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Outdoor air pollution exposure and cognitive performance: findings from the enrolment phase of the CONSTANCES cohort

Mohammad Javad Zare Sakhvidi, Jun Yang, Emeline Lequy, Jie Chen, Kees de Hoogh, Noémie Letellier, Marion Mortamais, Anna Ozguler, Danielle Vienneau, Marie Zins, Marcel Goldberg, Claudine Berr, Bénédicte Jacquemin

Summary

Background Air pollution exposure is one of the modifiable risk factors of cognitive decline. We aimed to test the association between exposure to several outdoor air pollutants and domain-specific cognitive performance.

Methods In this cross-sectional study, we used data from the enrolment phase of the French CONSTANCES cohort. From the 220 000 people (aged 18–69 years) randomly recruited in the French CONSTANCES cohort, participants aged 45 years old or older (104 733 people) underwent a comprehensive cognitive assessment (verbal episodic memory, language skills, and executive functions). After exclusion of those who were not suitable for our analysis, 61 462 participants with available data were included in the analyses. We used annual mean concentrations at residential addresses, derived from land-use regression models, to assign exposure to particulate matter with aerodynamic diameters less than 2·5 µm ($PM_{2·5}$), nitrogen dioxide (NO_2), and black carbon. We used multiple linear regression models with different covariate adjustments to test the associations between each pollutant and cognitive outcomes. We did several sensitivity analyses, including multilevel modelling, meta-analysis by centre of recruitment, and exclusion of specific population groups.

Findings We found significantly poorer cognitive function, especially on semantic fluency and domains of executive functions, with an increase in exposure to black carbon and NO_2. Exposure to $PM_{2·5}$ was mainly significant for the semantic fluency test. We found that decrease in cognitive performance with an increase of one interquartile range of exposure ranged from 1% to nearly 5%. The largest effect size (percentage decrease) for both $PM_{2·5}$ and NO_2 was found for the semantic fluency test ($PM_{2·5}$ 4·6%, 95% CI 2·1–6·9 and NO_2 3·8%, 1·9–5·7), whereas for black carbon, the largest effect size was found for the digit symbol substitution test of the domains of executive functions (4·5%, 2·7–6·3). Monotonic and linear exposure–response associations were found between air pollution exposure and cognitive performance, starting from a low level of exposures.

Interpretation Significantly poorer cognitive performance was associated with exposure to outdoor air pollution even at low levels of exposure. This highlights the importance of further efforts to reduce exposure to air pollution.

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For the French translation of the abstract see Online for appendix 1

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Introduction

Age-related cognitive decline and dementia are a global public health concern. The number of cases of dementia is forecasted to triple in the coming decades, and the underlying economic burden is estimated to reach around US$2 trillion by 2030.[1] In addition to non-modifiable risk factors (eg, age and genetic factors), several modifiable risk factors are recognised to prevent or delay cognitive decline and dementia cases by up to 40%.[2–4] The population-attributed fraction (PAF) for air pollution for dementia is 2%, which is similar to the calculated PAF for physical activity or hypertension.[4] Particulate matter with aerodynamic diameters less than 2·5 µm ($PM_{2·5}$), black carbon, and nitrogen dioxide (NO_2) are among the most important outdoor air pollutants.[5] A link between outdoor air pollution exposure and cognitive performance has been reported in human and animal studies.[6–11] Oxidative stress, systemic neuroinflammation, or vascular damages are hypothesised to be biological pathways of the neurotoxic effect of air pollutants.[12]

Increasing urbanisation, which is often associated with exposure to higher concentrations of outdoor air pollution,[13] in parallel with an increasingly ageing population, raises concerns about the neurodegenerative effects of air pollution. Given that the neurodegenerative process in Alzheimer's disease is likely to begin decades before the onset of clinical symptoms,[14] there is potentially a wide time window to prevent or slow the onset of cognitive impairments. Recently, air pollution has been recognised as a modifiable risk factor of Alzheimer's

Research in context

Evidence before this study

Exposure to air pollution has been suggested to be associated with different health consequences including neurodegenerative outcomes, such as Alzheimer's disease. We did a PubMed search using keywords related to air pollution as exposure ("air pollution" OR "air pollutant*" OR "particulate matter*" OR "traffic related"), related to cognitive function as outcome ("Dementia" OR "Alzheimer's disease" OR "cognition" OR "cognitive"), and human adults as a population. The evidence on the association between air pollution exposure and different cognitive outcomes has been accumulating in recent years. However, the evidence for which cognitive domains are most affected is still limited. Findings on the comparison of several air pollutants (especially black carbon) in terms of their effect on the cognitive outcomes in the available studies showed discrepancy and seem to need more in-depth examination. Additionally, few studies considered exposure–response associations at different concentrations of air pollution, and most of the available studies were done in urban and suburban areas on populations with relatively high exposure concentration compared with those living in rural areas or small cities.

Added value of this study

In this study, we have examined the association between exposure to different air pollutants including $PM_{2·5}$, black carbon, NO_2, and residuals of black carbon on $PM_{2·5}$ (to disentangle black carbon and $PM_{2·5}$, which has not been done until now for air pollution and cognition performance studies) with different domains of cognitive performance. Additionally, we studied three different domains of cognition on a large sample (about 62 000) of participants aged at least 45 years across all urban areas, suburban areas, small cities, and rural areas of metropolitan France.

Implications of all the available evidence

In line with the previous studies, we found that air pollution has a negative role in cognitive performance (especially NO_2). The study adds to available evidence for the need to control current air pollution exposure concentrations. Our study suggests that the degree of associations depends on the pollutant and the cognitive domain. In terms of pollutants, our findings suggest that the most harmful pollutants (among the ones selected in this study) are NO_2 and black carbon, whereas we found a less robust negative association for $PM_{2·5}$. In terms of cognitive domain, our findings were highly suggestive for the negative role of air pollution on executive functions, and the semantic part of language skills domains.

disease and dementia.[4] However, research on the associations between air pollution exposure and cognition is not conclusive, depending on the type of pollutant and the domain of cognition. Additionally, evidence is accumulating on the hazardous effects of outdoor air pollution at very low concentrations of exposure, which resulted in the lowering of the air-quality guideline values by WHO.

Our objective is to assess the association between outdoor air pollution exposure and cognitive function in a large cohort of adults from all over metropolitan France. We hypothesised that participants more greatly exposed to outdoor air pollution would have poorer cognitive performance, and such associations would be different depending on the components of outdoor air pollutants and the cognitive domains.

Methods

Participants

In this cross-sectional study, we used data from the enrolment phase of the CONSTANCES cohort, launched in late 2012 across metropolitan France.[15,16] About 220 000 members (aged 18–69 years) of the French national health insurance were recruited. The CONSTANCES cohort team selected 22 health-screening centres (hereafter referred to as centres) located in 20 departmental regions of metropolitan France (appendix 2 p 21). Within each departmental region, eligible people were then selected randomly from the national social security database (which covers 85% of the population of France). A sampling scheme stratified by age, sex, and socioeconomic status was used to obtain the most representative sample of the source population.[15] At enrolment, a wide range of data were collected by self-administered questionnaires, face-to-face interviews, and medical examination.

See Online for appendix 2

All participants underwent a clinical examination, including cognitive tests for people 45 years of age and older (by end of December, 2019; n=104733). Despite the logistical issues involved in the selection of participants of this age range for neurocognitive assessments, 45 years of age is decades before clinical manifestation of Alzheimer's disease, but early enough to detect early subclinical changes in cognition caused by ageing. We excluded participants with tests in paper format, non-French speakers, test results with problems or that were not complete, participants with Parkinson's disease at the time of enrolment, and individuals with incomplete residential addresses. We finally retained 61 462 participants in our analysis with both exposure and outcome data (figure 1; appendix 2 pp 5, 10).

Exposure assessment

We estimated annual mean concentrations of $PM_{2·5}$, black carbon, and NO_2 at the residential addresses of the participants at the time of enrolment. This estimation was based on fine spatial resolution (100×100 m) land-use regression models (developed for 2010), which incorporated ground-based measurements, satellite-derived and

chemical transport-modelled estimates, road density, land-use variables, and altitude.[17] Ground-based monitoring data representing annual mean concentrations in 2010 were obtained from 543 sites for $PM_{2.5}$, 436 sites for black carbon, and 2399 sites for NO_2. The models explained 72% of the spatial variation in measured $PM_{2.5}$ concentrations, 54% of the spatial variation in black carbon concentrations, and 59% of the spatial variation in NO_2 concentrations across western Europe (appendix 2 pp 5–6).

Cognitive performance assessment

After a centralised training programme, neuropsychologists did standardised evaluations of the neurocognitive capacities of the participants.[18,19] The neuropsychological tests for verbal episodic memory (comprising four different subscores of the Free and Cued Selective Reminding Test, including the fast free recall test [FRT] and the fast free cued recal test [TRT], and the delayed free recall test [DFRT] and delayed free and cued recal test [DTRT]),[20] language skills (lexical and semantic verbal fluency tasks),[21] and executive functions (the digit–symbol substitution task [DSST] of the Wechsler adult intelligence scale IV,[22] and parts A and B of the trail making test [TMT-A and TMT-B])[23] were used in the present study (appendix 2 p 11). We constructed a global cognitive score using the first component of the principal component analysis on the six tests (including FRT, semantic fluency, lexical fluency, DSST, TMT-A, and TMT-B), which represented the largest fraction of the dataset variance (appendix 2 pp 6–8, 22).[24] For all outcomes, higher scores represented better cognitive performance, except in the case of TMT-A and TMT-B, for which higher scores represented poorer performance.

We also defined poor cognitive status dichotomously (yes or no) using the cutoff of the norms of neuropsychological tests that were prepared and published previously in percentiles stratified by sex, age, and education, on the basis of the CONSTANCES cohort data.[18,19] Poor cognitive status was defined on the basis of a score lower than or equal to the 25th percentile of the test-score distributions in each population stratum (for TMT-A and TMT-B, scores greater than or equal to the 75th percentile of the corresponding distribution were regarded as indicative of poor cognitive status; appendix 2 p 8).

Covariates

Covariates used as potential confounders included age, sex, education, marital status, smoking status, alcohol consumption (on the basis of the Alcohol Use Disorders Identification Test classification),[25] non-occupational physical activity (on the basis of a questionnaire measuring frequency and intensity of different activities), body-mass index, geographical origin (France *vs* other countries), living alone at home (on the basis of the answer to the question "do you live as a couple at home or not?"), mobility limitation (defined as having difficulty going up or down the stairs or walking 1 km without stopping), monthly household income, retirement status, neighbourhood deprivation, and rural or urban status of the commune of residence of the participant. We also used information on health and medical history, including self-assessment of perceived general health, a doctor's diagnosis of cardiovascular diseases, respiratory diseases, hearing loss, depression symptoms, self-reported type-2 diabetes, hypercholesterolaemia, hypertriglyceridaemia, parental history of Alzheimer's disease, and self-reported hypertension.

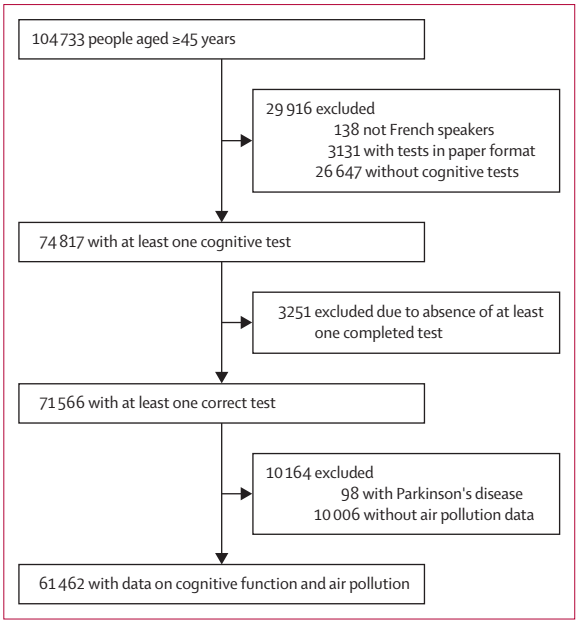


Figure 1: **Flowchart of population selection for this analysis**

Statistics

Data were analysed using R version 3.5. The percentage of missing data across the selected variables ranged from 0% and 7·8% (for the household income variable). We used multiple imputations (using the mice package in R) to treat missing values.[26] All analyses were run on an imputed dataset (appendix 2 p 8).

We normalised the cognitive tests before including them into the model. For the main analysis, we used multiple linear-regression models, and hypothesised that associations between exposure and outcome would be linear. As air pollutants in this study were highly correlated (eg, for NO_2 and $PM_{2.5}$, the Spearman's coefficient was 0·85), using two-pollutant models was methodologically questionable, and the regression model could not reliably estimate the main effects or the interaction of pollutants.[27] Therefore, throughout the manuscript we used single-pollutant models.

The sex-specific *Z* score of each cognitive performance test (computed from the mean and SD of the tests scores) along with the global cognitive score were used as the

	Men (n=29 280)	Women (n=32 182)	p value	Total (n=61 462)
Age in years, mean (SD)	57·98 (7·14)	57·62 (7·12)	<0·0001	57·79 (7·13)
Years of education	..	..	<0·0001	..
<5 years	1091 (3·7%)	1033 (3·2%)	..	2124 (3·5%)
5–12 years	14 791 (50·5%)	15 194 (47·2%)	..	29 985 (48·8%)
>12 years	13 398 (45·8%)	15 955 (49·6%)	..	29 353 (47·8%)
Smoking status	..	..	<0·0001	..
Non-smoker	10 974 (37·5%)	16 531 (51·4%)	..	27 505 (44·8%)
Smoker	4092 (14·0%)	4241 (13·2%)	..	8333 (13·6%)
Ex-smoker	14 214 (48·5%)	11 410 (35·5%)	..	25 624 (41·7%)
Alcohol drinking	..	..	<0·0001	..
Abstinent	788 (2·7%)	1843 (5·7%)	..	2631 (4·3%)
No abuse or dependence	21 794 (74·4%)	26 357 (81·9%)	..	48 151 (78·3%)
Abuse	5037 (17·2%)	3282 (10·2%)	..	8319 (13·5%)
Dependence	1661 (5·7%)	700 (2·2%)	..	2361 (3·8%)
Country of origin, France	26 439 (90·3%)	29 385 (91·3%)	<0·0001	55 824 (90·8%)
Familial status	..	..	<0·0001	..
Non-married	3614 (12·3%)	4321 (13·4%)	..	7935 (12·9%)
Partnership or married	21 226 (72·5%)	20 576 (63·9%)	..	41 802 (68·0%)
Separated or divorced	3935 (13·4%)	5656 (17·6%)	..	9591 (15·6%)
Widow	505 (1·7%)	1629 (5·1%)	..	2134 (3·5%)
Income >€2100 per month	24 011 (82·0%)	24 809 (77·1%)	<0·0001	48 820 (79·4%)
Socio-occupational status	..	..	<0·0001	..
Farmer or craftsman	921 (3·1%)	592 (1·8%)	..	1513 (2·5%)
Executive or intellectual profession	10 730 (36·6%)	7004 (21·8%)	..	17 734 (28·9%)
Middle-level profession	8321 (28·4%)	10 508 (32·7%)	..	18 829 (30·6%)
Employee or manual workers	8173 (27·9%)	12 479 (38·8%)	..	20 652 (33·6%)
Never worked or not in another status	1135 (3·9%)	1599 (5·0%)	..	2734 (4·4%)
Exposed to occupational solvents	7114 (24·3%)	2754 (8·6%)	<0·0001	9868 (16·1%)
Type of living area	..	..	<0·0001	..
Urban	10 976 (37·5%)	12 744 (39·6%)	..	23 720 (38·6%)
Suburban	10 784 (36·8%)	11 734 (36·5%)	..	22 518 (36·6%)
Isolated city	2215 (7·6%)	2263 (7·0%)	..	4478 (7·3%)
Rural	5305 (18·1%)	5441 (16·9%)	..	10 746 (17·5%)
French deprivation index	..	..	<0·0001	..
First tertile	9965 (34·0%)	11 662 (36·2%)	..	21 627 (35·2%)
Second tertile	10 047 (34·3%)	10 860 (33·7%)	..	20 907 (34·0%)
Third tertile	9268 (31·7%)	9660 (30·0%)	..	18 928 (30·8%)
Living alone at home	5401 (18·4%)	9280 (28·8%)	<0·0001	14 681 (23·9%)
Retired	11 274 (38·5%)	11 187 (34·8%)	<0·0001	22 461 (36·5%)
Physical activity, mean (SD)	4·63 (1·57)	4·80 (1·53)	<0·0001	4·72 (1·55)
Parental history of Alzheimer's disease	2399 (8·2%)	2712 (8·4%)	0·29	5111 (8·3%)
Body mass index in kg/m², mean (SD)	26·51 (3·89)	25·01 (4·73)	<0·0001	25·73 (4·42)
Self-rated health status, mean (SD)	2·93 (1·24)	2·94 (1·24)	0·20	2·94 (1·24)
Depressive symptoms	4525 (15·5%)	8609 (26·8%)	<0·0001	13 134 (21·4%)
Respiratory disease	2707 (9·2%)	2985 (9·3%)	0·90	5692 (9·3%)
Self-reported type-2 diabetes	1573 (5·4%)	874 (2·7%)	<0·0001	2447 (4·0%)

(Table 1 continues on next page)

outcome. We used a sequential adjustment approach based on a priori knowledge to define the models with different levels of adjustment. The first model (hereafter referred to as the parsimonious model) was adjusted for age, sex, education (given that their effects on neuropsychological performance are well documented), and enrolment centre (to consider the clustering role of the centres). The second model (hereafter referred to as the main model) was additionally adjusted for personal-level and area-level variables (comprising smoking status, alcohol drinking, familial situation, body-mass index, history of Alzheimer's disease in parents, non-occupational physical activity, living alone at home, country of origin, depression symptoms, self-reported hypertension, self-reported type-2 diabetes, cardiovascular diseases, hearing loss, household income, living area including urban living, suburban living, isolated city living, or rural living, and French Deprivation Index). Results of multiple linear regressions (β and 95% CIs) were reported per SD change in cognitive outcome for an IQR increase in air pollutant. We also converted the β values to percent of change in outcome to communicate the results in the text (with percent change=exponential (β)−1). For dichotomous outcomes (based on cognitive norms), we used logistic regression and reported the odds ratios (ORs) for an IQR increase in air pollution exposure.

To test the possible non-linearity of the shape of the exposure–response associations, we applied restricted cubic spline functions.[28] We also reported associations on the basis of quartiles of exposure (appendix 2 pp 8–9).

We also did stratified analyses on the basis of sex and type of residential area (urban, suburban, isolated city, and rural). We formally tested the interaction by sex by entering the product of sex and exposure terms into the models and using the likelihood-ratio test.

We tested the sensitivity of the findings by additionally adjusting the main model for retirement status, self-rated health status, hypercholesterolaemia, hypertriglyceridaemia, respiratory disease, and mobility limitation (hereafter referred to as the fully adjusted model), and by using complete-case datasets (datasets without imputation). We also reported the main models separately by: exclusion of participants from Paris centres (because of the higher exposure to air pollutants and higher education compared with other centres); inclusion only of cases with all tests results; and exclusion of people aged 65 years or older (given that we expected that beyond age 65 years, the probability of the participants having pathological cognitive ageing increased, and because many factors, including air pollution, might contribute to cognitive impairment, we excluded these people to reduce potential residual bias).

Finally, we combined centre-specific findings using fixed-effects meta-analysis to report the pooled β values (and corresponding 95% CI), heterogeneity as I^2, and p values of the Cochran's Q test. Because we found high interclass correlation for pollutants across the centres,

we also applied a multilevel modelling approach, including a random effect for centres.[29] We further did a residual analysis to assess the role of exposure to black carbon, holding constant the exposure to $PM_{2·5}$ (using $PM_{2·5}$ as a dependent variable, and black carbon as the independent variable).[30] To take into account the possible multiple testing (because of multiple comparisons with related neuropsychological tests), we computed p values for the association between exposures and outcomes and adjusted them considering false discovery rate.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study population included 61 462 participants of the CONSTANCES cohort, aged 45 years and older (mean age at enrolment 57·79 years, SD 7·13), of whom 32 182 were women and 29 280 were men, 29 353 (47·8%) were educated for more than 12 years, and 46 238 (75·2%) resided in urban and suburban areas. Among the selected comorbidities, depressive symptoms were the most frequent (13 134 [21·4%]; table 1). Participants across the centres were similar in terms of age, sex, and education, except in the Paris centres, where they were more educated.

Median exposure to $PM_{2·5}$ was 16·07 µg/m³ (IQR 3·79), median exposure to black carbon was 1·62 10^{-5}/m (IQR 0·74), and median exposure to NO_2 was 25·54 µg/m³ (IQR 13·93). Air pollution exposure was different across the centres. Exposure for all three pollutants was significantly higher in Paris than other centres (appendix 2 pp 23–25). Around 59 168 (96%) of the selected participants lived in areas with NO_2 concentrations higher than WHO guideline values (10 µg/m³) and 61 462 (100%) lived in areas with $PM_{2·5}$ concentrations higher than WHO guideline values (5 µg/m³). A significant positive correlation was found between all pollutants. The highest correlation in total and in centre-specific analyses was found between NO_2 and black carbon (ranging from 0·84 to 0·95 across the centres). No significant difference was observed in the exposure to air pollutants between included and excluded participants. We found a high interclass correlation coefficient (ICC) especially for $PM_{2·5}$ (ICC 0·84) across the centres, indicating a high between-cluster variance compared to within-cluster variances.

Exposure to air pollution including $PM_{2·5}$, black carbon, and NO_2 was associated with significantly poorer cognitive performance in terms of total recall of episodic memory, language skills (semantic fluency), and executive functions. In the main models, we found similar but attenuated effect sizes for black carbon and NO_2. The main model findings on $PM_{2·5}$ remained significant only for semantic fluency (table 2). After considering the false discovery rate and adjusted p value, only one previously significant association became non-significant and the rest of the associations remained significant (appendix 2 p 12).

	Men (n=29 280)	Women (n=32 182)	p value	Total (n=61 462)
(Continued from previous page)				
Cardiovascular diseases	3565 (12·2%)	2557 (7·9%)	<0·0001	6122 (10·0%)
Hypercholesterolaemia	5272 (18·0%)	3444 (10·7%)	<0·0001	8716 (14·2%)
Hypertriglyceridaemia	1002 (3·4%)	427 (1·3%)	<0·0001	1429 (2·3%)
Self-reported hypertension	6417 (21·9%)	5252 (16·3%)	<0·0001	11 669 (19·0%)
Stroke	440 (1·5%)	326 (1·0%)	<0·0001	766 (1·2%)

Data are n (%) unless otherwise specified.

Table 1: **General characteristics of the CONSTANCES cohort participants at enrolment (n=61 462)**

The strongest associations were observed across different domains of cognition depending on the pollutant types. For both $PM_{2·5}$ and NO_2, semantic fluency was the most strongly affected test, equal to a 4·6% (95% CI 2·1–6·9) decrease for an IQR increase in $PM_{2·5}$ concentration and a 3·8% (1·9–5·7) decrease for an IQR increase in NO_2 concentration. The observed associations for tests of executive functions ranged from 3·1% (95% CI 1·3–5·0; for TMT-A and NO_2) to 4·5% (2·7–6·3; for DSST and black carbon) decrease for an IQR increase in exposure (table 2).

We found similar results in the analyses on the basis of the dichotomous outcomes (except for $PM_{2·5}$ and TRT in the parsimonious model; appendix 2 p 13). In the main model, we found significant 7–15% increases in odds of having poor cognition (according to the norms) for an IQR increase in exposure. For both the NO_2 and black carbon, the largest effect sizes were observed for DSST followed by TMT-B.

The effect sizes were typically higher and more often significant among people living in suburban areas than urban areas (table 3). We found an indication of effect modification by sex, indicating stronger association in women (except for semantic fluency; appendix 2 p 14). We found robust findings for all cognitive performance measures in the sensitivity analysis after excluding different groups, and in the analyses on complete cases (appendix 2 pp 15–16). The residual analysis also showed that for a fixed amount of $PM_{2·5}$ there was still an effect of black carbon on cognitive performance (appendix 2 p 17). Further adjustment (the fully adjusted model) did not change the significance and the magnitude of the observed associations (appendix 2 pp 15–16).

Using restricted cubic splines and exposure categorised by quartiles, we found a linear and monotonic exposure–response relationship for executive functions (DSST, TMT-A, and TMT-B) for black carbon and NO_2. Trend analysis was significant for semantic fluency in relation to $PM_{2·5}$ and NO_2, and TRT for black carbon (figure 2; appendix 2 pp 18–19).

A meta-analysis by centre showed a significant association for semantic fluency for all pollutants without

	Number	Parsimonious model, β (95% CI)	Main model, β (95% CI)
$PM_{2·5}$			
FRT	57 854	0·006 (–0·016 to 0·028)	0·007 (–0·017 to 0·030)
TRT	57 854	–0·020 (–0·037 to –0·004)	–0·007 (–0·025 to 0·011)
DFRT	57 854	–0·006 (–0·027 to 0·016)	–0·003 (–0·026 to 0·020)
DTRT	57 854	–0·017 (–0·029 to –0·005)	–0·010 (–0·023 to 0·003)
Lexical fluency	59 544	–0·003 (–0·027 to 0·020)	–0·001 (–0·026 to 0·024)
Semantic fluency	60 692	–0·086 (–0·110 to –0·062)	–0·047 (–0·072 to –0·021)
DSST	59 385	–0·034 (–0·056 to –0·012)	–0·007 (–0·030 to 0·016)
TMT-A	59 227	0·050 (0·027 to 0·073)	0·015 (–0·010 to 0·040)
TMT-B	58 353	0·047 (0·025 to 0·069)	0·009 (–0·015 to 0·032)
Global cognitive score	53 544	0·033 (–0·011 to 0·076)	0·010 (–0·037 to 0·057)
Black carbon			
FRT	57 854	0·005 (–0·011 to 0·021)	0·005 (–0·014 to 0·025)
TRT	57 854	–0·029 (–0·041 to –0·017)	–0·019 (–0·034 to –0·005)
DFRT	57 854	–0·010 (–0·026 to 0·005)	–0·009 (–0·028 to 0·010)
DTRT	57 854	–0·016 (–0·025 to –0·007)	–0·010 (–0·020 to 0·001)
Lexical fluency	59 544	0·003 (–0·014 to 0·020)	0·011 (–0·009 to 0·032)
Semantic fluency	60 692	–0·074 (–0·091 to –0·056)	–0·033 (–0·054 to –0·012)
DSST	59 385	–0·073 (–0·090 to –0·057)	–0·046 (–0·065 to –0·027)
TMT-A	59 227	0·077 (0·060 to 0·094)	0·041 (0·021 to 0·061)
TMT-B	58 353	0·083 (0·067 to 0·100)	0·045 (0·026 to 0·065)
Global cognitive score	53 544	0·046 (0·014 to 0·079)	0·039 (–0·000 to 0·077)
NO_2			
FRT	57 854	0·001 (–0·015 to 0·016)	0·002 (–0·017 to 0·020)
TRT	57 854	–0·025 (–0·037 to –0·014)	–0·015 (–0·028 to –0·001)
DFRT	57 854	–0·012 (–0·027 to 0·003)	–0·010 (–0·028 to 0·007)
DTRT	57 854	–0·015 (–0·023 to –0·006)	–0·008 (–0·018 to 0·002)
Lexical fluency	59 544	0·002 (–0·015 to 0·018)	0·009 (–0·010 to 0·028)
Semantic fluency	60 692	–0·076 (–0·093 to –0·059)	–0·039 (–0·059 to –0·019)
DSST	59 385	–0·062 (–0·078 to –0·047)	–0·033 (–0·051 to –0·016)
TMT-A	59 227	0·068 (0·051 to 0·084)	0·032 (0·013 to 0·051)
TMT-B	58 353	0·072 (0·057 to 0·088)	0·035 (0·017 to 0·053)
Global cognitive score	53 544	0·041 (0·010 to 0·072)	0·031 (–0·005 to 0·067)

For all the tests (except TMT-A and TMT-B) and for the global cognitive score, negative β indicates worse cognitive performance. For TMT-A and TMT-B, positive β indicates worse cognitive performance. The parsimonious model is adjusted for age, education, sex, and centre. The main model is adjusted for variables in the parsimonious model and smoking status, alcohol drinking, familial situation, body-mass index, history of Alzheimer's disease in parents, non-occupational physical activity, living alone at home, country of origin, depression symptoms, hypertension, type-2 diabetes, cardiovascular diseases, hearing loss, income, living area (urban, suburban, isolated city, or rural), and French Deprivation Index. Associations are change in cognitive performance (one SD change in *Z* scores) with an IQR increase in exposure to air pollutants (3·79 μg/m³ for $PM_{2·5}$, $0·74 \times 10^{-5}$/m for black carbon, and 13·93 μg/m³ for NO_2). $PM_{2·5}$=particulate matter with aerodynamic diameters less than 2·5 μm. FRT=fast free recall test. TRT=fast free and cued recall test. DFRT=delayed free recall test. DTRT=delayed free and cued recall test. DSST=digit–symbol substitution test. TMT-A=trail making test part A. TMT-B=trail making test part B. NO_2=nitrogen dioxide.

Table 2: **Results of multiple linear regression for the association between air pollution exposure and cognitive performance in the CONSTANCES cohort**

indication of heterogeneity. For black carbon and NO_2, the results of DSST, TMT-A, and TMT-B were also significant. However, we found heterogeneity indication for DSST and TMT-B for NO_2 (appendix 2 p 20). By considering centres as a clustering variable, the results of multilevel models were similar to the findings of the linear regression model (especially black carbon and NO_2; appendix 2 pp 15–16).

Discussion

In this large population-based study of French people aged 45 years or older, air pollution exposure (mostly to NO_2 and black carbon) was associated with poorer cognitive performance, especially in language skills and domains of executive functions. Our findings were robust to different sensitivity analyses and covariates adjustment.

Our findings support those from previous studies on the association between exposure to air pollution and cognitive performance.[10,31,32] The observed effect estimates in this study were in the range of 1% to nearly 5% decrease in cognitive performance for each IQR increase in exposure to air pollution depending on the cognitive outcome and pollutant, which is quite considerable. Additionally, using neuropsychological norms as a stricter criterion to define cognitive impairment (changing cognitive status from healthy to poor) again showed a significant association between air pollutants and poorer cognitive impairment. Moreover, considering the large number of people exposed to air pollutants globally, the population burden would be of great importance even with small effect sizes. Our findings on NO_2 and black carbon are highly important, because these pollutants are largely attributed to combustion sources and traffic, we observed robust association between exposure to NO_2 and black carbon and poorer cognitive performance. Stronger associations between air pollution and cognitive outcomes in people living in major cities and areas with higher traffic were reported in other studies,[33] indicating exposure to traffic-related air pollution (TRAP) might be particularly relevant. Despite relatively high exposure to $PM_{2·5}$ in nearly all of our study participants, the majority of our findings for $PM_{2·5}$, a less specific marker of TRAP, were not significant. Our non-significant findings for $PM_{2·5}$ especially for rural and isolated cities could be caused by power issues. This finding could also be caused by lower exposure intensity in the participants living in rural and isolated cities compared with urban and suburban residents.

We found our results to be mostly significant when associated with language skills (semantic fluency test) and executive functions domains. The prodromal stage of Alzheimer's dementia has been shown to be associated with impairment in semantic, but not lexical, fluency.[34,35] Our findings are also in accordance with those of Amieva and colleagues,[36] who reported a decline in semantic memory function as the earliest indication of Alzheimer's disease, appearing as much as 12 years before clinical manifestation of the disease. Semantic fluency tests localise to the temporal lobe.[37] Our findings on semantic fluency are consistent with another brain structural study that found that exposure to air pollution is most strongly associated with impairment in the temporal lobe.[38]

Regarding episodic memory, we found different results according to subscores (mostly significant on total recall scores). It has been reported that free recall significantly improves with the introduction of semantic cues in

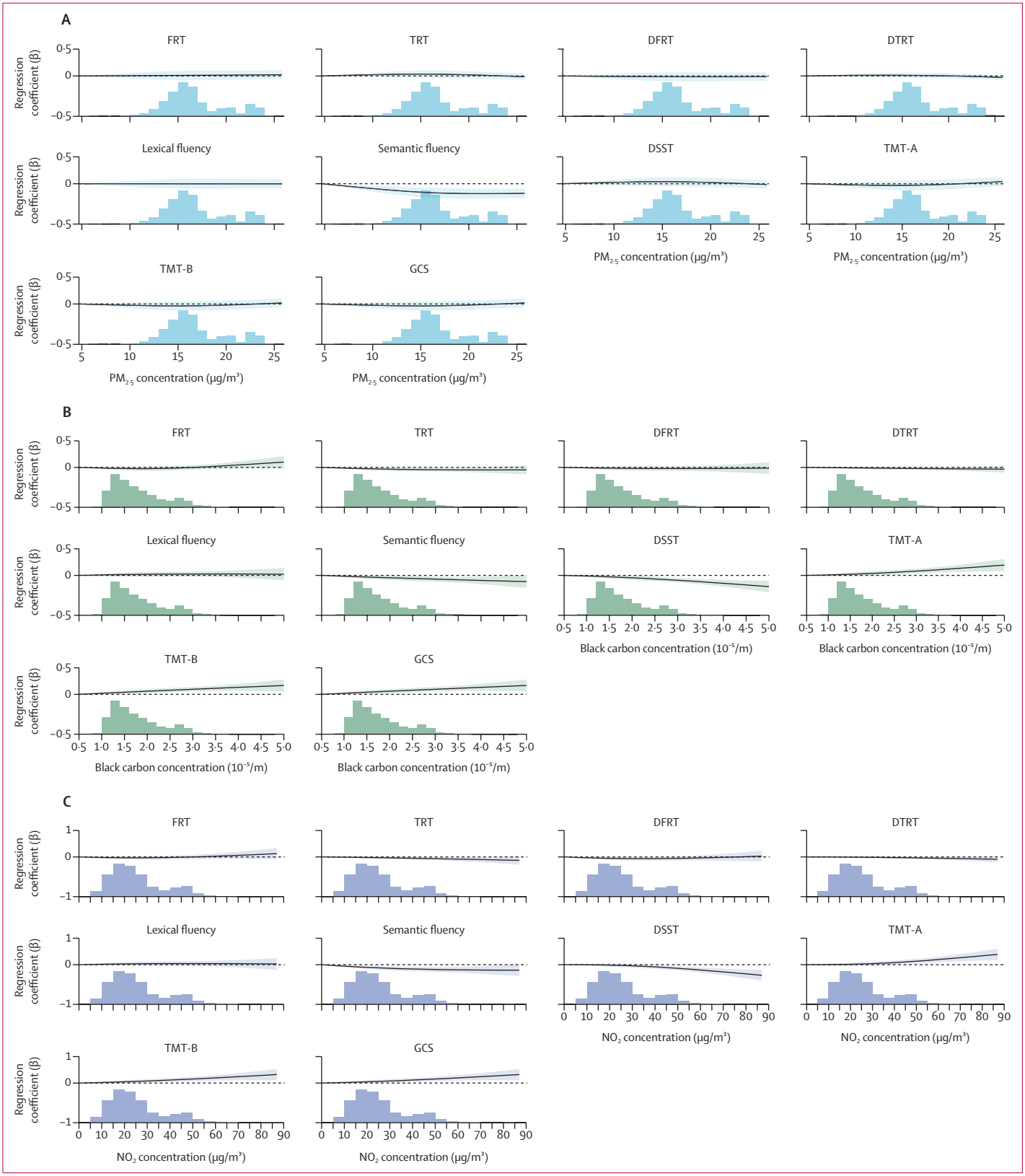
	Urban, β (95% CI)	Suburban, β (95% CI)	Isolated city, β (95% CI)	Rural, β (95% CI)
$PM_{2.5}$				
FRT	0·017 (–0·028 to 0·062)	–0·003 (–0·041 to 0·034)	0·012 (–0·081 to 0·106)	0·011 (–0·040 to 0·061)
TRT	–0·007 (–0·040 to 0·026)	–0·016 (–0·045 to 0·012)	0·001 (–0·072 to 0·073)	0·002 (–0·039 to 0·042)
DFRT	–0·008 (–0·051 to 0·035)	–0·002 (–0·039 to 0·034)	–0·021 (–0·112 to 0·070)	0·003 (–0·047 to 0·052)
DTRT	–0·004 (–0·028 to 0·020)	–0·013 (–0·034 to 0·008)	–0·005 (–0·057 to 0·047)	–0·012 (–0·042 to 0·018)
Lexical fluency	0·008 (–0·039 to 0·055)	0·002 (–0·038 to 0·042)	0·067 (–0·030 to 0·163)	–0·043 (–0·097 to 0·012)
Semantic fluency	–0·014 (–0·062 to 0·034)	–0·075 (–0·117 to –0·034)	–0·037 (–0·136 to 0·062)	–0·049 (–0·104 to 0·007)
DSST	0·001 (–0·044 to 0·046)	–0·032 (–0·068 to 0·004)	0·025 (–0·059 to 0·109)	0·020 (–0·029 to 0·069)
TMT–A	0·010 (–0·037 to 0·057)	0·049 (0·010 to 0·088)	–0·080 (–0·174 to 0·013)	0·002 (–0·051 to 0·055)
TMT–B	0·006 (–0·037 to 0·049)	0·038 (–0·000 to 0·075)	–0·060 (–0·150 to 0·029)	–0·028 (–0·081 to 0·025)
Global cognitive score	–0·070 (–0·159 to 0·018)	0·051 (–0·024 to 0·125)	0·048 (–0·133 to 0·229)	0·006 (–0·097 to 0·109)
Black carbon				
FRT	0·019 (–0·008 to 0·046)	0·007 (–0·026 to 0·039)	–0·096 (–0·241 to 0·049)	–0·031 (–0·126 to 0·064)
TRT	–0·016 (–0·035 to 0·004)	–0·013 (–0·038 to 0·012)	–0·070 (–0·181 to 0·041)	–0·045 (–0·120 to 0·030)
DFRT	–0·003 (–0·028 to 0·023)	0·002 (–0·030 to 0·034)	–0·082 (–0·222 to 0·059)	–0·045 (–0·138 to 0·048)
DTRT	–0·008 (–0·022 to 0·007)	–0·003 (–0·022 to 0·015)	–0·061 (–0·141 to 0·020)	–0·023 (–0·079 to 0·033)
Lexical fluency	0·016 (–0·012 to 0·044)	0·026 (–0·009 to 0·062)	0·071 (–0·078 to 0·219)	–0·059 (–0·161 to 0·044)
Semantic fluency	–0·029 (–0·058 to –0·000)	–0·018 (–0·054 to 0·018)	–0·110 (–0·261 to 0·041)	–0·042 (–0·147 to 0·063)
DSST	–0·033 (–0·060 to –0·006)	–0·054 (–0·085 to –0·022)	–0·011 (–0·139 to 0·118)	–0·040 (–0·131 to 0·052)
TMT–A	0·037 (0·009 to 0·066)	0·045 (0·011 to 0·080)	–0·053 (–0·196 to 0·090)	0·055 (–0·045 to 0·155)
TMT–B	0·037 (0·011 to 0·063)	0·044 (0·011 to 0·077)	0·021 (–0·117 to 0·159)	0·055 (–0·045 to 0·155)
Global cognitive score	0·031 (–0·022 to 0·085)	0·050 (–0·016 to 0·116)	0·128 (–0·152 to 0·407)	–0·023 (–0·218 to 0·172)
NO_2				
FRT	0·008 (–0·019 to 0·035)	0·008 (–0·022 to 0·038)	–0·022 (–0·115 to 0·072)	–0·022 (–0·083 to 0·039)
TRT	–0·016 (–0·035 to 0·004)	–0·011 (–0·033 to 0·012)	–0·001 (–0·072 to 0·071)	–0·019 (–0·067 to 0·030)
DFRT	–0·002 (–0·028 to 0·024)	–0·006 (–0·035 to 0·023)	–0·052 (–0·143 to 0·038)	–0·030 (–0·090 to 0·030)
DTRT	–0·004 (–0·019 to 0·010)	–0·008 (–0·025 to 0·009)	–0·028 (–0·079 to 0·024)	–0·013 (–0·049 to 0·023)
Lexical fluency	0·008 (–0·021 to 0·036)	0·031 (–0·000 to 0·063)	0·040 (–0·056 to 0·136)	–0·040 (–0·106 to 0·026)
Semantic fluency	–0·035 (–0·064 to –0·006)	–0·032 (–0·064 to 0·001)	–0·086 (–0·184 to 0·013)	–0·048 (–0·116 to 0·020)
DSST	–0·032 (–0·059 to –0·005)	–0·037 (–0·065 to –0·008)	–0·012 (–0·096 to 0·071)	–0·002 (–0·061 to 0·057)
TMT–A	0·038 (0·009 to 0·066)	0·040 (0·008 to 0·071)	–0·043 (–0·136 to 0·049)	0·014 (–0·051 to 0·078)
TMT–B	0·036 (0·010 to 0·062)	0·035 (0·005 to 0·065)	0·004 (–0·086 to 0·093)	0·007 (–0·058 to 0·072)
Global cognitive score	0·004 (–0·049 to 0·058)	0·062 (0·002 to 0·121)	0·143 (–0·037 to 0·323)	–0·050 (–0·176 to 0·076)

For all the tests (except TMT-A and TMT-B) and for the global cognitive score, negative β indicates worse cognitive performance. For TMT-A and TMT-B, positive β indicates worse cognitive performance. All models are adjusted for age, education, sex, centre, smoking status, alcohol drinking, familial situation, body-mass index, history of Alzheimer's disease in parents, non-occupational physical activity, living alone at home, country of origin, depression symptoms, hypertension, type-2 diabetes, cardiovascular diseases, hearing loss, income, living area (urban, suburban, isolated city, or rural), and French Deprivation Index. Associations are change in cognitive performance (one SD change in *Z* scores) with an IQR increase in exposure to air pollutants (3·79 μg/m³ for $PM_{2.5}$, 0·74 10^{-5}/m for black carbon, and 13·93 μg/m³ for NO_2). $PM_{2.5}$=particulate matter with aerodynamic diameters less than 2·5 μm. FRT=fast free recall test. TRT=fast free and cued recall test. DFRT=delayed free recall test. DTRT=delayed free and cued recall test. DSST=Digit-Symbol Substitution Test. TMT-A= Trail Making Test part A. TMT-B=Trail Making Test part B. NO_2=nitrogen dioxide.

Table 3: **Results of multiple linear regression for the association between air pollution exposure and cognitive performance in the CONSTANCES cohort according to the residential area (urban, suburban, isolated city, and rural area)**

Alzheimer's disease dementias.[39] Additionally, total recall is a more specific memory measure in settings with a higher prevalence of amnestic mild cognitive impairments or patients with Alzheimer's disease. Alzheimer's disease dementias frequently present memory disorders associated with semantic dysfunction. Therefore, assuming air pollution is a risk factor of Alzheimer's disease,[4] the observed results on total recall scores (and not free recalls) are plausible. However, available evidence on the association between air pollution exposure and episodic memory are contradictory.[40] Younan and colleagues[7] found that long-term exposure to ambient $PM_{2.5}$ at residential locations was associated with accelerated decline in episodic memory, specifically in the measures of immediate recall and new learning.

We found no significant association between exposure to air pollutants and global cognitive score in our analyses, which is in accordance with Gatto and colleagues,[32] who found no significant association between exposure to $PM_{2.5}$, NO_2, and ozone, and global cognitive score. However, some other studies found significant associations between air pollution exposure and decreased cognitive performance or cognitive decline in terms of global cognitive score.[6,41] The global cognitive


A
FRT
TRT
DFRT
DTRT
Lexical fluency
Semantic fluency
DSST
TMT-A
TMT-B
GCS
Regression coefficient (β)
0·5
0
−0·5
5 10 15 20 25
PM2·5 concentration (μg/m³)
B
0·5 1·0 1·5 2·0 2·5 3·0 3·5 4·0 4·5 5·0
Black carbon concentration (10⁻⁵/m)
C
1
0
−1
0 10 20 30 40 50 60 70 80 90
NO2 concentration (μg/m³)

score in our study only comprised 44–47% of the variance in the data. Additionally, global cognitive scores across studies might be different from one study to another in terms of definition of the component domains and method by which the global cognitive score is constructed. Therefore, the discrepancy in the findings across the studies are perceivable.

In our study, women showed stronger associations with air pollution than men in all outcomes except semantic fluency. Considering the higher prevalence of risk factors of poor cognitive performance in men than in women in this study, and adjustment for these variables in the models, this finding could be of high importance. A stronger association between air pollution exposure and cognitive performance in women has also been highlighted in other studies.[42,43] However, some other studies reported associations in the opposite direction, finding higher risk in men or risk that was no different between men and women.[38,44] In accordance with our findings on the absence of gender difference for semantic fluency associations, Mura and colleauges[19] also reported negligible effect size of gender for semantic fluency.

The major strength of this study is its large sample size, with participants residing in different regions of metropolitan France. Further, using an extensive battery of cognitive tests and several air pollutants (especially black carbon) at the residential address is an asset. Our participants were younger than those included in previous studies on air pollution and cognition, shedding light on the association between air pollution and cognitive performance among a middle-aged population. Additionally, the numerous sensitivity analyses in this study indicate the robustness of our results. The concurrent results on three different outdoor air pollutants increase the understanding on the neurotoxicity of air pollutants. These pollutants are products of the main sources of outdoor air pollution, such as traffic and combustion-related sources in most of the regions (especially black carbon and NO_2). However, further studies are needed to explore the role of other outdoor air pollutants, such as ozone or components of particulate matter on cognitive performance.

The cross-sectional nature of our study limited us to draw a cause–effect association from the findings, even though it is most likely that exposure at the year of recruitment reflects the chronic exposure of several years, at least for people who did not move to a different location.[45] However, because of reduction of air pollution concentration in past decades, using air pollution exposure at the time of enrolment can underestimate the cumulative past exposure of the participants. In our study, data on changes in the residential address of the participants were unavailable. This missing data can introduce exposure misclassification, especially because of possible moving of the participants to areas with different air pollution concentrations, and also because of temporal changes in air pollution concentrations. As the probability of residential mobility might have been similar for most of the participants, this misclassification should be mostly of the non-differential type, thus making the effect estimates closer to the null value than they probably are.

Despite widely reported long-term effects of air pollution on cognitive performance, short-term effects of environmental factors including air pollution and temperature on human cognitive performance and brain activity have also been reported.[46–47] As air pollution concentration and temperature fluctuate during the day, timing of the tests should be included as a covariate in the models to compensate possible short-term associations between air pollution or thermal exposure or both.

Additionally, results of the stability analyses of the land-use regression models that were used for our study showed that different temporal correlations could be observed between modelled concentrations in 2010 and extrapolated correlations for other years according to the regions.[17] Therefore, even for participants with no change of residential address in the years before recruitment in the CONSTANCES cohort, using single-year exposure values can introduce the risk of exposure misclassification. Predicted air pollution from the land-use regression model explained 54–72% of spatial variation, which is good for spatial models. However, it also means that land-use regression models are subject to error, especially for areas without measurements. Additionally, some of the participants in the CONSTANCES cohort did not do all the cognitive tests. This raises concerns about possible selection bias because it is probable that tests that were not administered or incompletely assessed were hard to do for people with impaired cognitive performance (caused by exposure to various risk factors, possibly including air pollution). However, such a phenomenon, assuming it occurred in our study, could lead to an underestimation of the effect sizes, because in this case we would exclude participants with impaired cognitive performance.

In conclusion, air pollution has been suggested as a modifiable risk factor of cognitive impairment. In our study, we found robust associations between exposure to different air pollutants and poor cognitive performance. We found significant and robust links between exposure to NO_2 and black carbon and poor cognitive performance. Our results highlight the

Figure 2: **Exposure–response association between exposure to $PM_{2·5}$, NO_2, and black carbon, and cognitive performance in the CONSTANCES cohort**
For all the tests (except TMT-A and TMT-B) and for the global cognitive score, negative β indicates worse cognitive performance. For TMT-A and TMT-B, positive β indicates worse cognitive performance. The x-axis is the concentration of the pollutants (for $PM_{2·5}$ and NO_2 in μg/m^3 and for black carbon in 10^{-5}/m); the y-axis is the regression coefficient. DFRT=delayed free recall of FCSRT. DSST=Digit–Symbol Substitution Test. DTRT=delayed free and cued recall of FCSRT. FCSRT=Free and Cued Selective Reminding Test. FRT=free recall trials of the FCSRT. GCS=global cognitive score. TMT-A=Trail Making Test part A. TMT-B=Trail Making Test part B. TRT=free and cued recall trials of FCSRT.

importance of considering the role of traffic-related air pollutants in cognitive ageing.

Contributions

MJZS contributed to conceptualising the study, the methodology, data curation, software use, formal data analysis, data visualisation, and writing of the original draft before editing and reviewing secondary drafts. JY, EL, and CB contributed to the study conceptualisation, methodology, and reviewing and editing of the manuscript. JC contributed to the reviewing and editing of the manuscript. KdH and DV contributed to the conceptualisation, the methodology, the reviewing and editing of the manuscript, and exposure data resources. NL contributed to the methodology and reviewing and editing of the manuscript. MM and AO reviewed and edited the manuscript. MZ and MG contributed to the conceptualisation of the study, the methodology, reviewing and editing the manuscript, investigation, and financial and data gathering resources. BJ contributed to the funding acquisition, supervision, project administration, study conceptualisation, methodology, and review and editing of the manuscript. BJ, MZ, and MG had data access.

Declaration of interests

We declare no competing interests.

Data sharing

All the data in this study is collected in the framework of the CONSTANCES cohort and the POCOMO project. All the data is available upon request to the corresponding author (benedicte.jacquemin@inserm.fr) and with agreement of the steering committee of the CONSTANCES cohort.

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