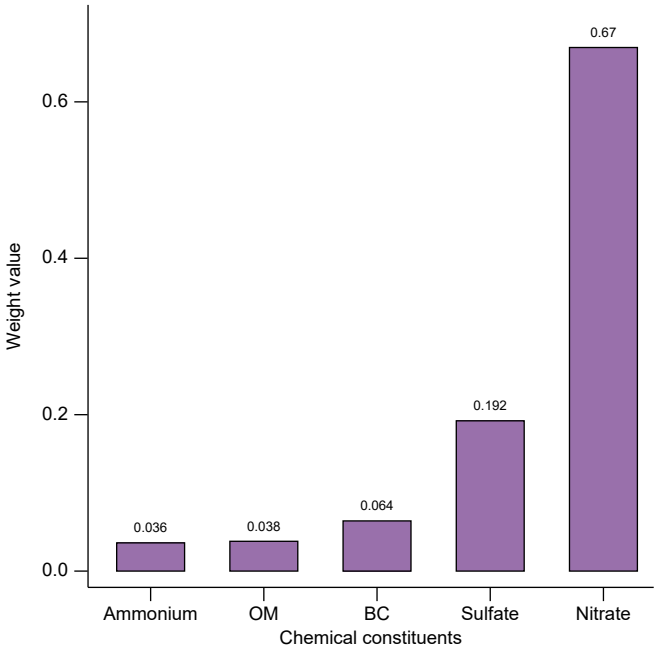


Fig. 2. Weight of each constituent in the association between $PM_{2.5}$ joint exposure and MAFLD by weighted quantile sum regression. Weighted quantile sum regression model was adjusted for age, sex, ethnicity and admission sites, urban area, education level, annal household income, alcohol consumption, smoke status, high-fat diet, low fruit and vegetable intake, physical activity, second-hand smoking exposure, biomass fuel exposure, 3-year average temperature and 3-year average humidity. BC, black carbon; MAFLD, metabolic dysfunction-related fatty liver disease; OM, organic matter; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter.

contribute to the development of evidence-based clinical approaches for assessing ambient particulate pollution risk, identifying vulnerable individuals, and providing interventions.[24,25]

Given the paucity of studies on $PM_{2.5}$ constituents and MAFLD, we interpret the results of this paper with reference to the available evidence on $PM_{2.5}$ constituents and metabolic disorders or metabolic diseases.

Regarding $PM_{2.5}$ mass, we estimated that each SD increase in $PM_{2.5}$ may give rise to an OR of 1.480 (95% CI 1.366-1.605). This finding is broadly consistent with previous epidemiologic studies investigating the association of ambient $PM_{2.5}$ with either MAFLD or NAFLD.[5–7,23] Besides, numerous studies have found positive associations between the mass concentrations of $PM_{2.5}$ and increased incidences of metabolic disorders or diseases.[26–30] For example, a study of middle-aged and elderly Chinese adults found that an IQR increase in $PM_{2.5}$ was related to higher odds of MetS (OR 1.39, 95% CI 1.11-1.75).[13] Our findings are consistent with recent literature demonstrating an increased risk of metabolic disorders or diseases (including MAFLD) associated with long-term exposure to $PM_{2.5}$.

The pollutant-specific analysis indicated that the five $PM_{2.5}$ constituents were all positively associated with MAFLD, with sulfate having the highest effect (OR 1.618, 1.501–1.744). Further, the joint exposure analysis found that the effect of the five-constituent mixture is similar to $PM_{2.5}$ mass, and nitrate (67.0%) contributed most to the association of MAFLD with the five-constituent mixture, followed by sulfate (19.2%). Our findings point to the need to better control the sources of particulate matter as targets for risk prevention. Typically, nitrate particles are formed by the oxidation of nitrogen oxides emitted from vehicles and other combustion sources;[31] sulfate particles are formed by the oxidation of gaseous sulfur dioxide emitted from coal or oil burning; OM and BC may predominantly result from vehicle emissions, coal combustion, and biomass burning;[32,33] and ammonium is related to the concentration of ammonia, which is dominated by agriculture activities.[34] To our knowledge, this is the first epidemiologic study that evaluates the health effect of $PM_{2.5}$ constituents on MAFLD and quantifies the relative contributions of these constituents.

Table 2. Odds ratio (95% CIs) of MAFLD associated with each SD increase in 3-year exposure to $PM_{2.5}$ and its major chemical constituents.

	Model 0	Model 1	Model 2
$PM_{2.5}$	1.141 (1.121–1.161)	1.133 (1.053–1.219)	1.480 (1.366–1.605)
Black carbon	1.152 (1.132–1.173)	1.130 (1.055–1.210)	1.426 (1.323–1.538)
Organic matter	1.135 (1.115–1.155)	1.018 (0.948–1.093)	1.294 (1.196–1.401)
Ammonium	1.139 (1.118–1.159)	1.236 (1.147–1.332)	1.561 (1.440–1.692)
Sulfate	1.137 (1.116–1.157)	1.367 (1.272–1.469)	1.618 (1.501–1.744)
Nitrate	1.138 (1.118–1.158)	1.059 (0.986–1.139)	1.368 (1.262–1.482)

MAFLD, metabolic dysfunction-associated fatty liver disease; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter; SD, standard deviation.
Model 0: unadjusted.
Model 1: adjusted for age, sex, ethnicity and admission sites, urban area, education level, annal household income.
Model 2: additionally adjusted for alcohol consumption, smoke status, high-fat diet, low fruit and vegetable intake, physical activity, second-hand smoking exposure, biomass fuel exposure, 3-year average temperature and 3-year average humidity.

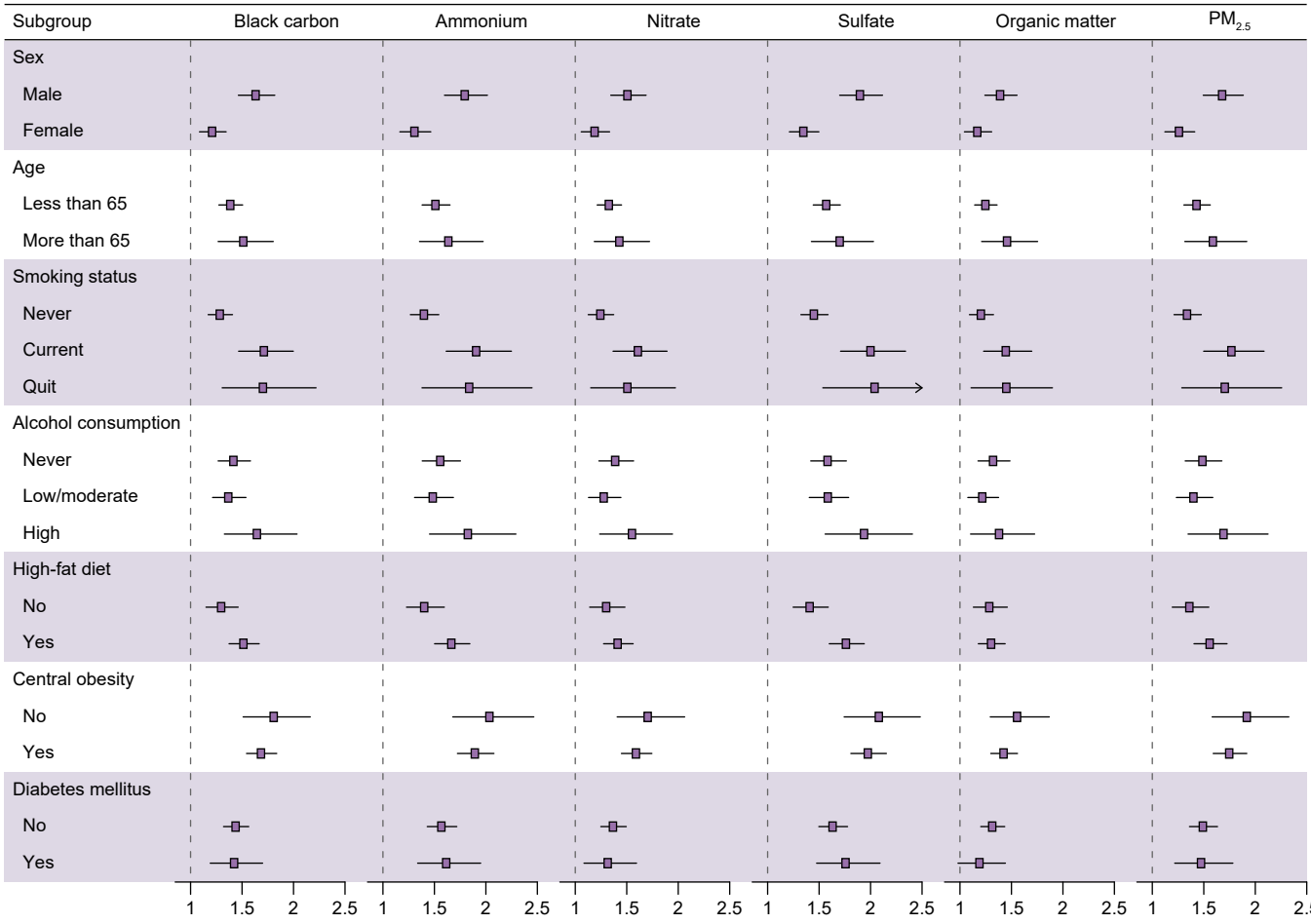


Fig. 3. Odds ratio (95% CIs) of MAFLD associated with each SD increase in 3-year exposure to $PM_{2.5}$ and its five components stratified by demographic and lifestyle factors. $PM_{2.5}$, particulate matter 2.5 μm or less in diameter.

Our epidemiologic findings are consistent with previous mechanistic evidence that linked ambient $PM_{2.5}$ to the liver. Key biological mechanisms that explain the metabolic effects of $PM_{2.5}$ on the liver include oxidative stress, inflammatory responses, and fibrosis.[8,35–38] Human and animal studies have shown that $PM_{2.5}$ exposure may alter the plasma lipidome and hepatic lipid metabolism,[39,40] which further promotes systemic and hepatic inflammation.[38] $PM_{2.5}$ may also impair oxidative homeostasis and induce oxidative injury, further activating hepatic stellate cells.[41] In addition, after long-term exposure, $PM_{2.5}$ particles will accumulate in Kupffer cells and trigger inflammation and hepatic stellate cell collagen synthesis.[42]

Inorganic compounds, such as particulate sulfate, nitrate, and ammonium, make up a large fraction of ambient $PM_{2.5}$. Nitrate and sulfate in particulate matter are mainly produced as a secondary aerosol by oxidizing sulfur dioxide (SO_2) and nitrogen oxides (NO_x). Two population-level studies separately found that exposure to sulfate could affect levels of IL1β, IL5, IL7, IL12, and IFN-γ and increase the risk of MetS, suggesting that sulfate affects systemic inflammation and metabolic diseases.[13,43] However, evidence on nitrate and metabolic disorders or diseases is inconsistent. A study in children and adolescents found that nitrate may increase the risk of several metabolic disorders, including MetS, central obesity, and high blood pressure,[44] but similar results were not observed in middle-aged and elderly adults.[13] Previous epidemiologic studies on particulate ammonium and metabolic disorders or diseases are inconsistent.[12,13] The underlying biological mechanisms by which inorganic particulate compounds affect metabolic health remain to be further explored by future studies.

As for carbon species, BC and OM were positively associated with MAFLD. Several epidemiologic studies have demonstrated associations between exposure to carbon species and metabolic diseases or other biomarkers. For instance, a longitudinal study found that exposure to BC was associated with increased risks of total cardiovascular disease and hypertension in Chinese adults.[45] Also, organic carbon was positively associated with cytokines, including IL8 and MIP-1β, indicating that organic compounds may induce systemic inflammation.[43]

Generally stronger positive associations were also observed for all constituents in males, for most of the constituents in smokers, and for sulfate and ammonium in participants with a high-fat diet. Previous studies reported favorable gene expression in females in response to long-term exposure to air pollution, while sex hormone levels may be associated with differential effects of air pollution.[46] In addition, smoking is generally considered a risk factor for metabolic diseases. Our findings indicate that smoking and $PM_{2.5}$ and most of its constituents may have additional effects on the risk of MAFLD. A high-fat diet may lead to obesity, bringing higher metabolism-related risks. This study found that, in people on a high-fat diet, sulfate and ammonium were more strongly positively

associated with MAFLD, similar to other studies' findings. However, this study did not find statistically significant heterogeneity in the effect of sulfate and ammonium on the presence of central obesity and diabetes. More studies are required to validate the mechanisms underlying these associations.

No matter the concentration, ambient air pollution will threaten people's health and bring a heavy disease burden to society, considering its ubiquitous existence and the large number of people affected. Therefore, interventions to reduce the harmful health impacts of $PM_{2.5}$ and its constituents are critical. The findings of this study could help the government develop more targeted air pollution regulations, promote the development of individual precise protective equipment, and also inspire physicians to protect susceptible patients in MAFLD-related clinical practice.

This study benefits from the large-scale population sizes (76,727 participants included) of CMEC and the wide range of ambient $PM_{2.5}$ concentrations in southwest China. The CMEC was conducted with well-established standard operating procedures and rigorous quality control measures, which were reported elsewhere.[15,16] Also, the exposure data were simulated using the same method used in the assessment of ambient air pollution for the Global Burden of Disease study, which has been shown to have minor errors.[17,47] Further strengths are the WQS method to evaluate the association of joint exposure to $PM_{2.5}$ constituents with MAFLD. WQS can estimate the weights of each constituent and their joint effect simultaneously; thus, it gives easy-to-understand results to guide the control of the most harmful particulate constituents. Evidence on the positive associations of $PM_{2.5}$ and its constituents with liver fibrosis indices and MAFLD phenotypes also strengthened this work.

Nevertheless, we also acknowledge several limitations. First, there may be some risk of exposure misclassification because pollution exposures were matched to the participant's most recent residential address without considering individual mobility. In addition, as a cross-sectional study, our study evaluated pollution exposures during a prespecified period of 3 years before baseline enrollment but did not allow us to examine associations with the progression of MAFLD. Longitudinal analyses using MAFLD measurements from follow-up surveys will provide better evidence of the relationship between long-term exposure to $PM_{2.5}$ constituents and MAFLD. Last, future work should consider the source apportion of $PM_{2.5}$ constituents to provide stricter regulation of the human sources of emissions that form these constituents.

To our knowledge, this study is the first large-scale epidemiologic study exploring the associations between $PM_{2.5}$ constituents and MAFLD. We observed positive associations between a mixture of $PM_{2.5}$ chemical constituents and MAFLD and quantified specific weights of individual chemical constituents on MAFLD using WQS regression methods. This research indicates that particulate nitrate and sulfate of $PM_{2.5}$ play major harmful roles on MAFLD and thus should be paid more attention. Moves to mitigate these ambient chemical constituents might bring greater benefits to public health. This study also suggests that males and smokers were more susceptible to the association between $PM_{2.5}$ constituents and MAFLD.

Abbreviations

BC, black carbon; CMEC, China Multi-Ethnic Cohort; MAFLD, metabolic dysfunction-associated fatty liver disease; MetS, metabolic syndrome; OM, organic matter; OR, odds ratio; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter; SD, standard deviation; T2DM, type 2 diabetes mellitus; WQS, weighted quantile sum.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Yin J. and Zhao X. served as co-senior authors. Concept and design: Guo B., Huang S., Li S., and Zhao X. Acquisition of data: Zhao X., Yin J., Lin H., Li Y., Qin Z., Jiang X., Wang Z., Pan Y., Li S., and Guo B. Analysis or interpretation of data: Guo B., Huang S., Li S., Han X., Lin H., and Zhao X. Drafting of the manuscript: Guo B., Huang S., and Li S. Critical revision of the manuscript for important intellectual content: Guo B., Huang S., Zhang J., and Zhao X. Statistical analysis: Huang S. and Guo B. Obtained funding: Guo B., Zhao X., and Zhang J. Administrative, technical, or material support: Guo B., Huang S., Han X., Lin H., Li Y., Qin Z., Jiang X., and Wang Z. Supervision: Zhao X., Yin J., and Zhang J.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100912.

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Author names in bold designate shared co-first authorship

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