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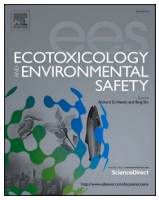

The association between air pollutant exposure and cerebral small vessel disease imaging markers with modifying effects of PRS-defined genetic susceptibility

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ABSTRACT

Studies have highlighted a possible link between air pollution and cerebral small vessel disease (CSVD) imaging markers. However, the exact association and effects of polygenic risk score (PRS) defined genetic susceptibility remains unclear. This cross-sectional study used data from the UK Biobank. Participants aged 40–69 years were recruited between the year 2006 and 2010. The annual average concentrations of NO_X, NO_2, $PM_{2.5}$, $PM_{2.5-10}$, $PM_{2.5}$ absorbance, and PM_{10}, were estimated, and joint exposure to multiple air pollutants was reflected in the air pollution index (APEX). Air pollutant exposure was classified into the low (T1), intermediate (T2), and high (T3) tertiles. Three CSVD markers were used: white matter hyper-intensity (WMH), mean diffusivity (MD), and fractional anisotropy (FA). The first principal components of the MD and FA measures in the 48 white matter tracts were analysed. The sample consisted of 44,470 participants from the UK Biobank. The median (T1–T3) concentrations of pollutants were as follows: NO_2, 25.5 (22.4–28.7) μg/m^3; NOx, 41.3 (36.2–46.7) μg/m^3; PM_{10}, 15.9 (15.4–16.4) μg/m^3; $PM_{2.5}$, 9.9 (9.5–10.3) μg/m^3; $PM_{2.5}$ absorbance, 1.1 (1.0–1.2) per metre; and $PM_{2.5-10}$, 6.1 (5.9–6.3) μg/m^3. Compared with the low group, the high group's APEX, NO_X, and $PM_{2.5}$ levels were associated with increased WMH volumes, and the estimates (95 %CI) were 0.024 (0.003, 0.044), 0.030 (0.010, 0.050), and 0.032 (0.011, 0.053), respectively, after adjusting for potential confounders. APEX, PM_{10}, $PM_{2.5}$ absorbance, and $PM_{2.5-10}$ exposure in the high group were associated with increased FA values compared to that in the low group. Sex-specific analyses revealed associations only in females. Regarding the combined associations of air pollutant exposure and PRS-defined genetic susceptibility with CSVD markers, the associations of NO_2, NO_X, $PM_{2.5}$, and $PM_{2.5-10}$ with WMH were more profound in females with low PRS-defined genetic susceptibility, and the associations of PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ absorbance with FA were more profound in females with higher PRS-defined genetic susceptibility. Our study demonstrated that air pollutant exposure may be associated with CSVD imaging markers, with females being more susceptible, and that PRS-defined genetic susceptibility may modify the associations of air pollutants.

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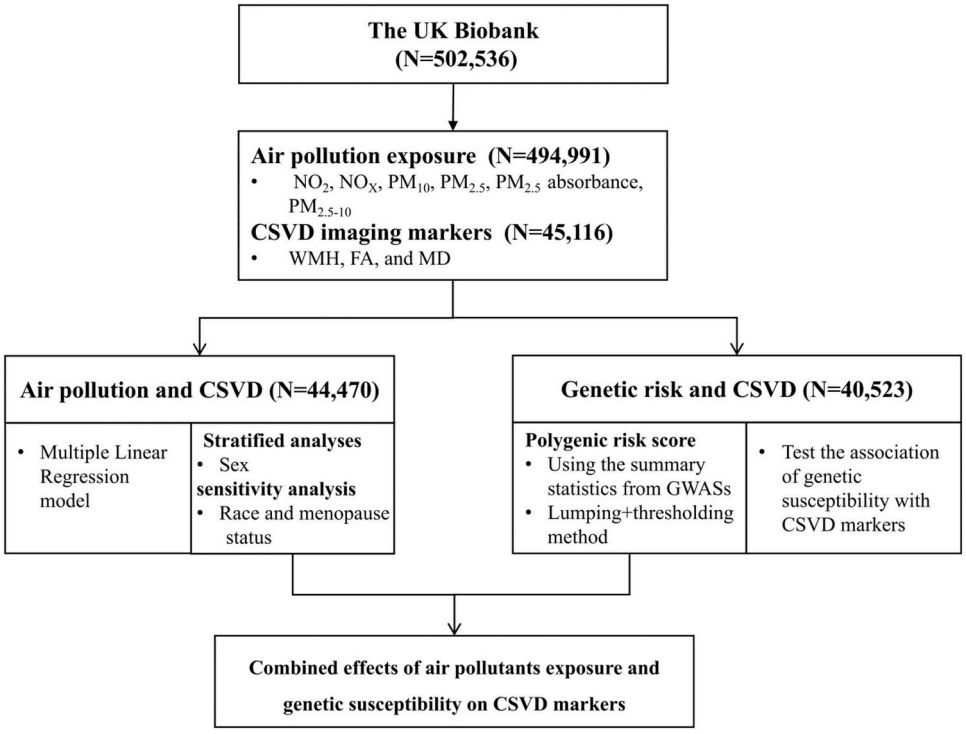

Fig. 1. Study flow diagram for participant inclusion.

1. Introduction

Cerebral small vessel disease (CSVD) refers to pathological changes in small penetrating vessels in the brain. As a major public health concern, CSVD accounts for up to one-third of the stroke cases and approximately 45 % of the dementia cases worldwide, particularly among old adults. CSVD is one of the most common causes of neurological diseases and related disabilities (Gorelick et al., 2011; Pasi et al., 2016; Sudlow and Warlow, 1997). With the development of neuroimaging techniques, the diagnosis of CSVD has become increasingly common in older adults, especially in the presence of hypertension, cardiovascular disease, and diabetes (Tap et al., 2023). Despite the high prevalence and serious consequences of CSVD, the pathogenesis and risk factors contributing to its development are poorly understood (De Silva and Faraci, 2020). Additionally, there are currently no effective treatments for CSVD, thus, unveiling the risk factors related to CSVD and identifying effective prevention strategies are of crucial importance in reducing the burden of CSVD disease.

Air pollution, which comprises particulate matter (PM) and several toxic gases, is a critical health concern. PM is classified by particle size, for example, fine PM (diameter $\leq$2.5μm, $PM_{2.5}$), coarse PM (diameter between 2.5 and 10 μm, $PM_{2.5–10}$), and PM 10 (diameter $\leq$10 μm, PM_{10}). Nitrogen oxides (NO_X), including nitrogen dioxide (NO_2), are some commonly observed gaseous pollutants (Verhoeven et al., 2021). The association of air pollutant exposure with stroke, cardiovascular disease, cognitive decline, and dementia have been reported (Delgado-Saborit et al., 2021; Parra et al., 2022; Tian et al., 2022; Wolf et al., 2021; S. Y. Zhang et al., 2023).

Although the effect of air pollutants on the morbidity and mortality rates of stroke and dementia is well-established, studies on the association between air pollutants and CSVD imaging markers have yielded conflicting results. A study in South Korea reported that exposure to PM_{10} was positively associated with white matter hyper-intensity (WMH) volume and the risk of silent lacunar infarction in the adult population, suggesting that exposure to PM_{10} is a potential risk factor for CSVD (Jeong et al., 2022). A study in Massachusetts showed that exposure to $PM_{2.5}$ was associated with lower WMH volume in patients with memory concerns (Wilker et al., 2016). However, the Northern Manhattan Study did not find an association between residential traffic pollutants exposure and WMH volume (Kulick et al., 2017).

In addition to environmental factors, genetic factors can affect CSVD progression (Taylor-Bateman et al., 2022). Genome-wide association studies (GWAS) can identify genetic susceptibilities to various diseases, including cerebrovascular and metabolic diseases (Bakker et al., 2020; Ge et al., 2022; Lu et al., 2022; O'Sullivan et al., 2023). The polygenic risk score (PRS) quantifies the effect of various genetic variants (Lu et al., 2022, 2021). Mounting evidence has indicated that genetic susceptibility can partially determine the influence of environmental factors (Fu et al., 2022; Gao et al., 2023). However, evidence regarding the combined associations of air pollution and genetic susceptibility with CSVD imaging markers is limited. Clarifying the interaction between the environment and genetic susceptibility can improve the accuracy of prediction and intervention of CSVD (Gao et al., 2023; J. Zhang et al., 2023).

Therefore, using a large sample of nearly 50,000 adults, and comprehensive data on individual characteristics, lifestyles, air pollutant exposure, brain imaging, and genetic information from the UK Biobank, this study aimed to quantify the association between air pollutants exposure and CSVD imaging markers in adults. We assessed the combined associations of air pollutants exposure and PRS-defined genetic susceptibility with CSVD imaging markers.

2. Materials and methods

2.1. Study population

The UK Biobank study protocol has been previously published (Li et al., 2022). In brief, 502,536 participants in the United Kingdom aged 40–69 years were recruited between the year 2006 and 2010. Information on the participants' lifestyles and health was collected during the baseline visit. Physical measurements were performed, and urine, blood, and saliva samples were collected. Prior to data collection, all

Table 1
Characteristics of the included participants.

Characteristics	N (%)
Age, mean (SD), years	55.0 (7.5)
Sex	
Female	23,530 (52.9)
Male	20,940 (47.1)
BMI, kg/m^2	26.57 (4.2)
Race	
White British	40,523 (91.2)
Other	3935 (8.8)
Tobacco smoking	
Never	27,036 (60.8)
Previous	14,617 (32.9)
Current	2718 (6.1)
Unknown	87 (0.2)
Alcohol drinking	
Never	1080 (2.4)
Previous	936 (2.1)
Current	42,427 (95.4)
Unknown	15 (0.1)
Household income range, £	
<18000	4648 (10.6)
18000–30999	8832 (20.2)
31000–51999	12,111(27.6)
52000–100000	11,389(26.0)
100000	3129(7.1)
Unknown	3733(8.5)
Menopause	
Yes	18,173 (77.2)
No	1808 (7.7)
Not sure or prefer not to answer	3549 (15.1)
Hypertension	
Yes	9791 (25.7)
No	28,380(74.3)
Diabetes	
Yes	2077 (5.4)
No	36,094 (94.6)
Dyslipidemia	
Yes	5079 (13.3)
No	33,092 (86.7)
Air pollution	
NO_2, median (T1-T3), μg/m^3	25.5 (22.4–28.7)
NO_x, median (T1-T3), μg/m^3	41.3 (36.2–46.7)
PM_{10}, median (T1-T3), μg/m^3	15.9 (15.4–16.4)
$PM_{2.5}$, median (T1-T3), μg/m^3	9.9 (9.5–10.3)
$PM_{2.5}$ absorbance, median (T1-T3), per meter	1.1 (1.0–1.2)
$PM_{2.5-10}$, median (T1-T3), μg/m^3	6.1 (5.9–6.3)

Abbreviations BMI: Body Mass Index; NO_2: Nitrogen dioxide; NOx: Nitrogen oxides; PM_{10}: Particles with aerodynamic diameters ≤10 μm; $PM_{2.5}$: Particles with aerodynamic diameters ≤2.5 μm; $PM_{2.5}$ absorbance: a measurement of the blackness of $PM_{2.5}$ filters, a proxy for elemental carbon, which is the dominant light absorbing substance; $PM_{2.5-10}$: Particles with aerodynamic diameters between 2.5 and 10 μm; T1: lowest tertile; T3: highest tertile.

participants needed to sign informed consent forms (Bycroft et al., 2018). A diagram of the study flow with participant inclusion is shown in Fig. 1.

2.2. Air pollution exposure

The annual average concentrations of air pollutants, including NO_X, NO_2, PM_{10}, $PM_{2.5-10}$, $PM_{2.5}$, and $PM_{2.5}$ absorbance (a proxy for elemental carbon), were modelled for participants' residential addresses by using the land use regression model. A detailed description of the air pollution measurements has been provided in the literature (Beelen et al., 2013; Eeftens et al., 2012). Specifically, the land use regression model assesses spatial variations in air pollutant levels by using several geospatial predictive variables, such as land use, population intensity, traffic intensity, and altitude. Information on each participant's air pollutants exposure levels was collected between 26 January 2010 and 18 January 2011. The air pollutants estimates represented the year 2010.

2.3. Assessment of CSVD magnetic resonance imaging (MRI) markers

We used the multimodal MRI data released by the UK Biobank in February 2023. Multimodal MRI data collected from 44,470 individuals between 2014 and 2015 were available for analysis. Three CSVD imaging markers (continuous variables) were used: WMH volume, diffusion tensor imaging (DTI) metrics fractional anisotropy (FA), and DTI mean diffusivity (MD) in various white matter tracts. WMH is a marker used to identify CSVD, and the DTI metrics FA and MD are markers that measure the microstructural integrity of white matter, which is typically abnormal in CSVD. To approximate a normal distribution, WMH volumes were log-transformed in the analyses. We removed outliers outside the ±8 SD range for each multimodal MRI marker (Taylor-Bateman et al., 2022). To derive a comprehensive global assessment of white matter FA and white matter MD, we conducted principal component analysis on the FA and MD obtained from the analysis of 48 different white matter tracts. The first principal components of the white matter FA and white matter MD measures in 48 white mattresses were considered (Persyn et al., 2020; Taylor-Bateman et al., 2022; Zhang et al., 2022), and accounted for 40.5 % (FA) and 42.3 % (MD) of the variance in these measures, respectively. We also calculated the combined value of multiple principal components to achieve a variance of 80 % for FA and MD.

2.4. PRS analyses

We conducted PRS analyses to estimate the genetic susceptibility of the CSVD markers by calculating the target genotype and GWAS data. To obtain the GWAS summary statistics in the PRS analyses, we downloaded the GWAS data for WMH volume and the first principal components of white matter FA and MD from https://www.kp4cd.org/dataset_downloads/stroke (Persyn et al., 2020). We used the UK Biobank imputed data as the target data, with 430,112 White British individuals and 21,566,456 variants after quality control. We then calculated and analysed the PRS by using a clumping and thresholding method with a *P*-value threshold of 0.001 (Choi et al., 2020). The PRS of the three CSVD markers was included in the statistical analyses as an interaction term for air pollutants.

2.5. Statistical analyses

Sociodemographic and lifestyle factors, air pollution exposure, and CSVD imaging markers for the included participants were summarised using descriptive statistics. We primarily used a generalised additive model to examine the potential nonlinear associations between air pollution exposure and the three CSVD imaging markers, which suggested nonlinearity in some scenarios (nonlinear plots of WMH volumes versus multiple air pollutants exposure are shown in Figure S1). Therefore, air pollution exposure was classified into three groups based on the concentration: low (first tertile; T1), intermediate (second tertile; T2), and high (third tertile; T3). Multiple linear regression models were conducted to examine the association between air pollution exposure and WMH volume, white matter FA, and white matter MD, with age, sex, household income, BMI, race, tobacco smoking, and alcohol consumption as covariates. Brain volume was included as an additional covariate for the analysis of WMH. We calculated the air pollution index (APEX) using the equation: $APEX=(\beta_{NO2}\times NO_2+\beta_{NOX}\times NO_X+\beta_{PM10}\times PM_{10}+\beta_{PM25-10}\times PM_{2.5-10}+\beta_{PM2.5}\times PM_{2.5}+\beta_{PM2.5\ absorbance}\times PM_{2.5}\ absorbance)\times(6/\text{sum of the }\beta\text{ coefficients})$, which was also categorised into three groups by tertiles (Li et al., 2022). We used the false discovery rate (FDR) correction to solve the multiple comparisons problem, and *P*-values corrected by FDR were calculated. We included an interaction term between each air pollutant and sex in the regression model to explore the possible modification effect by sex, and presented the results separately for females and males.

To evaluate whether genetic susceptibility can modify the

Table 2
The associations between air pollutants exposure and WMH volume in participants.

Air pollution	Groups	All (N=44470)			Women (N=23530)			Men (N=20940)			*P*-value for interaction
		β[#]	*P*	95 %CI	β[#]	*P*	95 %CI	β[#]	*P*	95 %CI	
APEX	T1	ref			**ref**			**ref**			0.012*
	T2	-0.009	0.363	-0.030, 0.011	-0.003	0.838	-0.030, 0.025	-0.007	0.647	-0.037, 0.023	
	T3	**0.024**	**0.024***	**0.003, 0.044**	**0.038**	**0.006***	**0.011, 0.066**	0.010	0.542	-0.021, 0.041	
NO_2	T1	ref			ref			ref			0.032*
	T2	0.001	0.911	-0.019, 0.021	-0.004	0.788	-0.030, 0.023	0.003	0.819	-0.026, 0.033	
	T3	0.019	0.069	-0.001, 0.039	0.026	0.058	-0.001, 0.053	0.009	0.537	-0.021, 0.039	
NO_x	T1	ref			ref			ref			0.008
	T2	-0.002	0.846	-0.022, 0.018	0.004	0.763	-0.022, 0.031	-0.010	0.494	-0.040, 0.019	
	T3	**0.030**	**0.003***	**0.010, 0.050**	**0.042**	**0.002***	**0.016, 0.069**	0.015	0.331	-0.015, 0.045	
PM_{10}	T1	ref			ref			ref			0.011*
	T2	-0.009	0.412	-0.029, 0.012	0.006	0.642	-0.021, 0.034	-0.026	0.093	-0.056, 0.004	
	T3	-0.005	0.634	-0.025, 0.015	0.012	0.407	-0.016, 0.039	-0.024	0.127	-0.054, 0.007	
$PM_{2.5}$	T1	ref			ref			ref			0.041*
	T2	-0.007	0.485	-0.028, 0.013	-0.009	0.523	-0.036, 0.018	-0.008	0.622	-0.038, 0.023	
	T3	**0.032**	**0.002***	**0.011, 0.053**	**0.043**	**0.002***	**0.016, 0.071**	0.017	0.286	-0.014, 0.048	
$PM_{2.5\ absorbance}$	T1	ref			ref			ref			0.193
	T2	-0.006	0.595	-0.026, 0.015	-0.019	0.185	-0.046, 0.009	0.009	0.572	-0.022, 0.039	
	T3	-0.015	0.167	-0.035, 0.006	-0.020	0.160	-0.048, 0.008	-0.010	0.511	-0.041, 0.021	
$PM_{2.5–10}$	T1	ref			ref			ref			0.077
	T2	-0.016	0.119	-0.036, 0.004	-0.001	0.942	-0.028, 0.026	**-0.035**	**0.026***	**-0.065, −0.004**	
	T3	0.003	0.810	-0.018, 0.023	0.011	0.443	-0.017, 0.038	-0.009	0.573	-0.039, 0.022	

Note: 1) Abbreviations APEX: Air pollution index; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; PM_{10}: Particles with aerodynamic diameters ≤10 μm; $PM_{2.5}$: Particles with aerodynamic diameters ≤2.5 μm; $PM_{2.5}$ absorbance: a measurement of the blackness of $PM_{2.5}$ filters, a proxy for elemental carbon, which is the dominant light absorbing substance; $PM_{2.5–10}$: Particles with aerodynamic diameters between 2.5 and 10 μm; WMH: White matter hyperintensity.
2) [#]Models adjusted for age, sex, household income, BMI, race, tobacco smoking, alcohol drinking, and brain volume.
3) *There are statistically significant differences.
4) Defined by air pollutants concentrations: T1 (lowest tertile), T2 (intermediate tertile), T3 (highest tertile).

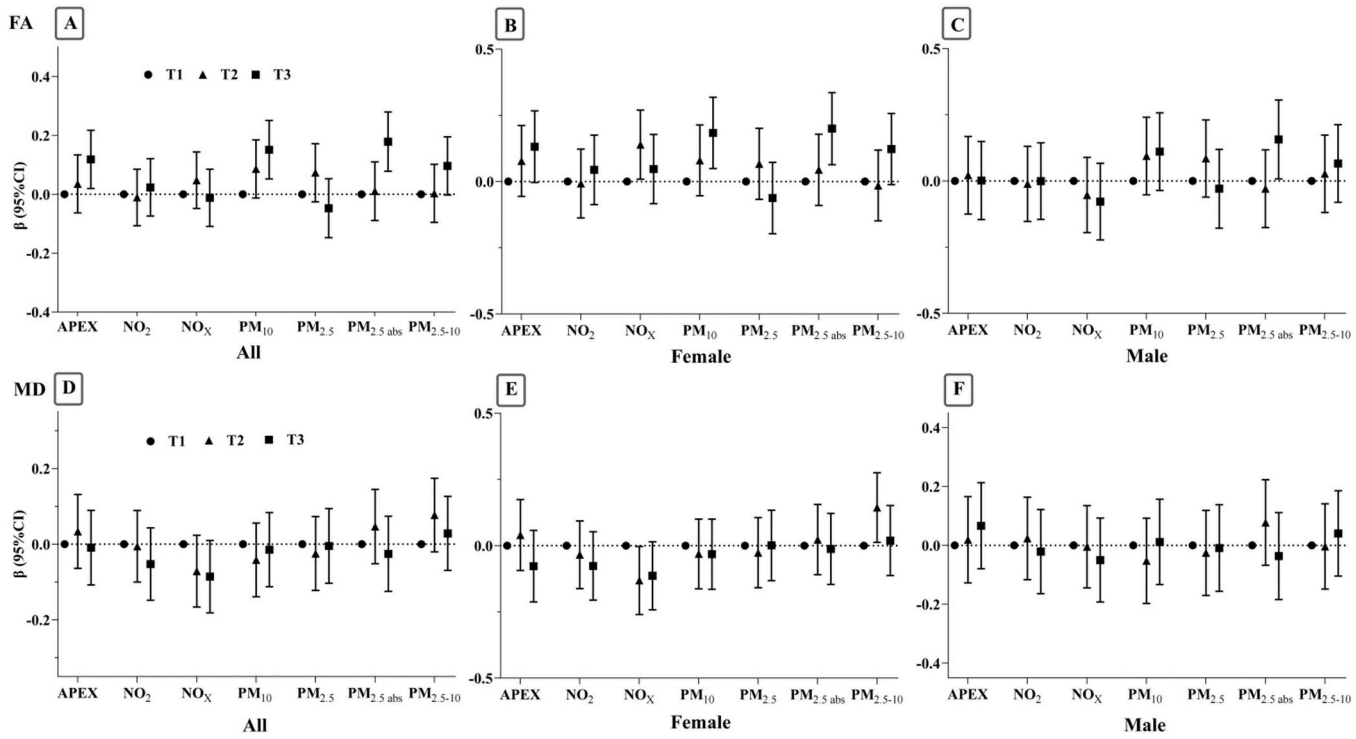

Fig. 2. The associations of air pollutants exposure with the first principal component of white matter FA and MD in participants. Note: (A) Air pollution exposure and the first principal component of FA in all participants; (B)Air pollution exposure and the first principal component of FA in female; (C) Air pollution exposure and the first principal component of FA in male; (D) Air pollution exposure and the first principal component of MD in all participants; (E) Air pollution exposure and the first principal component of MD in female; (F) Air pollution exposure and the first principal component of MD in male. 1) Dots indicate the estimate, and vertical lines indicate the 95 % CI. 2) Abbreviations APEX: Air pollution index; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; PM_{10}: Particles with aerodynamic diameters ≤10 μm; $PM_{2.5}$: Particles with aerodynamic diameters ≤2.5 μm; $PM_{2.5}$ abs: $PM_{2.5}$ absorbance, a measurement of the blackness of $PM_{2.5}$ filters, a proxy for elemental carbon, which is the dominant light absorbing substance; $PM_{2.5–10}$: Particles with aerodynamic diameters between 2.5 and 10 μm; FA: Fractional anisotropy; MD: Mean diffusivity. 3) Models adjusted for age, sex, household income, BMI, race, tobacco smoking, and alcohol drinking. 4) Defined by air pollutants concentrations: T1 (lowest tertie), T2 (intermediate tertile), T3 (highest tertile).

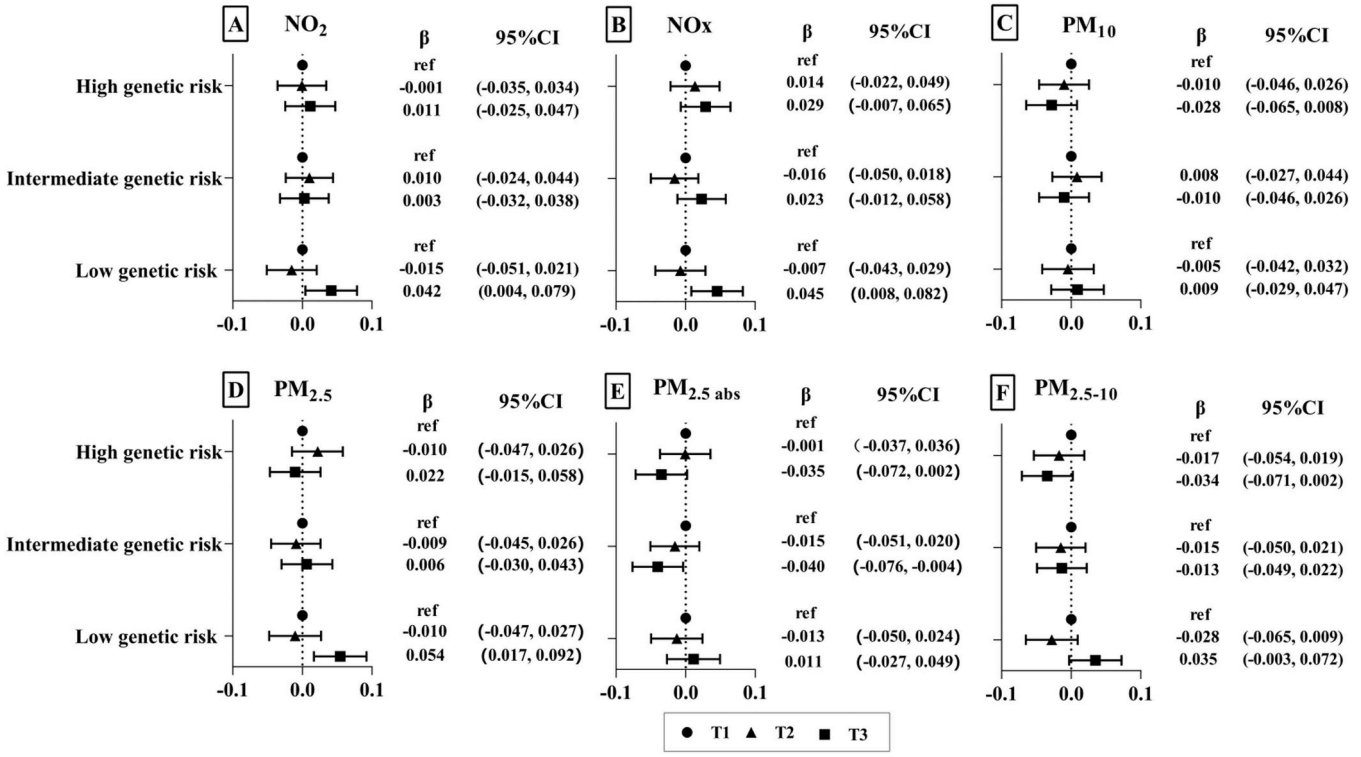

Fig. 3. Additive joint interaction for air pollutants exposure and PRS-defined genetic risk categories on WMH volume in all participants. Note: (A) NO_2 exposure and PRS categories on WMH volume; (B) NO_X exposure and PRS categories on WMH volume; (C)PM_{10} exposure and PRS categories on WMH volume; (D) $PM_{2.5}$ exposure and PRS categories on WMH volume; (E) $PM_{2.5\ abs}$ exposure and PRS categories on WMH volume; (F) $PM_{2.5-10}$ exposure and PRS categories on WMH volume. 1) Dots indicate the estimate, and vertical lines indicate the 95 % CI. 2) Abbreviations PRS: polygenic risk score; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; PM_{10}: Particles with aerodynamic diameters ≤10 μm; $PM_{2.5}$: Particles with aerodynamic diameters ≤2.5 μm; $PM_{2.5}$ abs: $PM_{2.5}$ absorbance, a measurement of the blackness of $PM_{2.5}$ filters, a proxy for elemental carbon, which is the dominant light absorbing substance; $PM_{2.5-10}$: Particles with aerodynamic diameters between 2.5 and 10 μm; WMH: White matter hyperintensity. 3) Models adjusted for age, sex, household income, BMI, race, tobacco smoking, alcohol drinking, and brain volume. 4) Defined by air pollutants concentrations: T1 (lowest tertile), T2 (intermediate), T3 (highest tertile). Defined by genetic categories: Low (lowest tertile), Intermediate (intermediate), High (highest tertile).

association between air pollution and CSVD imaging markers, we tested genetic-air pollutant interactions by adding interaction terms (air pollutants × PRS) to the model. We generated a categorical variable based on the air pollution tertiles. Moreover, a categorical variable based on the PRS tertiles was generated to show the joint association between both factors and CSVD imaging markers.

In order to examine the robustness of the main results, we conducted several sensitivity analyses. We examined the association of air pollutants exposure with CSVD imaging markers in White British citizens and menopausal women. We also examined the joint associations of air pollutants exposure and PRS categories [defined as low (≤P20), intermediate (P20–P80), and high (≥P80)] with WMH volumes in multiple regression models for a potential threshold effect of genetic susceptibility. SAS version 9.4 and R version 4.3.1 were used to conduct the analyses. Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of participants

A total of 44,470 participants (mean [SD] age, 55.0 [7.5] years; 23,530 females [52.9 %]; 20,940 males [47.1 %]) were included in the analysis. Most of the participants were White British (91.2 %) and most of the female participants were menopausal. Detailed data are presented in Table 1. The median (T1–T3) concentrations of pollutants were as follows: NO_2, 25.5 (22.4–28.7) μg/m^3; NO_x, 41.3 (36.2–46.7) μg/m^3; PM_{10}, 15.9 (15.4–16.4) μg/m^3; $PM_{2.5}$, 9.9 (9.5–10.3) μg/m^3; $PM_{2.5}$ absorbance, 1.1 (1.0–1.2) per metre; $PM_{2.5-10}$, 6.1 (5.9–6.3) μg/m^3 (Table 1).

3.2. Association between multiple air pollutants exposure and MRI markers of CSVD

Air pollution was divided into tertiles based on concentration. Exposure to APEX, NO_X, and $PM_{2.5}$ in the T3 was associated with increased WMH volumes compared with that of the T1 after adjusting for potential confounders. The estimates of β coefficients for APEX, NO_X, and $PM_{2.5}$ exposure (95 %CI) were 0.024 (0.003, 0.044), 0.030 (0.010, 0.050), and 0.032 (0.011, 0.053), respectively. Next, a sex-stratified analysis was performed. The associations of APEX, NO_X, and $PM_{2.5}$ with WMH volumes were mainly observed in females and not observed in males (Table 2). The *P*-values corrected by FDR for (borderline) statistically significant associations of air pollutants exposure with WMH volumes are presented in Table S1.

We then examined the associations of multiple air pollutants exposure with the first principal components of white matter FA and white matter MD. Exposure to APEX, PM_{10}, $PM_{2.5}$ absorbance, and $PM_{2.5-10}$ in the T3 was associated with higher white matter FA values than that of the T1. Using sex-stratified analyses, we found that these associations were more prominent in female participants than in male participants (Fig. 2). Specifically, in females, the T3 of APEX, PM_{10}, $PM_{2.5}$ absorbance, $PM_{2.5-10}$, and the T2 of NO_X exposure, were associated with higher white matter FA values than that of the T1. The T2 of $PM_{2.5-10}$ exposure was associated with a statistically significant increase in white matter MD values only in females compared with the T1 (Fig. 2).

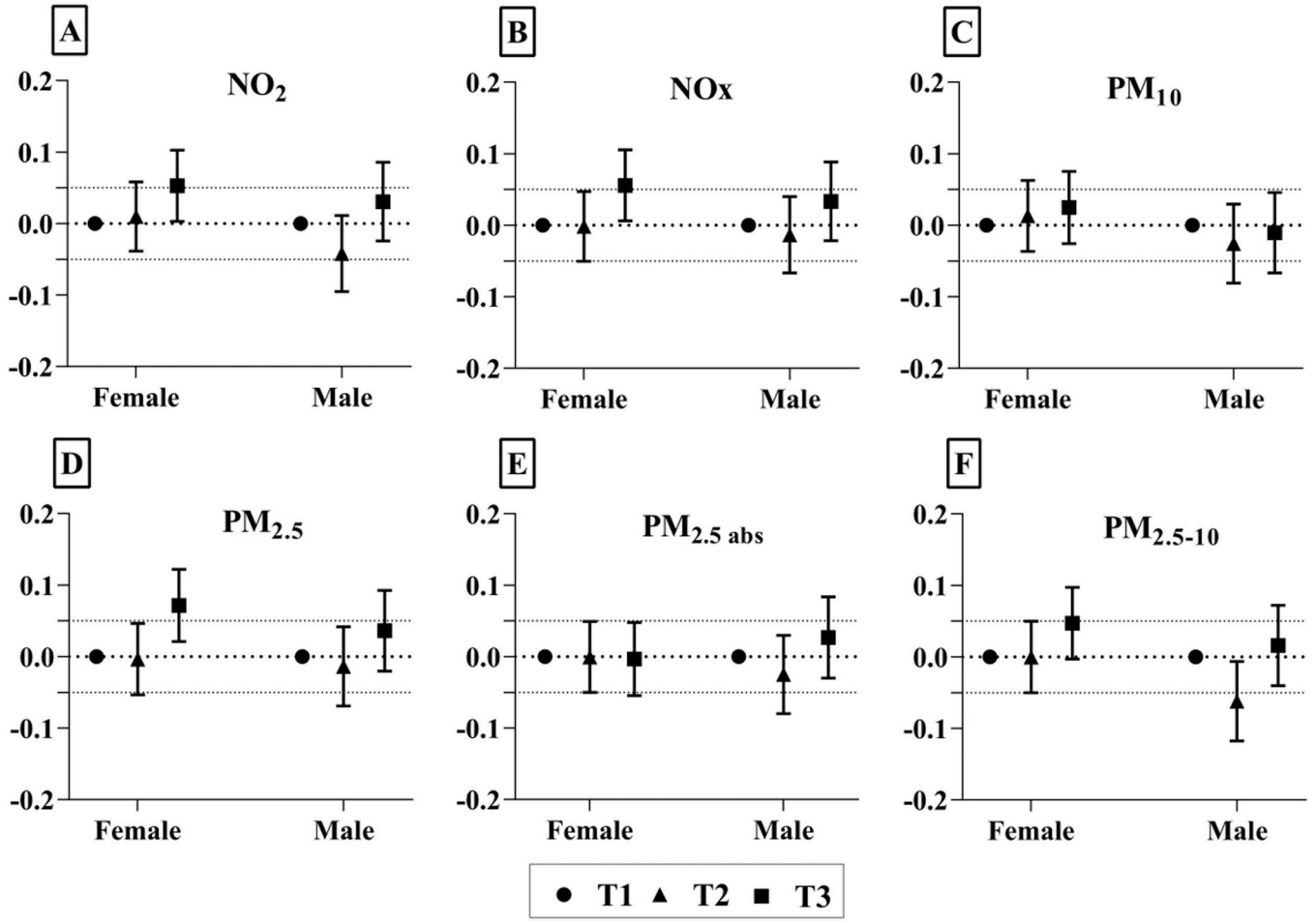

Fig. 4. The associations between air pollutants exposure and WMH volume in participants with low PRS-defined genetic susceptibility. Note: (A) NO_2 exposure and WMH volume; (B) NO_x exposure and WMH volume; (C) PM_{10} exposure and WMH volume; (D) $PM_{2.5}$ exposure and WMH volume; (E) $PM_{2.5\ abs}$ exposure and WMH volume; (F) $PM_{2.5\text{-}10}$ exposure and WMH volume. 1) Dots indicate the estimate, and vertical lines indicate the 95 % CI. 2) Abbreviations PRS: polygenic risk score; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; PM_{10}: Particles with aerodynamic diameters ≤10 μm; $PM_{2.5}$: Particles with aerodynamic diameters ≤2.5 μm; $PM_{2.5}$ abs: $PM_{2.5}$ absorbance, a measurement of the blackness of $PM_{2.5}$ filters, a proxy for elemental carbon, which is the dominant light absorbing substance; $PM_{2.5\text{–}10}$: Particles with aerodynamic diameters between 2.5 and 10 μm; WMH: White matter hyperintensity. 3) Models adjusted for age, sex, household income, BMI, race, tobacco smoking, alcohol drinking, and brain volume. 4) Defined by air pollutants concentrations: T1 (lowest tertile), T2 (intermediate tertile), T3 (highest tertile).

Moreover, similar associations were observed between multiple air pollutants exposure and the combined values of the multiple principal components of white matter FA and MD (data not shown). A sensitivity analysis restricted to White British citizens confirmed the robustness of our results (Table S2). When further adjusted for updated covariates in the model, the associations of air pollutants exposure with WMH volume were robust (Table S3). In addition, we observed strong associations of air pollutants exposure with CSVD imaging markers in menopausal women (Table S4).

3.3. Association of multiple air pollutants exposure and PRS-defined genetic susceptibility with CSVD imaging markers

Next, we examined the association of PRS with CSVD imaging markers and found positive associations between the PRS score and WMH volumes, and white matter FA and MD (data not shown). As the interactions between PRS-defined genetic susceptibility to CSVD imaging markers and air pollutants were significant in several models ($P<0.1$), we generated a categorical variable based on the PRS tertiles to show the joint association of air pollutants and PRS-defined genetic susceptibility with CSVD imaging markers. The associations of NO_2, NO_X, $PM_{2.5}$, and $PM_{2.5\text{–}10}$ with WMH volumes were (marginally) statistically significant in individuals with low PRS-defined genetic susceptibility but not in the intermediate and high PRS-defined genetic susceptibility groups (Fig. 3). Sex-stratified analyses revealed that these associations were presented only among female participants (Fig. 4). When PRS categories were defined as low (≤P20), intermediate (P20–P80), and high (≥P80), similar results were obtained (Table S5).

We also examined joint associations of air pollutants exposure and genetic categories with white matter FA and MD. The associations of PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ absorbance with FA were more profound in individuals with higher PRS-defined genetic susceptibility, and the aforementioned associations were only observed among female participants (Figure S2). Regarding joint associations of air pollutants exposure and genetic categories on white matter MD, the T3 of NO_2, NO_X, and $PM_{2.5}$ exposure were associated with a decreased MD value compared with those of the T1 exposure in female participants with intermediate PRS-defined genetic susceptibility (Figure S3).

4. Discussion

This study evaluated the combined associations of multiple air pollutants exposure and PRS-defined genetic susceptibility with CSVD imaging markers in the general population. We identified sex-specific

associations between multiple air pollutants exposure and CSVD imaging markers. Air pollutants exposure is associated with increased WMH volume and white matter FA in females. In addition, females with low PRS-defined genetic susceptibility were more likely to have increased WMH volumes, those with higher PRS-defined genetic susceptibility were more likely to have increased white matter FA values, and those with intermediate PRS-defined genetic susceptibility were more likely to have decreased white matter MD values when exposed to high levels of air pollutants. Our study indicates that exposure to relatively high concentrations of multiple air pollutants may be associated with CSVD imaging markers, with females being more susceptible, and that PRS-defined genetic susceptibility may modify the associations of air pollutants.

WMH volumes are indicative of the pathological alterations observed on MRI and are commonly attributed to CSVD in the general population. White matter FA and white matter MD as DTI measures, are used to assess white matter damage. Still, they are expected to exhibit higher sensitivity to disturbances in regular functioning and structural integrity, than solely measuring pathological changes (Persyn et al., 2020). Although epidemiological studies have indicated clear associations of multiple air pollutants exposure with the risk of stroke and dementia, contradictory findings on the associations between air pollutants exposure and CSVD imaging markers have been reported. Jeong et al. evaluated the associations of annual air pollutants exposure with CSVD markers in South Korean adults and found that only PM_{10} exposure was associated with a significant increases in WMH volume (Jeong et al., 2022). Other studies have reported no associations of $PM_{2.5}$, NOx, NO_2, and O_3 exposure with WMH volume in females with concerns about memory loss or in the general adults (Kulick et al., 2017; Wilker et al., 2016). The inconsistent results across these studies may be partially attributed to the differences in air pollution types, exposure levels, and participants. The results of the aforementioned studies suggest that the associations of air pollutants exposure with WMH vary according to area, demographic characteristics, disease history, and other factors. Two animal studies have examined the associations between traffic-related air pollutants exposure and DTI in mice and demonstrated that diesel exhaust particulate exposure resulted in decreased FA (Chakhoyan, 2023; Chen et al., 2023). Aa FA served as a comprehensive measurement in the present epidemiological study, a direct comparison of our findings with those of animal studies is challenging. Nevertheless, the findings of these studies emphasis the susceptibility of white matter to air pollutants exposure.

The biological mechanisms of the link between air pollution and the CSVD imaging markers remain unclear. Gaseous pollutants and small particles can reach the brain directly via the nose. In addition, small particles may enter the circulation through the respiratory system and subsequently enter the brain (Hahad et al., 2020). Air pollution exposure may also induce brain's oxidative stress and immune responses, which is indicated by higher levels of pro-inflammatory cytokines, such as tumour necrosis factor-α in the blood and cerebrospinal fluid (Brockmeyer and D'Angiulli, 2016). An epidemiological study reported that the presence of WMH was related to neuro-inflammation, indicated by an increase in tumour necrosis factor-α (Calderón-Garcidueñas et al., 2012). In addition, epidemiological and experimental studies have shown that exposure to PM can reduce cerebral blood flow (Huuskonen et al., 2021; Wellenius et al., 2013), which is associated with an increased WMH burden in older adults (Crane et al., 2015; van Dalen et al., 2016). Those findings may provide a plausible biological explanation for the associations of air pollutants exposure with CSVD imaging markers. Further research is required to elucidate the exact mechanisms of our findings.

In addition to our study, other epidemiological studies have demonstrated higher susceptibility to air pollutants exposure among women (Clougherty, 2010; Kim et al., 2019). These results may be attributed to potential variations in brain structure or function between sexes. For instance, Gallart-Palau et al. investigated sex-specific molecular disparities in the progression of Alzheimer's disease to cerebrovascular disease and observed that women exhibited greater susceptibility to white matter pathology (Gallart-Palau et al., 2016). Additionally, an animal study examined sex-specific transcriptome responses to PM in the cerebral cortex and revealed a two-fold increase in the number of genes that respond to PM in female mice. These responsive genes encompass neuronal pathways, inflammation, antioxidants, and hypoxic signalling (Haghani et al., 2020). It is plausible to assume a similar phenomenon in human females.

Our study had two notable strengths. First, we used a large-scale prospective cohort from the UK Biobank to accurately measure each participant's daily air pollutant exposure levels. Second, we extracted brain multimodal MRI and GWAS data to explore the combined associations of air pollutants exposure and PRS-defined genetic susceptibility with CSVD imaging markers. Our study also has several limitations. As a volunteer cohort, participants in the UK Biobank cohort were probably healthier than the general population, which may have resulted in an underestimation of the impact of air pollution (Gao et al., 2023). Second, the measurement of air pollutant exposure was based on the participants' residential addresses; thus, a lack of information on exposure at other locations they may have visited or had lived before could result in exposure misclassification. Further studies using personal exposure data are required to corroborate our findings. Third, we used air pollutants exposure values from 2010 because this was the only year with available data for all components. The observed associations of air pollution exposure with CSVD imaging markers might be biased without considering exposure after or before 2010. However, studies have shown that land use regression models are temporally stable over 7–12–year time–frames (Cesaroni et al., 2012; Eeftens et al., 2011). Therefore, our exploration of the associations between air pollutants exposure and CSVD imaging markers is reasonable. However, further studies using temporal air pollutants exposure data are required to confirm these findings. Additionally, the impact of individual PM components and other gaseous pollutants, such as sulphur dioxide and ozone, on CSVD imaging markers also warrants further investigation.

5. Conclusion

Our results provided evidence that air pollutants exposure may be associated with cerebrovascular health in females and that PRS-defined genetic susceptibility may modify the associations with air pollutants. The WMH volume increased as the exposure levels of air pollutants increased in females with low PRS-defined genetic susceptibility, and the white matter FA increased as the exposure levels of air pollutants increased in females with high PRS-defined genetic susceptibility. As this study used data from areas with relatively low air pollution concentrations, the combined effect of air pollutants exposure and PRS-defined genetic risk on CSVD imaging markers in areas with higher air pollution deserves further exploration.

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Writing – original draft, Writing – review & editing. **Shiyang Ma:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Yunlu Guo:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Caiyang Chen:** Formal analysis, Writing – review & editing. **Lijun Pan:** Formal analysis, Writing – review & editing. **Yidan Cui:** Data curation, Writing – review & editing. **Zengai Chen:** Visualization, Writing – review & editing. **Rick M Dijkhuizen:** Supervision, Writing – review & editing. **Yan Zhou:** Supervision, Writing – review & editing. **Johannes Boltze:** Supervision, Funding acquisition, Writing – review & editing. **Zhangsheng Yu:** Resources, Supervision, Writing – review & editing. **Peiying Li:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.116638.

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