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Original Research Article

Ambient air pollution exposure in relation to cerebral small vessel disease in Chinese population: A cranial magnetic resonance imaging-based study

Yudiyang Ma [a,b,1], Ying Hui [c,1], Linxi Tang [a,b], Jianing Wang [a,b], Meiqi Xing [a,b], Lei Zheng [a,b], Feipeng Cui [a,b], Shuohua Chen [c], Shouling Wu [d,*], Zhenchang Wang [e,*], Yaohua Tian [a,b,*]

[a] Ministry of Education Key Laboratory of Environment and Health, and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[b] Department of Maternal and Child Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[c] Department of Medical Imaging, Kailuan General Hospital, Tangshan 063000, China
[d] Department of Cardiology, Kailuan General Hospital, Tangshan 063000, China
[e] Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

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ABSTRACT

Cerebral small vessel disease (CSVD), a chronic and progressive vascular disorder closely associated with stroke and dementia, is primarily identified and diagnosed in cranial magnetic resonance imaging (MRI). Given the limited evidence on the relationship between air pollution and CSVD, this study aimed to investigate the links between multiple air pollutants exposure and CSVD risk. Eligible subjects and their cranial MRI data were obtained from the Multi-modality Medical Imaging Study Based on Kailuan Study, totaling 1216 participants. Ordinal and binary logistic regression models were utilized to evaluate the associations between air pollution exposure and the neuroimaging markers of CSVD. For each interquartile range increase in air pollutant exposure during the examination year, the odds ratios and 95% confidence intervals of the increased white matter hyperintensity burden were 1.45 (1.15, 1.84) for $PM_{2.5}$, 1.72 (1.27, 2.34) for PM_{10}, 1.26 (1.05, 1.51) for SO_2, 1.52 (1.16, 2.00) for NO_2, and 1.63 (1.26, 2.13) for CO. The results remained consistent even when the model was fitted using air pollution from different exposure windows. Furthermore, the estimated effect sizes for the total burden of CSVD were 1.20 (1.01, 1.43) for $PM_{2.5}$, 1.39 (1.12, 1.74) for PM_{10}, 1.26 (1.03, 1.53) for NO_2, and 1.30 (1.08, 1.58) for CO. These findings suggest that a positive link between air pollutants exposure and neuroimaging markers of CSVD in the Chinese population, revealing the importance of controlling environmental pollutants to protect the population against cerebral small vessel damage.

1. Introduction

Cerebral small vessel disease (CSVD) is a common neurological condition characterized by pathological changes in the vessels of 50–500 μm in diameter in the brain [1]. These small vessels, including arterioles, venules, and capillaries, play a crucial role in regulating cerebral blood flow and upholding the integrity of the blood–brain barrier [2]. CSVD encompasses a spectrum of structural and functional abnormalities, such as lipohyalinosis, arteriolosclerosis, microaneurysms, and microinfarcts, predominantly in the deep white matter and subcortical regions of the brain [3]. These changes can lead to cerebral hypoperfusion, chronic ischemia, and ultimately, cognitive impairment, dementia, and even stroke. Due to the slow and insidious progression of CSVD in its early stages, coupled with the absence of prominent clinical manifestations, cranial magnetic resonance imaging (MRI) is the preferred radiological modality for diagnosing CSVD [4]. Its neuroimaging features encompass cerebral white matter hyperintensities (WMH), lacunes (LA), cerebral microbleed (CMB), enlarged perivascular spaces (EPVS), and brain atrophy [2,5]. Given that CSVD accounts for over a quarter of ischemic strokes and approximately half of dementia [2], it is critical to explore its risk factor profile and develop targeted strategies to reduce the burden of the disease.

Ambient air pollution is recognized as the primary environmental risk factor, contributing to a range of health issues, including stroke, dementia,

* Corresponding authors.
E-mail addresses: drwusl@163.com (S. Wu), cjr.wzhch@vip.163.com (Z. Wang), yaohua_tian@hust.edu.cn (Y. Tian).
[1] The authors contributed equally.

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and Alzheimer's disease [6–9]. Nevertheless, it remains unclear whether air pollution exposure is a risk factor for CSVD due to the relative paucity of research evidence based on brain MRI data. For instance, population studies have reported that long-term exposure to particulate matter was related to an increase in brain WMH volume [10–12]. Both the Framingham Offspring Study and the Korean National Health Insurance Service-based study have found positive relationships between long-term particulate matter with aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$) and particulate matter with aerodynamic diameter $\leq$ 10 μm (PM_{10}) exposure and covert brain infarcts, but not with WMH volume [12,13]. Similarly, another study conducted in the U.S. failed to find a significant link between air pollution exposure and WMH volume, but it reported an increased risk of CMB was associated with air pollutant exposure [14]. Moreover, there is also a dearth of studies focused on the effects of gaseous pollutants, such as sulfur dioxide (SO_2), nitrogen dioxide (NO_2), or carbon monoxide (CO), etc., on the risk of CSVD [15]. Additionally, CSVD is often characterized by the coexistence of multiple radiologic markers. Previous studies that solely focused on an individual radiological metric have resulted in a limited and incomplete understanding of this disease [15,16].

Therefore, this study investigated the associations between air pollution exposure and CSVD neuroimaging features, including WMH burden, which integrates deep WMH (DWMH) and periventricular WMH (PWMH), perivascular spaces surrounding the basal ganglia (BG-EPVS), LA, and CMB, utilizing brain MRI data from the Multi-modality Medical Imaging Study Based on Kailuan Study (META-KLS). Moreover, we explored the unfavorable influence of air pollutants on the total burden of CSVD, which encompasses a comprehensive evaluation of four CSVD imaging characteristics: WMH burden, BG-EPVS, LA, and CMB. The total burden of CSVD was scored on a scale ranging from 0 to 4 points, with higher scores indicating more severe CSVD lesions.

2. Methods

2.1. Study design and participants

The META-KLS is a sub-cohort of the Kailuan Study, a prospective cohort study initiated in 2006 that employs a population-based approach to thoroughly investigate risk factors contributing to overall mortality [17–19]. Since December 2020, META-KLS has been recruiting eligible participants (no history of stroke, tumors, or traumatic brain injury) from the Kailuan Study. All selected participants have undergone multimodal medical imaging, such as brain MRI scan, retinal fundus photography, and clinical assessment (including blood pressure, blood glucose, and lipid profile, etc.) [19–21]. All study subjects completed an informed consent form prior to the start of the META-KLS.

Among the 1530 participants included in this cross-sectional study, we excluded individuals with missing health records (n = 78) and individuals who lacked specific residential address information required for air pollution exposure assessment (n = 236). Finally, 1216 study subjects were entered into the final analysis.

2.2. Exposure assessment

Ambient air pollutant data employed in this study were acquired from the ChinaHighAirPollutants dataset (https://weijing-rs.github.io/product.html). The generation of the dataset took into account the spatiotemporal heterogeneity of air pollution and integrated big data sources such as ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations [22–25]. This dataset contains $PM_{2.5}$ and PM_{10} data (1 km ground-level) for China from 2013 to 2022, as well as SO_2, NO_2, and CO data (1 km ground-level) from 2019 to 2022. The overall performance of the model in estimating near-surface air pollutant concentrations was evaluated using a 10-fold cross-validation method conducted on out-of-sample data, and the performance statistics of the model indicated good performance [22–25]. In addition, a previous study utilized $PM_{2.5}$ data from the ChinaHighAirPollutants dataset to construct an exposure model in Tangshan City, Hebei Province, China, and the statistical indicators of model performance demonstrated that the exposure assessment was good ($R^2 = 0.94$, RMSE = 4.64 μg/m^3) [26].

According to the method employed in our previous publications, we first geocoded the addresses of each participant and then extracted the corresponding values from the Raster object provided in the ChinaHighAirPollutants dataset according to their respective locations [17,27,28]. During the process of exposure assessment, we considered the changes in the residential addresses of the study participants (the rate of relocation was 2.3%). Next, we calculated individual exposure across different time windows: the year of the medical examination, namely, the average of the 365 days prior to the date of the medical examination (lag 0 year), two years prior to the year of the medical examination (lag 2 years), the average of the three years prior to the medical examination (average 3 years), and the average of the five years prior to the medical examination (average 5 years, only for $PM_{2.5}$ and PM_{10}).

2.3. MRI data collection and definitions

The brain MRI scan was conducted using a 3.0 T scanner equipped with an eight-channel phased-array coil (MR750w, General Electric, Waukesha, WI) in Kailuan General Hospital. Brain imaging data were in the Digital Imaging and Communications in Medicine format. The radiologists completed the cerebral MRI examinations of the study participants. The interpretation of brain MRI images and the quantification of CSVD neuroimaging features were independently performed by two neuroradiologists from Kailuan General Hospital. In cases of disagreement, a third neuroradiologist intervened to arbitrate, and the final results were determined through consultation and discussion. Neuroimaging markers of CSVD were defined based on the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) [29]. DWMH and PWMH were scored based on the Fazekas scale from 0 to 3 [30]. The WMH burden was assessed by considering the DWMH and PWMH (DWMH $\geq$ 2 or PWMH = 3), ranging from 0 to 1 [31]. The BG-EPVS was assessed based on the number of EPVS in the basal ganglia of the brain, ranging from 0 to 4 [32,33]. CMB and LA were rated based on the size, shape, and location of neuroimaging features, ranging from 0 to 1 [29]. Moreover, because CSVD is a composite outcome with varied imaging features, individual neuroimaging markers cannot fully reflect overall brain damage. Therefore, we utilized the well-established Wardlaw group methodology to calculate the total burden of CSVD, aiming to comprehensively and systematically assess the CSVD imaging profile and cumulative brain damage in our study subjects [34,35]. The total burden of CSVD was calculated by assigning one point to each of the four imaging features present in the study subjects' MRI images (including WMH burden = 1, BG-EPVS $\geq$ 2, CMB $\geq$ 1, or LA $\geq$ 1), and then summing these points. See Table 1 for specific definitions and rating scales [29,30,32,35].

2.4. Covariates

In the investigation of the adverse effects of ambient air pollution exposure on CSVD, previous studies have indicated that the presence of certain confounding factors may affect the true associations between air pollution exposure and CSVD [36,37]. Therefore, our study incorporated factors potentially related to CSVD, including age (years), sex (male or female), body mass index (BMI, kg/m^2), smoking history (never, previous smoking, or current smoking), drinking history (never, previous drinking, or current drinking), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), fasting blood glucose (FBG, mmol/L), total cholesterol (TC, mmol/L), low-density lipoprotein (LDL, mmol/L), as well as variables potentially related to air pollution exposure, such as temperature (°C) and relative humidity (%). The temperature dataset was spatially downscaled from CRU TS v4.02 with WorldClim datasets based on the Delta downscaling method [38]. The humidity dataset was estimated using observational data from meteorological stations and multiple covariates, including surface temperature,

Table 1
Definitions of neuroimaging markers of CSVD.

MRI feature	Visual assessment standard	Rating scale	Score range	Ref.
DWMH/PWMH	Fazekas scale	Absence (*0 point*); Punctate foci (*1 point*); Beginning confluence of foci (*2 points*); large confluent areas (*3 points*).	0–3	[30]
WMH burden	Fazekas scale	DWMH $\geq$ 2 or PWMH = 3 (*1 point*); other (*0 point*).	0–1	[30]
BG-EPVS	Semiquantitative scale	No EPVS (*0 point*); 1–10 EPVS (*1 point*); 11–20 EPVS (*2 points*); 21–40 EPVS (*3 points*); over 40 EPVS (*4 points*).	0–4	[32]
CMB	International consensus definition	Absence (*0 point*); small (<5 mm), homogeneous, round foci of low signal intensity on gradient echo images in cerebellum, brainstem, basal ganglia, white matter, or cortico-subcortical junction (*1 point*).	0–1	[29]
LA	International consensus definition	Absence (*0 point*); Rounded or ovoid lesions, 3–20 mm diameter, in the basal ganglia, internal capsule, centrum semiovale, or brainstem (*1 point*).	0–1	[29]
Total burden of CSVD	Wardlaw group method	*1 point* is assigned to each of the four imaging features that appeared (WMH burden = 1, BG-EPVS $\geq$ 2, CMB $\geq$ 1, or LA $\geq$ 1), and these points are then summed.	0–4	[35]

CSVD, cerebral small vessel disease; WMH, white matter hyperintensities; DWMH, deep white matter hyperintensities; PWMH, periventricular white matter hyperintensities; BG-EPVS, perivascular spaces surrounding the basal ganglia; CMB, cerebral microbleed; LA, lacune.

vapor pressure, and land cover, etc., employing the Light Gradient Boosting Machine algorithm [39].

2.5. Statistical analysis

Depending on the data type, the distribution of covariates in this study was presented as mean (standard deviation, SD) or frequency (percentage). For ordinal categorical outcomes (DWMH, PWMH, BG-EPVS, and total burden of CSVD), ordinal logistic regression models were employed to explore the relationships between air pollution exposure and the neuroimaging metrics of CSVD. For dichotomous outcomes (WMH burden, CMB, and LA), binary logistic regression models were used. Models incorporated several potential confounders, including age, sex, BMI, smoking history, drinking history, SBP, DBP, FBG, TC, and LDL. Temperature and relative humidity were also adjusted in the model using a natural cubic spline function with 3 degrees of freedom [40,41]. Results were presented as odds ratios (ORs) accompanied by their 95% confidence intervals (CIs).

We further fitted models to calculate the corresponding effect size estimations of air pollution exposure across different time windows (including lag 0 year, lag 2 years, average 3 years, and average 5 years) on the radiological markers of CSVD. To explore dose–response relationships between air pollutants and the risk of CSVD, we fitted a logistic regression model with a restricted cubic spline. To identify the potentially vulnerable populations, this study conducted subgroup analyses by age (<60 or $\geq$60 years), sex (male or female), BMI (<24 or $\geq$24 kg/m^2), smoking history (never, ever or current smoking), and drinking history (never, ever or current drinking). Considering that participants were exposed to multiple pollutants, we employed a weighted quantile sum (WQS) regression model to assess the overall influence of air pollution mixtures [42,43].

A range of sensitivity tests were performed to evaluate the robustness of the results: (1) we substituted waist circumference for BMI during the model fitting; (2) we replaced SBP, DBP and FBG with hypertension and diabetes during the model fitting; (3) we fitted a multi-pollutant model that simultaneously considered the influence of various air pollutants in the regression analysis. The R programming language (version 4.2.2) was utilized for all statistical analyses.

3. Results

3.1. Baseline characteristics of the study population

Table 2 shows the characteristics of study subjects. A total of 1216 participants were involved in this analysis, including 641 men and 575 women. The geographical distribution of the study subjects and the temporal changes in air pollutant exposure concentrations are depicted in Fig. S1 and Fig. S2. In general, the average (SD) age was 55.57 (12.17) years, while the BMI stood at 25.23 (3.55) kg/m^2. The average (SD) of SBP, FBG, and LDL was 133.47 (19.67) mmHg, 5.61 (1.61) mmol/L, and 3.12 (0.78) mmol/L, respectively. There were 895 (73.60%) subjects with WMH burden equal to 0. The numbers of subjects with the following radiological markers were as follows: DWMH of 0–3 points, 286 (23.52%), 609 (50.08%), 267 (21.96%), and 54 (4.44%), respectively; PWMH of 0–3 points, 773 (63.57%), 276 (22.70%), 120 (9.87%), and 47 (3.86%), respectively; BG-EPVS of 1–4 points, 500 (41.12%), 465 (38.24%), 208 (17.11%), and 43 (3.53%), respectively; LA of 0–1 point, 1023 (84.13%) and 193 (15.87%), respectively; CMB of 0–1 point, 888 (73.03%) and 328 (26.97%), respectively; and total burden of CSVD of 0–4 points, 401 (32.98%), 370 (30.43%), 239 (19.65%), 114 (9.38%), and 92 (7.56%), respectively. Table S1 provides a summary of the distribution of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO exposures in the different time windows. Pearson correlation coefficients for air pollutants, as well as meteorological factors, are displayed in Fig. S3.

3.2. Association between exposure to air pollution and CSVD

Binary logistic regression results indicated that exposure to air pollutants increased the risk of WMH burden after adjusting for a series of covariates (Table 3). For each interquartile range (IQR) increase of air pollution exposure (lag 0 year), the ORs and 95% CIs of the worsened WMH burden were 1.45 (1.15, 1.84) for $PM_{2.5}$, 1.72 (1.27, 2.34) for PM_{10}, 1.26 (1.05, 1.51) for SO_2, 1.52 (1.16, 2.00) for NO_2, and 1.63 (1.26, 2.13) for CO. These findings remained statistically significant when the exposure window was changed (lag 2 years, average 3 years, and average 5 years). In Table 4, there were positive relationships between air pollution exposure (lag 0 year) and the total burden of CSVD, with ORs of 1.20 (1.01, 1.43) for $PM_{2.5}$, 1.39 (1.12, 1.74) for PM_{10}, 1.26 (1.03, 1.53) for NO_2, and 1.30 (1.08, 1.58) for CO. Furthermore, the total burden of CSVD was also significantly associated with each IQR increase in the 3-year average of PM_{10} [OR and 95% CI: 1.25 (1.02, 1.54)] and CO [OR and 95% CI: 1.25 (1.01, 1.55)] exposure. Figs. 1 and 2 exhibit the exposure–response relationships of air pollution exposure in different time windows with WMH burden and the total burden of CSVD. In the majority of cases, the exposure-response curves typically increased when air pollutants were at low concentrations but tended to plateau or displayed a slight decline at higher concentrations.

For other neuroimaging markers of CSVD, apart from DWMH, which was positively associated with air pollutant exposure (Table S2), we did not observe any pronounced associations between air pollutants across different exposure windows and neuroimaging markers such as PWMH (Table S3), BG-EPVS (Table S4), LA (Table S5), and CMB (Table S6). Figs. S4-S8 illustrate the exposure-response curves of these neuroimaging markers to air pollutants across different time windows.

Table 2
Baseline characteristics of included participants.

Variables	Participants (n = 1216)	$PM_{2.5}$ exposure				*P* value
		Q1 (n = 314)	Q2 (n = 317)	Q3 (n = 281)	Q4 (n = 304)	
Age (years)	55.57 (12.17)	53.02 (13.87)	55.64 (11.58)	58.48 (11.12)	55.46 (11.24)	**<0.001**
Sex, n (%)						**<0.001**
Female	575 (47.29)	173 (55.10)	161 (50.79)	109 (38.79)	132 (43.42)	
Male	641 (52.71)	141 (44.90)	156 (49.21)	172 (61.21)	172 (56.58)	
BMI (kg/m^2)	25.23 (3.55)	25.26 (3.50)	25.13 (3.92)	25.30 (3.31)	25.26 (3.44)	0.935
Smoking history, n (%)						**0.014**
Never	919 (75.58)	261 (83.12)	238 (75.08)	200 (71.17)	220 (72.37)	
Previous smoking	90 (7.40)	17 (5.41)	27 (8.52)	21 (7.47)	25 (8.22)	
Current smoking	207 (17.02)	36 (11.46)	52 (16.40)	60 (21.35)	59 (19.41)	
Drinking history, n (%)						**0.020**
Never	828 (68.09)	228 (72.61)	224 (70.66)	177 (62.99)	199 (65.46)	
Previous smoking	76 (6.25)	23 (7.32)	10 (3.15)	22 (7.83)	21 (6.91)	
Current smoking	312 (25.66)	63 (20.06)	83 (26.18)	82 (29.18)	84 (27.63)	
SBP (mmHg)	133.47 (19.67)	130.85 (19.06)	131.23 (19.64)	138.75 (19.71)	133.64 (19.39)	**<0.001**
DBP (mmHg)	79.08 (12.28)	77.80 (12.12)	78.31 (12.48)	80.80 (12.19)	79.62 (12.17)	**0.013**
FBG (mmol/L)	5.61 (1.61)	5.79 (1.25)	5.50 (1.44)	5.79 (2.33)	5.39 (1.20)	**0.002**
TC (mmol/L)	5.18 (0.99)	5.27 (1.02)	5.16 (1.05)	5.17 (0.96)	5.14 (0.93)	0.375
LDL (mmol/L)	3.12 (0.78)	3.05 (0.78)	3.09 (0.81)	3.19 (0.74)	3.15 (0.78)	0.124
Temperature (°C)	12.93 (0.35)	12.92 (0.38)	13.06 (0.28)	12.78 (0.38)	12.94 (0.27)	**<0.001**
Relative humidity (%)	54.09 (1.84)	54.08 (1.83)	54.18 (2.08)	53.72 (1.94)	54.33 (1.39)	**0.001**
DWMH, n (%)						**<0.001**
0	286 (23.52)	90 (28.66)	78 (24.61)	45 (16.01)	73 (24.01)	
1	609 (50.08)	169 (53.82)	159 (50.16)	133 (47.33)	148 (48.68)	
2	267 (21.96)	45 (14.33)	69 (21.77)	82 (29.18)	71 (23.36)	
3	54 (4.44)	10 (3.18)	11 (3.47)	21 (7.47)	12 (3.95)	
PWMH, n (%)						**0.003**
0	773 (63.57)	212 (67.52)	211 (66.56)	151 (53.74)	199 (65.46)	
1	276 (22.70)	73 (23.25)	69 (21.77)	77 (27.40)	57 (18.75)	
2	120 (9.87)	21 (6.69)	24 (7.57)	37 (13.17)	38 (12.50)	
3	47 (3.86)	8 (2.55)	13 (4.10)	16 (5.69)	10 (3.29)	
WMH burden, n (%)						**<0.001**
0	895 (73.60)	259 (82.48)	237 (74.76)	178 (63.35)	221 (72.70)	
1	321 (26.40)	55 (17.52)	80 (25.24)	103 (36.65)	83 (27.30)	
BG-EPVS, n (%)						**0.028**
1	500 (41.12)	140 (44.59)	143 (45.11)	87 (30.96)	130 (42.76)	
2	465 (38.24)	112 (35.67)	114 (35.96)	123 (43.77)	116 (38.16)	
3	208 (17.11)	52 (16.56)	46 (14.51)	61 (21.71)	49 (16.12)	
4	43 (3.53)	10 (3.18)	14 (4.42)	10 (3.56)	9 (2.96)	
LA, n (%)						**<0.001**
0	1023 (84.13)	278 (88.54)	280 (88.33)	216 (76.87)	249 (81.91)	
1	193 (15.87)	36 (11.46)	37 (11.67)	65 (23.13)	55 (18.09)	
CMB, n (%)						**<0.001**
0	888 (73.03)	239 (76.11)	243 (76.66)	174 (61.92)	232 (76.32)	
1	328 (26.97)	75 (23.89)	74 (23.34)	107 (38.08)	72 (23.68)	
Total burden of CSVD, n (%)						**<0.001**
0	401 (32.98)	121 (38.54)	118 (37.22)	66 (23.49)	96 (31.58)	
1	370 (30.43)	102 (32.48)	97 (30.60)	71 (25.27)	100 (32.89)	
2	239 (19.65)	53 (16.88)	58 (18.30)	68 (24.20)	60 (19.74)	
3	114 (9.38)	20 (6.37)	24 (7.57)	42 (14.95)	28 (9.21)	
4	92 (7.56)	18 (5.73)	20 (6.31)	34 (12.10)	20 (6.58)	

Participants were grouped by quartiles of $PM_{2.5}$ exposure in lag 0 year. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; LDL, low density lipoprotein; Q, quartile.

Table 3
Binary regression results for the associations between air pollutants exposure and WMH burden.

Air pollutants (per IQR increase)	Lag 0 year		Lag 2 years		Average 3 years		Average 5 years	
	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value
$PM_{2.5}$	1.45 (1.15, 1.84)	**0.002**	1.53 (1.15, 2.05)	**0.004**	1.52 (1.15, 2.02)	**0.004**	1.43 (1.09, 1.89)	**0.009**
PM_{10}	1.72 (1.27, 2.34)	**<0.001**	1.55 (1.19, 2.01)	**0.001**	1.60 (1.21, 2.13)	**0.001**	1.44 (1.12, 1.86)	**0.004**
SO_2	1.26 (1.05, 1.51)	**0.010**	1.50 (1.06, 2.14)	**0.023**	1.55 (1.13, 2.13)	**0.007**	–	–
NO_2	1.52 (1.16, 2.00)	**0.002**	1.82 (1.22, 2.74)	**0.004**	1.83 (1.27, 2.66)	**0.001**	–	–
CO	1.63 (1.26, 2.13)	**<0.001**	1.63 (1.19, 2.23)	**0.002**	1.65 (1.21, 2.25)	**0.001**	–	–

Models were adjusted for age, sex, BMI, smoking history, drinking history, SBP, DBP, FBG, TC, LDL, temperature, and relative humidity. Interquartile range (IQR) for $PM_{2.5}$ in lag 0 year, lag 2 years, average 3 years, and average 5 years were 5.23, 5.40, 5.40, and 5.76 $\mu g/m^3$, respectively. IQR for PM_{10} in lag 0 year, lag 2 years, average 3 years, and average 5 years were 16.20, 11.90, 12.33, and 9.73 $\mu g/m^3$, respectively. IQR for SO_2 in lag 0 year, lag 2 years, and average 3 years were 2.20, 5.30, and 4.93 $\mu g/m^3$, respectively. IQR for NO_2 in lag 0 year, lag 2 years, and average 3 years were 6.62, 7.20, and 7.03 $\mu g/m^3$, respectively. IQR for CO in lag 0 year, lag 2 years, and average 3 years were 0.18, 0.21, and 0.20 $\mu g/m^3$, respectively.

Table 4
Ordinal logistic regression results for the associations between air pollutants exposure and total burden of CSVD.

Air pollutants (per IQR increase)	Lag 0 year		Lag 2 years		Average 3 years		Average 5 years	
	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value
$PM_{2.5}$	1.20 (1.01, 1.43)	**0.037**	1.17 (0.95, 1.44)	0.146	1.16 (0.95, 1.42)	0.158	1.11 (0.91, 1.35)	0.302
PM_{10}	1.39 (1.12, 1.74)	**0.003**	1.19 (0.98, 1.44)	0.073	1.25 (1.02, 1.54)	**0.029**	1.13 (0.94, 1.35)	0.196
SO_2	1.12 (0.98, 1.28)	0.099	1.18 (0.92, 1.52)	0.201	1.19 (0.95, 1.50)	0.128	–	–
NO_2	1.26 (1.03, 1.53)	**0.023**	1.36 (1.01, 1.84)	**0.041**	1.29 (0.99, 1.67)	0.057	–	–
CO	1.30 (1.08, 1.58)	**0.007**	1.24 (0.99, 1.55)	0.059	1.25 (1.01, 1.55)	**0.044**	–	–

Models were adjusted for age, sex, BMI, smoking history, drinking history, SBP, DBP, FBG, TC, LDL, temperature, and relative humidity. IQR for $PM_{2.5}$ in lag 0 year, lag 2 years, average 3 years, and average 5 years were 5.23, 5.40, 5.40, and 5.76 μg/m^3, respectively. IQR for PM_{10} in lag 0 year, lag 2 years, average 3 years, and average 5 years were 16.20, 11.90, 12.33, and 9.73 μg/m^3, respectively. IQR for SO_2 in lag 0 year, lag 2 years, and average 3 years were 2.20, 5.30, and 4.93 μg/m^3, respectively. IQR for NO_2 in lag 0 year, lag 2 years, and average 3 years were 6.62, 7.20, and 7.03 μg/m^3, respectively. IQR for CO in lag 0 year, lag 2 years, and average 3 years were 0.18, 0.21, and 0.20 μg/m^3, respectively.

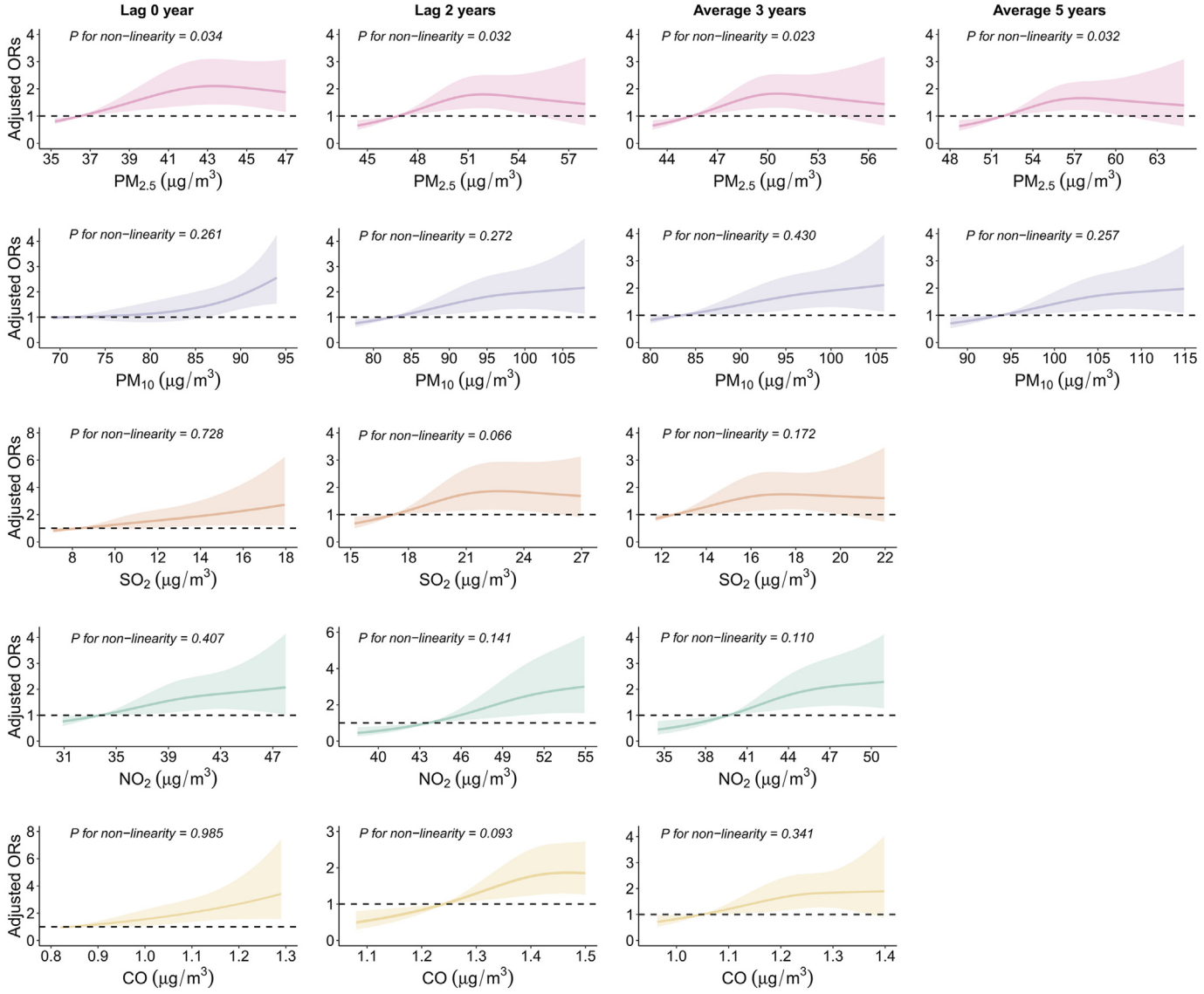

Fig. 1. Exposure–response relationships of air pollutants exposure with WMH burden. A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure–response relationships between air pollutants exposure and WMH burden. ORs (solid lines) and 95% CIs (shaded areas) were adjusted for age, sex, BMI, smoking history, drinking history, SBP, DBP, FBG, TC, LDL, temperature, and relative humidity.

Fig. S9 and Fig. S10 display ORs and 95% CIs of air pollution exposure on WMH burden and the total burden of CSVD stratified by age, sex, BMI, smoking history, and drinking history. Although we observed variations in the effect sizes of air pollutants among different subgroups, these differences did not reach statistical significance (*P* for interaction > 0.05). In the context of exposure to multiple air pollutants (Fig. S11), this study revealed a positive relationship between the WQS indices and WMH burden [ORs and 95% CIs: 1.43 (1.15, 1.78) for lag 0 year; 1.36 (1.10, 1.68) for lag 2 years; and 1.43 (1.14, 1.78) for average 3 years], as well as the total burden of CSVD [OR and 95% CI: 1.29 (1.03, 1.62) for

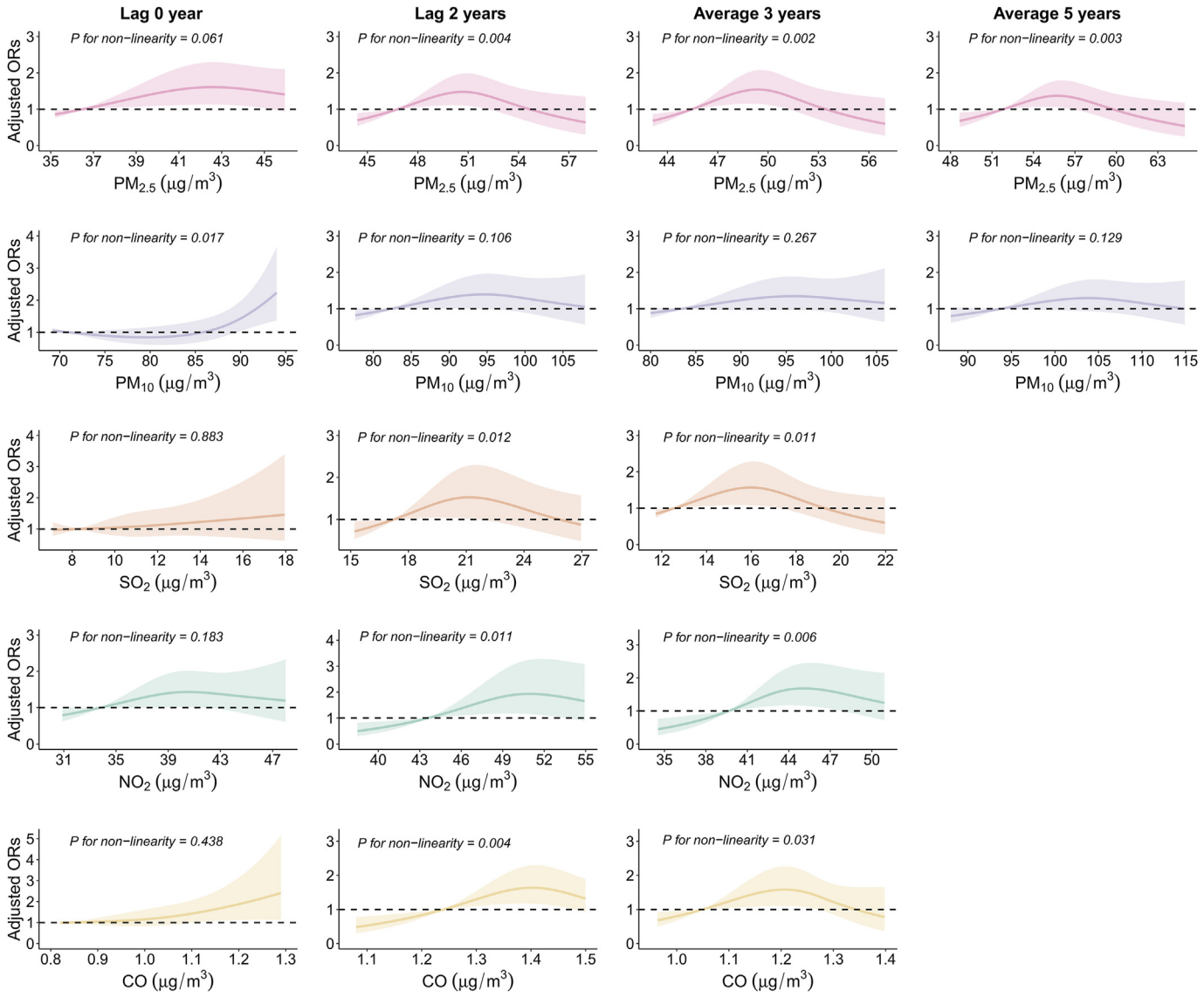

Fig. 2. Exposure–response relationships of air pollutants exposure with the total burden of CSVD. A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure–response relationships between air pollutants exposure and total burden of CSVD. ORs (solid lines) and 95% CIs (shaded areas) were adjusted for age, sex, BMI, smoking history, drinking history, SBP, DBP, FBG, TC, LDL, temperature, and relative humidity.

lag 0 year]. In the sensitivity analyses (Tables S7-S9), it was found that the results of the study remained virtually unchanged.

4. Discussion

The current study is the first to comprehensively investigate the relationships between air pollution exposure and radiological markers of CSVD. One notable discovery was the significant associations between $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO exposures across various time windows and the increased risk of WMH burden and the total burden of CSVD. Another key finding highlighted a positive link between exposure to multiple air pollution mixtures and the risk of CSVD.

4.1. Comparison with other studies

Similar to our findings, the Cardiovascular Health Study reported the associations between PM_{10} (per 10 μg/m^3 increase) and NO_2 (per 10 ppb increase) exposure and the deterioration of white matter grade, with estimated effect sizes of 0.14 (0.01, 0.37) and 0.37 (0.04, 0.61), respectively [44]. As well, in the Framingham Offspring Study, community-dwelling participants exposed to $PM_{2.5}$ (per 2 μg/m^3 increase) exhibited an elevated OR of covert brain infarcts [1.37 (1.02, 1.85)] [13]. While a study based on the Korean population found that exposure to PM_{10} (per 11.6 μg/m^3 increase) could elevate the risk of covert brain infarction, no significant association was uncovered between PM_{10}, NO_2, SO_2, and CO and the risk of CMB [12], aligning with our findings. Likewise, WMH volume has attracted considerable attention in many prior studies, yet the findings have been inconsistent. For example, a population-based analysis utilizing data from the French Three-City Montpellier study (n = 582) demonstrated an association between $PM_{2.5}$ exposure and an elevated risk of increased WMH volume [16]. Conversely, a study conducted at the Massachusetts Alzheimer's Disease Research Center (n = 236) reported that an increase in $PM_{2.5}$ was associated with a decrease in WMH volume [14]. The negative associations were also observed in the Women's Health Initiative Memory Study [45,46]. Moreover, findings from the Framingham Offspring Study (n = 943) and the Northern Manhattan Study (n = 1075) indicated that the relationship between $PM_{2.5}$ and NO_2 exposure and cerebral WMH volume was not statistically significant [13,47]. The heterogeneity of findings may be attributed to the sample size, as the identification and

diagnosis of CSVD rely on cranial MRI techniques, making it challenging to collect a large number of cranial MRI images of study subjects. Another possible reason lies in the varying concentrations of air pollutants in different study areas. A meta-analysis denoted that the risk of cerebrovascular disease in the Asian region was associated with particulate matter exposure, whereas in Europe and South America, this association no longer held statistical significance. This was largely due to differences in pollutant concentrations (median level of PM_{10}: 71.6 μg/m^3 in the Asian region vs. 20.6 μg/m^3 and 23.1 μg/m^3 in Europe and South America), respectively [48,49].

Delineating exposure windows facilitates a more precise identification of susceptible period through which air pollutant exposure impacts CSVD. Yet, previous studies have focused solely on a single time window, such as pollution exposure in the year of health examination or average exposure of several years, overlooking the impact of air pollution exposure on CSVD across different exposure windows [10,12,16]. Our study demonstrated that air pollutant exposure across different exposure windows was consistently associated with an increased WMH burden. For the total burden of CSVD, this study uncovered the positive links between $PM_{2.5}$, PM_{10}, SO_2, and CO exposure and small blood vessel damage in the brain, which has not yet been reported in existing studies.

4.2. Potential mechanism

Several mechanisms have been proposed regarding the harmful impact of air pollution on cerebrovascular health. According to the classical inflammation hypothesis, inhaled particles are engulfed by pulmonary macrophages, leading to the secretion of inflammatory mediators that subsequently affect the vascular system [50–52]. Similarly, ultrafine particles have the ability to penetrate the alveolar-capillary barrier, exerting a direct influence on blood vessels and circulating blood cells [53,54]. Another hypothesis suggests that inhalation of air pollutants activates neural sensory receptors, triggering changes in autonomic nervous system function, which ultimately leads to alterations in vascular homeostasis [55,56]. The proper functioning of these biological pathways is crucial for maintaining brain health. When disrupted by air pollutants, they may adversely affect the cerebral microvasculature, thereby influencing the onset of CSVD. Future studies should delve deeper into the mechanisms underlying the association between air pollution exposure and CSVD.

4.3. Strengths and limitations

To the best of our knowledge, this study represents the pioneering investigation to comprehensively explore the hazardous effects of air pollutant exposure on cerebral microvascular health through multiple CSVD MRI features in the Chinese population. An additional strength of this study is that we assessed the effects of environmental pollutants across different exposure windows to gain a deeper understanding of the role of varying exposure patterns in triggering CSVD. Nevertheless, this study is still subject to some limitations. Initially, since this study involved only one instance of cranial MRI and employed a cross-sectional study design, future longitudinal research is required to validate the relationships between air pollutant exposure and neuroimaging features of CSVD. Secondly, the study, using an observational design, was unable to establish definitive causal relationships. Thirdly, the assessment of ambient air pollution exposure for each subject was based on their home addresses, potentially leading to unavoidable exposure misclassification Finally, study subjects were recruited from the META-KLS conducted in Tangshan City, Hebei Province, China, necessitating caution when extrapolating the research findings.

5. Conclusion

In Chinese adults, $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO exposures were associated with an increased risk of CSVD. The relationships between exposure to ambient air pollutants and neuroimaging markers of CSVD remained significant even when considering different exposure windows. Our study suggested that air pollution may serve as a potential independent risk factor for CSVD, which emphasizes the importance of controlling environmental pollutants to prevent cerebral small vessel damage.

CRediT authorship contribution statement

Yudiyang Ma: Writing – review & editing, Writing – original draft, Software, Methodology. **Ying Hui:** Resources, Investigation. **Linxi Tang:** Writing – review & editing. **Jianing Wang:** Writing – review & editing. **Meiqi Xing:** Writing – review & editing. **Lei Zheng:** Writing – review & editing. **Feipeng Cui:** Writing – review & editing. **Shuohua Chen:** Investigation. **Shouling Wu:** Supervision, Resources, Methodology, Data curation. **Zhenchang Wang:** Supervision, Resources, Investigation, Conceptualization. **Yaohua Tian:** Writing – review & editing, Supervision, Conceptualization.

Ethical approval

The Medical Ethics Committee of Kailuan General Hospital approved the META-KLS study (IRB number: 2021002). This study was registered on Clinicaltrials.gov (Clinical Indicators and Brain Image Data: a Study Based on Kailuan Cohort; No. NCT05453877; https://clinicaltrials.gov/ct2/show/NCT05453877). This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and principles of the Declaration of Helsinki.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eehl.2024.10.004.

References

[1] H.S. Markus, F.E. de Leeuw, Cerebral small vessel disease: recent advances and future directions, Int. J. Stroke 18 (2023) 4–14.
[2] J.M. Wardlaw, C. Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications, Lancet Neurol. 18 (2019) 684–696.
[3] A. Ter Telgte, E.M.C. van Leijsen, K. Wiegertjes, C.J.M. Klijn, A.M. Tuladhar, F.E. de Leeuw, Cerebral small vessel disease: from a focal to a global perspective, Nat. Rev. Neurol. 14 (2018) 387–398.
[4] S. Debette, S. Schilling, M.G. Duperron, S.C. Larsson, H.S. Markus, Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis, JAMA Neurol. 76 (2019) 81–94.
[5] S. Wan, C. Dandu, G. Han, Y. Guo, Y. Ding, H. Song, et al., Plasma inflammatory biomarkers in cerebral small vessel disease: a review, CNS Neurosci. Ther. 29 (2023) 498–515.
[6] K.C. Paul, M. Haan, E.R. Mayeda, B.R. Ritz, Ambient air pollution, noise, and late-life cognitive decline and dementia risk, Annu. Rev. Publ. Health 40 (2019) 203–220.

[7] J.I. Verhoeven, Y. Allach, I.C.H. Vaartjes, C.J.M. Klijn, F.E. de Leeuw, Ambient air pollution and the risk of ischaemic and haemorrhagic stroke, Lancet Planet. Health 5 (2021) e542–e552.

[8] E.H. Wilker, M. Osman, M.G. Weisskopf, Ambient air pollution and clinical dementia: systematic review and meta-analysis, BMJ Clinical Research Ed 381 (2023) e071620.

[9] H. Xu, Y. Jia, Z. Sun, J. Su, Q.S. Liu, Q. Zhou, et al., Environmental pollution, a hidden culprit for health issues, Eco-Environment & Health 1 (2022) 31–45.

[10] C. Chen, K.M. Hayden, J.D. Kaufman, M.A. Espeland, E.A. Whitsel, M.L. Serre, et al., Adherence to a MIND-like dietary pattern, long-term exposure to fine particulate matter air pollution, and MRI-based measures of brain volume: the women's health initiative memory study-MRI, Environ. Health Perspect. 129 (2021) 127008.

[11] U. Clancy, Y. Cheng, A. Brara, F.N. Doubal, J.M. Wardlaw, Occupational and domestic exposure associations with cerebral small vessel disease and vascular dementia: a systematic review and meta-analysis, Alzheimer's Dementia : the journal of the Alzheimer's Association 20 (2024) 3021–3033.

[12] H.Y. Jeong, H.J. Kim, K.W. Nam, S.M. Jeong, H. Kwon, J.H. Park, et al., Annual exposure to PM(10) is related to cerebral small vessel disease in general adult population, Sci. Rep. 12 (2022) 19693.

[13] E.H. Wilker, S.R. Preis, A.S. Beiser, P.A. Wolf, R. Au, I. Kloog, et al., Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure, Stroke 46 (2015) 1161–1166.

[14] E.H. Wilker, S. Martinez-Ramirez, I. Kloog, J. Schwartz, E. Mostofsky, P. Koutrakis, et al., Fine particulate matter, residential proximity to major roads, and markers of small vessel disease in a memory study population, J. Alzheim. Dis. 53 (2016) 1315–1323.

[15] X. Sun, S. Ma, Y. Guo, C. Chen, L. Pan, Y. Cui, et al., The association between air pollutant exposure and cerebral small vessel disease imaging markers with modifying effects of PRS-defined genetic susceptibility, Ecotoxicol. Environ. Saf. 281 (2024) 116638.

[16] J. Duchesne, I. Carrière, S. Artero, A.M. Brickman, J. Maller, C. Meslin, et al., Ambient air pollution exposure and cerebral white matter hyperintensities in older adults: a cross-sectional analysis in the three-city montpellier study, Environ. Health Perspect. 131 (2023) 107013.

[17] D. Li, S. Wu, L. Tang, S. Chen, F. Cui, Y. Ma, et al., Long-term exposure to reduced specific-size ambient particulate matter and progression of arterial stiffness among Chinese adults, J. Hazard Mater. 466 (2024) 133482.

[18] P. Liu, Y. Wang, X. Zhang, Z. Zhang, N. Zhao, W. Ou, et al., Obesity and cardiac conduction block disease in China, JAMA Netw. Open 6 (2023) e2342831.

[19] H. Shi, L. Cui, Y. Hui, S. Wu, X. Li, R. Shu, et al., Enlarged perivascular spaces in relation to cumulative blood pressure exposure and cognitive impairment, Hypertension 80 (2023) 2088–2098.

[20] J. Sun, Y. Hui, J. Li, X. Zhao, Q. Chen, X. Li, et al., Protocol for Multi-modality medical imaging study based on KaiLuan Study (META-KLS): rationale, design and database building, BMJ Open 13 (2023) e067283.

[21] J. Sun, N. Zeng, Y. Hui, J. Li, W. Liu, X. Zhao, et al., Association of variability in body size with neuroimaging metrics of brain health: a population-based cohort study, The Lancet regional health–Western Pacific 44 (2024) 101015.

[22] J. Wei, Z. Li, A. Lyapustin, L. Sun, Y. Peng, W. Xue, et al., Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: spatiotemporal variations and policy implications, Rem. Sens. Environ. 252 (2021) 112136.

[23] J. Wei, Z. Li, J. Wang, C. Li, P. Gupta, M. Cribb, Ground-level gaseous pollutants (NO_2, SO_2, and CO) in China: daily seamless mapping and spatiotemporal variations, Atmos. Chem. Phys. 23 (2023) 1511–1532.

[24] J. Wei, Z. Li, W. Xue, L. Sun, T. Fan, L. Liu, et al., The ChinaHighPM(10) dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China, Environ. Int. 146 (2021) 106290.

[25] J. Wei, S. Liu, Z. Li, C. Liu, K. Qin, X. Liu, et al., Ground-level NO(2) surveillance from space across China for high resolution using interpretable spatiotemporally weighted artificial intelligence, Environ. Sci. Technol. 56 (2022) 9988–9998.

[26] Y. Zhong, J. Wei, Y. Zheng, F. Yan, Spatial refinement method of the $PM_{2.5}$ emission inventory based on the quiescent period pollutant, Journal of Geo-information Science 23 (2021) 1971–1983.

[27] Y. Zhu, Y. Ma, L. Tang, H. Li, C. Miao, H. Cao, et al., The adverse impact of maternal ozone exposure on fetal growth in utero and the interaction with residential greenness, J. Hazard Mater. 461 (2024) 132562.

[28] Y. Ma, D. Li, F. Cui, J. Wang, L. Tang, Y. Yang, et al., Air pollutants, genetic susceptibility, and abdominal aortic aneurysm risk: a prospective study, Eur. Heart J. 45 (2024) 1030–1039.

[29] J.M. Wardlaw, E.E. Smith, G.J. Biessels, C. Cordonnier, F. Fazekas, R. Frayne, et al., Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration, Lancet Neurol. 12 (2013) 822–838.

[30] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJNR Am J Neuroradiol 149 (1987) 351–356.

[31] H. Lv, J. Sun, T. Zhang, Y. Hui, J. Li, X. Zhao, et al., Associations of serum uric acid variability with neuroimaging metrics and cognitive decline: a population-based cohort study, BMC Med. 22 (2024) 256.

[32] F.N. Doubal, A.M. MacLullich, K.J. Ferguson, M.S. Dennis, J.M. Wardlaw, Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease, Stroke 41 (2010) 450–454.

[33] G.M. Potter, F.M. Chappell, Z. Morris, J.M. Wardlaw, Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability, Cerebrovascular diseases (Basel, Switzerland) 39 (2015) 224–231.

[34] P. Klarenbeek, R.J. van Oostenbrugge, R.P. Rouhl, I.L. Knottnerus, J. Staals, Ambulatory blood pressure in patients with lacunar stroke: association with total MRI burden of cerebral small vessel disease, Stroke 44 (2013) 2995–2999.

[35] J. Staals, S.D. Makin, F.N. Doubal, M.S. Dennis, J.M. Wardlaw, Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden, Neurology 83 (2014) 1228–1234.

[36] V.L. Feigin, M.D. Abate, Y. Abate, S. ElHafeez, F. Abd-Allah, A. Abdelalim, et al., Global, regional, and national burden of stroke and its risk factors, 1990–2021: a systematic analysis for the global burden of disease study 2021, Lancet Neurol. 23 (2024) 973–1003.

[37] A. Saad, L. Cherian, K. Benameur, Lifestyle factors and stroke prevention: from the individual to the community, Curr. Neurol. Neurosci. Rep. 24 (2024) 507–515.

[38] S. Peng, 1-km Monthly Mean Temperature Dataset for China (1901-2023), National Tibetan Plateau/Third Pole Environment Data Center, 2019, https://doi.org/10.11888/Meteoro.tpdc.270961.

[39] H. Zhang, M. Luo, W. Zhan, Y. Zhao, Y. Yang, E. Ge, et al., HiMIC-Monthly:A 1km high-resolution atmospheric moisture index collection over China, 2003–2020, Sci. Data 11 (2024) 425.

[40] W. Li, S.M. Bertisch, E. Mostofsky, C. Buettner, M.A. Mittleman, Weather, ambient air pollution, and risk of migraine headache onset among patients with migraine, Environ. Int. 132 (2019) 105100.

[41] L. Chu, K. Chen, Z. Yang, S. Crowley, R. Dubrow, A unified framework for assessing interaction effects among environmental exposures in epidemiologic studies: a case study on temperature, air pollution, and kidney-related conditions in New York state, Environ. Res. 248 (2024) 118324.

[42] J. Bai, Y. Ma, Y. Zhao, D. Yang, S. Mubarik, C. Yu, Mixed exposure to phenol, parabens, pesticides, and phthalates and insulin resistance in NHANES: a mixture approach, Sci. Total Environ. 851 (2022) 158218.

[43] Y. Ma, Q. Hu, D. Yang, Y. Zhao, J. Bai, S. Mubarik, et al., Combined exposure to multiple metals on serum uric acid in NHANES under three statistical models, Chemosphere 301 (2022) 134416.

[44] E.O.B. Semmens, Effects of Traffic-Related Air Pollution on Cognitive Function, Dementia Risk and Brain MRI Findings in the Cardiovascular Health Study, University of Washington, 2013. Doctoral dissertation.

[45] R. Casanova, X. Wang, J. Reyes, Y. Akita, M.L. Serre, W. Vizuete, et al., A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women, Front. Hum. Neurosci. 10 (2016) 495.

[46] J.C. Chen, X. Wang, G.A. Wellenius, M.L. Serre, I. Driscoll, R. Casanova, et al., Ambient air pollution and neurotoxicity on brain structure: evidence from women's health initiative memory study, Ann. Neurol. 78 (2015) 466–476.

[47] E.R. Kulick, G.A. Wellenius, J.D. Kaufman, J.T. DeRosa, P.L. Kinney, Y.K. Cheung, et al., Long-term exposure to ambient air pollution and subclinical cerebrovascular disease in NOMAS (the northern manhattan study), Stroke 48 (2017) 1966–1968.

[48] W.S. Yang, X. Wang, Q. Deng, W.Y. Fan, W.Y. Wang, An evidence-based appraisal of global association between air pollution and risk of stroke, Int. J. Cardiol. 175 (2014) 307–313.

[49] S. Shi, W. Wang, X. Li, C. Xu, J. Lei, Y. Jiang, et al., Evolution in disparity of PM2.5 pollution in China, Eco-Environment & Health 2 (2023) 257–263.

[50] A. Bhatnagar, Cardiovascular effects of particulate air pollution, Annu. Rev. Med. 73 (2022) 393–406.

[51] B. Hoffmann, S. Moebus, N. Dragano, A. Stang, S. Möhlenkamp, A. Schmermund, et al., Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers, Environ. Health Perspect. 117 (2009) 1302–1308.

[52] M. Pedde, T.V. Larson, J. D'Souza, A.A. Szpiro, I. Kloog, L.D. Lisabeth, et al., Coarse particulate matter and markers of inflammation and coagulation in the multi-ethnic study of atherosclerosis (mesa) population: a repeat measures analysis, Environ. Health Perspect. 132 (2024) 27009.

[53] H.H. Aung, M.W. Lame, K. Gohil, G. He, M.S. Denison, J.C. Rutledge, et al., Comparative gene responses to collected ambient particles in vitro: endothelial responses, Physiol. Genom. 43 (2011) 917–929.

[54] G. Oberdörster, Z. Sharp, V. Atudorei, A. Elder, R. Gelein, A. Lunts, et al., Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats, J. Toxicol. Environ. Health, Part A 65 (2002) 1531–1543.

[55] M.A. Bind, A. Peters, P. Koutrakis, B. Coull, P. Vokonas, J. Schwartz, Quantile regression analysis of the distributional effects of air pollution on blood pressure, heart rate variability, blood lipids, and biomarkers of inflammation in elderly American men: the normative aging study, Environ. Health Perspect. 124 (2016) 1189–1198.

[56] B.Z. Simkhovich, M.T. Kleinman, R.A. Kloner, Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms, J. Am. Coll. Cardiol. 52 (2008) 719–726.