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Ambient Air Pollution Exposure and Cerebral White Matter Hyperintensities in Older Adults: A Cross-Sectional Analysis in the Three-City Montpellier Study

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BACKGROUND: Growing epidemiological evidence suggests an adverse relationship between exposure to air pollutants and cognitive health, and this could be related to the effect of air pollution on vascular health.

OBJECTIVE: We aim to evaluate the association between air pollution exposure and a magnetic resonance imaging (MRI) marker of cerebral vascular burden, white matter hyperintensities (WMH).

METHODS: This cross-sectional analysis used data from the French Three-City Montpellier study. Randomly selected participants 65–80 years of age underwent an MRI examination to estimate their total and regional cerebral WMH volumes. Exposure to fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and black carbon (BC) at the participants' residential address during the 5 years before the MRI examination was estimated with land use regression models. Multinomial and binomial logistic regression assessed the associations between exposure to each of the three pollutants and categories of total and lobar WMH volumes.

RESULTS: Participants' (*n* = 582) median age at MRI was 70.7 years [interquartile range (IQR): 6.1], and 52% (*n* = 300) were women. Median exposure to air pollution over the 5 years before MRI acquisition was 24.3 (IQR: 1.7) μg/m³ for PM_{2.5}, 48.9 (14.6) μg/m³ for NO₂, and 2.66 (0.60) 10⁻⁵/m for BC. We found no significant association between exposure to the three air pollutants and total WMH volume. We found that PM_{2.5} exposure was significantly associated with higher risk of temporal lobe WMH burden [odds ratio (OR) for an IQR increase = 1.82 (95% confidence interval: 1.41, 2.36) for the second volume tercile, 2.04 (1.59, 2.61) for the third volume tercile, reference: first volume tercile]. Associations for other regional WMH volumes were inconsistent.

CONCLUSION: In this population-based study in older adults, PM_{2.5} exposure was associated with increased risk of high WMH volume in the temporal lobe, strengthening the evidence on PM_{2.5} adverse effect on the brain. Further studies looking at different markers of cerebrovascular damage are still needed to document the potential vascular effects of air pollution. <https://doi.org/10.1289/EHP12231>

Introduction

Evidence on the detrimental effect of ambient air pollution on cognitive health in older adults is accumulating. Exposure to air pollution, and particularly to particulate matter, is associated with increased risk of dementia and accelerated cognitive decline.^{1,2}

The effects of air pollution on cognitive health might, in part, be related to its detrimental effect on cardiovascular health. Short- and long-term air pollution exposure is associated with vascular risk factors, such as increased blood pressure, atrial fibrillation, and diabetes.^{3–6} Vascular risk factors are major determinants of cognitive health. Hypertension and diabetes are now well-recognized risk factors for dementia⁷ and have also been associated with cognitive impairment.^{8,9} Associations between

atrial fibrillation and cognitive health have also been reported.¹⁰ Recent mediation studies suggest that the relationship of air pollution with dementia risk could be mediated by incident cardiovascular events or type 2 diabetes.^{11,12}

White matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI) are markers of white matter deterioration, frequently observed in older individuals.¹³ In addition to age, WMH severity is associated with hypertension and other vascular risk factors,¹⁴ and WMH are generally considered a marker of cerebral small vessel disease.¹⁵ Accordingly, WMH are associated with increased risk of incident stroke, dementia, and cognitive decline.^{16,17} As a marker of long-term vascular burden and cumulative subclinical cerebrovascular damage, WMH constitute an interesting factor when evaluating the evidence for the effect of air pollution on cognition and improve our understanding of the mechanisms involved.

To date, few epidemiological studies have examined the association between air pollution exposure and WMH. Three studies did not find any significant associations,^{18–21} and one study reported unexpected protective associations with lower WMH volume with increasing air pollution.²¹ Moreover, no study has investigated whether the relationship may vary depending on localization of WMH in the brain. Recent epidemiological studies suggest that anterior regions of the brain might be more susceptible to vascular damage.^{22–25} In the ALFA study, frontal and parietal WMH were more consistently associated with hypertension than temporal or occipital WMH, even after taking age into

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account.²² In the Northern Manhattan Study (NOMAS), participants with low levels of diastolic blood pressure (<80 mmHg) had decreased WMH volume in the frontal and parietal lobes compared to participants with high diastolic blood pressure (≥ 90 mmHg).²³ Both systolic and diastolic blood pressure were associated with increased risk of WMH in the frontal and parietal lobes in the 1000BRAINS study.²⁵ Only frontal WMH were associated with the Framingham risk score for cardiovascular disease in the Dementia Disease Initiation study.²⁴

Using data from a French study in older adults, we evaluated the association between exposure to three air pollutants [fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and black carbon (BC)] and both total and regional WMH volumes.

Methods

Study Population

We used baseline data from the Three-City Montpellier study, a French prospective cohort.²⁶ Briefly, community-dwelling ≥ 65 -year-old adults were recruited randomly from the electoral rolls of the Montpellier district between 1999 and 2001. The baseline assessment and the follow-up visits included standardized questionnaires, clinical examination, and detailed cognitive evaluations allowing active dementia screening. Among the 2,259 participants included in the study in Montpellier, 760 participants under the age of 80 who had no contraindication for MRI were randomly selected and agreed to have an MRI brain scan at the baseline visit. We excluded participants with prevalent dementia, with history of stroke, with addresses that could not be geocoded, who had lived at their declared address at MRI examination for <5 years, with T2-weighted MRI images of insufficiently good quality to quantify the WMH volume, and with missing data for covariates of the main model (Figure 1, whole sample; $n = 582$). We further excluded participants with T1-weighted images of insufficiently good quality to use the lobar atlas and thus to estimate regional WMH volumes (Figure 1, sub-sample; $n = 444$).

The study protocol was approved by the Ethics Committee of the Hospital of Kremlin-Bicêtre, and each participant signed an informed consent.

MRI Data

MRI scan acquisition. A 1.5 T GE Signa Imaging System (GE HealthCare, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence [repetition time (TR) = 12 ms, echo time (TE) = 2.8 ms, inversion time = 600 ms, matrix size = 256 \times 256, in-plane resolution = 0.9375 \times 0.9375 mm, number of excitations = 1, and slice thickness = 1.0 mm]. Slices were then converted to be isotropic (0.9375 mm³) and resliced to 1.0 mm³. T2-weighted data were acquired axially with a 2-dimensional double-echo sequence (TR = 4,400 ms, TE1/TE2 = 16 ms/98 ms, slice thickness = 4 mm with a 0.4-mm gap, 256 \times 256 matrix size, and a 0.98 \times 0.98-mm in-plane resolution).

WMH volume estimation. Total WMH volume was determined with a semiautomatic method that has been described previously.²⁷ Supratentorial areas that appeared hyperintense on the T2-weighted sequences were segmented with a manual intensity threshold using MRICro software.²⁸ In a second step, areas identified as containing hyperintense signal were manually outlined on each slide, making sure to include hyperintense voxels in the parenchyma but to exclude areas that appear as hyperintense outside of the brain. The intersection between the first and second steps defined the WMH areas, and volume was determined by

multiplying labeled areas by the voxel dimensions. A neurologist examined 80 randomly chosen scans to assess the interrater reliability, and intraclass correlation coefficients showed good to excellent agreement (interrater: 0.79; intrarater: 0.95).

To estimate regional WMH volumes in the frontal, temporal, parietal, and occipital lobes, a lobar atlas was spatially normalized to each subject's T2-weighted image. Regional volumes were defined by the intersection of each atlas lobe with the labeled WMH voxels in that region; labeled voxel values were multiplied by voxel dimensions and summed. All volumes were expressed in centimeters cubed.

Intracranial volume estimation. T1-weighted sequences were segmented with SPM5 (Wellcome Department of Cognitive Neurology) to derive gray matter, white matter, and cerebrospinal fluid (CSF) volumes. The intracranial volume was calculated as the sum of gray matter, white matter, and CSF volumes.

Air Pollution Exposure

As previously described,^{29,30} ambient concentrations of PM_{2.5}, NO₂, and BC were estimated using hybrid land use regression (LUR) models developed for Western Europe within the framework of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) study.³¹ PM_{2.5} and NO₂ concentration data for the year 2010 were extracted from the European Environment Agency AirBase database that compiles data recorded at routine monitoring stations (including traffic, industrial, and background sites). The annual mean BC concentrations (measured as PM_{2.5} absorbance based on reflectance measurement of the filters) for the 2009–2010 period were extracted from the European Study of Cohorts for Air Pollution Effects (ESCAPE).³² Potential predictor variables of the LUR models included land use characteristics, population density, roads, altitude, pollutant estimates for 2010 from chemical transport models (MACC-II ENSEMBLE³³), and satellite-derived PM_{2.5} and NO₂ estimates. The final models, described in detail elsewhere,³¹ explained 72% (66% in hold-out validation), 59% (58%), and 54% (51%) of the spatial variation in the measured concentrations of PM_{2.5}, NO₂, and BC, respectively. Models were derived, validated, and mapped at 100 \times 100 m across Western Europe, and assigned to the geocoded baseline residential address of each participant. Mapping of the LUR models across Montpellier at 100 \times 100 m are presented in Figure S1 [maps produced with ArcGIS ArcMap 10.6.1 (ESRI 2018); background: OpenStreetMap]. To derive exposures relevant to the MRI acquisition period, the 2010 model estimates were back-extrapolated to the period of 1994–2000 according to the method used in ELAPSE. Backward extrapolation was applied on regional level data [i.e., European Classification of Territorial Units for Statistics (level 1: NUTS-1); the study center is located within one region, so the spatial pattern was therefore preserved in back extrapolation]. Specifically, exposures for an earlier year were estimated by multiplying the 2010 exposures by a coefficient, which was the ratio of annual mean estimates of that year and year 2010, derived from the 26 \times 26-km Danish Eulerian hemispheric model.³⁴

The annual exposure estimates were finally aggregated to obtain the mean PM_{2.5}, NO₂, and BC exposures in the 5 years before the MRI acquisition. Correlations between participants' exposure to the three pollutants are presented in Table S1. All exposures were analyzed as continuous variables.

Other Variables

Socio-demographic variables at MRI examination included age (years), sex, and education level (primary education: ≤ 5 years; lower secondary education: up to 9 years; and higher secondary education: >9 years). Health behavior variables at MRI included

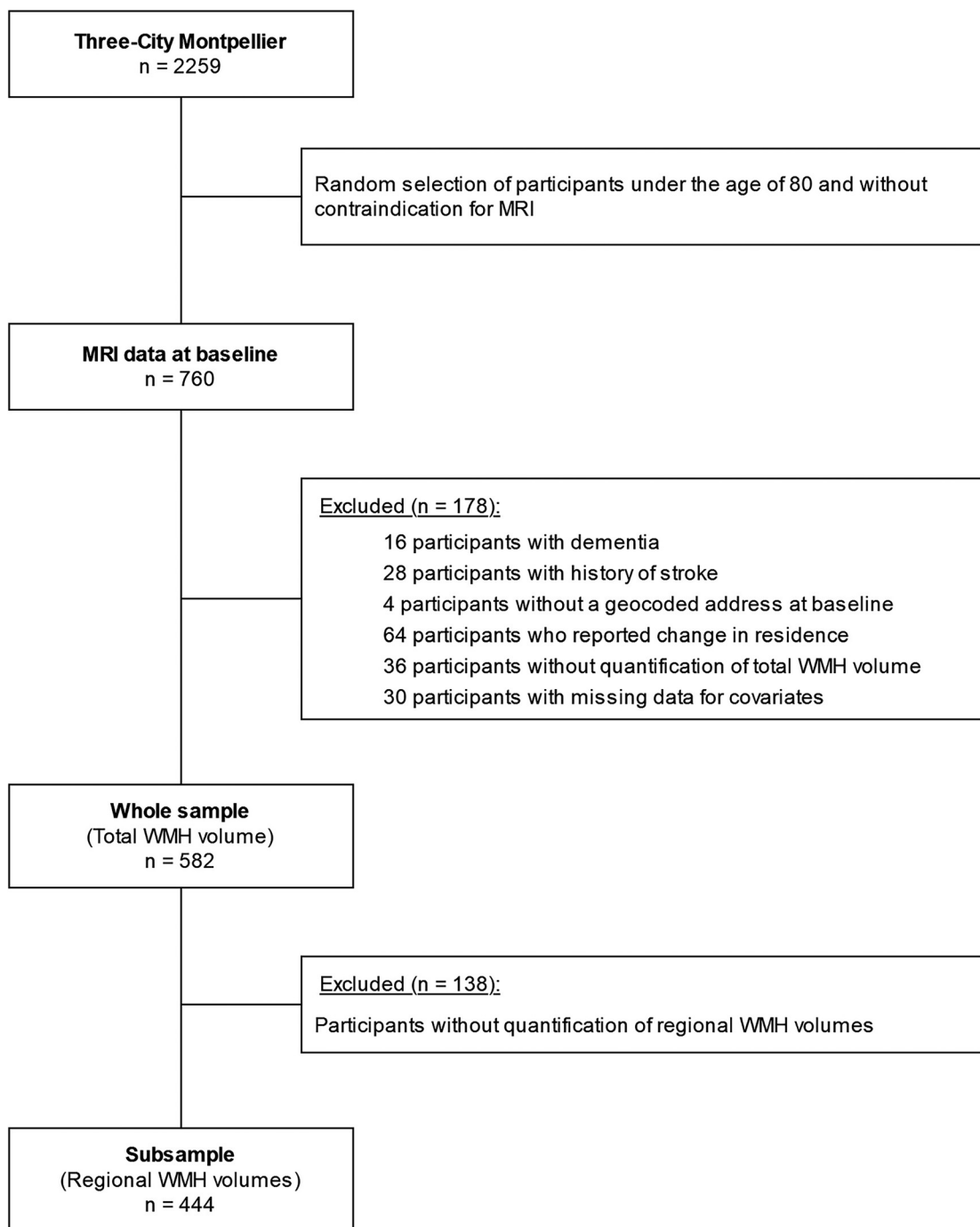


Figure 1. Flow chart for the selection of the final analytical samples from the Three-City Montpellier study.

smoking habits (never/former or current smoker) and alcohol intake (none, moderate if <36 g per day, or heavy if ≥ 36 g). Apolipoprotein E (APOE) $\epsilon 4$ carrier was defined as the presence of at least one $\epsilon 4$ allele. Vascular factors included history of cardiovascular disease (self-reported history of stroke, angina pectoris, myocardial infarction, coronary surgery, coronary angioplasty, arterial surgery of lower limbs), diabetes (glycemia ≥ 7.0 mmol/L, or taking anti-diabetic treatment), hypertension (systolic/diastolic blood pressure $\geq 140/\geq 90$ mmHg or taking antihypertensive drugs), dyslipidemia (plasma cholesterol >6.20 mmol/L or using lipid-lowering drugs), body mass index (kg/m^2). Except for systolic/diastolic blood pressure, glycemia, and plasma cholesterol that were measured at baseline, all variables were self-reported by

questionnaire. Performance at the Mini Mental State Examination (MMSE) (global cognitive score ranging from 0 to 30) was evaluated by neuropsychologists during the cognitive assessment undergone at baseline by all participants. Participants were included in the study independently of their MMSE score. The score was dichotomized according to the clinical cut-off below which dementia is suspected (MMSE <24).

Statistical Analyses

WMH volume distributions were highly skewed, with most participants having null or low WMH volumes. As log-transformation did not correct the distribution, we categorized total, frontal,

temporal, and parietal WMH volume into terciles. Categorization of occipital volume into terciles was not possible, as distribution was even more skewed toward zero; we therefore dichotomized the variable into occipital volume = 0/occipital volume > 0.

We performed separate analyses for each pollutant and studied their association with WMH volume using multinomial logistic regression for total, frontal, temporal, and parietal volumes and binomial logistic regression for occipital volume. Odds ratios (ORs) [95% confidence intervals (CIs)] for the associations are presented for an interquartile range (IQR) increase in PM_{2.5}, NO₂, and BC exposure. Global *p*-values for the pollutant term of each model were obtained using the likelihood-ratio test. Analysis of total WMH volume was performed in the whole sample (*n* = 582) and then replicated in the subsample of 444 participants with regional volume estimations to evaluate the potential impact of selection bias. Analyses of regional volume could only be performed on the subsample of 444 participants.

The linearity of associations with pollutants was assessed using second-degree fractional polynomials (FP). The R package *mfp*³⁵ was used to include FP in separate binomial logistic models for the second and third WMH terciles (i.e., two models for each air pollutant and WMH volume variable: one comparing tercile 2 to tercile 1 and one comparing tercile 3 to tercile 1). Selection of the best model was performed automatically according to the *mfp* package selection process described elsewhere.³⁶ Briefly, successive likelihood ratio tests comparing the best-fitting second-degree FP with less complex models (null or linear or best first-degree FP model) are performed. The tests with the linear model indicated a linear effect for PM_{2.5}, NO₂, and BC on WMH volumes.

The main analyses were adjusted for variables identified in the literature as associated with WMH: age, sex, intracranial volume, and APOE genotype. We did not adjust for vascular factors in the main analyses, as we considered them as potential mediators in the studied relationship.

In sensitivity analyses, we further adjusted the main models for education level, alcohol intake, and smoking habits. We also tested additional adjustment of the main models with vascular factors to examine how it affected our results. We explored modification of air pollution exposure's effect by APOE genotype by including an interaction term between air pollution and APOE genotype. To evaluate the influence of the categorization of WMH volumes according to terciles on our results, we additionally studied the effect of air pollution using dichotomized WMH volumes variables as follows: *a*) first, using a median split and *b*) second, using the 66th percentile as the cut-off value. The obtained binary variables were used as the outcomes in logistic regression models adjusted for age, sex, intracranial volume, and APOE genotype. Finally, we studied the WMH volume normalized to WM volume. For these analyses, the WMH volume-to-WM volume ratios were categorized into terciles and used as the outcomes, and models were adjusted for age, sex, and APOE genotype.

Analyses were performed using R version 4.0.2.³⁷ Multinomial logistic regression models were estimated using the R *nnet* package, and fractional polynomials were tested with the *mfp* package. Statistical significance level was set to 0.05.

Results

Among the 582 participants included in the study, median age (IQR) was 70.7 (6.1), 52% were women, and 47% had more than 9 years of education (Table 1). Median exposure to air pollution over the 5 years before MRI acquisition was 24.3 (IQR: 1.7) μg/m³ for PM_{2.5}, 48.9 (14.6) μg/m³ for NO₂ and 2.66 (0.60) 10⁻⁵/m for BC. Terciles for total WMH volume and regional WMH volumes are presented in Table 2. Due to the high number of participants with null temporal WMH volume, all participants included in

the first temporal volume tercile had a temporal volume = 0. The second and third temporal volume terciles comprised participants with a temporal WMH volume in (0, 0.02) cm³ and (0.02, 2.32) cm³, respectively (Table 2).

When comparing total WMH volume terciles, participants in the third tercile were older, slightly more exposed to PM_{2.5} and had reported more frequently a history of cardiovascular disease compared to participants in the first tercile (Table 1). Participants in the second tercile were older compared to those in the first tercile.

Comparison of participants' characteristics according to regional volume terciles are presented in Tables S2–S5. Partitioned into terciles of frontal WMH volume, participants differed by age, PM_{2.5}, and NO₂ exposure, history of cardiovascular disease, and hypertension status (Table S2). Regarding parietal WMH volume, participants differed by age, APOE genotype, and hypertension status according to tercile distribution (Table S3). Regarding temporal WMH volume, participants differed by age, APOE genotype, and exposure to the three pollutants according to tercile distribution (Table S4).

Finally, participants partitioned into two categories of occipital WMH volume differed by age, sex, APOE genotype, and PM_{2.5} exposure (Table S5). The 138 participants excluded from the whole sample were less educated, had a higher total WMH volume, and were less exposed to the three air pollutants (Table 3).

In adjusted analyses in the whole sample (Table 4), we found a tendency for a higher risk of being in the third total WMH volume tercile with increased PM_{2.5} exposure, but the association was not significant. Associations for NO₂ and BC were also not significant.

In the subsample focusing on specific regions (described in Table 3), PM_{2.5} exposure was significantly associated with increased risk of being in the third total WMH volume tercile [OR (95% CI) for a 1.7-μg/m³ increase: 1.44 (1.09, 1.89), reference: first tercile] (Table 4). PM_{2.5} exposure was also significantly associated with increased risk of higher temporal lobe WMH volume [OR = 1.82 (1.41, 2.36) for the second tercile, 2.04 (1.59, 2.61) for the third tercile, reference: first tercile]. Regarding NO₂, higher exposure was significantly associated with increased risk of being in the third total WMH volume tercile compared to the second [OR = 1.64 (1.10, 2.44)]. Exposure to NO₂ was also significantly associated with lower risk of being in the second frontal WMH volume tercile compared to the first one [OR for a 14.6-μg/m³ increase: 0.63 (0.43, 0.93)]. We found no significant associations between the three pollutants and parietal or occipital WMH volumes and, on the whole, no significant associations with BC exposure.

These results were not modified by additional adjustment for education level, alcohol intake, and smoking habits (Table S6) or by additional adjustment for vascular factors (Table S7). There was no modification of the effect of air pollution according to APOE genotype. When WMH volumes were dichotomized according to the median (Table S8), PM_{2.5} exposure was significantly associated with high WMH volume in the temporal lobe [OR = 1.64 (1.26, 2.14)], but there were no significant associations for the other brain regions or for total WMH volume. When WMH volumes were dichotomized according to the 66th percentile (Table S9), PM_{2.5} exposure was significantly associated with high total WMH volume in the subsample [OR = 1.54 (1.14, 2.09)] and high WMH volume in the temporal lobe [OR = 1.57 (1.18, 2.09)]. Results of the normalized WMH volumes analyses were similar to those of the main analyses (Table S10).

Discussion

In this population-based study in French older adults, we found no association between PM_{2.5}, NO₂, and BC exposure and total

Table 1. Characteristics of the Three-City Montpellier participants included in the whole sample ($n = 582$) and comparison between total WMH volume tertiles.

Characteristic [n (%)]	Whole sample ($n = 582$)	First WMH tertile ^a ($\leq 0.3 \text{ cm}^3$) ($n = 196$)	Second WMH tertile ^a ($0.3\text{--}1.5 \text{ cm}^3$) ($n = 196$)	Third WMH tertile ^a ($> 1.5 \text{ cm}^3$) ($n = 190$)	p -Value ^b
Age at MRI [years, median (IQR)]	70.7 (6.1)	69.8 (5.4)	70.6 (5.8)	71.6 (6.8)	<0.001
Sex	—	—	—	—	0.922
Women	300 (51.5)	103 (52.6)	99 (50.5)	98 (51.6)	—
Men	282 (48.5)	93 (47.4)	97 (49.5)	92 (48.4)	—
Education ^c	—	—	—	—	0.479
≤ 5 years	149 (25.7)	44 (22.5)	58 (29.7)	47 (24.7)	—
5–9 years	161 (27.7)	53 (27.0)	54 (27.7)	54 (28.4)	—
> 9 years	271 (46.6)	99 (50.5)	83 (42.6)	89 (46.9)	—
Missing	1	0	1	0	—
APOE $\epsilon 4$ carriers	—	—	—	—	0.193
Yes	120 (20.6)	34 (17.3)	39 (19.9)	47 (24.7)	—
No	462 (79.4)	162 (82.7)	157 (80.1)	143 (75.3)	—
MMSE score $< 24^d$	—	—	—	—	0.163
Yes	26 (4.5)	7 (3.6)	6 (3.1)	13 (6.8)	—
No	556 (95.5)	189 (96.4)	190 (96.9)	177 (93.2)	—
Air pollution exposure ^e [median (IQR)]	—	—	—	—	—
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	24.3 (1.7)	24.2 (1.5)	24.2 (1.9)	24.7 (2.0)	0.030
NO ₂ ($\mu\text{g}/\text{m}^3$)	48.9 (14.6)	48.6 (13.7)	48.4 (14.3)	50.1 (15.6)	0.327
BC ($10^{-5}/\text{m}$)	2.66 (0.60)	2.63 (0.56)	2.64 (0.59)	2.70 (0.72)	0.771
Smoking habits	—	—	—	—	0.352
Never	322 (55.3)	112 (57.1)	113 (57.7)	97 (51.1)	—
Former or current smoker	260 (44.7)	84 (42.9)	83 (42.3)	93 (48.9)	—
Alcohol intake ^c	—	—	—	—	0.770
None	92 (16.2)	36 (18.9)	29 (15.0)	27 (14.8)	—
Moderate	411 (72.5)	132 (69.1)	144 (74.2)	135 (74.2)	—
Heavy	64 (11.3)	23 (12.0)	21 (10.8)	20 (11.0)	—
Missing	15	5	2	8	—
History of cardiovascular disease	—	—	—	—	0.044
Yes	100 (17.2)	26 (13.3)	31 (15.8)	43 (22.6)	—
No	482 (82.8)	170 (86.7)	165 (84.2)	147 (77.4)	—
Diabetes ^c	—	—	—	—	0.850
Yes	57 (9.8)	21 (10.7)	19 (9.7)	17 (9.0)	—
No	524 (90.2)	175 (89.3)	177 (90.3)	172 (91.0)	—
Missing	1	0	0	1	—
Hypertension	—	—	—	—	0.077
Yes	402 (69.1)	128 (65.3)	131 (66.8)	143 (75.3)	—
No	180 (30.9)	68 (34.7)	65 (33.2)	47 (24.7)	—
Dyslipidemia ^c	—	—	—	—	0.339
Yes	306 (52.7)	110 (56.4)	96 (49.0)	100 (52.6)	—
No	275 (47.3)	85 (43.6)	100 (51.0)	90 (47.4)	—
Missing	1	1	0	0	—
Body mass index ^c [kg/m^2 ; median (IQR)]	24.6 (4.3)	24.3 (4.4)	24.8 (4.5)	24.9 (4.2)	0.289
Missing	4	1	2	1	—

Note: —, no data; APOE, apolipoprotein E; BC, black carbon; IQR, interquartile range; MMSE, Mini Mental State Examination; PM, particulate matter; WMH, white matter hyperintensities.

^aTerciles for total WMH volume.

^bUnadjusted multinomial logistic regression.

^cVariables with missing data, not included in the main model but used in sensitivity analyses.

^dMMSE score < 24 , clinical cut-off below which dementia is suspected.

^eAir pollution exposure over the 5 years preceding the MRI examination.

WMH volume. We observed that PM_{2.5} exposure was associated with increased WMH volume in the temporal lobe. There were no consistent associations between PM_{2.5}, NO₂, and BC exposure and WMH in other cerebral regions.

Regarding the relationship between air pollution exposure and total WMH volume, our results are consistent with existing studies. Previous work on total WMH volume in cognitively normal older adults did not evidence any significant association,^{18–20}

Table 2. Distribution of WMH volumes in the Three-City Montpellier study.

WMH volume (cm^3)	Minimum	33rd percentile	Median	66th percentile	Maximum
Total volume ($n = 582$)	0	0.30	0.700	1.50	126.60
Total volume ($n = 444$)	0	0.30	0.600	1.10	43.60
Regional volume ($n = 444$)					
Frontal lobe	0	0.18	0.358	0.73	22.88
Parietal lobe	0	0.04	0.089	0.22	16.75
Temporal lobe	0	0	0.003	0.02	2.32
Occipital lobe	0	0	0	0	1.84

Note: WMH, white matter hyperintensities.

Table 3. Characteristics of the Three-City Montpellier participants in the analysis on regional WMH volumes, comparing those included in the subsample ($n = 444$) with those excluded from the whole sample ($n = 138$).

Characteristic [n (%)]	Subsample ($n = 444$)	Excluded participants ($n = 138$)	p -Value ^a
Age at MRI [years, median (IQR)]	70.8 (6.7)	70.2 (4.6)	0.305
Sex	—	—	0.420
Women	233 (52.5)	67 (48.6)	—
Men	211 (47.5)	71 (51.4)	—
Education ^b	—	—	0.009
≤ 5 years	101 (22.8)	48 (34.8)	—
5–9 years	122 (27.5)	39 (28.3)	—
> 9 years	220 (49.7)	51 (36.9)	—
Missing	1	0	—
APOE $\epsilon 4$ carriers	—	—	0.555
Yes	94 (21.2)	26 (18.8)	—
No	350 (78.8)	112 (81.2)	—
MMSE score < 24 ^c	—	—	0.186
Yes	17 (3.8)	9 (6.5)	—
No	427 (96.2)	129 (93.5)	—
Total WMH volume (cm^3)	0.6 (1.5)	1.1 (6.1)	< 0.001
Air pollution exposure ^d [median (IQR)]	—	—	—
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	24.5 (1.6)	24.1 (2.1)	0.002
NO ₂ ($\mu\text{g}/\text{m}^3$)	50.1 (12.5)	43.3 (16.1)	< 0.001
BC ($10^{-3}/\text{m}$)	2.67 (0.54)	2.37 (0.82)	< 0.001
Smoking habits	—	—	0.295
Never	251 (56.5)	71 (51.4)	—
Former or current smoker	193 (43.5)	67 (48.6)	—
Alcohol intake ^b	—	—	0.466
None	67 (15.5)	25 (18.4)	—
Moderate	318 (73.8)	93 (68.4)	—
Heavy	46 (10.7)	18 (13.2)	—
Missing	13	2	—
History of cardiovascular disease	—	—	0.225
Yes	81 (18.2)	19 (13.8)	—
No	363 (81.8)	119 (86.2)	—
Diabetes	—	—	0.149
Yes	48 (10.8)	9 (6.6)	—
No	396 (89.2)	128 (93.4)	—
Hypertension	—	—	0.484
Yes	310 (69.8)	92 (66.7)	—
No	134 (30.2)	46 (33.3)	—
Dyslipidemia ^b	—	—	0.105
Yes	225 (50.8)	81 (58.7)	—
No	218 (49.2)	57 (41.3)	—
Missing	1	0	—
Body mass index ^b [kg/m^2 , median (IQR)]	24.6 (4.2)	25.0 (4.7)	0.063
Missing	2	2	—

Note: The subsample comprises participants with available data on regional WMH volumes ($n = 444$). Participants with no data on regional WMH volumes were excluded ($n = 138$). —, no data; APOE, apolipoprotein E; BC, black carbon; IQR, interquartile range; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PM, particulate matter; WMH, white matter hyperintensities.

^aUnadjusted binomial logistic regression.

^bVariables with missing data, not included in the main model but used in sensitivity analyses.

^cMMSE score < 24 , clinical cut-off below which dementia is suspected.

^dAir pollution exposure over the 5 years preceding the MRI examination.

even in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) that benefitted from a large sample size and where various exposure windows up to 20 years before the MRI were available.¹⁹ Despite nonsignificance, the associations found in the Framingham Offspring Study and in NOMAS indicated lower WMH volumes as PM_{2.5}^{18,20} or NO₂¹⁸ exposure increased. The same direction of association was observed among cognitively impaired participants of the Massachusetts Alzheimer's Disease Research Center study, where higher exposure to PM_{2.5} was significantly associated with lower WMH volume.²¹ As suggested by the authors, such unexpected negative associations

could be related to decreased white matter volume with PM_{2.5} exposure, as observed for example in the Women's Health Initiative Memory Study.^{38,39} In our population, results also suggested negative associations for the second total WMH tercile, despite not reaching significance. This could be due to a lack of contrast between WMH levels in the first two terciles, as our population was somewhat younger than in previous studies and most participants had low WMH volumes. Odds of being in the third total volume tercile compared to the first one, however, were increased with higher PM_{2.5} exposure, and it is noteworthy that we had higher PM_{2.5} exposure levels in our population compared to previous studies. However, comparison between studies remains difficult. As opposed to other studies,^{18,20,21} we were not able to study WMH continuously because WMH volume distributions were highly skewed, and log-transformation did not correct them. In the absence of a clinically relevant cut-off, we chose to categorize WMH volume into terciles, while in the ARIC-NCS study, WMH volume was dichotomized.¹⁹

Regional WMH volumes have not previously been studied in relation to air pollution exposure. Most studies on WMH usually distinguish between periventricular and subcortical WMH, as histopathology studies have highlighted different tissue changes, thus suggesting different possible etiologies.^{40,41} There is, however, less indication of different etiologies depending on cerebral lobe distribution. WMH observed in anterior regions of the brain (frontal and parietal lobes) have been associated with vascular factors in recent epidemiological studies.^{22–25} Accordingly, the frequency of hypertension, a main predictor of WMH, was significantly different between frontal and parietal WMH terciles in our population. However, while our hypothesis was on the vascular effects of air pollution, we found no significant associations between air pollution exposure and WMH in these two lobes, except for an isolated but significant negative association between NO₂ exposure and frontal WMH volume.

In our population, increased air pollution exposure was consistently associated with higher risk of high WMH volume in the temporal lobe, even in sensitivity analyses using a different cut-off for the categorization of WMH volumes. These results argue for a detrimental effect of PM_{2.5} exposure on cognition, as previous work in the 3C Montpellier study has shown that a specific WMH pattern characterized by high WMH burden in the temporal lobe was associated with increased risk of mild cognitive decline and dementia.⁴² The association was significant for PM_{2.5} only, which is consistent with previous longitudinal analyses in the whole population of the 3C study where PM_{2.5} exposure was associated with accelerated cognitive decline and increased risk of dementia.^{29,30} Of the pollutants considered, the LUR models for NO₂ and BC had lower performance compared to PM_{2.5}. There is a higher spatial variability in NO₂ and BC levels, as their emissions are mainly related to traffic. This may have contributed to greater nondifferential misclassification and thus to associations tending toward the null for these two pollutants.

Whether the temporal WMH observed in our population are associated with vascular damage or with other types of lesions is debatable, as hypertension frequency did not differ among temporal WMH terciles in our population and as additional adjustment for vascular factors did not change the main results. In the same way, additional adjustment on vascular factors did not change the results observed in previous work on all-cause dementia risk and cognitive decline in the 3C study.^{29,30} In other studies on air pollution exposure and WMH, the impact of additional adjustment for vascular factors was inconsistent, with attenuated associations toward the null in NOMAS,¹⁸ while for other studies there was little change observed.^{20,21} The temporal region is affected early in Alzheimer's disease⁴³; thus, the association of air pollution and

Table 4. Adjusted associations between air pollution exposure and WMH volumes in the Three-City Montpellier study.

	OR (95% CI) ^a		Global <i>p</i> -value ^c	OR (95% CI) ^b	
	2nd volume tercile	3rd volume tercile		WMH volume >0	Global <i>p</i> -value ^c
Whole sample, <i>n</i> = 582					
Total WMH volume					
PM _{2.5}	0.90 (0.72,1.11)	1.20 (0.96,1.50)	0.10	—	—
NO ₂	0.84 (0.61,1.16)	1.01 (0.72,1.41)	0.45	—	—
BC	0.85 (0.64,1.12)	0.85 (0.64,1.15)	0.44	—	—
Subsample, <i>n</i> = 444					
Total WMH volume					
PM _{2.5}	0.89 (0.70,1.14)	1.44 (1.09,1.89)	0.01	—	—
NO ₂	0.74 (0.51,1.07)	1.21 (0.79,1.84)	0.04 ^d	—	—
BC	0.80 (0.57,1.13)	1.12 (0.76,1.65)	0.18	—	—
Frontal lobe					
PM _{2.5}	0.87 (0.67,1.12)	1.20 (0.92,1.55)	0.14	—	—
NO ₂	0.63 (0.43,0.93)	1.00 (0.67,1.49)	0.03	—	—
BC	0.79 (0.55,1.12)	1.05 (0.73,1.51)	0.24	—	—
Parietal lobe					
PM _{2.5}	0.86 (0.66,1.11)	1.10 (0.84,1.44)	0.27	—	—
NO ₂	1.18 (0.80,1.73)	1.19 (0.80,1.77)	0.63	—	—
BC	1.05 (0.74,1.50)	1.02 (0.71,1.48)	0.96	—	—
Temporal lobe					
PM _{2.5}	1.82 (1.41,2.36)	2.04 (1.59,2.61)	<0.001	—	—
NO ₂	1.60 (1.09,2.37)	1.36 (0.94,1.99)	0.05	—	—
BC	1.45 (1.02,2.07)	1.24 (0.88,1.76)	0.12	—	—
Occipital lobe					
PM _{2.5}	—	—	—	1.35 (1.00,1.81)	0.05
NO ₂	—	—	—	1.21 (0.84,1.73)	0.30
BC	—	—	—	1.09 (0.78,1.51)	0.62

Note: Total volume (*n* = 582): tercile 1, (0, 0.30) cm³; tercile 2, (0.30, 1.50) cm³; tercile 3, (1.50, 126.60) cm³. Total volume (*n* = 444): tercile 1, (0, 0.30) cm³; tercile 2, (0.30, 1.10) cm³; tercile 3, (1.10, 43.60) cm³. Frontal volume: tercile 1, (0, 0.18) cm³; tercile 2, (0.18, 0.73) cm³; tercile 3, (0.73, 22.88) cm³. Parietal volume: tercile 1, (0, 0.04) cm³; tercile 2, (0.04, 0.22) cm³; tercile 3, (0.22, 16.75) cm³. Temporal volume: tercile 1, Volume = 0; tercile 2, (0, 0.02) cm³; tercile 3, (0.02, 2.32) cm³. Models adjusted for age, sex, intracranial volume, and APOE genotype. OR expressed for an IQR increment in PM_{2.5}, NO₂, and BC exposure (1.7 μg/m³, 14.6 μg/m³ and 0.6 × 10⁻⁵/m, respectively). —, no data; BC, black carbon; CI, confidence interval; OR, odds ratio; PM, particulate matter; WMH, white matter hyperintensities.

^aReference: first volume tercile.

^bReference: no WMH detected.

^cLikelihood-ratio test.

^dGlobal *p*-value reflects a significant difference between third and second terciles (OR = 1.64; 95% CI: 1.10, 2.44).

WMH observed here may be independent of the vascular burden and reflect neurodegenerative processes. In Alzheimer's disease, WMH could be related to Wallerian degeneration, especially for WMH observed in temporo-parietal regions.^{44,45} Moreover, we used T2-weighted images without fluid attenuation; thus, hyperintense signal could be confounded by atrophy (the CSF in atrophied areas would be bright on T2-weighted images). Evidence on gray matter atrophy in relation to air pollution exposure is still sparse,^{1,2,46} but a recent meta-analysis of epidemiological studies suggests that PM_{2.5} exposure could be associated with lower volumes of the hippocampus,⁴⁷ a structure located in the temporal lobe. This observation made from neuroimaging studies in humans adds to a series of experimental studies that pinpointed that in mice, PM exposures led to selective changes in hippocampal CA1 neurons.^{48–50} As PM exposure triggers peripheral and brain inflammation,^{48,51} the particular vulnerability of the hippocampus could be related to the abundance of receptors for pro-inflammatory cytokines in this brain region.⁵²

This study has several strengths. We were able to estimate air pollution exposure at the participants' residential address using fine-scale LUR models. The exclusion of participants who moved during the 5 years preceding the MRI visit reduced the risk of exposure classification bias. Data on regional WMH volumes provided additional insight into the potential mechanisms by which air pollution could affect the brain, as the restriction of our results to the temporal lobe question the vascular etiology of the lesions caused by PM_{2.5} exposure. However, our analyses of regional volumes may be limited by selection bias. Participants excluded for missing data on regional volumes were less exposed to the three air pollutants and had higher total WMH volume, thus explaining the

stronger associations observed for total WMH volume in the subsample. However, given the CIs obtained for the association between PM_{2.5} and temporal WMH volume, the main result of the present study appears to be robust. Another limitation is related to the exposure window. The LUR models were developed for 2010, and back-extrapolation was performed to reflect air pollution levels at the time of the MRI. The back-extrapolation was solely a temporal correction and was assumed appropriate given the relatively small size of the study area. Further, the stability of the spatial pattern over time, which was assessed over almost 6,500 randomly selected points across France, was shown to be good between 2000 and 2010.³¹ Still, we cannot entirely rule out misclassification of exposure at a finer scale. If such misclassification occurred, it was probably nondifferential, leading estimations toward the null.

In conclusion, we found that PM_{2.5} exposure was associated with increased risk of high WMH volume in the temporal lobe. This result on an MRI marker that has been linked to cognitive decline and dementia strengthens our knowledge of an adverse effect of air pollution exposure on cognitive health. However, we cannot conclude that air pollution has a detrimental cerebrovascular effect, as the associations observed here could be related to other underlying mechanisms. Further studies looking at different markers of cerebrovascular diseases are still needed.

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