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Original Article

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Long-Term Exposure to Fine Particulate Constituents and Vascular Damage in a Population with Metabolic Abnormality in China

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Aim: To date, $PM_{2.5}$-associated vascular damage in metabolic abnormalities has remained controversial. We knew little about the vascular damage of $PM_{2.5}$ constituents. Thus, this study aimed to investigate the relationship between long-term exposure to $PM_{2.5}$ and its constituents and vascular damage in metabolic abnormalities.

Methods: A total of 124,387 participants with metabolic abnormalities (defined as at least one metabolic disorder, such as obesity, elevated blood pressure, elevated triglyceride level, elevated fasting glucose level, or low HDL cholesterol level) were recruited in this study from 11 representative centers in China between January 2011 and December 2017. $PM_{2.5}$ and its constituents (black carbon [BC], organic matter [OM], sulfate [SO_4^{2-}], nitrate [NO_3^-], and ammonium salts [NH_4^+]) were extracted. Elevated brachial-ankle pulse wave velocity (baPWV) (≥ 1,400 cm/s) and declined ankle-brachial index (ABI) (＜0.9) indicated vascular damage. Multivariable logistic regression and Quantile g-Computation models were utilized to explore the impact on outcomes.

Results: Of the 124,387 participants (median age, 49 years), 87,870 (70.64%) were men. One-year lag exposure to $PM_{2.5}$ and its constituents was significantly associated with vascular damage in single pollutant models. The adjusted odds ratios (OR) for each 1-μg/m^3 increase in $PM_{2.5}$ was 1.013 (95% CI, 1.012–1.015) and 1.031 (95% CI, 1.025–1.037) for elevated baPWV and decreased ABI, respectively. $PM_{2.5}$ constituents were also associated with vascular damage in multi-pollutant models. Among the $PM_{2.5}$ constituents, BC (47.17%), SO_4^{2-} (33.59%), and NH_4^+ (19.23%) have the highest contribution to elevated baPWV and NO_3^- (47.89%) and BC (23.50%) to declined ABI.

Conclusion: Chronic exposure to $PM_{2.5}$ and $PM_{2.5}$ constituents was related to vascular damage in the abnormal metabolic population in China. The heterogeneous contribution of different $PM_{2.5}$ constituents to vessel bed damage is worthy of attention when developing targeted strategies.

Key words: Ambient air pollution, $PM_{2.5}$ constituents, Brachial-ankle pulse wave velocity, Ankle-brachial index, Vascular injury

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, especially in low- and middle-income countries[1, 2]. In China, the age-standardized mortality rate of CVD significantly increased from 1990 to 2019 [3]. This high mortality and increased trend pose a huge disease burden on China. Thus, it is essential to investigate its associated risk factors and prevent the disease at its onset. Furthermore, all CVDs are accompanied by vascular damage in their initial stages. Brachial-ankle pulse wave velocity (baPWV) and ankle-brachial index (ABI) are indirect indicators of arterial stiffness and peripheral artery atherosclerosis. They have been proposed as risk indicators for CVDs with a potential clinical application in CVD risk assessment[4-8]. Therefore, it is crucial and urgent to investigate the associated risk factors of vascular injury to develop targeted preventive measures so as to help alleviate the disease burden posed by CVDs.

Metabolic abnormalities are mainly characterized by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, and adiposity, which affect up to 24.50% of the Chinese population[9]. The existence of these conditions significantly increased the risk factors for CVDs[10, 11]. It has been reported that participants with metabolic disorders are twice as likely to develop CVDs over the next 10 years as those without any metabolic disorders[12]. Therefore, participants with metabolic disorders require further attention in preventing CVD risks[13]. Ambient fine particulate matter ($PM_{2.5}$) air pollution has been widely recognized as a major environmental risk factor of CVDs[14-17]. Several studies have explored the effect of long- or short-term exposure to PM mass and other pollutants (such as carbon oxide, sulfur dioxide, nitrogen dioxide, and ozone) on the risk of vascular injury[18-22]. However, the impact of chronic exposure to $PM_{2.5}$ and its chemical constituents on vascular injury in metabolic disorders is poorly understood.

Therefore, to address the research gap in the literature, we conducted a retrospective study to investigate the chronic effects of $PM_{2.5}$ and its chemical constituents on the prevalence of early vascular injury, as represented by elevated baPWV and declined ABI, in a population with metabolic abnormalities.

Aim

This cross-sectional study aimed to examine the association between long-term exposure to fine PM and its constituents and vascular damage in a population with metabolic abnormalities in China.

Materials and Methods

Study Population

A total of 128,905 participants with metabolic disorders were recruited in this study from 11 health management centers representing the southern and northern regions of China between January 2011 and December 2017. All participants voluntarily participated in the health examinations. Metabolic disorders were characterized by the existence of at least one of the following metabolic abnormalities: elevated body mass index (BMI) (25 kg/m^2 or greater), elevated triglyceride (TG) level (150 mg/dL or greater), reduced high-density lipoprotein cholesterol (HDL-C) ($<$40 mg/dL in men and $<$50 mg/dL in women), elevated blood pressure (130/85 mmHg or greater), or elevated fasting blood glucose (FBG) level (100 mg/dL or greater)[10, 11]. A total of 559 participants aged below 18 years and 3,959 participants with a history of atherosclerotic CVD (such as coronary heart disease, stroke, or myocardial infarction) were excluded from the study. Finally, a total of 124,387 participants were included **(Fig. 1)**.

All medical records related to personal identification were removed, and each participant remained anonymous throughout the study. The study complied with the principles of the Declaration of Helsinki. The ethical review committee of Renmin Hospital of Wuhan University, Wuhan, China, approved the study. Subsequently, the study was recognized by the ethics center in each collaborative health management center. The ethical committees waived the requirement for informed consent documentation for the analysis of existing data with anonymous personal identification.

Outcome Assessment

The measurements of baPWV and ABI were assessed as follows. The participants rested in bed for at least 5 min in the supine position, and the ABI and baPWV measurements were assessed by qualified senior professionals using an automated waveform

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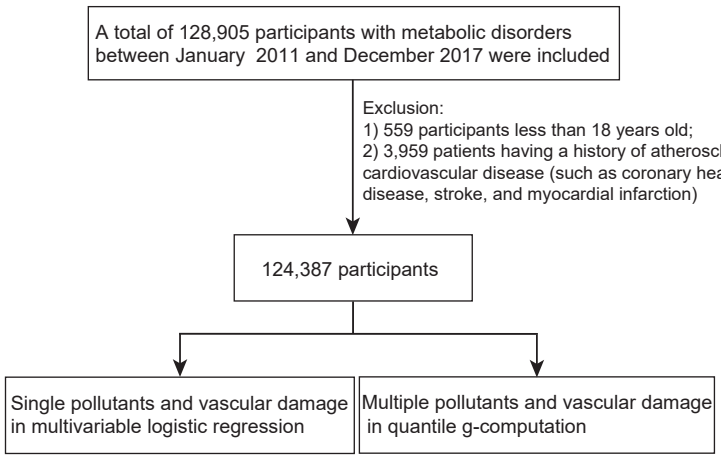

Fig. 1. Flowchart of participant inclusion and exclusion in the study
BaPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index.

analyzer. The brachial and ankle waveforms were recorded during sampling, and the time interval between the wavefront of the brachial waveform and the ankle waveform, defined as T, was automatically measured. Based on the patient's height, the path lengths from the suprasternal notch to the elbow (La) and from the suprasternal notch to the ankle (Lb) were automatically determined. Then, baPWV was calculated using the formula baPWV (cm/s)=(Lb–La)/T, and the average value of the left and right baPWV was taken for data analysis[23]. The baPWV measurements were taken twice or thrice if the difference in baPWV between the first two measurements was larger than 0.5 cm/s[24]. The result was the average of multiple measurements. In addition, the right and left ankle systolic blood pressure (SBP) and brachial SBP were measured, and the ABI was calculated using the formula ABI=ankle SBP/brachial SBP. A third measurement was performed if the difference between the two values of one limb was greater than 10 mmHg. The lowest value of the right and left ABI was used for analysis[23].

The measurements of baPWV or ABI was performed twice for each participant, and the average of the two measurement results was considered the final value. The present study defined early vascular damage as baPWV ≥ 1,400 cm/s[25] and ABI <0.9 [8].

Estimates of Individual Air Pollution Exposure

The daily gridded concentrations of ambient $PM_{2.5}$ total mass and its five chemical constituents (black carbon [BC], organic matter [OM], sulfate [SO_4^{2-}], nitrate [NO_3^-], and ammonium salt [NH_4^+]) at a 10×10-km spatial resolution were obtained from the Tracking Air Pollution in China (TAP, http://tapdata.org.cn/). This dataset was based on a synthesis of in situ measurements collected from literature and satellite-based estimates using aerosol optical depth data and the GEOS-Chem chemical transport model. The prediction model for $PM_{2.5}$ and its components has been described elsewhere[26]. We used the daily average temperature and relative humidity of each city obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn/) to account for meteorological factors.

Assuming that most participants visited the health management center close to their residential address, daily air pollutant concentrations at each health management center were assigned to all participants who visited. We calculated the average exposure levels of $PM_{2.5}$ and its constituents in a 10-km radius buffer zone around the health management center at two exposure time windows: 1- and 2-year average levels of air pollutant exposure[21]. Specifically, based on the date of each participant's visit to the health screening center, the average concentrations for the previous 365 and 730 days were calculated as 1- and 2-year lag pollutant concentrations, respectively.

Covariates

Each health screening center was equipped with highly trained and experienced physicians, and all participants underwent comprehensive anthropometric examinations and laboratory testing. Sociodemographic data, including age, sex, height, weight, smoking status, systolic and diastolic blood pressures, self-reported medical history, and medication history, were obtained. BMI was calculated by dividing weight by the square of height (kg/m^2). The mean arterial

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pressure was calculated as mean arterial pressure (MAP) = [(2 × diastolic blood pressure) + systolic blood pressure]/3. After overnight fasting, the participants underwent laboratory tests conducted by trained researchers, including routine blood, lipid, liver function, and kidney function tests. The estimated glomerular filtration rate (eGFR) (mL/min per 1.73 m^2) was calculated using the modified Chinese method, $eGFR = 175 \times Scr^{-1.234} \times age^{-0.179}$ [if women, ×0.79], where serum creatinine (Scr) is expressed in mg/dL and age in years[27]. In addition, data on gross domestic product (GDP) per capita were collected from the National Bureau of Statistics of China.

The definitions of the comorbidities have been reported in our previous studies[28-30]. In short, metabolic syndrome (Mets) was characterized by the existence of at least three of the following pre-defined metabolic abnormalities: elevated BMI [25 kg/m^2 or greater], elevated TG level [150 mg/dL or greater], reduced HDL-C level [< 40 mg/dL in men and < 50 mg/dL in women], elevated blood pressure [130/85 mmHg or greater], and elevated FBG level [100 mg/dL or greater][10, 11]. Hypertension was defined as SBP ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a history of hypertension according to the 2018 Chinese hypertension management guidelines[31]. Type 2 diabetes mellitus (T2DM) was characterized by FBG level ≥ 7.0 mmol/L, 2-h postprandial glucose level ≥ 11.1 mmol/L, or a history of diabetes[32]. Dyslipidemia was defined as having any of the following: TG level ≥ 2.3 mmol/L, total cholesterol (TC) level ≥ 6.2 mmol/L, HDL-C level < 1.0 mmol/L, low-density lipoprotein cholesterol (LDL-C) level ≥ 4.1 mmol/L, or a history of dyslipidemia[33].

Statistical Analysis

We conducted descriptive analysis on all variables. Categorical variables were expressed as numbers (percentages) and continuous variables as median (interquartile range, IQR). Student's *t*-test or Kruskal–Wallis test was employed to compare continuous variables and the chi-squared test or Fisher's exact test to compare categorical variables.

The effects of the 1-year lag average concentrations of $PM_{2.5}$ and its constituents on vascular injury were assessed via logistic regression. Three sets of models were constructed separately. Model 1 was constructed with crude model. Model 2 was constructed with each participant's sex and age adjusted. In model 3, all individual-level risk factors at baseline, including sex, age, BMI, MAP, GDP per capita, smoking status, white blood cell count, alanine aminotransferase (ALT), eGFR, TG, LDL-C, HDL-C, FBG, temperature, and relative humidity, were considered[18-20].

To further explore the mixture impact of $PM_{2.5}$ components on vascular injury and to quantify the impact value of mixture exposures, we adopted Quantile g-Computation (QgC) to assess the joint effects of the $PM_{2.5}$ component mixture on vascular injury and to the positive or negative contributions of different components to vascular injury[34, 35]. This novel approach, including the inferential simplicity of weighted quantile sum regression with the flexibility of QgC, appeared to be less biased and more robust[34]. In the QgC model, the $PM_{2.5}$ components were transformed into quartiles[34, 35], and a linear model was fitted as follows (omitting covariates):

$$Y_{vascular\ injury} = \beta_0 + \sum_{j=1}^{p} \beta_j \text{PM2.5 component}_j^q + \varepsilon_i$$

where β_0 denotes the model intercept; $\text{PM2.5 component}_j^q$ a quartile version of the jth component, component_j; $\sum_{j=1}^{p} \beta_j$, the weighted quantile sum representing the classification values of vascular injury in all components; and ε_i, the error term.

The weight of each component was calculated as positive or negative, indicating the proportion of the $PM_{2.5}$ components contributing to vascular damage in the same direction, thus sum to one for the positive direction and to −1 for the negative direction. The overall association, representing the effects of all five $PM_{2.5}$ components as a mixture, was interpreted on the classification values of vascular injury in all $PM_{2.5}$ components, controlling for covariates. In the QgC model, the covariates were consistent with the fully adjusted logistic regression model.

All statistical analyses were conducted using the SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) and R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). The "lme4" package was used to evaluate the relationship between PM component exposure and outcome[36] and the "qgcomp" and "knitr" packages to build a multiple PM component model[34]. $P < 0.05$ on both sides was considered to indicate statistical significance.

Sensitivity Analysis

To check the robustness of our results, we conducted sensitivity analyses in both single- and mixed-pollutant models. First, we used the average concentrations of fine particulate pollutants with lags of 2 years in the adjusted model. Second, quartile rank variable for fine particulate pollutants was used in the regression model. Third, we used a generalized linear mixed model (GLMM) to analyze the association between air pollutants and vascular injury, including a

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random effect, to account for the multicenter study setting. Fourth, in addition to the risk factors in the fully adjusted logistic regression model, we adjusted the medication history for metabolic disorders, such as antihypertensive, hypoglycemic, and lipid-lowering drugs.

Results

Characteristics of the Participants

About 124,387 participants in this study had metabolic disorders. Furthermore, 53,022 (42.63%) participants had baPWV ≥ 1,400 cm/s, and 1,293 (1.04%) had ABI < 0.9. Their median age was 49 years (IQR: 43–55 years), and their median BMI was 25.58 kg/m^2 (IQR: 23.64–27.52 kg/m^2); moreover, 70.64% of them were men **(Table 1)**.

Participants with elevated baPWV were older, accounted for a higher percentage of men and the smoking population, had higher BMI and blood pressure, and accounted for a higher percentage of the population with Mets, obesity, hypertension, and T2DM than those with normal baPWV. Consistently, participants with decreased ABI had similar characteristics to those with elevated baPWV **(Table 1)**.

The median concentrations of $PM_{2.5}$ total mass were 57.70 (42.24–84.54) per μg/m^3 and 71.28 (55.91–84.88) per μg/m^3 in the normal and elevated baPWV groups, respectively, during the 1-year lag exposure. Accordingly, exposure to $PM_{2.5}$ constituents was also higher in the elevated baPWV group than in the normal group. The participants with decreased ABI also had higher exposure to $PM_{2.5}$ mass and its constituents than the normal ABI group **(Table 1)**.

Characteristics of Air Pollutants

The map of the 11 health management centers is presented in **Supplementary Fig. 1**, and the 1-year lag average concentrations of pollutants for the descriptive statistics are presented in **Supplementary Tables 1 and 2**. The minimum level was 22.98 μg/m^3 with 1-year lag $PM_{2.5}$, which far exceeded the level in the World Health Organization Air Quality Guidelines[37]. The median levels were 2.97, 8.61, 13.24, 15.94, and 11.49 μg/m^3 for BC, NH_4^+, NO_3^-, OM, and SO_4^{2-}, respectively, in 1-year lag average concentrations. Furthermore, the concentration of the same pollutant dramatically varied among cities, which indicated that the pollutant concentrations in northern cities were higher than those in southern cities **(Supplementary Table 2)**. For example, C03 had the highest 1-year lag average concentration of $PM_{2.5}$, and C11 had the lowest 1-year lag average concentration of $PM_{2.5}$. The participants' maximum exposure to $PM_{2.5}$ was 99.28 μg/m^3 and the minimum was 25.48 μg/m^3 **(Supplementary Table 2)**. In addition, Spearman's correlations of air pollutant concentrations in the study population are presented in **Supplementary Table 3**. Overall, $PM_{2.5}$ and its chemical constituents were inter-correlated.

Association of $PM_{2.5}$ and its Constituents with Vascular Injury in the Logistic Model

Vascular injury was observed to be associated with increased exposure to $PM_{2.5}$ mass and its constituents **(Table 2, Fig. 2)**. After adjusting for potential confounding factors, an increase of 1 μg/m^3 of 1-year lag $PM_{2.5}$ (1.013, 95% confidence interval [CI]: 1.012–1.015, $P<0.001$) and its constituents BC (1.081, 95% CI: 1.056–1.107, $P<0.001$), NH_4^+ (1.213, 95% CI: 1.197–1.230, $P<0.001$), NO_3^- (1.119 95% CI: 1.110–1.128, $P<0.001$), OM (1.005, 95% CI: 1.000–1.009, $P<0.001$), and SO_4^{2-} (1.121, 95% CI: 1.113–1.129, $P<0.001$) had significantly higher odds ratios (ORs) of baPWV ≥ 1400 cm/s. Consistently, a 1-μg/m^3 increase of 1-year lag $PM_{2.5}$ (1.031, 95% CI: 1.025–1.037, $P<0.001$) and its constituents BC (1.332, 95% CI: 1.202–1.476, $P<0.001$), NH_4^+ (1.489, 95% CI: 1.398–1.588, $P<0.001$), NO_3^- (1.300, 95% CI: 1.254–1.349, $P<0.001$), OM (1.034, 95% CI: 1.016–1.053, $P<0.001$), and SO_4^{2-} (1.191, 95% CI: 1.149–1.235, $P<0.001$) was also significantly associated with ABI < 0.9 in the full adjusted model **(Table 2, Fig. 2)**.

Association of $PM_{2.5}$ Constituents with Vascular Injury in the Quantile g-Computation Model

We found a significant positive association between multiple $PM_{2.5}$ particles (five $PM_{2.5}$ constituents) as a whole and vascular injury by using the QgC model. After fully adjusting for confounders, the effect of multiple $PM_{2.5}$ particles remained significant on vascular injury, with the ORs being 1.061 (95% CI: 1.034–1.088, $P<0.001$) for elevated baPWV and 2.250 (95% CI: 1.984–2.551, $P<0.001$) for reduced ABI **(Table 3)**. OM and NO_3^- had a negative effect on elevated baPWV, whereas the other three air pollutants, namely, BC (47.17%), SO_4^{2-} (33.59%), and NH_4^+ (19.23%), had a positive correlation with elevated baPWV. Only SO_4^{2-} had a negative effect on the overall pollutants for ABI reduction, whereas NO_3^- (47.89%), BC (23.50%), NH_4^+ (22.39%), and OM (6.23%) had a positive effect on the overall mixture effects of $PM_{2.5}$ constituents and ABI reduction **(Table 3)**.

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Table 1. Characteristic of the participant with and non-vascular injury in a cross-sectional study

Characteristic	Total (N = 124,387)	baPWV < 1,400 cm/s (N = 71,365)	baPWV ≥ 1,400 cm/s (N = 53,022)	*p* value	ABI ≥ 0.9 (N = 123,094)	ABI < 0.9 (N = 1,293)	*p* value
Social demographics							
Age (years, median [IQR])	49 [43-55]	48 [42-54]	50 [44-57]	< 0.001	49 [43-55]	53 [45-63]	< 0.001
Sex, *n* (%)	87,870 (70.64%)	49,926 (69.96%)	37,944 (71.56%)	< 0.001	87,190 (70.83%)	680 (52.59%)	< 0.001
BMI (kg/m^2, median [IQR])	25.58 [23.64-27.52]	25.48 [23.50-27.37]	25.72 [23.81-27.71]	< 0.001	25.58 [23.64-27.51]	26.32 [24.19-28.66]	< 0.001
SBP (mmHg, median [IQR])	127 [116-139]	123 [112-134]	133 [122-145]	< 0.001	127 [116-139]	130 [119-145]	< 0.001
DBP (mmHg, median [IQR])	81 [73-89]	79 [71-86]	84 [76-91]	< 0.001	81 [73-89]	80 [72-89]	0.327
MAP (mmHg, median [IQR])	96.67 [88-105.33]	93.33 [85.33-102]	100.33 [92.33-109]	< 0.001	96.67 [88-105.33]	97.33 [88.67-106.67]	< 0.001
Lifestyle							
Smoke, *n* (%)	36,786 (29.57%)	20,764 (29.10%)	16,022 (30.22%)	0.001	36,507 (29.66%)	279 (21.58%)	< 0.001
Medical history							
Medication history for metabolic disorders[a], *n* (%)	16,160 (12.99%)	8,152(11.42%)	8,008 (15.10%)	< 0.001	15,984 (12.99%)	176 (13.61%)	< 0.001
Environmental factors							
Temperature (K)	286.49 (284.95-290.92)	286.85 (285.16-290.9)	285.7 (284.82-290.92)	< 0.001	286.52 (284.96-290.92)	285.48 (284.76-286.18)	< 0.001
Relative humidity (%)	57.11 (51.06-75.88)	72.86 (51.21-75.81)	52.62 (50.9-76.08)	< 0.001	59.31 (51.06-75.88)	51.72 (50.51-53.43)	< 0.001
Economic indicators							
Per GDP (× 10^4/yuan, median [IQR])	9.28 [5.25-11.37]	8.62 [3.84-11.37]	9.80 [5.83-11.37]	< 0.001	9.28 [5.25-11.37]	7.59 [4.66-10.06]	< 0.001
Laboratory indicators							
WBC (× 10^9/L, median [IQR])	6.05 [5.15-7.14]	5.96 [5.07-7.02]	6.17 [5.26-7.29]	< 0.001	6.05 [5.14-7.13]	6.48 [5.50-7.60]	< 0.001
ALT (IU/L, median [IQR])	23.00 [16.00-34.00]	22.00 [15.50-33.00]	23.70 [16.70-35.00]	< 0.001	23.00 [16.00-34.00]	22.20 [16.50-33.25]	0.742
eGFR(ml/min per 1.73 m^2, median [IQR])	104.96 [88.50-122.75]	101.11 [84.64-119.26]	109.57 [94.08-126.75]	< 0.001	104.96 [88.53-122.75]	103.08 [84.46-125.07]	0.085
FBG (mmol/L, median [IQR])	5.45 [5.02-6.00]	5.38 [4.98-5.87]	5.55 [5.09-6.21]	< 0.001	5.44 [5.02-5.99]	5.53 [5.03-6.23]	< 0.001
TC (mmol/L, median [IQR])	4.90 [4.29-5.58]	4.86 [4.25-5.53]	4.96 [4.33-5.63]	< 0.001	4.90 [4.29-5.58]	4.98 [4.28-5.65]	0.152
TG (mmol/L, median [IQR])	1.71 [1.16-2.45]	1.66 [1.12-2.36]	1.77 [1.23-2.59]	< 0.001	1.71 [1.16-2.45]	1.70 [1.17-2.34]	0.424
LDL-C (mmol/L, median [IQR])	2.92 [2.41-3.48]	2.92 [2.41-3.48]	2.92 [2.41-3.47]	0.512	2.92 [2.41-3.47]	3.02 [2.47-3.70]	< 0.001
HDL-C (mmol/L, median [IQR])	1.16 [0.98-1.36]	1.15 [0.97-1.35]	1.17 [0.99-1.37]	< 0.001	1.16 [0.98-1.36]	1.19 [1.01-1.36]	0.004
Comorbidities							
Mets (%)	50,264 (40.41%)	25,453 (35.67%)	24,811 (46.79%)	< 0.001	49,659 (40.34%)	605 (46.79%)	< 0.001
Obesity (%)	83,297 (66.97%)	45,796 (64.17%)	37,501 (70.73%)	< 0.001	82,358 (66.91%)	939 (72.62%)	< 0.001
Hypertension (%)	42,253 (33.97%)	17,739 (24.86%)	24,514 (46.23%)	< 0.001	41,682 (33.86%)	571 (44.16%)	< 0.001
T2DM (%)	17,583 (14.14%)	7,152 (10.02%)	10,431 (19.67%)	< 0.001	17,304 (14.06%)	279 (21.58%)	< 0.001
Dyslipidemia (%)	63,208 (50.82%)	27,547 (51.95%)	35,661 (49.97%)	< 0.001	62,594 (50.85%)	614 (47.49%)	0.017
Vascular injury outcomes							
baPWV ≥ 1,400 cm/s, *n* (%)	53,022 (42.63%)	0 (0%)	53,022 (98.23%)	< 0.001	52,682 (42.80%)	340 (26.30%)	< 0.001
ABI < 0.9, *n* (%)	1,293 (1.04%)	0 (0%)	1,293 (2.40%)	< 0.001	0 (0%)	1,293 (100%)	< 0.001
$PM_{2.5}$ constituents							
$PM_{2.5}$ total mass (μg/m^3, median [IQR])	68.91 [54.82-84.66]	57.70 [42.24-84.54]	71.28 [55.91-84.88]	< 0.001	68.64 [54.82-84.62]	86.15 [73.96-94.66]	< 0.001
$PM_{2.5}$ BC (μg/m^3, median [IQR])	2.97 [2.76-4.07]	2.91 [2.47-3.93]	3.11 [2.90-4.10]	< 0.001	2.96 [2.75-4.06]	4.17 [3.25-4.76]	< 0.001
$PM_{2.5}$ NH_4^+ (μg/m^3, median [IQR])	8.61 [7.34-9.66]	8.10 [6.90-9.60]	8.84 [7.88-9.72]	< 0.001	8.61 [7.26-9.64]	9.78 [9.30-10.42]	< 0.001
$PM_{2.5}$ NO_3^- (μg/m^3, median [IQR])	13.24 [10.77-14.78]	11.91 [9.28-14.73]	13.99 [11.43-14.91]	< 0.001	13.20 [10.77-14.78]	15.05 [14.31-15.85]	< 0.001
$PM_{2.5}$ OM (μg/m^3, median [IQR])	15.94 [13.05-22.37]	14.34 [11.18-22.27]	16.59 [13.78-22.37]	< 0.001	15.92 [13.05-22.27]	23.34 [17.33-24.96]	< 0.001
$PM_{2.5}$ SO_4^{2-} (μg/m^3, median [IQR])	11.49 [10.15-13.25]	10.86 [8.66-13.15]	12.02 [10.81-13.29]	< 0.001	11.49 [10.15-13.25]	13.57 [12.02-15.29]	< 0.001

[a]The medication history for metabolic disorders, such as antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs.
BaPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; per GDP, gross domestic product per capita; WBC, white blood cell; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C. high-density lipoprotein cholesterol; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; $PM_{2.5}$, fine particulate matter < 2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate.

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Table 2. Associations between long-term exposure to $PM_{2.5}$ mass and vascular damage outcomes

Model	$PM_{2.5}$ mass per 1 μg/m³ increase			
	baPWV ≥ 1400 cm/s		ABI < 0.9	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Model 1 [a]	1.017 (1.017, 1.018)	< 0.001	1.067 (1.063, 1.072)	< 0.001
Model 2 [b]	1.017 (1.016, 1.017)	< 0.001	1.062 (1.058, 1.067)	< 0.001
Model 3 [c]	1.013 (1.012, 1.015)	< 0.001	1.031 (1.025, 1.037)	< 0.001

[a] Model 1, unadjusted model; [b] Model 2, adjusting sex and age; [c] Model 3, adjusting age, sex, BMI, MAP, per GDP, smoke, Temp, RH, WBC, ALT, eGFR, TG, LDL-C, HDL-C, and FBG.

BaPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; OR, odds ratio; CI, confidence interval; $PM_{2.5}$, fine particulate matter < 2.5 μm; BMI, body mass index; MAP, mean arterial pressure; per GDP, gross domestic product per capita; Temp, temperature; RH, relative humidity; WBC, white blood cell; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose.

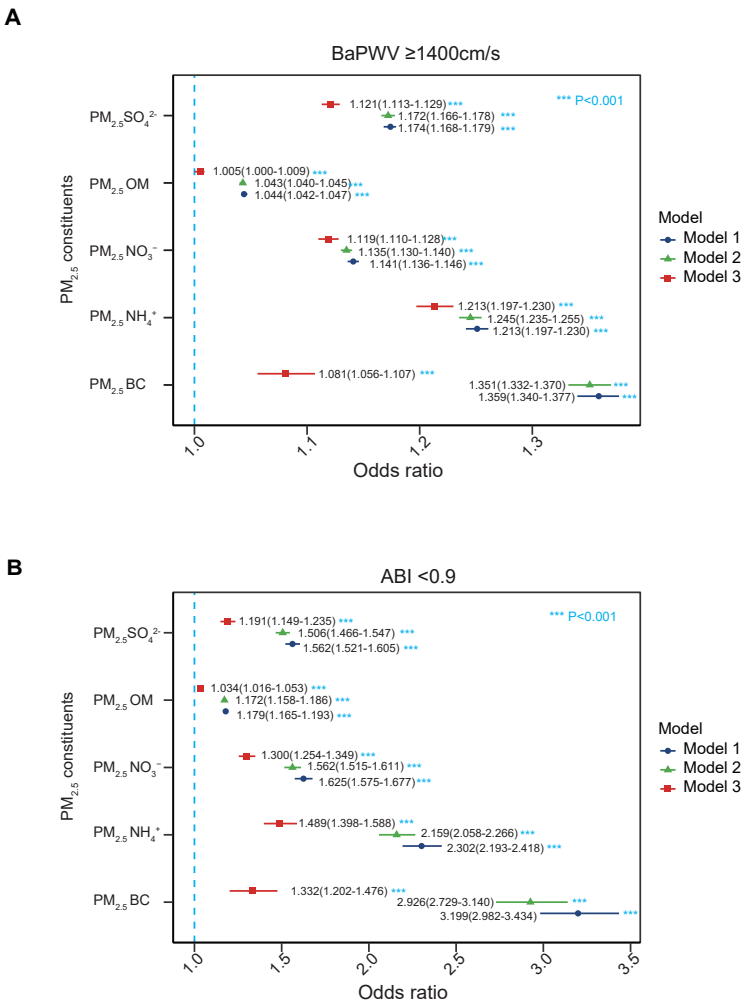

Fig. 2. Associations between long-term exposure to $PM_{2.5}$ constituents with brachial-ankle pulse wave velocity ≥ 1400 cm/s (A) and ankle-brachial index < 0.9 (B)

Model 1, unadjusted model; model 2, adjusting sex and age; model 3, adjusting age, sex, body mass index, mean arterial pressure, gross domestic product per capita, smoking status, temperature, relative humidity, white blood cell count, alanine aminotransferase, estimated glomerular filtration rate, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose. $PM_{2.5}$, fine particulate matter < 2.5 μm; BC, black carbon; NH_4^+, ammonium salt; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate.

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Table 3. Adjusted ORs and 95% CIs of vascular damage outcomes associated with air pollution in multi-pollutant models

Exposures	Outcomes	Index weight	Odds ratio per quartile increase[a] (95%CI)	*p* value
$PM_{2.5}$ constituents				
$PM_{2.5}$ BC (μg/m³)	baPWV ≥ 1400 cm/s	0.601	1.061 (1.034, 1.088)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)		0.245		
$PM_{2.5}$ NO_3^- (μg/m³)		-0.147		
$PM_{2.5}$ OM (μg/m³)		-1.068		
$PM_{2.5}$ SO_4^{2-} (μg/m³)		0.428		
$PM_{2.5}$ constituents				
$PM_{2.5}$ BC (μg/m³)	ABI <0.90	0.317	2.250 (1.984, 2.551)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)		0.302		
$PM_{2.5}$ NO_3^- (μg/m³)		0.646		
$PM_{2.5}$ OM (μg/m³)		0.084		
$PM_{2.5}$ SO_4^{2-} (μg/m³)		-0.539		

[a]Model adjusting age, sex, BMI, MAP, per GDP, smoke, Temp, RH, WBC, ALT, eGFR, TG, LDL-C, HDL-C, and FBG.
CI, confidence interval; $PM_{2.5}$, fine particulate matter <2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; BMI, body mass index; MAP, mean arterial pressure; per GDP, gross domestic product per capita; Temp, temperature; RH, relative humidity; WBC, white blood cell; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C. high density lipoprotein cholesterol; FBG, fasting blood glucose.

Sensitivity Analysis

To validate the robustness of our findings, we conducted several sensitivity analyses to confirm the relationship between a single pollutant and vascular injury. First, with a 1-μg/m³ increase of a 2-year lag $PM_{2.5}$ and its components, the ORs of vascular injury were still statistically significant. Second, the correlation between increased $PM_{2.5}$ and its components per IQR and vascular injury remained significant. We switched to a GLMM model to further adjust for urban random effects, and the correlation between $PM_{2.5}$ and its components and vascular injury remained significant. Finally, we further adjusted the information on medication for metabolic disorders; the results remained consistent **(Supplementary Table 4)**.

The sensitivity analyses for mixture pollutants generated similar results. In addition, 2-year lag average concentrations of $PM_{2.5}$ components were used instead in the QgC model did not change the significant associations between multiple $PM_{2.5}$ components and vascular injury. Similar results were obtained using the GLMM model with additional adjustment for the random effects of cities or for information on medication for metabolic disorders **(Supplementary Table 5)**.

Discussion

To the best of our knowledge, this is the largest epidemiological study to explore the relationship between long-term exposure to $PM_{2.5}$ and its constituents and vascular injury in a population with metabolic disorders in China. This study demonstrated that long-term exposure to either $PM_{2.5}$ total mass or its five chemical constituents was associated with the prevalence of vascular injury (including baPWV ≥ 1400 cm/s and ABI<0.9). Among the $PM_{2.5}$ constituents, BC (47.17%) and SO_4^{2-} (33.59%) contributed the most to the elevated baPWV whereas NO_3^- (47.89%) and BC (23.50%) to the declined ABI. Our findings may have important implications in developing intervention measures for specific $PM_{2.5}$ constituents to more effectively reduce the risk of atherosclerotic CVD caused by air pollution.

The effect of $PM_{2.5}$ exposure on arterial stiffness has been controversial in the general population[38-42]. We found a consistent and positive association between chronic exposure and $PM_{2.5}$ and its five chemical constituents, with elevated baPWV representing arterial stiffness in participants with metabolic disorders. The inconsistent results from the preexisting studies may help us to find the reasonable explanation. In more detail, previous studies conducted in high-income countries demonstrated no association between exposure to $PM_{2.5}$ and arterial stiffness, possibly due to the relatively low levels of $PM_{2.5}$ [38, 42]. Furthermore, previous studies on household $PM_{2.5}$ air pollution in women and the elderly in China did not find associations with arterial stiffness, which may be due to the difference between

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indoor and outdoor pollution and the bias brought by the study population sample selection[39, 40]. Notably, short-term exposure to $PM_{2.5}$ may induce vascular stiffness in the general population in China and India[41, 43], consistent with our results from studies that included participants with metabolic disorders. In particular, we focused on the population with metabolic disorders, and previous studies suggested a higher susceptibility risk for $PM_{2.5}$ exposure in these participants[44, 45], which has not been elucidated in China. Therefore, the present study fills this knowledge gap.

Our results indicated the detrimental effects of $PM_{2.5}$ on ABI reduction, reflecting the impacts of air pollution on peripheral atherosclerosis. In the early studies in Europe and the USA, no association was observed between $PM_{2.5}$ and ABI, possibly due to the limited number of studies[46]. However, a cross-sectional study reported significant associations between long-term PM exposure and ABI reduction in the general population, which is consistent with our results[19]. Furthermore, previous studies have been supported by the positive correlation between air pollution and the prevalence and progression of atherosclerosis in other vessel beds, such as carotid intima-media thickness[43, 47], coronary calcification[47], and thoracic aortic calcification[48]. Notably, a recent study demonstrated that vascular dysfunction associated with short-term environmental PM exposure may be exacerbated in glucose-metabolizing populations[44], which may partly explain the underlying effect of abnormal metabolism on peripheral arterial disease.

This study also showed the effects of exposure to $PM_{2.5}$ constituents on elevated baPWV and reduced ABI in participants with metabolic disorders. Among them, BC and NH_4^+ exerted significant effects on arterial stiffness and peripheral atherosclerosis. Existing relevant research on the relationship between BC and other indicators of vascular damage or other diseases may support our finding[43, 49]. Furthermore, a nationwide multicenter study in China suggested that NH_4^+ in $PM_{2.5}$ is the main cause of the association with the increasing risk of blood pressure and fasting glucose level, which may partly explain the underlying mechanisms for the $PM_{2.5}$ constituents in atherosclerosis[50].

We also found that OM might exert a positive effect on the development of peripheral atherosclerosis. The formation of OM in the particulate phase was mainly caused by the emission of volatile organic compounds[51, 52]. Previous study demonstrated that the removal of organic matters from $PM_{2.5}$ mass significantly reduced the cardiovascular toxic effects of ambient air pollution exposure[53]. The potential mechanism between the $PM_{2.5}$ components and atherosclerosis still need further study.

We found that BC contributed the most to the elevated baPWV and that NO_3^- was strongly associated with reduced ABI. Elevated baPWV indicates increased arterial stiffness in the large vessel[4, 5], whereas reduced ABI indicates peripheral arterial disease due to conditions causing arterial narrowing, indicating more advanced atherosclerosis compared with increased arterial stiffness at an early stage[6-8]. The different constituents of $PM_{2.5}$ associated with baPWV and ABI may indicate the different mechanisms underlying BC- and NO_3^--mediated vascular damages. The possible mechanisms of increased arterial stiffness caused by BC are autonomic nervous system disorders, oxidative stress, and inflammation as well as free radicals that reduce nitric oxide and increase vasoconstrictors, such as angiotensin, endothelin, and prostaglandins, which exacerbate arterial stiffness[54, 55]. BC was found to have a lesser effect on endothelial function impairment[55]. Contrarily, the mechanisms of increased atherosclerosis are caused by NO_3^- mainly through pathways such as oxidative stress and inflammatory response, which leads to leukocyte migration, infiltration, and arterial foam cell formation, resulting in endothelial cell damage[56].

The potential biological mechanisms linked to the effect of fine PM and vascular injury in participants with metabolic disorder are accountable. Some studies indicated that PM pollutants might cause circadian rhythm disturbances, leading to abnormal liver lipid metabolism[57]. Furthermore, several studies have demonstrated that air pollutant-mediated alterations in autonomic homeostasis can further exacerbate systemic insulin resistance through the sympathetic nervous system over activity, which can further contribute to the development of diabetes[58]. In particular, elevated blood pressure may force endothelial cells and arterial smooth muscle cells to accelerate vascular damage[59]. Hyperglycemia also induces massive changes in the cellular level of vascular tissue, which may accelerate the atherosclerotic process[60]. Hence, the combination of metabolic disorders and fine PM may accelerate vascular injury.

The present study included a large population. When analyzing the effects of $PM_{2.5}$ and its constituents on vascular injury, we adjusted for various potential vascular injury confounding factors. Furthermore, the sensitivity analysis showed consistent results. However, several limitations of the study

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should be considered. First, this is a cross-sectional design, which does not allow for the interpretation of causality between the $PM_{2.5}$ components and vascular injury. Second, we only used baPWV and ABI as the vascular injury indices. Carotid-femoral PWV is usually considered the gold standard for the measurement of central arterial stiffness[61]. Future studies are needed to elucidate the effects on central arterial stiffness. Third, health examinations were often sponsored by employers. Health check-up centers are usually located nearby institutions or companies. Therefore, the concentration of air pollution was estimated based on the address of the health check-up centers, representing the air condition at the addresses. Finally, some potential confounding factors, including individual income status and in-house environment, should have been considered due to the lack of relevant data.

Conclusions

This large multicenter study demonstrated a positive association between long-term exposure to $PM_{2.5}$ and its constituents and vascular injury in a population with metabolic disorders in China. BC contributed more to vascular injury risk than the other $PM_{2.5}$ constituents. The heterogeneous contribution of different $PM_{2.5}$ constituents to vessel bed damage is worthy of attention when developing targeted preventive strategies.

Author Contributions

In our research, L.L. and H.H. designed the study, collected and analyzed data, wrote the manuscript, and substantively revised it. F.L., T.S., Z.C., K. Q., M.L., and Y.H. performed the statistical analysis and interpreted data. X.H. and X.Z. wrote codes for data analysis. P.Z., X.-J.Z., Z.-G.S., J.C., and S.Y. reviewed and checked the data. P.J. and H.L. contributed equally to the project design, manuscript editing, and research supervision. We confirm that the work has never been published previously. The manuscript is an original work and is not being considered for publication elsewhere.

All authors read, reviewed, and approved the submitted manuscript.

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Conflicts of Interest

All authors declare that there are no conflicts of interest.

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Supplementary Fig. 1. Map of the cities where the health check-up centres were located

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Supplementary Table 1. Distribution of one-year average exposure levels of $PM_{2.5}$ mass and its constituents in China from 2011 to 2017

Air pollutants	Mean	Median	SD	Minimum	Maximum	IQR
$PM_{2.5}$ mass (μg/m³)	66.33	68.91	18.65	22.98	109.63	29.84
$PM_{2.5}$ BC (μg/m³)	3.22	2.97	0.82	1.33	5.32	1.31
$PM_{2.5}$ NH_4^+ (μg/m³)	8.40	8.61	1.50	3.07	12.57	2.32
$PM_{2.5}$ NO_3^- (μg/m³)	12.55	13.24	2.74	3.91	19.36	4.01
$PM_{2.5}$ OM (μg/m³)	17.16	15.94	5.40	6.57	28.45	9.32
$PM_{2.5}$ SO_4^{2-} (μg/m³)	11.41	11.49	2.36	4.80	18.49	3.10

SD, standard deviation; IQR, interquartile range; $PM_{2.5}$, fine particulate matter <2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate.

Supplementary Table 2. Distribution of one-year average exposure levels of $PM_{2.5}$ mass and its constituents in 11 health management centers

Centers	*n* (%) (N=124,387)	City	Median [IQR]					
			$PM_{2.5}$ mass (μg/m³)	$PM_{2.5}$ BC (μg/m³)	$PM_{2.5}$ NH_4^+ (μg/m³)	$PM_{2.5}$ NO_3^- (μg/m³)	$PM_{2.5}$ OM (μg/m³)	$PM_{2.5}$ SO_4^{2-} (μg/m³)
C01	1269 (1.02%)	Hohhot	51.78 [46.57-61.51]	2.59 [2.24-3.37]	5.41 [5.16-6.07]	8.18 [7.37-15.73]	12.92 [10.94-15.73]	8.06 [7.00-10.15]
C02	51194 (41.16%)	Beijing	84.30 [73.11-86.68]	3.79 [2.99-4.24]	9.54 [9.08-9.87]	14.73 [14.13-24.70]	22.08 [17.44-24.70]	12.85 [10.88-13.58]
C03	5952 (4.79%)	Shijiazhuang	99.28 [91.53-100.88]	4.95 [4.36-5.10]	10.65 [9.84-10.99]	16.03 [14.81-25.99]	25.01 [23.04-25.99]	15.98 [14.20-16.19]
C04	947 (0.76%)	Tianjin	86.25 [82.96-103.96]	4.23 [4.03-5.04]	9.60 [9.25-11.50]	14.55 [14.13-26.00]	21.99 [21.23-26.00]	13.32 [12.70-16.57]
C05	1272 (1.02%)	Linfen	68.76 [67.94-71.22]	3.23 [3.21-3.28]	9.43 [9.32-9.92]	14.51 [14.22-17.27]	16.98 [16.81-17.27]	12.00 [11.85-12.36]
C06	2105 (1.69%)	Zhengzhou	87.30 [86.68-88.48]	4.25 [4.22-4.28]	9.87 [9.75-10.30]	14.91 [14.77-24.90]	24.75 [24.51-24.90]	13.91 [13.61-14.42]
C07	4461 (3.59%)	Wuhan	69.56 [68.64-82.70]	3.51 [3.34-4.25]	8.65 [8.45-9.72]	14.33 [14.08-21.06]	17.82 [17.21-21.06]	12.68 [12.28-15.49]
C08	20694 (16.64%)	Shiyan	38.33 [37.80-41.31]	2.10 [2.07-2.35]	6.38 [6.22-6.78]	8.51 [8.19-10.98]	10.31 [10.16-10.98]	7.56 [7.48-8.42]
C09	20930 (16.83%)	Chongqiang	55.91 [55.16-58.78]	2.94 [2.91-3.03]	7.95 [7.86-8.27]	10.84 [10.76-13.78]	13.13 [12.96-13.78]	11.72 [11.49-12.39]
C10	13492 (10.85%)	Changsha	55.23 [54.57-55.39]	2.76 [2.74-2.76]	7.34 [7.14-7.38]	11.84 [11.79-14.34]	14.18 [14.13-14.34]	10.50 [10.15-10.70]
C11	2071 (1.66%)	Zhanjiang	25.48 [24.74-29.95]	1.50 [1.48-1.91]	3.49 [3.27-4.10]	4.41 [4.12-8.55]	7.32 [7.17-8.55]	5.15 [5.10-6.39]

$PM_{2.5}$, fine particulate matter <2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate.

Supplementary Table 3. Spearman's correlation between $PM_{2.5}$ mass and its constituents in all subjects

Exposure	$PM_{2.5}$ total mass (μg/m³)	$PM_{2.5}$ BC (μg/m³)	$PM_{2.5}$ NH_4^+ (μg/m³)	$PM_{2.5}$ NO_3^- (μg/m³)	$PM_{2.5}$ OM (μg/m³)	$PM_{2.5}$ SO_4^{2-} (μg/m³)
$PM_{2.5}$ total mass (μg/m³)	1.000	0.944	0.960	0.911	0.968	0.901
$PM_{2.5}$ BC (μg/m³)	0.944	1.000	0.894	0.801	0.925	0.951
$PM_{2.5}$ NH_4^+ (μg/m³)	0.960	0.894	1.000	0.955	0.908	0.893
$PM_{2.5}$ NO_3^- (μg/m³)	0.911	0.801	0.955	1.000	0.892	0.785
$PM_{2.5}$ OM (μg/m³)	0.968	0.925	0.908	0.892	1.000	0.850
$PM_{2.5}$ SO_4^{2-} (μg/m³)	0.901	0.951	0.893	0.785	0.850	1.000

$PM_{2.5}$, fine particulate matter <2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate.

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Supplementary Table 4. Sensitive analyses of ORs [95% CIs] for associations between single-pollutants and vascular damage outcomes

Exposures	Outcomes	Cases, *n*	Sensitive analysis 1 OR per 1 μg/m³ increase (95% CI)	*p* value	Sensitive analysis 2 OR per IQR increase (95% CI)	*p* value	Sensitive analysis 3 OR per 1 μg/m³ increase (95% CI)	*p* value	Sensitive analysis 4 OR per 1 μg/m³ increase (95% CI)	*p* value
$PM_{2.5}$ mass (μg/m³)	baPWV ≥	53,022	1.017 (1.016, 1.019)	<0.001	1.403 (1.373, 1.434)	<0.001	1.059 (1.057, 1.061)	<0.001	1.015 (1.014, 1.016)	<0.001
$PM_{2.5}$ BC (μg/m³)	1400 cm/s	(42.63%)	1.195 (1.167, 1.224)	<0.001	1.435 (1.410, 1.461)	<0.001	2.314 (2.238, 2.392)	<0.001	1.187 (1.160, 1.214)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)			1.280 (1.263, 1.299)	<0.001	1.444 (1.416, 1.472)	<0.001	1.596 (1.557, 1.636)	<0.001	1.214 (1.208, 1.240)	<0.001
$PM_{2.5}$ NO_3^- (μg/m³)			1.130 (1.120, 1.139)	<0.001	1.268 (1.244, 1.293)	<0.001	1.472 (1.452, 1.493)	<0.001	1.095 (1.086, 1.104)	<0.001
$PM_{2.5}$ OM (μg/m³)			1.018 (1.013, 1.022)	<0.001	1.132 (1.108, 1.157)	<0.001	1.156 (1.150, 1.163)	<0.001	1.015 (1.011, 1.019)	<0.001
$PM_{2.5}$ SO_4^{2-} (μg/m³)			1.143 (1.135, 1.152)	<0.001	1.352 (1.332, 1.373)	<0.001	1.324 (1.309, 1.339)	<0.001	1.133 (1.125, 1.141)	<0.001
$PM_{2.5}$ mass (μg/m³)	ABI < 0.9	1,293	1.030 (1.023, 1.038)	<0.001	1.367 (1.242, 1.506)	<0.001	1.032 (1.024, 1.041)	<0.001	1.039 (1.034, 1.045)	<0.001
$PM_{2.5}$ BC (μg/m³)		(1.04%)	1.224 (1.091, 1.375)	0.003	1.153 (1.052, 1.265)	<0.001	1.571 (1.386, 1.782)	<0.001	1.570 (1.419, 1.737)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)			1.538 (1.417, 1.672)	<0.001	1.742 (1.589, 1.912)	<0.001	1.425 (1.309, 1.550)	<0.001	1.613 (1.516, 1.717)	<0.001
$PM_{2.5}$ NO_3^- (μg/m³)			1.345 (1.283, 1.411)	<0.001	1.857 (1.704, 2.026)	<0.001	1.279 (1.218, 1.343)	<0.001	1.355 (1.308, 1.405)	<0.001
$PM_{2.5}$ OM (μg/m³)			1.013 (0.992, 1.034)	<0.001	1.333 (1.199, 1.485)	<0.001	1.082 (1.058, 1.108)	0.231	1.058 (1.040, 1.078)	<0.001
$PM_{2.5}$ SO_4^{2-} (μg/m³)			1.182 (1.134, 1.233)	0.001	1.135 (1.052, 1.226)	<0.001	1.220 (1.168, 1.275)	<0.001	1.258 (1.215, 1.302)	<0.001

Sensitive analysis 1: The exposures used were two-year lag of $PM_{2.5}$ and the constituents; Sensitive analysis 2: transferring $PM_{2.5}$ and the constituents from continuous variables to quartiles; Sensitive analysis 3: using GLMM model to account for a random effect of multi-centre study setting; The sensitive analysis 1, 2, and 3 models adjusting age, sex, BMI, MAP, per GDP, smoke, Temp, RH, WBC, ALT, eGFR, TG, LDL-C, HDL-C, and FBG; Sensitive analysis 4 model additionally adjusting the information on medication for metabolic disorders.

OR, odds ratio; CI, confidence interval; IQR, interquartile range; GLMM model, generalized linear mixed model; $PM_{2.5}$, fine particulate matter < 2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^- , nitrate; OM, organic matter; SO_4^{2-}, sulfate; BMI, body mass index; MAP, mean arterial pressure; per GDP, gross domestic product per capita; Temp, temperature; RH, relative humidity; WBC, white blood cell; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C. high-density lipoprotein cholesterol; FBG, fasting blood glucose.

Supplementary Table 5. Sensitive analyses of ORs [95% CIs] for associations between multiple-pollutants and vascular damage outcomes

Exposures	Outcomes	Cases, *n*	Sensitive analysis 1 OR per quartile increase (95% CI)	*p* value	Sensitive analysis 2 OR per quartile increase (95% CI)	*p* value	Sensitive analysis 3 OR per quartile increase (95% CI)	*p* value
$PM_{2.5}$ constituents								
$PM_{2.5}$ BC (μg/m³)	baPWV ≥	53,022	1.150 (1.120, 1.181)	<0.001	1.061 (1.034, 1.088)	<0.001	1.060 (1.033, 1.087)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)	1400 cm/s	(42.63%)						
$PM_{2.5}$ NO_3^- (μg/m)								
$PM_{2.5}$ OM (μg/m³)								
$PM_{2.5}$ SO_4^{2-} (μg/m³)								
$PM_{2.5}$ constituents								
$PM_{2.5}$ BC (μg/m³)	ABI <0.9	1,293	2.476 (2.175, 2.819)	<0.001	2.250 (1.984, 2.551)	<0.001	2.253 (1.986, 2.554)	<0.001
$PM_{2.5}$ NH_4^+ (μg/m³)		(1.04%)						
$PM_{2.5}$ NO_3^- (μg/m³)								
$PM_{2.5}$ OM (μg/m³)								
$PM_{2.5}$ SO_4^{2-} (μg/m³)								

Sensitive analysis 1: The exposures used were two-year lag of $PM_{2.5}$ and the constituents; Sensitive analysis 2: using GLMM model to account for a random effect of multi-centre study setting; The sensitive analysis 1 and 2 models adjusting age, sex, BMI, MAP, per GDP, smoke, Temp, RH, WBC, ALT, eGFR, TG, LDL-C, HDL-C, and FBG; Sensitive analysis 3 model additionally adjusting the information on medication for metabolic disorders.

OR, odds ratio; CI, confidence interval; IQR, interquartile range; GLMM model, generalized linear mixed model; $PM_{2.5}$, fine particulate matter < 2.5 μm; BC, black carbon; NH_4^+, ammonium salts; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate; BMI, body mass index; MAP, mean arterial pressure; per GDP, gross domestic product per capita; Temp, temperature; RH, relative humidity; WBC, white blood cell; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C. high-density lipoprotein cholesterol; FBG, fasting blood glucose.

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