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ORIGINAL RESEARCH

Associations of Long-Term Exposure to Fine Particulate Constituents With Cardiovascular Diseases and Underlying Metabolic Mediations: A Prospective Population-Based Cohort in Southwest China

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BACKGROUND: The health effects of particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) might differ depending on compositional variations. Little is known about the joint effect of $PM_{2.5}$ constituents on metabolic syndrome and cardiovascular disease (CVD). This study aims to evaluate the combined associations of $PM_{2.5}$ components with CVD, identify the most detrimental constituent, and further quantify the mediation effect of metabolic syndrome.

METHODS AND RESULTS: A total of 14 427 adults were included in a cohort study in Sichuan, China, and were followed to obtain the diagnosis of CVD until 2021. Metabolic syndrome was defined by the simultaneous occurrence of multiple metabolic disorders measured at baseline. The concentrations of $PM_{2.5}$ chemical constituents within a 1-km^2 grid were derived based on satellite- and ground-based detection methods. Cox proportional hazard models showed that black carbon, organic matter (OM), nitrate, ammonium, chloride, and sulfate were positively associated with CVD risks, with hazard ratios (HRs) ranging from 1.24 to 2.11 (all $P<0.05$). Quantile g-computation showed positive associations with 4 types of CVD risks (HRs ranging from 1.48 to 2.25, all $P<0.05$). OM and chloride had maximum weights for CVD risks. Causal mediation analysis showed that the positive association of OM with total CVD was mediated by metabolic syndrome, with a mediation proportion of 1.3% (all $P<0.05$).

CONCLUSIONS: Long-term exposure to $PM_{2.5}$ chemical constituents is positively associated with CVD risks. OM and chloride appear to play the most responsible role in the positive associations between $PM_{2.5}$ and CVD. OM is probably associated with CVD through metabolic-related pathways.

Key Words: cardiovascular disease ■ fine particulate matter constituents ■ mediation analysis ■ metabolic syndrome ■ multiple exposure analysis

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CLINICAL PERSPECTIVE

What Is New?

- Specific particulate matter with an aerodynamic diameter ≤2.5 μm chemical constituents are key drivers of the associations between long-term exposure to fine particulate matter and the risk of developing cardiovascular disease.
- Metabolic syndrome and its components underpin these associations, especially obesity, raised triglycerides, and blood pressure.

What Are the Clinical Implications?

- Controlling specific constituents such as organic matter may be essential for preventing incident cardiovascular disease.
- Interventions for metabolic risk factors such as obesity, triglycerides, and blood pressure could provide additional benefits in lowering incident cardiovascular disease risks associated with fine particulate matter.

Nonstandard Abbreviations and Acronyms

BC	black carbon
CAR	cardiac arrest
CBVD	cerebrovascular disease
CHAP	ChinaHighAirPollutants
Cl^-	chloride
CMEC	China Multi-Ethnic Cohort
DASH	Dietary Approaches to Stop Hypertension
IHD	ischemic heart disease
MetS	metabolic syndrome
NH_4^+	ammonium
NO_3^-	nitrate
OM	organic matter
PAH	polycyclic aromatic hydrocarbon
$PM_{2.5}$	particulate matter with an aerodynamic diameter ≤2.5 μm
QGC	quantile g-computation
SO_4^{2-}	sulfate

Cardiovascular disease (CVD) remains a predominant threat to public health, being the leading cause of mortality.[1] In 2019, ischemic heart disease (IHD) accounted for an aggregate of 182 million disability-adjusted life-years, while for stroke it was 143 million.[2] As a ubiquitous risk factor, ambient air pollution contributes heavily to the CVD-related disease burden for the entire population.[3,4] Recent research indicates that disease burden attributed to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) has notably shifted from developed to developing countries.[2] Therefore, research on $PM_{2.5}$-related topics to combat CVD is both necessary and urgent.

The composition of $PM_{2.5}$ encompasses a range of chemical constituents. These include black carbon (BC), organic matter (OM), nitrate (NO_3^-), chloride (Cl^-), sulfate (SO_4^{2-}), and ammonium (NH_4^+), among others.[5] While the $PM_{2.5}$ concentration, known as $PM_{2.5}$ mass, is undeniably important, the chemical constituents of $PM_{2.5}$ are of greater significance. This is because the composition can differ depending on the environment in which one resides, which, in turn, can cause varying health effects of $PM_{2.5}$.[6] Most of the current studies focusing on $PM_{2.5}$ and CVD have used $PM_{2.5}$ mass concentration as exposure. However, the toxicity and underlying mechanisms associated with the chemical components of $PM_{2.5}$ remain to be fully understood.[7] In addition, given that multiple chemical constituents coexisted in $PM_{2.5}$, exposure to $PM_{2.5}$ essentially equates to simultaneous exposure to these various constituents. Hence, it is reasonable to evaluate the joint associations between these constituents and CVD risks and determine the most detrimental one. However, current research used each $PM_{2.5}$ constituent as a single exposure,[8] and more evidence on joint exposure is required.

Further, based on existing research, it is theorized that metabolic disorders mediate the health impacts of $PM_{2.5}$ on CVD.[5,9,10] Specifically, the mechanisms of $PM_{2.5}$ on CVD have involved endothelial damage, vascular dysfunction, and thrombosis. Especially under long-term exposure, these changes may accumulate and not be resolved, leading to metabolic disorders, possibly metabolic syndrome (MetS), and even CVD events.[5] However, detailed epidemiological evidence about $PM_{2.5}$ chemical constituents on this topic remains lacking. Quantifying the mediation effect of MetS in these associations and further identifying the most responsible constituent to CVD could help clinicians refine treatment schedules and the public mitigate specific polluted sources.

Therefore, this study used a prospective population-based cohort to: (1) evaluate associations between $PM_{2.5}$ chemical constituents and CVD and identify which constituents contribute most to the association with CVD risk; and (2) explore the potential mediated roles of MetS in the association between the most contributable constituent and CVD risk. Research efforts focused on uncovering the potential mechanisms linking $PM_{2.5}$ chemical constituents to CVD could shed new light on cardioprotective action for reducing air pollution risk.

METHODS

Study Design and Participants

The data that support the findings of this study are available on reasonable request to the corresponding author. In this study, we collected data from a subcohort of CMEC (China Multi-Ethnic Cohort) in Sichuan, China. Sichuan is a representative province in Southwest China, with an approximate permanent population of 84 million. Briefly, the cohort included 21 592 adults of Han ethnicity aged 30 to 79 years in 2018. Baseline data for this study were gathered by a team of well-trained researchers and medical technicians. This collection process included face-to-face interviews using electronic questionnaires, medical examinations, and clinical laboratory tests. All participants signed informed consent forms before enrollment. Detailed information on this cohort is described in Data S1.[11] Ethical approval for the study was granted by the Sichuan University's medical ethical review board (K2016038 and K2020022).

The data on CVD histories during the follow-up period from 2018 to 2021 were sourced from the hospital surveillance system of Sichuan Province. CVD diagnoses were conducted by local physicians and formally recorded in the system based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*). The outcomes in this study were defined by incident CVD-related *ICD-10* codes (Table S1). In summary, we included 4 types of CVD outcomes in the analysis: (1) total CVD, (2) IHD, (3) cardiac arrests (CARs), (4) cerebrovascular disease (CBVD). To ensure the integrity and validity of the study, we excluded: (1) participants who had resided in their present location for no more than 3 years at baseline; (2) participants who were diagnosed with CVD or cancer before baseline; and (3) participants with missing information on covariate data. Finally, 14 427 adults were included in this study (Figure S1).

Exposure Assessment

Annual concentration data for $PM_{2.5}$ chemical constituents, including BC, OM, NO_3^-, NH_4^+, Cl^-, and SO_4^{2-}, were collected from the ChinaHighAirPollutants (CHAP) database, which was apportioned from the satellite-derived 1-km $PM_{2.5}$ product[12,13] at a high spatial resolution of 0.01°×0.01°, integrating a large density of ground-based measurements of $PM_{2.5}$ components, chemical-model simulations of components, meteorology reanalysis, land use information, pollution emissions, and other spatial and temporal predictors.[14] A developed deep-learning spatiotemporal deep forest model was used for the apportion, and the cross-validation illustrates high data quality with high correlations of 0.93 to 0.95 and root mean squared error of 0.5 to 1.8 μg/m^3 on an annual basis. Based on the geocoded address, the 3-year average concentrations of $PM_{2.5}$ chemical constituents before baseline were assigned to each participant as the exposure surrogates.

Mediators

In this study, mediators were considered as MetS and its 5 components at baseline. Based on previously published criteria and recommendation,[15–17] MetS was defined using a modified definition to suit Chinese people as obesity,[18] which includes central obesity (waist circumference ≥90 cm for Chinese men and ≥85 cm for Chinese women) and peripheral obesity (body mass index ≥28 kg/m^3 for Chinese people), along with any combination of 2 of the 4 factors as follow: (1) raised triglycerides: ≥1.7 mmol/L; (2) reduced high-density lipoprotein: <1.03 mmol/L in men and <1.29 mmol/L in women, or self-reported prior diagnosed hyperlipidemia; (3) raised blood pressure (BP): systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg, or self-reported prior diagnosed hypertension; and (4) impaired fasting glucose: fasting plasma glucose ≥5.6 mmol/L, hemoglobin A_{1c} ≥5.7% (39 mmol/mol), or self-reported prior diagnosed diabetes. Considering the overlapping periods between the baseline survey and outcome assessment, we have ensured the MetS occurred before the CVD occurrence during the data linkage stage.

Statistical Analysis

Participants' demographic characteristics were assessed using χ^2 and t tests by total CVD status. We used the Spearman correlation coefficient to evaluate correlations among $PM_{2.5}$ chemical constituents. Cox proportional hazard models were used to evaluate the hazard ratio (HR) along with its 95% CI for the associations between $PM_{2.5}$ chemical constituents and both CVD and its subtypes. In this section, all associations were assessed by a strategy of gradually adding covariates to the model. In model 1, the initial models were adjusted for age and sex. Model 2 additionally adjusted for education, annual household income, marital status, urbanicity, family history of hypertension, and body mass index. Model 3 further adjusted for smoke, second-hand smoke, alcohol, indoor air pollution, physical activity,[19] the Dietary Approaches to Stop Hypertension (DASH) score,[20] and 3-year average temperature. Model 4 additionally adjusted for hypertension and diabetes. Details of each covariate are presented in Data S1. The directed acyclic graphs (R package "dagitty") are shown in Figure S2. Further, associations between $PM_{2.5}$ chemical constituents and MetS and its components were assessed by logistic

regression. All models were adjusted for the same covariates in model 4.

For multiple exposure analysis, quantile g-computation (QGC) was applied by the R package "qgcomp." We used this approach to evaluate the overall associations of constituents on CVD and its subtypes, adjusted for all covariates as mentioned above. As a new method to estimate joint associations of environmental pollutants, the QGC method provided a more flexible estimation.[21] Detailed information and code settings for QGC are shown in Data S1.

In addition, subgroup analyses were performed by using age (<65 years or ≥65 years) and sex (men and women) as potential effect modifiers. We conducted subgroup analyses for the associations in both the single- and multiple-exposure models. Heterogeneity among the different subgroups was assessed using χ^2 tests.

The potential mediation effects of MetS and its components on the associations of contributable constituents (determined by the maximum weight) with CVD risks were estimated by the R package "CMAverse" (version 0.1.0).[22] Mediation models were adjusted for age, sex, education, marital status, annual household income, urbanicity, family history of hypertension, smoke, second-hand smoke, alcohol, indoor air pollution, physical activity, DASH score, and 3-year average temperature. This package provides a suitable function for survival data to evaluate the natural direct effect and the natural indirect effect. The 95% CI in mediation analyses was assessed based on bootstrap methods.

Sensitivity analyses were performed by several strategies. First, the Cox proportional hazards assumption was evaluated through the examination of Schoenfeld plots and was satisfied. Second, *E* values were calculated to evaluate the unmeasured confounders (R package "EValue").[23] Third, to ensure robustness, exposure windows were altered using 2-year and 4-year average concentrations of exposures. Fourth, mediation analyses were also applied for the associations of NO_3^-, SO_4^{2-}, NH_4^+, and BC with CVD risks.

In this study, we conducted all analyses using R software (4.1.2) and used STROBE guidelines.[24] In addition, false-discovery rate correction was applied to adjust for multiple tests. Thus, the corrected $P<0.05$ was taken to indicate statistical significance. Detailed information on the false-discovery rate is shown in Data S1.

RESULTS

Table 1 summarizes the baseline characteristics of the participants. Among 14 427 adults, 1837 were diagnosed with CVD, 416 with IHD, 393 with CARs, and 916 with CBVD during 43 895 person-year follow-up (average, 3.04 years). In this study, participants were an average age of 50.3±11.8 years at baseline, and over half were women. The mean DASH score was 20.2 (SD, 4.4), and physical activity was 21.9 metabolic equivalent in hours per day (SD, 15.0 metabolic equivalent in hours per day). Of the participants, 52.9% were secondhand smokers, while 53.3% were drinkers. A total of 2744 adults were diagnosed with MetS at baseline.

Table 2 presents the distributions of pollutants' concentrations. The mean 3-year average concentration of $PM_{2.5}$ was 55.2 μg/m^3 (SD, 5.2 μg/m^3). For constituents, the mean exposure levels ranged from 2.27 μg/m^3 (interquartile range, 0.42 μg/m^3) for Cl^- to 21.60 μg/m^3 (6.60 μg/m^3) for OM. Further, the correlations and spatial distributions of $PM_{2.5}$ chemical constituents are shown in Figures S3 and S4. The correlations among chemical constituents were positive except for Cl^- (r_s=−0.06 for BC, r_s=−0.15 for OM).

Figure and Figure S5 display the associations between ambient $PM_{2.5}$ chemical constituents and CVD risks. We found ambient $PM_{2.5}$ (per interquartile range 8.11 μg/m^3) was positively and significantly associated with total CVD (HR, 1.67 [95% CI, 1.52–1.84]), IHD (HR, 1.26 [95% CI, 1.03–1.54]), CAR (HR, 1.49 [95% CI, 1.21–1.83]), and CBVD (HR, 2.11 [95% CI, 1.82–2.43]). For constituents, NO_3^-, NH_4^+, and BC were associated with all CVD outcomes. On the other hand, OM and SO_4^{2-} showed similar associations with CVD risks when compared with $PM_{2.5}$ mass, except for associations with IHD. In addition, no significant association was found between Cl^- and CAR. In the sensitivity analyses, the associations were not materially changed (Tables S2–S8).

The mixed pollutants derived by QGC models were positively associated with total CVD (HR, 1.79 [95% CI, 1.63–1.97]), IHD (HR, 1.48 [95% CI, 1.21–1.81]), CAR (HR, 1.70 [95% CI, 1.35–2.14]), and CBVD (HR, 2.25 [95% CI, 1.94–2.62]) (Figure). The highest weighted pollutants in QGC models were OM for total CVD and CAR and Cl^- for IHD and CBVD (Figure S6). Sensitivity analyses also show robustness (Table S9).

Figure S7 presents the associations between $PM_{2.5}$ chemical constituents and MetS and its components. We observed significant associations between $PM_{2.5}$ and MetS (odds ratio [OR], 1.37 [95% CI, 1.23–1.53]), as well as specific components such as obesity (OR, 1.48 [95% CI, 1.33–1.65]), raised triglycerides (OR, 1.14 [95% CI, 1.06–1.23]), and raised BP (OR, 1.42 [95% CI, 1.31–1.55]). Among associations of constituents with MetS and its components, NO_3^- showed the highest estimates for MetS (OR, 1.38 [95% CI, 1.26–1.52]) and obesity (OR, 1.54 [95% CI, 1.40–1.68]), whereas Cl^- and OM had the highest estimates for raised triglycerides (OR, 1.17 [95% CI, 1.07–1.28]) and raised BP (OR, 1.48 [95% CI, 1.34–1.64]), respectively. In addition, Cl^- was

Table 1. Baseline Characteristics of Participants by CVD Among CMEC in Sichuan

Characteristic	Total (N=14427)	CVD (n=1837)	No CVD (n=12590)	*P* value*
Age, y	50.29±11.78	58.62±10.99	49.08±11.40	<0.001
Sex, n (%)				0.361
Men	6321 (43.8)	823 (44.8)	5498 (43.7)	
Women	8106 (56.2)	1014 (55.2)	7092 (56.3)	
Education, n (%)				<0.001
No formal school	1607 (11.1)	337 (18.3)	1270 (10.1)	
Primary school	2713 (18.8)	464 (25.3)	2249 (17.9)	
Junior middle school	4674 (32.4)	589 (32.1)	4085 (32.4)	
High school	2619 (18.2)	277 (15.1)	2342 (18.6)	
College or above	2814 (19.5)	170 (9.3)	2644 (21.0)	
Annal household income (CNY), n (%)				<0.001
<12000	1290 (8.9)	224 (12.2)	1066 (8.5)	
12000–19999	1706 (11.8)	252 (13.7)	1454 (11.5)	
20000–59999	5340 (37.0)	711 (38.7)	4629 (36.8)	
60000–99999	2994 (20.8)	388 (21.1)	2606 (20.7)	
≥100000	3097 (21.5)	262 (14.3)	2835 (22.5)	
Marital status, n (%)				<0.001
Married or cohabitating	13119 (90.9)	1643 (89.4)	11476 (91.2)	
Separated or divorced	596 (4.1)	63 (3.4)	533 (4.2)	
Unmarried	164 (1.1)	11 (0.6)	153 (1.2)	
Widowed	548 (3.8)	120 (6.5)	428 (3.4)	
Urbanicity, n (%)				0.829
Rural	6524 (45.2)	835 (45.5)	5689 (45.2)	
Urban	7903 (54.8)	1002 (54.5)	6901 (54.8)	
Hypertension family history, n (%)				0.329
No	5862 (40.6)	755 (41.1)	5107 (40.6)	
Not sure	2727 (18.9)	324 (17.6)	2403 (19.1)	
Yes	5838 (40.5)	758 (41.3)	5080 (40.3)	
Smoke, n (%)				<0.001
Smoking	3674 (25.5)	455 (24.8)	3219 (25.6)	
Quitted	960 (6.7)	191 (10.4)	769 (6.1)	
Never	9793 (67.9)	1191 (64.8)	8602 (68.3)	
Secondhand smoke, n (%)				<0.001
No	6789 (47.1)	945 (51.4)	5844 (46.4)	
Yes	7638 (52.9)	892 (48.6)	6746 (53.6)	
Alcohol, n (%)				<0.001
No	6736 (46.7)	991 (53.9)	5745 (45.6)	
Yes	7691 (53.3)	846 (46.1)	6845 (54.4)	
Indoor air pollution, n (%)				0.005
No	2208 (15.3)	241 (13.1)	1967 (15.6)	
Yes	12219 (84.7)	1596 (86.9)	10623 (84.4)	
Hypertension, n (%)				<0.001
No	12580 (87.2)	1271 (69.2)	11309 (89.8)	
Yes	1847 (12.8)	566 (30.8)	1281 (10.2)	
Diabetes, n (%)				<0.001
No	13646 (94.6)	1636 (89.1)	12010 (95.4)	
Yes	781 (5.4)	201 (10.9)	580 (4.6)	

(*Continued*)

Table 1. Continued

Characteristic	Total (N=14427)	CVD (n=1837)	No CVD (n=12590)	*P* value*
MetS, n (%)				<0.001
No	11683 (81.0)	1288 (70.1)	10395 (82.6)	
Yes	2744 (19.0)	549 (29.9)	2195 (17.4)	
Obesity, n (%)				<0.001
No	10478 (72.6)	1134 (61.7)	9344 (74.2)	
Yes	3949 (27.4)	703 (38.3)	3246 (25.8)	
Raised triglycerides, n (%)				<0.001
No	9464 (65.6)	1065 (58.0)	8399 (66.7)	
Yes	4963 (34.4)	772 (42.0)	4191 (33.3)	
Raised high-density lipoprotein, n (%)				0.586
No	10084 (69.9)	1274 (69.4)	8810 (70.0)	
Yes	4343 (30.1)	563 (30.6)	3780 (30.0)	
Raised BP, n (%)				<0.001
No	8543 (59.2)	662 (36.0)	7881 (62.6)	
Yes	5884 (40.8)	1175 (64.0)	4709 (37.4)	
Impaired fasting glucose, n (%)				<0.001
No	8515 (59.0)	818 (44.5)	7697 (61.1)	
Yes	5912 (41.0)	1019 (55.5)	4893 (38.9)	
BMI	24.24±3.28	24.81±3.25	24.15±3.28	<0.001
Physical activity, MET-h/d	21.92±14.99	18.81±15.16	22.38±14.91	<0.001
DASH score	20.19±4.39	19.95±4.47	20.23±4.38	0.011
Temperature	13.39±1.37	13.45±1.27	13.38±1.38	0.038

Continuous variables are presented as the mean±SD. Categorical variables are presented as numbers (percentages). Differences between cardiovascular disease (CVD) and non-CVD were examined by *t* test (for continuous variables) and χ^2 test (for categorical variables). BMI indicates body mass index; BP, blood pressure; CMEC, China Multi-Ethnic Cohort; CNY, Chinese Yuan; DASH, Dietary Approaches to Stop Hypertension; MET, metabolic equivalent; and MetS, metabolic syndrome.

**P* value corresponds for the comparison of characteristics of patients with CVD vs those without CVD.

negatively associated with raised BP (OR, 0.90 [95% CI, 0.82–0.99]). In the sensitivity analyses, the associations remained robust (Tables S10–S16).

The results of the subgroup analysis are shown in Tables S17 and S18. The heterogeneity tests for the associations between $PM_{2.5}$ mass and CVD in these subgroups were not significant. However, the associations of BC with total CVD (HR, 1.58 [95% CI, 1.39–1.79]) and NO_3^- with CBVD (HR, 1.53 [95% CI, 1.35–1.73]) were stronger in the female group.

Mediation analyses were performed to assess the potential mediating roles of MetS and its components on the associations of OM with total CVD and CAR risks, Cl^- with IHD and CBVD risks, and $PM_{2.5}$ mass with 4 types of CVD risks (Table 3 and Tables S19–S23). MetS mediated the associations between $PM_{2.5}$ mass and total CVD, IHD, and CBVD risks. The mediation proportions for these associations ranged from 0.3% to 1.6%. For constituents, only the association between OM and total CVD risk was significantly

Table 2. Summary Distributions of 3-Year Average Concentrations of $PM_{2.5}$ Chemical Constituents

Variable	Mean	SD	Min	P_{25}	P_{50}	P_{75}	Max
$PM_{2.5}$, μg/m^3	55.23	5.22	26.67	51.60	56.60	59.71	64.41
NO_3^-, μg/m^3	9.18	0.55	3.48	8.81	9.22	9.54	12.62
NH_4^+, μg/m^3	7.32	0.53	3.82	7.18	7.54	7.64	8.58
OM, μg/m^3	21.60	3.38	11.36	18.17	22.18	24.77	27.30
BC, μg/m^3	6.58	0.91	1.56	5.78	6.81	7.29	8.66
Cl^-, μg/m^3	2.27	0.24	0.92	2.07	2.24	2.48	2.85
SO_4^{2-}, μg/m^3	10.66	0.45	7.57	10.48	10.73	11.00	12.19

P_{25}, P_{50}, and P_{75} denotes 25%, 50%, and 75% percentile separately. BC indicates black carbon; Cl^-, chloride; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; and SO_4^{2-}, sulfate.

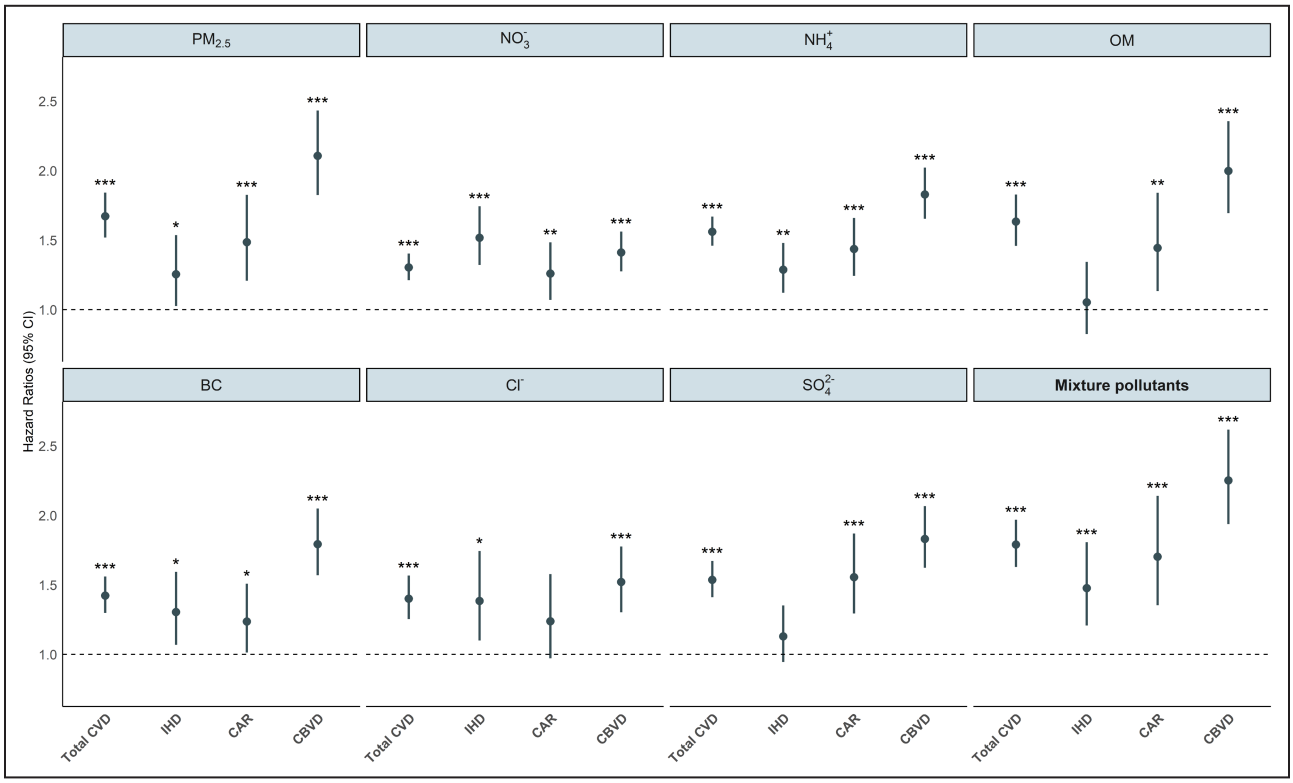

Figure. Hazard ratios with 95% CIs for subcategories of cardiovascular diseases, associated with per interquartile range increase in exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) chemical constituents.
All models were adjusted for age, sex, education, marital status, annual household income, urbanicity, family history of hypertension, body mass index, smoke, second-hand smoke, alcohol, indoor air pollution, physical activity, the Dietary Approaches to Stop Hypertension score, 3-year average temperature, hypertension, and diabetes. BC indicates black carbon; CAR, cardiac arrest; CBVD, cerebrovascular disease; Cl^-, chloride; CVD, cardiovascular disease; IHD, ischemic heart disease; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; and SO_4^{2-}, sulfate. *P<0.05; **P<0.01; ***P<0.001.

mediated by MetS, with a mediation proportion of 1.3%. Further, among the components of MetS, obesity, raised triglycerides, and BP were found to have significant mediation effects in these associations. Because some constituents showed positive associations with CVD risks, we also performed mediation analyses for these constituents (Tables S24–S29). These constituents showed similar results with $PM_{2.5}$. Further, results remain robust in the sensitivity analysis (Tables S30–S35).

Table 3. Estimated NDE, NIE, and Corresponding 95% CI of the Association Between the Most Responsible $PM_{2.5}$ Chemical Constituents and CVD Mediated by MetS

Outcome	Exposure	NDE*	*P* value for NDE	NIE*	*P* value for NIE	PM, %
Total CVD	OM	1.59 (1.42–1.77)	<0.001	1.01 (1.00–1.01)	0.020	1.3
	$PM_{2.5}$	1.63 (1.48–1.80)	<0.001	1.00 (1.00–1.01)	0.002	0.9
IHD	Cl^-	1.36 (1.05–1.76)	0.024	1.00 (1.00–1.01)	0.562	0.6
	$PM_{2.5}$	1.24 (1.01–1.56)	0.044	1.00 (1.00–1.01)	0.005	1.6
CAR	OM	1.42 (1.11–1.81)	0.002	1.00 (1.00–1.01)	0.052	1.1
	$PM_{2.5}$	1.47 (1.19–1.84)	<0.001	1.00 (1.00–1.01)	0.041	0.7
CBVD	Cl^-	1.50 (1.26–1.78)	<0.001	1.00 (1.00–1.00)	0.626	0.3
	$PM_{2.5}$	2.10 (1.81–2.46)	<0.001	1.00 (1.00–1.00)	0.017	0.3

All models were adjusted for age, sex, education, marital status, annual household income, urbanicity, family history of hypertension, smoke, secondhand smoke, alcohol, indoor air pollution, physical activity, Dietary Approaches to Stop Hypertension score, and 3-year average temperature. CAR indicates cardiac arrest; CBVD, cerebrovascular disease; CVD, cardiovascular disease; Cl^-, chloride; IHD, ischemic heart disease; MetS, metabolic syndrome; OM, organic matter; PM, proportion of mediation; and $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm.
*Estimated effects of natural direct effect (NDE) and natural indirect effect (NIE) are represented as hazard ratio with 95% CI.

DISCUSSION

In the current study, we found that NO_3^-, NH_4^+, OM, BC, Cl^-, and SO_4^{2-} may be positively associated with CVD risks. Among these chemical constituents, OM and Cl^- might play vital roles in the positive associations between joint exposure to $PM_{2.5}$ chemical constituents and CVD risks. Moreover, we observed that associations of OM with CVD risks were partially mediated by MetS. To the best of our knowledge, this population-based epidemiological study may be the first to analyze the joint associations of $PM_{2.5}$ chemical constituents with CVD and its subtypes and further evaluate the mediated role of metabolic mechanisms in the associations. This large-scale cohort provides a promising direction for exploring the cause underlying the associations of these pollutants with CVD risks.

Over the past decades, long-term $PM_{2.5}$ exposure has been linked to CVD by numerous studies.[4] Typically, current epidemiological studies use $PM_{2.5}$ mass or a single $PM_{2.5}$ constituent (ie, BC) as exposures. In contrast, little research has focused on the long-term associations of $PM_{2.5}$ chemical constituents on both CVD and its subtypes, especially in relatively highly polluted countries. Despite a few pieces of evidence suggesting the long-term associations of constituents on CVD mortality,[25] only 2 studies reported significant associations from constituents on incident CVD based on cohort design.[8,26] The first study involved 14 331 participants from 25 provincial regions in China, using self-reported total CVD as the outcome.[8] They found significant associations between CVD and $PM_{2.5}$ chemical constituents such as NO_3^-, NH_4^+, BC, and SO_4^{2-}. Similarly, the second study included 26 851 individuals from 3 highly polluted ($PM_{2.5}$ ranged from 67.7 to 77.9 $\mu g/m^3$) regions in Northern China, also using self-reported CVD as the outcome.[26] They reported BC and OM were significantly associated with incident CVD. Consistent with these studies, our findings indicate similar positive associations between constituents and total CVD. Further, we reported that the most responsible pollutant for the associations of mixture pollutants with total CVD was OM, which coincides with the findings of the second study. On the other hand, several recent studies have reported similar results concerning the associations between $PM_{2.5}$ chemical constituents and MetS. For example, a cross-sectional study included 13 418 older adults from 28 provinces in China that reported NO_3^-, NH_4^+, OM, BC, and SO_4^{2-} were associated with MetS.[27] Another study, also cross-sectional, with 10 066 children and adolescents in China, found significant associations between NO_3^-, OM, BC, and SO_4^{2-} and MetS.[28] Furthermore, a cohort study including 5453 children from Europe reported a significant association between BC and MetS.[29] Consistent with these findings, we reported similar results of the associations between constituents and MetS. By comparison, in addition to more outcome types and individual exposure assessments, we applied mediation analysis to further elucidate the potential causal relationships among $PM_{2.5}$ chemical constituents, MetS, and CVD. By focusing on *ICD-10*–based CVD diagnoses, this study may provide more precise and plausible evidence.

As secondary inorganic aerosols, NO_3^-, SO_4^{2-}, and NH_4^+ were found that might have detrimental impacts on CVD in this study. Previous research has reported similar associations of these constituents with CVD incidence and mortality.[8,25,30,31] Similarly, we found significant associations between BC and OM with CVD, which echoed with most existing evidence.[32,33] For example, Liang et al. reported the significant associations of BC and OM with CVD mortality risk.[34] Kazemiparkouhi et al provided evidence that coal combustion–related chemical constituents (such as organic carbon) were strongly associated with CVD mortality.[35]

However, mechanistic evidence underpinning these associations remains sparse. A panel study suggested that SO_4^{2-} might contribute to inflammation, oxidative stress, blood coagulation, and autonomic dysfunction.[36] Another panel study proved that elemental carbon, organic carbon, NO_3^-, and SO_4^{2-} might induce systematic inflammation (eg, fibrinogen and C-reactive protein) and coagulation (soluble CD40 ligand and plasminogen activator inhibitor 1).[37,38] A repeated-measure study reported positive associations of NO_3^- with antioxidant enzymes extracellular superoxide dismutase and glutathione peroxidase 1, supporting the activation of circulating antioxidant enzymes.[39]

Considering the real-world scenario that exposure to $PM_{2.5}$ is actual joint exposure to multiple chemical constituents,[6] QGC was applied to estimate the joint associations. The results showed the same direction as $PM_{2.5}$, and the maximum weights of OM and Cl^- suggested the vital contribution of these constituents in chronic associations of $PM_{2.5}$ on CVD risks. This finding coincided with other evidence that reported OM might mainly account for the associations of $PM_{2.5}$ with CVD risk factors.[40] Moreover, for some components of OM, such as polycyclic aromatic hydrocarbons (PAHs), the primary source is typically the incomplete combustion of organic materials.[41,42] Animal studies indicate that PAHs, such as benzo[a]pyrene, may initiate the aryl hydrocarbon receptor, which leads to lipid peroxidation and tissue damage.[43–45] In addition, the aryl hydrocarbon receptor has been suggested to interact with TCF21, a gene related to coronary artery disease, activating a gene expression program related to inflammation.[46] This process can be enhanced by PAHs and contribute to the risk of CVD. Research also suggests that PAHs are associated with oxidative

stress,[47] inflammation,[48] atherosclerosis,[49] endothelial dysfunction,[50] and hypertension.[51] On the other hand, the epidemiological evidence also indicates that PAHs are associated with inflammatory markers such as 1-hydroxypyrene levels[52] and elevated systolic BP.[53] Further, while the CIs for the association between mixture pollutant and IHD and that between $PM_{2.5}$ mass and IHD overlap, the lower bound for $PM_{2.5}$ mass approaches one. This observation may be explained by the nonsignificant associations of specific constituents, such as OM and SO_4^{2-}, with IHD. Moreover, consistent with previous studies,[26,54] the results of our subgroup analyses suggested that sex might be a potential effect modifier in the association between $PM_{2.5}$ chemical constituents and CVD. However, we found no significant heterogeneity among the associations of $PM_{2.5}$ mass with CVD among these groups, which further emphasizes the necessity of considering chemical constituents.

Another interesting finding was that some constituents, such as BC, NH_4^+, and SO_4^{2-}, were positively associated with CVD risks, yet in multiple pollutant models, they showed substantial negative weights. Similar results have also been observed in other studies. For example, in 2-pollutant models, the estimated associations between NH_4^+ and CVD were negative but not statistically significant,[26] which is also the case for the associations between SO_4^{2-} and CVD.[37] This may be explained by high correlations among these constituents. The correlations can lead to some constituents being nonsignificant in QGC, resulting in the overall negative effect being close to zero and negative weights being substantive.[21] Further, some constituents showed positive but low weights in QGC. The high correlation with OM may explain the relatively low weights of BC. A previous review suggested that because of the high correlation between OM and BC, their effects on cardiovascular end points may overlap, making it difficult to distinguish between their respective impacts.[32] Other constituents of low positive weights, such as NO_3^-, were also found to have a positive association with fasting glucose or cardiac electrophysiological properties in the 2-pollutant model by the previous study.[40] These findings emphasize the importance of key constituents in the associations between $PM_{2.5}$ and CVD. There is an urgent need to turn attention to the joint exposure mechanisms of chemical constituents in order to develop targeted strategies, such as personal protection.[55]

To explain the importance of OM and Cl^- on CVD, our research interest further focused on metabolic disorders as increasing studies emphasized the associations between $PM_{2.5}$ and MetS.[56] Given that MetS is an important risk factor of CVD, and considering the associations identified by recent studies between $PM_{2.5}$ and MetS, it is plausible that MetS may mediate the associations between $PM_{2.5}$ and CVD. Our results show that the association of OM with CVD was mediated by MetS, suggesting that OM may be involved in the metabolic mechanisms of CVD. This is consistent with afore evidence demonstrating the associations between OM and several metabolic risk factors, including fasting glucose, ECG, and hypertension, among others.[8,40] Further, recent studies have shown that components of MetS, such as obesity,[57] dyslipidemia,[58] fasting plasma glucose,[59] and BP,[60] are associated with $PM_{2.5}$. Our research identified obesity, triglycerides, and raised BP as mediators in the associations of $PM_{2.5}$ and OM with CVD. These findings may indicate the vital role these components potentially play in mediating the association between $PM_{2.5}$ and CVD. While our study did not find a mediating role for raised fasting plasma glucose, recent research has reported associations between $PM_{2.5}$ and its constituents and diabetes,[61–64] suggesting that further exploring these mechanisms is warranted. These findings not only indicate potential benefits from targeting metabolic mechanisms such as obesity, dyslipidemia, and hypertension in interventions but also highlight the urgent need to reduce pollutant sources such as industry-related combustion to mitigate the cardiovascular impact of OM. On the other hand, our findings indicate that while Cl^- was positively associated with CVD, it was marginally negatively associated with BP, as well as in the mediation analyses. Such seemingly contradictory results could also be found in existing studies. For example, Wu et al found Cl^- might be involved in the antioxidant process,[39] whereas Feng et al reported a negative association of Cl^- with inflammation biomarkers (monocyte chemoattractant protein 1).[65] Another explanation for this inconsistency may be the variety of study designs and regions. Further, Cl^- was closely related to sea salt and wind-blown dust.[37,66–68] While sea salt was sourced from natural processes, dust contains metal elements such as calcium and potassium ions, which have been associated with adverse health effects.[69,70] Further, a panel study involving 30 patients with chronic obstructive pulmonary disease reported negative associations between sodium and calcium ions and biomarkers of inflammation, such as monocyte chemoattractant protein, as well as biomarkers of coagulation such as plasminogen activator inhibitor 1.[37] Nevertheless, biological mechanisms of Cl^- in the airway remain rare, and further research is needed to clarify the long-term effects.

Our study has several strengths in addition to the large population of the cohort design, including a rich set of covariates based on questionnaires with fewer measurement errors and precise laboratory examinations, *ICD-10*–based outcome, and a series of methods that are broadly accepted in the realm of environmental joint exposure assessment, yielding consistent and

robust results. In addition, we performed a series of sensitivity analyses to confirm the robustness of our findings because the associations may vary with exposure windows. The robustness of our results performed well, and the assumption of proportional hazards was not violated. Nevertheless, there are still some limitations in this study. First, because the health condition of participants with no hospital records cannot be identified after the baseline survey, results may be underestimated. Second, the follow-up time for our cohort might be considered relatively short for CVD outcomes due to the availability of medical records. Third, we assessed the exposure levels of individuals by their residential addresses without detailed information on activity patterns. However, considering that living houses and workplaces were not distant, measurement error in the results due to residential addresses may be limited.

CONCLUSIONS

Our study indicates that among the $PM_{2.5}$ chemical constituents that are positively associated with CVD risks, OM and Cl^- might be significant contributors to the associations between $PM_{2.5}$ and CVD risks. Further mediation analysis showed that metabolic mechanisms might be involved in the associations between OM and CVD risks. This study provided brand new evidence on which chemical constituents are attributed most in the association of $PM_{2.5}$ with increased CVD risks and their underlying metabolic mechanisms. Therefore, more individualized treatment strategies concerning the main constituent (eg, OM) in the area where patients live are needed. The action to control the source of specific $PM_{2.5}$ chemical constituents (ie, OM) is urgent. Further, the mechanisms of chemical constituents still require in-depth research.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1: Supplemental Methods
Tables S1–S35
Figures S1–S7

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