GeoHealth

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Special Section:
Atmospheric PM2.5 in China: indoor, outdoor, and health effects

Association Between Long-Term Exposure to Fine Particulate Matter Constituents and Progression of Cerebral Blood Flow Velocity in Beijing: Modifying Effect of Greenness

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Abstract Few studies have explored the effects of fine particulate matter ($PM_{2.5}$) and its constituents on the progression of cerebral blood flow velocity (BFV) and the potential modifying role of greenness. In this study, we investigated the association of $PM_{2.5}$ and its constituents, including sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), organic matter (OM), and black carbon (BC), with the progression of BFV in the middle cerebral artery. Participants from the Beijing Health Management Cohort who underwent at least two transcranial Doppler sonography examinations during 2015–2020 were recruited. BFV change and BFV change rate were used to define the progression of cerebral BFV. Linear mixed effects models were employed to analyze the data, and the weighted quantile sum regression assessed the contribution of $PM_{2.5}$ constituents. Additionally, greenness was examined as a modifier. Among the examined constituents, OM exhibited the strongest association with BFV progression. An interquartile range increase in $PM_{2.5}$ and OM exposure concentrations was associated with a decrease of −16.519 cm/s (95% CI: −17.837, −15.201) and −15.403 cm/s (95% CI: −16.681, −14.126) in BFV change, and −10.369 cm/s/year (95% CI: −11.387, −9.352) and −9.615 cm/s/year (95% CI: −10.599, −8.632) in BFV change rate, respectively. Furthermore, stronger associations between $PM_{2.5}$ and BFV progression were observed in individuals working in areas with lower greenness, those aged under 45 years, and females. In conclusion, reducing $PM_{2.5}$ levels in the air, particularly the OM constituent, and enhancing greenness could potentially contribute to the protection of cerebrovascular health.

Plain Language Summary Fine particulate matter in the atmosphere has been shown to be associated with cerebrovascular disease, however, the adverse effects of fine particulate matter chemical constituents on cerebral hemodynamics and the role of greenness in this are yet to be evaluated. In this study, we evaluated the association of fine particulate matter and its constituents (sulfate, nitrate, ammonium, black carbon, and organic matter) with cerebral arterial blood flow velocity (BFV) and the modifying effect of greenness. We found that fine particulate matter and its constituents accelerate the reduction of cerebral arterial BFV and that the association is stronger where greenness levels are low. Our findings provide new evidence that reducing fine particle exposure and enhancing urban greenery may be an effective way to protect cerebrovascular health.

Key Points:

- $PM_{2.5}$ and its constituents were associated with a greater and faster reduction in the cerebral artery blood flow velocity
- The impacts of $PM_{2.5}$ and its constituents were modified by greenness
- Younger people and females were found to be more vulnerable

Supporting Information:

Supporting Information may be found in the online version of this article.

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1. Introduction

With the rapid urbanization in China, the resulting air pollution has received more and more attention in recent years (Kumar et al., 2023). Among pollution-related diseases, the effect of fine particulate matter ($PM_{2.5}$) on cerebrovascular disease is becoming one of the most concerning health issues. Evidence has confirmed the association of $PM_{2.5}$ with cerebrovascular disease, including stroke (Niu et al., 2021; Tian et al., 2018; Verhoeven et al., 2021). However, the possible mechanism behind this association is not clear. A study suggested that cerebral hemodynamics may be an important pathway in the association between $PM_{2.5}$ and cerebrovascular disease (Wellenius et al., 2013). $PM_{2.5}$ may cause cerebral ischemia through mechanisms such as oxidative stress, which, in turn, causes cerebrovascular disease (Z. Chen et al., 2022). Compared to previous studies that focused on specific cerebrovascular diseases (e.g., stroke), we focused more on the effects of air pollution on cerebral blood flow, which will help explain the mechanisms of air pollution-induced cerebrovascular diseases.

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Cerebrovascular diseases encompass a broad spectrum of symptoms related to alterations in cerebrovascular hemodynamics (Alwatban et al., 2021). Among the intracranial arteries, the middle cerebral artery (MCA), which is one of the most commonly studied cerebral vessels, is considered to be the most common site of lesion (Banerjee & Chimowitz, 2017). Transcranial Doppler (TCD) sonography, a non-invasive method for hemodynamic monitoring, is widely used to measure cerebral artery blood flow velocity (BFV) in clinical settings. The level of cerebral artery BFV tends to decrease with increasing age (Alwatban et al., 2021). A previous study investigated the effects of temperature and $PM_{2.5}$ on cerebrovascular hemodynamics in elderly people (Pan et al., 2015). They reported that an increases in the 28-days moving average $PM_{2.5}$ concentration was associated with lower BFV in MCA. However, few studies have examined the long-term effects of $PM_{2.5}$ on the progression of cerebral artery BFV in the Chinese population. Asians have a higher burden of cerebrovascular disease compared to whites (Gutierrez et al., 2022), so conclusions from other countries may not be applicable to the Chinese population. Additionally, previous studies have tended to focus on the health effects of $PM_{2.5}$ particles. In this study, we aim to investigate the effects of their specific chemical constituent, which will provide insights for controlling $PM_{2.5}$ emissions by targeting different sources of its constituents. Therefore, it is highly necessary to evaluate the associations of $PM_{2.5}$ and its constituents with cerebrovascular hemodynamics in the Chinese population.

The term "greenness" refers to the vegetation cover in the environment, often measured by several indices, including the normalized difference vegetation index (NDVI), enhanced vegetation index (EVI) and soil-adjusted vegetation index (SAVI) (He et al., 2022). Previous studies have investigated the health effects of greenness (Li et al., 2023; T. Liu et al., 2021; Zagnoli et al., 2022). It has been shown that vegetation can trap particulate matter in the atmosphere or absorb gaseous pollutants through leaf stomata (L. Chen et al., 2016). Greenness has been suggested to modify the association between air pollution and cardiovascular disease (CVD). A recent study (Zhu et al., 2022) demonstrated that living in residential areas with higher levels of greenness can mitigate the adverse effects of air pollution on the heart. Interestingly, a previous study reported that higher NDVI was associated with a higher risk of $PM_{2.5}$ induced CVD hospitalization (Klompmaker et al., 2021). The current evidence on the role of greenness in the health effects of air pollution is inconsistent, and further research is urgently needed. Moreover, previous studies investigating the modifying effect of greenness often relied on a single greenness indicator (NDVI). In our study, we aim to use multiple greenness indicators (NDVI, EVI, and SAVI) to obtain more comprehensive and convincing evidence regarding the modifying effects of greenness.

Our main objective is to investigate the associations of long-term exposure to $PM_{2.5}$ and its constituents with the progression of cerebral arterial BFV in the population who have a fixed workplace and stable working hours in Beijing. Additionally, we aim to explore whether greenness can modify this association. The importance and significance of this study lie in its contribution to the growing body of evidence concerning air pollution-related cerebrovascular diseases. By investigating the impact of air pollution on these conditions, this research aims to shed light on the potential risks to human health. Moreover, the findings of this study can serve as a relevant scientific basis for the development of effective air pollution management strategies and urban greening policies.

2. Methods

2.1. Study Design and Population

The Beijing Health Management Cohort (BHMC) is a large-scale prospective dynamic cohort established in 2008 in Beijing, China, with annual recruitment. Participants are mainly employees with a fixed working address and stable working hours in Beijing. Details of the BHMC have been described previously (J. Liu et al., 2018). We obtained data of 13,864 subjects who underwent at least two physical examinations of TCD from the BHMC between 2015 and 2020, and the first and last measurements were used. Because the workplace of participants was used to assess the exposure, we excluded 2,035 participants who were older than 60 years or retired. In addition, we also excluded 2,024 participants with incomplete physical examination data. We further excluded 186 participants with malignant tumor, stroke or other cerebrovascular disease from the analyses. Finally, 9,619 participants were included in the study.

2.2. Outcome Assessment

During the medical examination, BFV was measured using a TCD ultrasound device. We measured systolic BFV in the MCA, and the side that is more prone to cerebrovascular disease was used for the analysis (Foerch

et al., 2005; Hedna et al., 2013; Rodríguez Hernández et al., 2003). Progression of BFV in the MCA was defined as BFV change and BFV change rate. The BFV change was calculated as the measurement of MCA BFV at the second physical examination minus the first measurement. The BFV change rate was calculated as the value of the BFV change divided by the time interval between the first and second examination.

2.3. Environment Variables Assessment

Daily average concentrations of $PM_{2.5}$ and its chemical constituents in Beijing during the study period were obtained from the Tracking Air Pollution in China (TAP) website (http://tapdata.org.cn). The TAP team built a two-stage machine learning model to estimate daily full-coverage $PM_{2.5}$ data with a spatial resolution of 10×10 km (Geng et al., 2017, 2021; Xiao, Geng, et al., 2021; Xiao, Zheng, et al., 2021b). The model combined information from multiple data sources, including population, land use data, ground observations, operational chemical transport model simulations, satellite aerosol optical depth, and other ancillary data such as meteorological fields, and elevation. Subsequently, $PM_{2.5}$ component information was then obtained from the operational Community Multiscale Air Quality Modeling System simulation with $PM_{2.5}$ concentration as the total constraint. The $PM_{2.5}$ component data collected in this study included sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), black carbon (BC) and organic matter (OM). Organic matter refers to various soluble and insoluble organic substances (Gautam et al., 2016), which includes the mass of elements such as oxygen attached to organic carbon (OC). As the concentrations of OM cannot be directly measured, they were considered to be 1.6 times the concentrations of OC in this study (S. Liu et al., 2022).

To investigate whether greenness could modify the associations of $PM_{2.5}$ and its constituents with the progression of BFV in MCA, NDVI was used to quantify the levels of greenness. Based on the land surface reflectance of the visible red (RED) and the near-infrared parts of the light spectra, NDVI was calculated according to the following equations:

$$\mathrm{NDVI} = (\mathrm{NIR} - \mathrm{RED})/(\mathrm{NIR} + \mathrm{RED})$$

For further analysis, we calculated the mean NDVI within a 1,000 m circular buffer around each subject's work address. In addition, EVI and SAVI were also collected for sensitivity analysis. The two indicators were calculated respectively according to the following equations:

$$\mathrm{SAVI} = (1 + \mathrm{L}) \times (\mathrm{NIR} - \mathrm{RED})/(\mathrm{NIR} + \mathrm{RED} + \mathrm{L}) \text{ and}$$

$$\mathrm{EVI} = 2.5 \times (\mathrm{NIR} - \mathrm{RED})/(\mathrm{NIR} + 6\mathrm{RED} - 7.5\mathrm{BLUE} + 1)$$

where L is the correction factor and is set to 0.5 to reduce the impact of soil background. The EVI calculated by adding the blue band (BLUE) compensated for the effects of incomplete atmospheric correction and soil brightness when vegetation density was sparse. All three greenness indicators above ranged from -0.2 to $+1.0$, with higher values indicating higher levels of greenness. We dichotomized greenness into two categories of low or high levels using the median of the greenness indicator as the cut-off point.

We obtained the latitude and longitude of the subjects' work address (Gautam et al., 2020) from Baidu Maps. Based on the geocoding of each subject, we calculated the average environmental exposure between the two medical examinations for each individual, and these exposures were used for analysis.

2.4. Covariates Assessment

The participants' alcohol consumption status, smoking status, physical exercise intensity and excessive salt intake were assessed by a questionnaire. Physical exercise intensity was divided into three levels: low intensity (walking, Tai Chi, dancing), medium intensity (jogging, cycling, climbing) and high intensity (swimming, playing ball games, rope skipping). Participants were asked to take off their coats and shoes while their height and weight were measured. Their body mass index (BMI) was then calculated: BMI = weight (in kilograms)/height^2 (in meters squared). Participants were asked not to smoke or consume caffeine 30 min before blood pressure was measured. The staff used an electronic sphygmomanometer to measure the systolic blood pressure and diastolic blood pressure after the participants were seated. Mean arterial pressure (MAP) was calculated using the formula: MAP = 1/3SBP + 2/3DBP. Before blood sample collection, the participants were required to fast for at

least 12 hr. Triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG) were measured by the enzymatic method according to the operating manual of the central laboratory of the hospital.

2.5. Statistical Analysis

Descriptive statistical analyses were performed on all environmental variables and baseline characteristics. We performed linear mixed models with a random intercept to assess the associations of $PM_{2.5}$ and its constituents with the progression of BFV, with the participant's companies considered as a random effect. We assessed the health effects of $PM_{2.5}$ and its constituents on potentially susceptible subpopulations stratified by sex, age (age<45, age≥45) and NDVI (low NDVI, high NDVI). We used the weighted quantile sum (WQS) regression model to evaluate how much a $PM_{2.5}$ constituent contributed to the overall effect, which is a weighted quartile sum approach in conjunction with linear (continuous outcomes) regression (Carrico et al., 2015; Czarnota et al., 2015). This approach took all the $PM_{2.5}$ constituents into consideration, and $PM_{2.5}$ constituents included in this model were constrained to have the same direction of effect for the association. By grouping different chemicals into quartiles, the WQS regression model calculated a weighted linear index, which represented the whole burden of all five $PM_{2.5}$ constituents. The corresponding weight of each $PM_{2.5}$ constituent showed how much a constituent contributed to the WQS index. In WQS regression, the data were randomly split into two data sets (40% as training set and 60% as validation set). Based on the results of the single constituent model, we set an unconstrained negative coefficient. After bootstrapping 2,000 times, we obtained the degree of contribution of each chemical constituent. We also constructed restricted cubic splines (knot = 4) to graphically estimate the association between $PM_{2.5}$ and the progression of BFV.

The following three models were fitted to adjust for confounders: Model 1 (n = 9,619): adjusted for sex, age; Model 2 (n = 9,619): additionally adjusted for BMI, MAP, FBG, TG, LDL-C, and HDL-C; Model 3 (n = 5,273): additionally adjusted for exercise intensity, alcohol consumption, smoking, and excessive salt intake. As some subjects refused to complete the questionnaire, model 3 is for a subset, and the results of model 2 are reported primarily. All effects were expressed per interquartile range (IQR) increase. Finally, we performed sensitivity analyses to examine the robustness of our results: (a) We evaluate individual exposure based on residential address or based on both workplace and residential address. (b) We further excluded participants with heart disease such as coronary heart disease to assess the robustness of the estimated associations of $PM_{2.5}$ and its constituents with the outcome. (c) We further adjusted for the effects of antihypertensive, lipid-regulating, and antidiabetic drugs. (d) In order to illustrate the effect modification by greenness, we used two other greenness indices, SAVI and EVI with buffer sizes of 1–3 km. (e) To assess whether spatial resolution in the exposure estimates change the robustness of the results, based on the monitoring station data, we used kriging interpolation to calculate $PM_{2.5}$ concentration at a 1 × 1 km spatial resolution and performed subgroup analysis by greenness.

Two-tailed P values < 0.05 were considered statistically significant. ArcGis 10.6 software was used to complete the Kriging interpolation method. R 4.2.1 software was used to analyze the associations of $PM_{2.5}$ and its constituents with the progression of BFV in MCA and the modifying effect of greenness.

3. Results

3.1. Description of the Study Population and Exposure

Baseline characteristics of study participants and individual exposures to environmental factors are shown in Table 1 and Table S1 in Supporting Information S1. The median follow-up time was 23 months. At baseline, the median age of the study population was 41 years, and 57.03% of them were male. The median BMI was 24.16 kg/m^2. The mean exposure concentrations of $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM and BC were 52.63, 7.60, 10.63, 6.51, 12.40, 2.22 μg/m^3, respectively.

3.2. Associations Between Progression of BFV and Air Pollution Exposure

The associations of $PM_{2.5}$ and its constituents with the progression of BFV in MCA is depicted in Table 2. The associations of $PM_{2.5}$ and its constituents with the BFV progression were significantly negative in the model 1. Results were significant in model 2 and model 3 as well. In the main model (model 2), we found that per IQR

Table 1
Baseline Characteristics of the Study Participants

Variables	Total participants
Number of participants, *n*	9,619
Age (years), median (IQR)	41 (16)
<45, *n* (%)	5,655 (58.79)
≥45, *n* (%)	3,964 (41.21)
Sex, *n* (%)	
Male	5,486 (57.03)
Female	4,133 (42.97)
BMI (kg/m^2), median (IQR)	24.16 (4.84)
SBP (mmHg), median (IQR)	120.00 (20.00)
DBP (mmHg), median (IQR)	79.00 (14.00)
MAP (mmHg), median (IQR)	92.00 (16.33)
FBG (mmol/L), median (IQR)	5.20 (0.71)
TG (mmol/L), median (IQR)	1.19 (1.00)
LDL-C (mmol/L), median (IQR)	2.79 (1.02)
HDL-C (mmol/L), median (IQR)	1.27 (0.41)
Physical activity, *n* (%)	
Low intensity	4,006 (74.91)
Moderate intensity	818 (15.30)
High intensity	524 (9.79)
Current alcohol consumption, *n* (%)	1,008 (18.98)
Cigarette smoking, *n* (%)	
Never	4,064 (76.19)
Former	190 (3.56)
Current	1,080 (20.25)
Excessive salt intake, *n* (%)	1,140 (21.39)

Note. IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FBG, fasting blood glucose; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

increase in $PM_{2.5}$ concentrations was associated with −16.519 cm/s (95% CI: −17.837, −15.201) decrease in BFV change, and −10.369 cm/s/year (95% CI: −11.387, −9.352) decrease in BFV change rate. Each $PM_{2.5}$ constituent in the single-pollutant model showed similar effect values to the total $PM_{2.5}$ particles (Table 2). The estimated weight of $PM_{2.5}$ constituents for each WQS index is shown in Figure 2. The highest weighted $PM_{2.5}$ constituent in both BFV change and BFV change rate models was OM, followed by NO_3^-. NH_4^+, BC, SO_4^{2-} were given the lower weight (<0.2).

Stratified analysis showed that stronger associations of $PM_{2.5}$ and its constituents with the progression of BFV were presented in individuals aged <45 years and in females (Figure 1). The non-linear analysis showed an approximately linear exposure-response function of $PM_{2.5}$ concentration and BFV progression (Figure 3), which was consistent with the estimates from the other models (Table 2).

3.3. Modification Effect of Greenness

In the main analysis, we performed a stratified analysis by median of NDVI with 1 km buffer and observed that the associations of $PM_{2.5}$ and its constituents with the progression of BFV were stronger for subjects who working at sites with lower levels of greenness (Figure 1).

3.4. Sensitivity Analyses

The results of sensitivity analyses suggested that the models were generally robust. After assessing individual exposure based on only the residential address and based on both the workplace and residential address, the results showed that the associations of $PM_{2.5}$ and its constituents with the progression of BFV were broadly consistent with the main analysis (Table S2 in Supporting Information S1). The associations remained robust after adjusting for medication use and excluding cardiac patients (Tables S3 and S4 in Supporting Information S1). And the results were similar when using different greenness indices and buffer sizes (Figures 4 and 5). Regarding the sensitivity analyses of the kriging estimates, we explored the potential impact of spatial scale in the exposure estimates. While our main analysis utilized gridded $PM_{2.5}$ estimates at a spatial resolution of 10 × 10 km, we conducted additional analyses by estimating $PM_{2.5}$ concentrations at a higher spatial resolution of 1 × 1 km using kriging interpolation. This allowed us to investigate whether the spatial resolution affected the reliability of our conclusions. The results of the greenness stratification analysis were also robust after using kriging interpolation to estimate $PM_{2.5}$ concentration (Table S5 in Supporting Information S1), and the association between $PM_{2.5}$ and progression of BFV remains greater for populations with lower greenness. These findings suggest that the original TAP data at a spatial resolution of 10 × 10 km are sufficient to draw convincing conclusions regarding the association between $PM_{2.5}$ and the progression of BFV.

4. Discussion

In this study, we examined the associations between long-term exposure to $PM_{2.5}$ constituents and the progression of cerebral systolic BFV in the MCA, and we also examined the effect modification by greenness based on three indices (NDVI, EVI, and SAVI). The effect of each $PM_{2.5}$ constituent were very similar to that of total $PM_{2.5}$ particles, with OM making the largest contribution to the overall effect. We presented significant negative associations of $PM_{2.5}$ and its constituents with the progression of BFV in the MCA, during a median follow-up of 23 months. Greenness was shown to be a modifier of the $PM_{2.5}$-BFV association. People who exposed to lower greenness had a significantly greater $PM_{2.5}$-induced risk of BFV progression.

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Table 2
Associations of Long-Term $PM_{2.5}$ and Its Constituents Exposures With the Progression of BFV Per Interquartile Range Increase in Exposure

		Model 1 (n = 9,619)		Model 2 (n = 9,619)		Model 3 (n = 5,273)	
Outcome	Pollutant	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
Change of BFV	$PM_{2.5}$	−16.463 (−17.780, −15.147)	<0.001	−16.519 (−17.837, −15.201)	<0.001	−11.730 (−13.070, −10.390)	<0.001
	SO_4^{2-}	−16.377 (−17.747, −15.006)	<0.001	−16.447 (−17.820, −15.075)	<0.001	−11.608 (−12.996, −10.221)	<0.001
	NO_3^-	−17.519 (−18.920, −16.119)	<0.001	−17.579 (−18.981, −16.177)	<0.001	−11.698 (−13.054, −10.342)	<0.001
	NH_4^+	−17.158 (−18.535, −15.781)	<0.001	−17.226 (−18.604, −15.848)	<0.001	−11.619 (−12.979, −10.259)	<0.001
	OM	−15.370 (−16.644, −14.093)	<0.001	−15.403 (−16.681, −14.126)	<0.001	−11.261 (−12.587, −9.934)	<0.001
	BC	−15.879 (−17.211, −14.547)	<0.001	−15.922 (−17.255, −14.588)	<0.001	−11.440 (−12.797, −10.083)	<0.001
Change rate of BFV	$PM_{2.5}$	−10.341 (−11.358, −9.323)	<0.001	−10.369 (−11.387, −9.352)	<0.001	−6.845 (−7.801, −5.889)	<0.001
	SO_4^{2-}	−9.981 (−11.040, −8.923)	<0.001	−10.019 (−11.077, −8.961)	<0.001	−6.576 (−7.565, −5.588)	<0.001
	NO_3^-	−11.072 (−12.154, −9.990)	<0.001	−11.102 (−12.184, −10.020)	<0.001	−6.856 (−7.820, −5.891)	<0.001
	NH_4^+	−10.847 (−11.910, −9.784)	<0.001	−10.883 (−11.946, −9.820)	<0.001	−6.805 (−7.771, −5.838)	<0.001
	OM	−9.601 (−10.585, −8.617)	<0.001	−9.615 (−10.599, −8.632)	<0.001	−6.561 (−7.505, −5.616)	<0.001
	BC	−9.775 (−10.803, −8.748)	<0.001	−9.795 (−10.822, −8.768)	<0.001	−6.551 (−7.518, −5.583)	<0.001

Note. Model 1: adjusted for age and gender; Model 2: additionally adjusted for body mass index, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose; Model 3: additionally adjusted for smoking, alcohol consumption, diet habit and physical activities. BFV, blood flow velocity; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon.

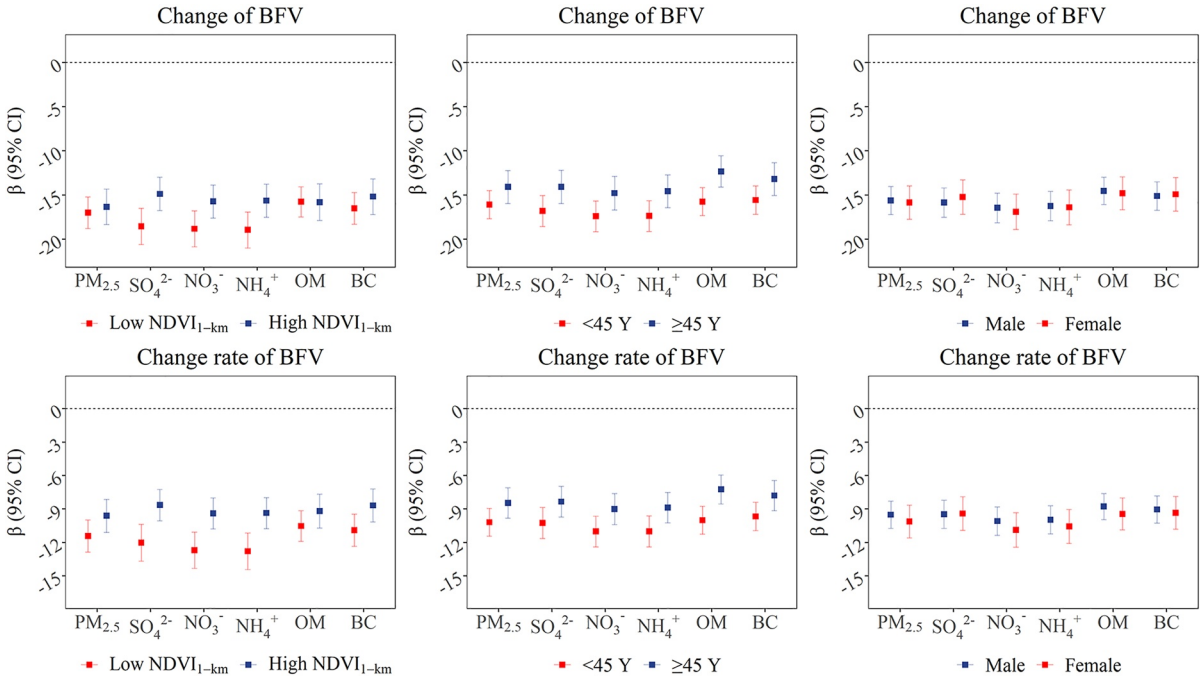

Figure 1. Associations of long-term $PM_{2.5}$ and its constituents exposures with the progression of blood flow velocity per interquartile range increase in exposure stratified by age, sex and normalized difference vegetation index with 1 km buffer. Abbreviations: Y, years old; BFV, blood flow velocity; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon; NDVI, normalized difference vegetation index.

There is limited information on the relationship between long-term exposure to air pollution exposure and cerebral arterial hemodynamics. Several previous studies have shown that long-term exposure to PM may lead to an increased risk of stroke (Amini et al., 2020) and cognitive decline (Kulick et al., 2020). Our research revealed the negative associations of $PM_{2.5}$ and its constituents with the progression of BFV in the MCA, which may be a potential mechanism for cerebrovascular disease caused by long-term exposure to air pollution. A study of the elderly population in Boston showed that short-term $PM_{2.5}$ levels were associated with a statistically significant decrease in cerebral BFV (Wellenius et al., 2013), which is consistent with the results of our study.

Previous studies have revealed that air pollution may affect vascular function, but cerebral hemodynamics have been poorly investigated. A systematic review and meta-analysis showed a positive association between ambient

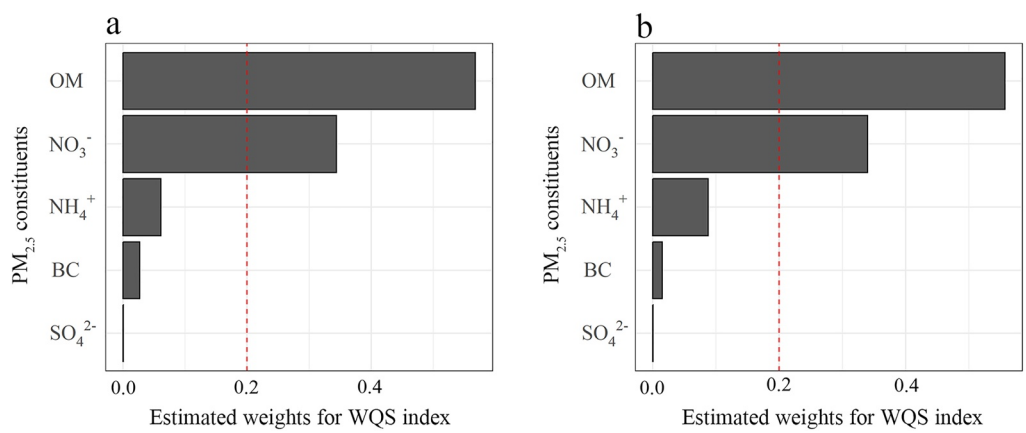

Figure 2. Weighted quantile sum model regression index weights for blood flow velocity (BFV) change (a) and BFV change rate (b). Adjusted for age, gender, body mass index, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose. Abbreviations: WQS, weighted quantile sum; BFV, blood flow velocity; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon; NDVI, normalized difference vegetation index.

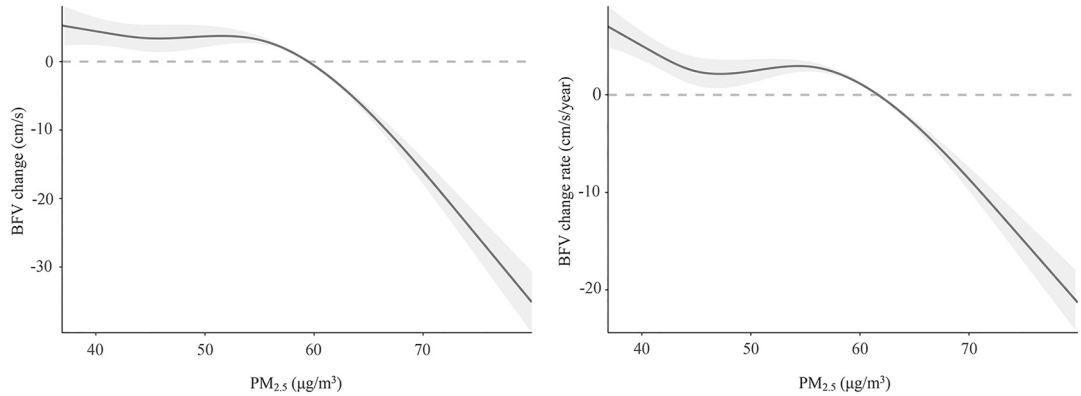

Figure 3. Nonlinear association of $PM_{2.5}$ concentration and progression of blood flow velocity. Shadows, pointwise 95% confidence intervals.

air pollution and increased blood pressure (B. Y. Yang et al., 2018). A study demonstrated that $PM_{2.5}$ damages blood vessels by increasing carotid intima-media thickness, carotid-femoral pulse wave velocity and augmentation index (Ranzani et al., 2020). A longitudinal cohort study (Kaufman et al., 2016) reported that increases in $PM_{2.5}$ concentrations were associated with progression of coronary calcification and atherosclerosis. In addition, experimental studies have shown that nanoscale particulate matter and chronic cerebral hypoperfusion synergistically contribute to white matter injury in a synergistic manner in a mouse model (Q. Liu et al., 2021). A prior study reported that ambient air pollution may affect vascular endothelial function through the induction of vascular inflammation and oxidative stress (Hahad et al., 2020). In the present study, we showed that a higher long-term exposure to $PM_{2.5}$ and its constituents was associated with a greater and faster reduction in BFV. The velocity of blood flow in the MCA may to some extent reflect the blood flow in the relevant brain area (Clark et al., 1996; Dahl et al., 1992; Larsen et al., 1994), indicating a higher likelihood of vascular dysfunction, hypoperfusion and hypoxia (Ashby & Mack, 2021). Previous studies have linked cerebrovascular dysfunction to cerebrovascular disease, including ischemic stroke (Fan et al., 2022), as well as cognitive decline (El Amki & Wegener, 2017; Findlay et al., 2019), depression (Jellinger, 2021) and dementia (Cortes-Canteli & Iadecola, 2020; Gupta & Iadecola, 2015). It is therefore reasonable to assume that a decrease in BFV, together with the above-mentioned vascular changes, plays a role in air pollution-induced cerebrovascular disease.

To our knowledge, there are no studies investigating the relationship between $PM_{2.5}$ chemical constituents and cerebral arterial BFV. Two studies (S. Y. Chen et al., 2014; Lin et al., 2016) explored the relationship between $PM_{2.5}$ constituents and stroke admissions and stroke deaths, respectively. They found that SO_4^{2-}, NO_3^-, NH_4^+, OM and elemental carbon were associated with stroke-related outcomes. In addition, a study investigating the association between $PM_{2.5}$ constituents and lung function, demonstrating that long-term exposure to ambient $PM_{2.5}$ and some constituents, especially OM and NO_3^-, were associated with lower airway function (T. Yang et al., 2021). Another study investigated the association between $PM_{2.5}$ constituents and gestational diabetes, and it suggested that OM, BC, and NO_3^- may be the main culprits for the association (Yu et al., 2020). In our study, we observed significant negative associations of $PM_{2.5}$ and all constituents (SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC) with cerebral artery BFV in the single-pollutant model. In the multi-pollutant model (WQS regression), OM had the largest contribution to the effect of $PM_{2.5}$. These findings align to some extent with previous studies, suggesting that OM may play a dominant role in the negative association between $PM_{2.5}$ and cerebral arterial BFV.

Subgroup analysis showed a generally stronger association in female and those aged <45 years. Gender differences in MCA blood velocity have been reported across the adult lifespan. A previous study compared the differences in BFV changes in MCA between males and females and indicated that the rate of MCA BFV decline was significantly greater in females compared with in males (Alwatban et al., 2021). This may explain why female's MCA BFV is more susceptible to air pollution. A study identified 4,837 cases of stroke and performed a case-crossover analysis (Yitshak Sade et al., 2015). They reported that a higher risk of ischemic stroke was associated with particulate matter in young adults, which is the consistent with our results. Young adults are more likely to be physically active than older adults (Kim et al., 2021), which increases their exposure to air pollution and makes them to be more susceptible.

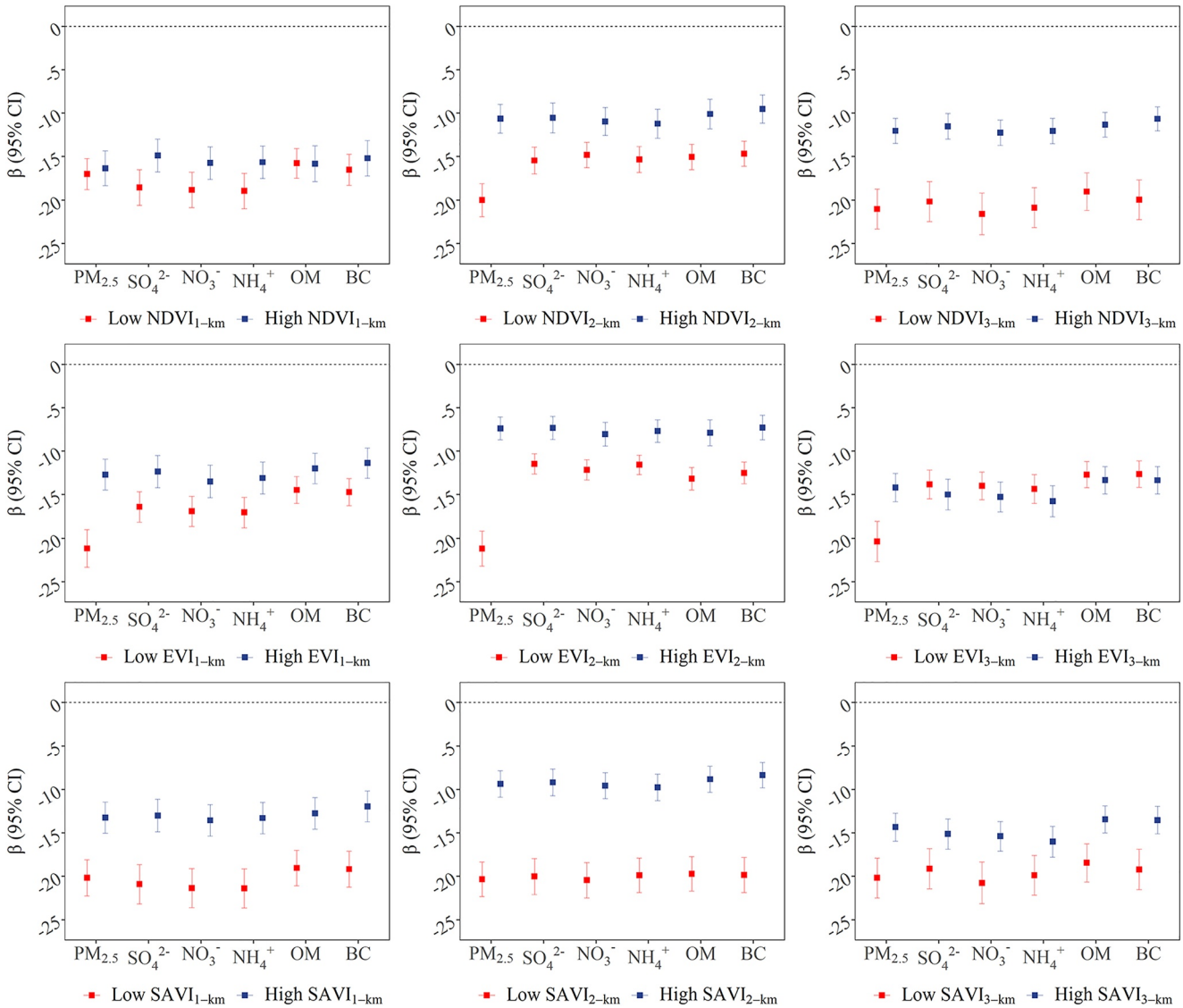

Figure 4. Sensitivity analyses of the associations of long-term $PM_{2.5}$ and its constituents exposures with the change of blood flow velocity per interquartile range increase in exposure, stratified by three different greenness indices for 1–3 km buffer sizes. Adjusted for age, gender, body mass index, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose. Abbreviations: BFV, blood flow velocity; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon; NDVI, normalized difference vegetation index; EVI, enhanced vegetation index; SAVI, soil-adjusted vegetation index.

In our study, we found a stronger effect of $PM_{2.5}$ and its constituents among participants who worked in areas with lower greenness levels. Some studies have investigated the modifying effects of greenness on the relationship between air pollution and disease, of which conclusions are inconsistent. A study found that the association between $PM_{2.5}$ and CVD hospitalization were stronger in areas with higher greenness (Klompmaker et al., 2021). However, another research reported that higher levels of greenness weaken the risk of air pollution to the heart (Zhu et al., 2022), which aligns with our findings. Similarly, a study showed that higher exposure to street-level greenspace was associated with lower prevalence of CVD (Wang et al., 2022). Greenness is often considered to be a protective factor for human health (Gascon et al., 2016). One explanation for the health benefits of greenness is that it purifies the air and reduces human exposure to air pollutants (Markevych et al., 2017). Greenness has also been shown to improve angiogenic capacity and reduce oxidative stress (Yeager et al., 2018). In our sensitivity analysis, we used three different buffer sizes (1–3 km) and three greenness indicators (NDVI, EVI, and SAVI) and obtained consistent results, indicating the robustness of our findings. These results demonstrated that greenness is a modifier of the $PM_{2.5}$-BFV association, and those who exposed to lower levels of greenness are

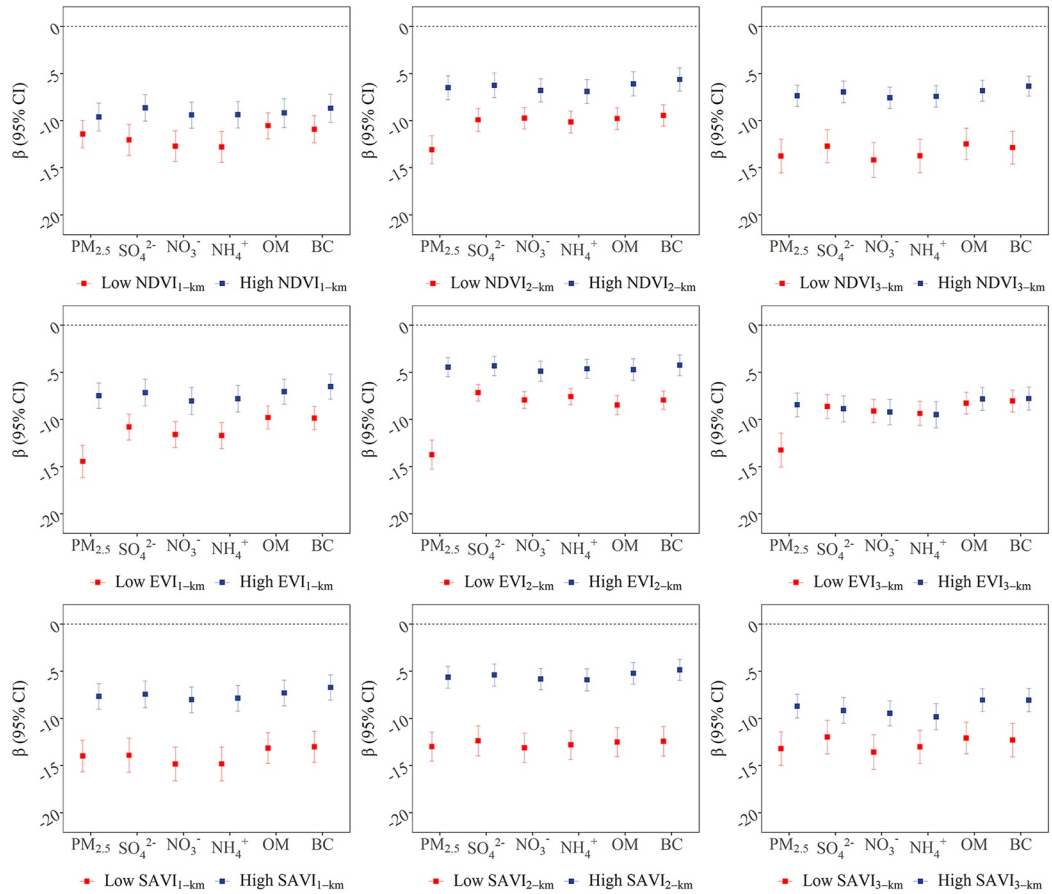

Figure 5. Sensitivity analyses of the associations of long-term $PM_{2.5}$ and its constituents exposures with the change rate of blood flow velocity per interquartile range increase in exposure, stratified by three different greenness indices for 1–3 km buffer sizes. Adjusted for age, gender, body mass index, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose. Abbreviations: BFV, blood flow velocity; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon; NDVI, normalized difference vegetation index; EVI, enhanced vegetation index; SAVI, soil-adjusted vegetation index.

indeed more susceptible to $PM_{2.5}$. Greenness is definitely a protective factor in many respects (Fong et al., 2018), what we are trying to emphasize that people in areas with low green levels should pay attention to the prevention of health hazards from air pollution, and policies to enhance greening levels and control air pollution should also be considered.

This is the first study to investigate the long-term effects of $PM_{2.5}$ on the progression of BFV in MCA. In addition, we estimated the effects of several $PM_{2.5}$ chemical constituents on BFV progression. We also examined the effect modification by greenness based on three indices and three buffer sizes. However, our study has some limitations. First, due to confidentiality restrictions on personal privacy, we mainly used the participants' workplace address to geocode and estimate the exposure. This could lead to some misclassification of exposure. However, based on subpopulations, we included residential addresses in our sensitivity analysis and confirmed the robustness of our analysis. In addition, we currently only have access to $PM_{2.5}$ constituents data at a spatial resolution of 10 km × 10 km, which results in coarse exposure estimates. Nevertheless, we calculated $PM_{2.5}$ concentrations using kriging interpolation based on monitoring station data in the sensitivity analysis, and the results were consistent with other analyses.

5. Conclusion

In conclusion, there is a significantly negative association of $PM_{2.5}$ and its constituents with progression of cerebral artery BFV, with OM dominating this association. Greenness serves as a modifier of this association, and

the effect of air pollutants is greater in areas with lower levels of greenness. The findings suggest that increasing greenness levels, as well as controlling $PM_{2.5}$ pollution in the air, particularly the OM constituent, may help protect the cerebrovascular health of the population.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

Air pollution data sets for this research are available at: $PM_{2.5}$ and its constituents (sulfate, nitrate, ammonium, black carbon, and organic matter), tapdata.org.cn; $PM_{2.5}$ data from air monitoring sites, https://quotsoft.net/air/; Data for Greenness (product number MOD13A2) was obtained from the following websites, https://ladsweb.modaps.eosdis.nasa.gov. The clinical data are not accessible to the public due to data policies of the Beijing Physical Examination Center in China. Detailed steps for downloading air pollutant and greenness data can be found in Supporting Information S1 "Data Download Tutorial" section. All analyses in this study are made with software R version 4.2.1.

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