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Exposure to ambient air pollution and cognitive decline: Results of the prospective Three-City cohort study

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ABSTRACT

Background: Growing epidemiological evidence suggests an adverse relationship between exposure to air pollutants and cognitive decline. However, there is still some heterogeneity in the findings, with inconsistent results depending on the pollutant and the cognitive domain considered. We wanted to determine whether air pollution was associated with global and domain-specific cognitive decline.

Methods: This analysis used data from the French Three-City prospective cohort (participants aged 65 and older at recruitment and followed for up to 12 years). A battery of cognitive tests was administered at baseline and every 2 years, to assess global cognition (Mini Mental State Examination, MMSE), visual memory (Benton Visual Retention Test), semantic fluency (Isaacs Set Test) and executive functions (Trail Making Tests A and B). Exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and black carbon (BC) at the participants' residential address during the 5 years before the baseline visit was estimated with land use regression models. Linear mixed models and latent process mixed models were used to assess the association of each pollutant with global and domain-specific cognitive decline.

Results: The participants' (n = 6380) median age was 73.4 years (IQR: 8.0), and 61.5% were women. At baseline, the median MMSE score was 28 (IQR: 3). Global cognition decline, assessed with the MMSE, was slightly accelerated among participants with higher $PM_{2.5}$ exposure: one IQR increment in $PM_{2.5}$ (1.5 $\mu g/m^3$) was associated with accelerated decline (β: −0.0060 [−0.0112; −0.0007] standard unit per year). Other associations were inconsistent in direction, and of small magnitude.

Conclusion: In this large population-based cohort, higher $PM_{2.5}$ exposure was associated with accelerated global cognition decline. We did not detect any significant association for the specific cognitive domains or the other pollutants. Evidence concerning $PM_{2.5}$ effects on cognition is growing, but more research is needed on other ambient air pollutants.

1. Introduction

Ambient air pollution is a complex mixture of particulate matter (PM), gases, organic volatile compounds and metals produced by combustion of fossil fuels and industrial and agricultural processes. The effects of air pollution on cardiovascular and respiratory health has been largely documented (Brunekreef and Holgate, 2002). More recently, findings from experimental and post-mortem studies suggest that air pollutants might also affect the central nervous system through different mechanisms (neuroinflammation, oxidative stress and cerebrovascular damage) (Block and Calderón-Garcidueñas, 2009; Block et al., 2012; Genc et al., 2012).

Growing epidemiological data are in agreement with these findings, suggesting an adverse relationship between air pollution and cognitive

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health in older adults (Peters et al., 2019; Delgado-Saborit et al., 2021). Although most studies found that air pollution exposure is associated with an increased dementia risk (Oudin et al., 2016; Cacciottolo et al., 2017; Oudin et al., 2018; Grande et al., 2020; Mortamais et al., 2021), results are heterogeneous on cognitive decline. Indeed, findings vary in function of the pollutants and cognitive domains considered (Cacciottolo et al., 2017; Weuve et al., 2012; Loop et al., 2013; Tonne et al., 2014; Oudin et al., 2017; Cleary et al., 2018; Cullen et al., 2018; Wurth et al., 2018; Kulick et al., 2020; Wang et al., 2020; Younan et al., 2020). Inconsistent associations could result from methodological differences in cognition and exposure assessments, but also from differences in air pollutant levels across populations and in population characteristics. Therefore, to strengthen the evidence, longitudinal studies combining the investigation of different cognitive domains and different air pollutants are needed, particularly in Europe because previous research was mainly performed in non-European countries (Cacciottolo et al., 2017; Weuve et al., 2012; Loop et al., 2013; Cleary et al., 2018; Wurth et al., 2018; Kulick et al., 2020; Wang et al., 2020; Younan et al., 2020). In a large population-based cohort of older adults in France, we sought to investigate the association between exposure to three different air pollutants [fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and black carbon (BC)] and decline in global cognition, visual memory, semantic fluency, and executive functions during a follow-up period of 12 years.

2. Methods

2.1. Study population

We used data from the Three-City study, a French prospective cohort (3C Study Group, 2003). Community-dwelling (i.e. not living in an institution) $\geq$ 65-year-old adults were recruited randomly from the electoral rolls of three French cities (Bordeaux, Dijon, Montpellier) between 1999 and 2001. Participants were followed for 12 years, with follow-up visits at 2, 4, 7, 10 and 12 years. The baseline assessment and the follow-up visits included standardized questionnaires, clinical examination, and detailed cognitive evaluations.

Among the 9294 participants originally included, 9251 had a baseline residential address that could be geocoded. Among them, we excluded participants who reported changes in residence during the 5 years preceding the baseline visit, who had prevalent dementia, who did not have any follow-up visit, and participants with missing data for covariates. Therefore, the final sample included 6380 individuals. For each cognitive test, we then excluded participants with fewer than two measurement points (Fig. 1).

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

2.2. Cognitive assessment

Five cognitive tests were administered by trained psychologists. The Mini Mental State Examination (MMSE) was used as a global measure of cognitive function (scores ranging from 0 to 30) (Folstein et al., 1975). The recognition form of the Benton Visual Retention Test (BVRT) assessed mainly visual memory (scores ranging from 0 to 15) (Amieva et al., 2006). Semantic fluency was measured using the Isaacs Set Test (IST), and the total number of words generated in four semantic categories (animals, colors, fruits and cities) within 30 s was calculated (Isaacs and Kennie, 1973). The Trail Making Test form A (TMTA), which

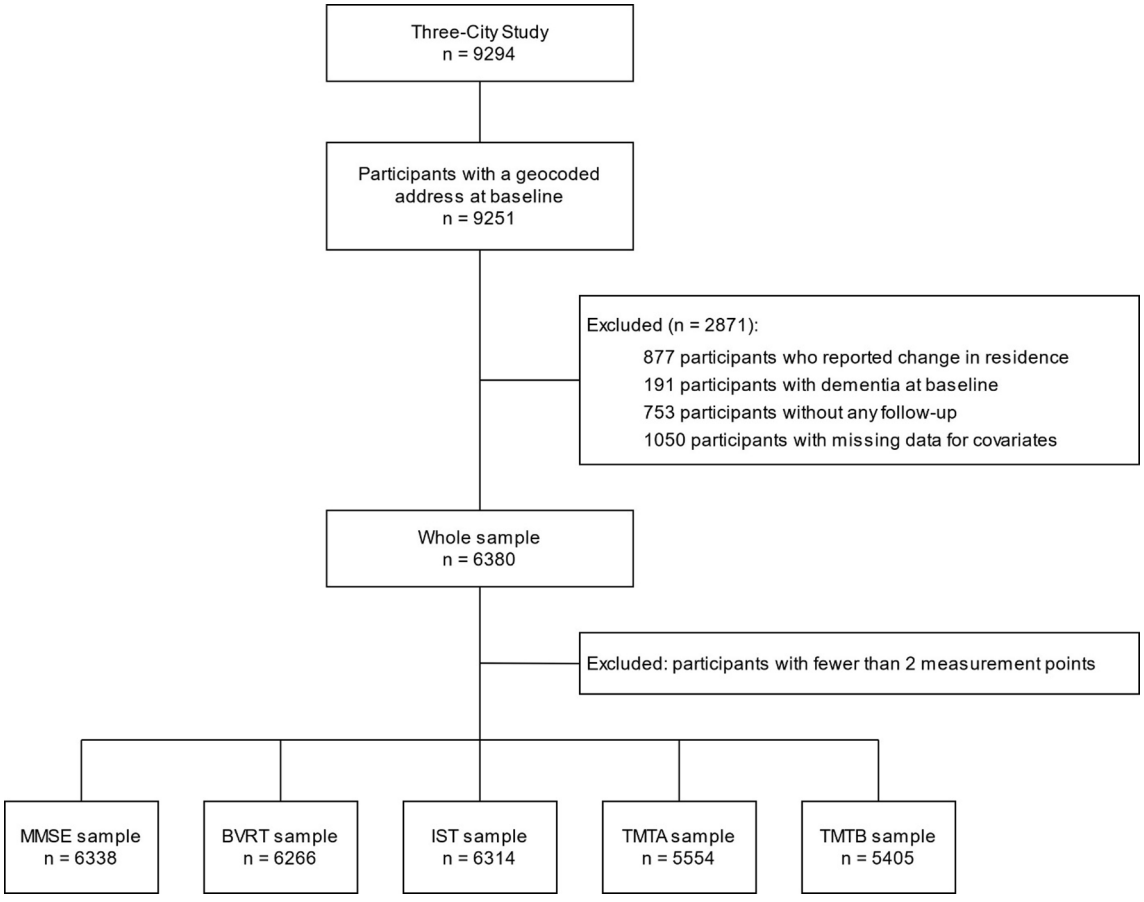

Fig. 1. Flowchart for the selection of the final analytical samples from the Three-City cohort. Abbreviations: BVRT: Benton Visual Retention Test; IST: Isaacs Set Test; MMSE: Mini Mental State Examination; TMTA-B: Trail Making Tests A and B.

requires participants to connect numbered circles in ascending order, was used to assess psychomotor speed. Executive function was evaluated with the Trail Making Test form B (TMTB) in which participants are asked to connect circles in alternating numerical and alphabetical sequences (Bowie and Harvey, 2006). For the TMTA and TMTB, the number of correct moves/time was calculated. Tests were administered at baseline and at each follow-up visit, except for the TMTA and TMTB that were not used at the first follow-up visit.

2.3. Air pollution exposure

Ambient concentrations of $PM_{2.5}$, NO_2 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 (de Hoogh et al., 2018). Methods of air pollution exposure assessment have been described in previous work (Mortamais et al., 2021). Briefly, $PM_{2.5}$ and NO_2 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) (Eeftens et al., 2012). Potential predictor variables of the LUR models included land use characteristics, population density, roads, altitude, pollutant estimates for 2010 from two long-range chemical transport models (MACC-II ENSEMBLE (Inness et al., 2013) and the Danish Eulerian Hemispheric Model (Brandt et al., 2012)), and satellite-derived $PM_{2.5}$ and NO_2 estimates. The final models, described in detail elsewhere (de Hoogh et al., 2018), explained 72%, 59% and 54% of the spatial variation in the measured concentrations of $PM_{2.5}$, NO_2 and BC, respectively. Models were derived, validated and mapped at 100x100m across Western Europe, and assigned to the geocoded baseline residential address of each participant.

To derive exposures relevant to the cohort baseline, the 2010 model estimates were extrapolated for the period 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), one level for each study center]. Specifically, the annual mean estimates from the 26x26km Danish Eulerian Hemispheric Model, previously downscaled from the original 50x50km resolution using bilinear interpolation (Brandt et al., 2012) were used. Stability of the spatial pattern in NO_2 after back extrapolation was evaluated at country level in the exposure assessment paper (de Hoogh et al., 2018); for NO_2 in 2000 the R^2 (RMSE) was 82.9% (1.9 μg/m^3) supporting the use of back extrapolation.

Exposure estimates were finally aggregated to obtain the mean $PM_{2.5}$, NO_2 and BC exposures in the 5 years before the baseline visit. All exposures were analyzed as continuous variables.

2.4. Other variables

Covariates that could be potential confounders were pre-selected based on literature review.

Socio-demographic variables at baseline included age (years), sex, education level (primary education: ≤5 years; lower secondary education: up to 9 years; and higher secondary education: >9 years), and study center. Health behavior variables at baseline included smoking habits (never/former or current smoker) and alcohol intake (none, moderate if < 36 g per day, or heavy if ≥ 36 g). APOEε4 carrier was defined as the presence of at least one ε4 allele. For each participant, the contextual neighborhood socioeconomic status was defined using a deprivation index based on the percentage of households without car, the percentage of tenants and single parents, unemployment rate, settlement index, and taxable household income (Letellier et al., 2018) at the IRIS level (Ilots Regroupés pour l'Information Statistique), the finest spatial census unit in France (2000 residents per unit). High deprivation index values indicate more deprived neighborhood areas.

2.5. Statistical analyses

To analyze the relationship between exposure to ambient air pollution and cognitive decline over time, linear mixed models for repeated measures were used, with a subject-specific random intercept and random slope for time. Separate analyses were performed for each cognitive test and for each pollutant. Because the MMSE and the BVRT have specific psychometric properties (curvilinearity and ceiling effect), latent process mixed models were used to study the association between pollutants and these two outcomes (Commenges and Jacqmin-Gadda, 2015). These models assume that there is a latent cognitive process (representing the cognition level) imperfectly assessed by the neuropsychological tests. The model is composed of two parts that are simultaneously estimated: (a) a standard linear mixed model that describes the change over time of the latent cognitive process and evaluates the effects of covariates on this change; and (b) a test-specific measurement model that links the neuropsychological test to the latent cognitive process using a beta cumulative function (flexible transformations) (Proust-Lima et al., 2017; Proust-Lima et al., 2011). The coefficients reported in this study are expressed in the latent process scale that is constrained to follow a Gaussian distribution N(0,1) at baseline.

For each cognitive test, minimally adjusted and fully adjusted models were estimated. Minimally adjusted models included terms for time (i.e. years since the baseline visit), air pollution, time-by-air pollution interaction, age, sex, education level, study center, and the interaction terms with time for these four covariates. Fully adjusted models also included terms for all the other pre-selected covariates, indicator of first completion of the cognitive test, and additional significant time-by-covariate interactions (covariates selected for each cognitive test when $p < 0.01$). The indicator of first completion of the cognitive test was used to handle the retest effect (i.e. getting used to the test, remembering the test content, or developing strategies) that may lead to practice-related improvement, and thus misdetection of cognitive decline (Weuve et al., 2015). Details on incremental adjustments are provided in Table S1. The linearity of pollutants' effects was also assessed. Associations are reported as the mean difference in cognitive score change per year and per interquartile range (IQR) increase in $PM_{2.5}$ (1.5 μg/m^3) and NO_2 (8.1 μg/m^3), and per unit increase in BC (10^{-5}/m). For all tests, negative coefficients indicate that high air pollution exposure is associated with accelerated cognitive decline.

In sensitivity analyses, we further adjusted our models for body mass index, family income and physical activity. As we excluded many participants due to missing data for covariates (especially the deprivation index, Table S3), we also performed additional analyses after imputing missing data using the fully conditional specification multiple imputation method (Liu and De, 2015). Finally, to evaluate the impact of non-response and drop-out on our results, we performed analyses where we included participants with fewer than 2 measurement points and where we added inverse probability of attrition (IPA) weights (Weuve et al., 2012) to the models. The procedures and results of these analyses are presented in Supplemental Material.

Analyses were performed using SAS version 9.4 and R version 4.0.2. Latent process mixed models were estimated using the R package lcmm (Proust-Lima et al., 2017).

3. Results

3.1. Participants' characteristics

Among the 6380 participants, the median age (IQR) at enrollment was 73.4 (8.0) years, 62% were women, and 37% had more than 9 years of education (Table 1). Participants were followed for a median duration

Table 1
Characteristics of the whole population at enrollment (n = 6380).

Characteristics	n (%) or median (IQR)
Age (years)	73.4 (8.0)
Women	3922 (61.5)
Study center	
Bordeaux	1469 (23.0)
Dijon	3636 (57.0)
Montpellier	1275 (20.0)
Education	
Primary (≤5 years)	2096 (32.9)
Lower secondary (5 – 9 years)	1908 (29.9)
Higher secondary (>9 years)	2376 (37.2)
Smoking habits	
Never	3947 (61.9)
Former or current smoker	2433 (38.1)
Alcohol intake	
None	1291 (20.2)
Moderate	4584 (71.8)
Heavy	505 (7.9)
APOE ε4 carriers	1261 (19.8)
Deprivation index[a]	−0.29 (2.02)
Cognitive performance at baseline	
MMSE (n = 6338)	28 (3)
BVRT (n = 6266)	12 (3)
IST (n. words generated in 30 s, n = 6314)	48 (14)
TMTA (n. correct items/second, n = 5554)	0.5 (0.2)
TMTB (n. correct items/second, n = 5405)	0.2 (0.2)
Follow-up duration (years)	9.1 (7.2)
Air pollution exposure	
$PM_{2.5}$ (μg/m^3)	25.4 (1.5)
NO_2 (μg/m^3)	36.1 (8.1)
BC (10^{-5}/m)	2.7 (0.4)

Abbreviations: APOE: apolipoprotein E; BC: black carbon; BVRT: Benton Visual Retention Test; IQR: interquartile range; IST: Isaacs Set Test; MMSE: Mini Mental State Examination; n.: number; PM: particulate matter; TMTA-B: Trail Making Tests A and B

[a] Higher score indicates more deprived neighborhood area (scores ranged from −4.19 to 10.75 in our study)

of 9.1 (IQR: 7.2) years. At the baseline visit, the median MMSE score was 28 (IQR: 3) and the median BVRT score was 12 (3). The median IST score was 48 (14) words in 30 s, and the median TMTA and TMTB scores were 0.5 (0.2) and 0.2 (0.2) correct moves/second, respectively. In the 5 years before enrollment, the median (IQR) exposure to pollution was 25.4 (1.5) μg/m^3 for $PM_{2.5}$, 36.1 (8.1) μg/m^3 for NO_2, and 2.7 (0.4) × 10^{-5}/m for BC (Table 1). Excluded participants (n = 2914) were slightly older than the study sample (median age: 74.0, $p < 0.0001$), and those who underwent baseline cognitive testing (n = 2878) had worse performance in the five cognitive tests ($p < 0.0001$).

3.2. Air pollution exposure and cognitive decline over time

Exposure to air pollution was not consistently associated with accelerated cognitive decline (Table 2). In the fully adjusted analyses, MMSE performance decline over time was accelerated in participants with higher air pollution exposure (Table 2). However, the association was statistically significant only for $PM_{2.5}$, with a slightly accelerated decline in the latent process scale: −0.0060 (95% CI: −0.0112; −0.0007) standard units per year for a 1.5 μg/m^3 increment in $PM_{2.5}$ exposure. This effect was equivalent to the difference in cognitive decline between individuals 1 year apart in age in our study. For the other cognitive tests, associations were inconsistent in direction, depending on the pollutant considered.

3.3. Sensitivity analyses

Additional adjustment on body mass index, household income and physical activity at baseline did not change the results of our primary analyses (Table S2). After imputation of missing data for covariates, coefficients for the associations were similar for $PM_{2.5}$ and NO_2, but the association between $PM_{2.5}$ and MMSE performance decline was attenuated and no longer significant (Table S4). There were variations in associations' direction for BC, but all remained non-significant (Table S4). Attrition varied slightly depending on the cognitive test considered (Table S5). However, there was no significant change in the results after IPA weighting (Table S6): all association coefficients were very similar and the association between $PM_{2.5}$ and MMSE performance decline remained significant. The only notable change was for $PM_{2.5}$ effect on IST performance decline, where the association became significant

4. Discussion

By using cognitive function data from a large prospective cohort of older adults in France, we found that higher exposure to $PM_{2.5}$ was associated with a slightly accelerated decline in global cognition, but not in the specific cognitive domains under study, during the 12-year follow-up. This accelerated decline was equivalent to 1 year of aging in our

Table 2
Differences (95% CI) in cognitive decline associated with air pollution exposure.

		$PM_{2.5}$				NO_2				BC			
	n	β[d]	95% CI			β[d]	95% CI			β[d]	95% CI		
Minimally adjusted models[a]													
MMSE (standard unit)[c]	6338	−0.0064	−0.0115	;	−0.0012	−0.0036	−0.0091	;	0.0019	−0.0027	−0.0170	;	0.0115
BVRT (standard unit)[c]	6266	−0.0004	−0.0052	;	0.0046	0.0021	−0.0029	;	0.0072	0.0009	−0.0111	;	0.0130
IST (n. words generated in 30 s)	6314	0.0263	−0.0044	;	0.0570	−0.0033	−0.0362	;	0.0296	0.0222	−0.0613	;	0.1056
TMTA (n. correct moves/second)	5554	−0.0004	−0.0010	;	0.0003	−0.0002	−0.0008	;	0.0005	0.0008	−0.0009	;	0.0025
TMTB (n. correct moves/second)	5405	0.0002	−0.0002	;	0.0006	0.0002	−0.0003	;	0.0006	0.0007	−0.0004	;	0.0017
Fully adjusted models[b]													
MMSE (standard unit)[c]	6338	−0.0060	−0.0112	;	−0.0007	−0.0037	−0.0092	;	0.0019	−0.0028	−0.0175	;	0.0119
BVRT (standard unit)[c]	6266	−0.0003	−0.0046	;	0.0041	0.0022	−0.0028	;	0.0072	0.0010	−0.0082	;	0.0102
IST (n. words generated in 30 s)	6314	0.0307	−0.0004	;	0.0618	−0.0022	−0.0355	;	0.0311	0.0249	−0.0596	;	0.1093
TMTA (n. correct moves/second)	5554	−0.0004	−0.0010	;	0.0002	−0.0002	−0.0009	;	0.0005	0.0008	−0.0009	;	0.0025
TMTB (n. correct moves/second)	5405	0.0002	−0.0002	;	0.0006	0.0002	−0.0002	;	0.0006	0.0007	−0.0004	;	0.0017

Abbreviations: BC: black carbon; BVRT: Benton Visual Retention Test; IST: Isaacs Set Test; MMSE: Mini Mental State Examination; n.: number; PM: particulate matter; TMTA-B: Trail Making Tests A and B

[a] Adjusted for age, sex, education level and study center, and their interactions with time

[b] Adjusted also for smoking habits, alcohol intake, apolipoprotein E genotype, contextual deprivation index, indicator of first completion of the test and additional significant time*covariate interactions (MMSE and IST: apolipoprotein E genotype)

[c] Coefficients are expressed in the latent process scale that is constrained to follow a Gaussian distribution N(0,1) at baseline

[d] β (time*air pollution coefficient) indicates the mean difference in cognitive decline per year and per interquartile range increase in $PM_{2.5}$ (1.5 μg/m^3) and NO_2 (8.1 μg/m^3), and per one unit increase in BC (10^{-5}/m)

study population. Conversely, for exposure to NO_2 and BC, two pollutants for which emissions are mainly traffic-related, we did not observe any significant association with cognitive decline.

Our results are consistent with those reported in previous epidemiological studies, suggesting an adverse association between exposure to $PM_{2.5}$ and decline in global cognition in middle-aged and older adults (Cacciottolo et al., 2017; Weuve et al., 2012; Kulick et al., 2020; Wang et al., 2020). In the Nurses' Health Study (Weuve et al., 2012), a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a cognitive decline equivalent to aging by approximately 2 years. Similarly, in the Washington Heights/Inwood Community Aging Project (WHICAP) study (Kulick et al., 2020), one IQR increment in $PM_{2.5}$ (4.84 μg/m^3) was associated with accelerated decline in global cognition. In the Women's Health Initiative Memory Study, in which a binary definition of cognitive decline was used, the risk of decline was increased by 81% in people exposed to $PM_{2.5}$ levels that exceeded the US Environmental Protection Agency standards (>12 μg/m^3) (Cacciottolo et al., 2017). Finally, in China (Wang et al., 2020), where $PM_{2.5}$ exposure is higher (median exposure: 50.1 (IQR: 19.5) μg/m^3), the risk of poor cognitive function (defined with a non-standardized MMSE score cut-off of 18) increased by 5.1% for each 10 μg/m^3 increase. Three studies did not find any significant effect of $PM_{2.5}$, but their short follow-up duration (4–5 years) may have precluded the detection of cognitive decline (Loop et al., 2013; Tonne et al., 2014; Cleary et al., 2018). The effect size we observed in our study reflects a rather minor clinical change in cognitive performance over time, despite slightly higher air pollution levels in our study compared with the literature, except for the study in China. However, comparison with the effects observed in other studies on cognitive decline remains difficult due to differences in the cognitive tests employed and in the definition of cognitive decline. Moreover, $PM_{2.5}$ exposure was less heterogeneous in our population, which might be related to the homogeneity in the residence place environment (urban/suburban). Other studies in European cities also reported small variability in $PM_{2.5}$ exposure (Raaschou-Nielsen et al., 2013).

The small heterogeneity in $PM_{2.5}$ exposure levels observed in our cohort did not prevent the detection of an effect of $PM_{2.5}$ on global cognition, but may explain the absence of any significant association with specific cognitive domains. Yet, some cognitive functions are affected earlier during aging. For instance, decline in episodic memory has been observed in patients with mild cognitive impairment and preclinical Alzheimer's disease, while other cognitive functions remain stable (Collie and Maruff, 2000). The PAQUID study found that other cognitive functions, such as visuo-spatial memory and semantic memory, also decline before the onset of dementia (Amieva et al., 2005; Amieva et al., 2008). Therefore, several studies identified associations between $PM_{2.5}$ exposure and decline in different cognitive functions. In the WHICAP study, $PM_{2.5}$ exposure was associated with accelerated cognitive decline in memory, language and executive functions (Kulick et al., 2020). Accelerated decline in memory related to $PM_{2.5}$ exposure was also found in the Women's Health Initiative Study of Cognitive Aging and in the Women's Health Initiative Memory Study (Younan et al., 2020; Petkus et al., 2020). In these studies with significant associations, $PM_{2.5}$ exposure was more variable in the populations (Weuve et al., 2012; Kulick et al., 2020; Wang et al., 2020; Younan et al., 2020), which could explain the discrepancy with our findings. Moreover, attrition bias could be particularly marked for tests assessing specific cognitive domains because participants experiencing cognitive difficulties may refuse to undergo an extensive cognitive assessment, besides the MMSE. Indeed, the median MMSE score at the last follow-up was lower in participants who did not do the BVRT than in those who did it during the same visit (25 vs 28). However, this hypothesis was not confirmed by our sensitivity analyses to account for attrition bias.

Literature data on the effect of $PM_{2.5}$ exposure on dementia risk are more consistent. Most studies reported an increased dementia risk for people exposed to higher $PM_{2.5}$ levels (Peters et al., 2019), whatever the study design (active or passive dementia diagnosis using health administrative databases). Experimental studies support the hypothesis that PM could be particularly harmful in the central nervous system. Overall, air pollutants can affect the central nervous system remotely, through systemic inflammation (Block and Calderón-Garcidueñas, 2009; Block et al., 2012; Genc et al., 2012). Because of their size and the related physical properties, small and ultrafine particles can reach the brain through the systemic circulation or through olfactory or sensory neuronal pathways, adding direct neurotoxicity to their systemic effects (Block and Calderón-Garcidueñas, 2009; Block et al., 2012; Heusinkveld et al., 2016). In addition, they can act as carrier of toxic compounds adsorbed on their surface, and deliver them to the brain (Block and Calderón-Garcidueñas, 2009; Genc et al., 2012).

Evidence regarding the effect of NO_2 and BC on cognitive decline is lacking. A limited number of studies evaluated the association between NO_2 or nitrogen oxides (NO_x) and cognitive decline in older adults. The analysis of the UK Biobank cohort did not find any evidence of an effect of NO_x or NO_2 exposure on decline in several cognitive domains (reasoning, memory, and reaction time) between two time points of cognitive evaluation (Cullen et al., 2018). A study in Sweden, where NO_x levels are rather low and lower than what estimated for our population, did not show any significant association between NO_x exposure and episodic memory decline (Oudin et al., 2017). Conversely, in the WHICAP study, where NO_2 exposure was higher than in our study (mean: 31.88 ppb), worse decline in both global cognition and specific functions was observed in participants living in areas with higher NO_2 levels (Kulick et al., 2020). Evidence on BC and cognitive decline is even scarcer, but one study on Puerto Rican older adults in Greater Boston found consistent associations between BC exposure and accelerated decline in several cognitive domains, such as memory, visuo-spatial memory and executive functions/verbal fluency (Wurth et al., 2018).

The heterogeneity observed in the literature can also be related to the diversity of air pollution exposures. For instance, PM chemical composition can vary in function of the emission source, and consequently also its toxicity. Therefore, PM effects on the central nervous system can be of different magnitude even for similar levels of exposure, if only PM mass and not composition is evaluated, as done in most studies. Another reason for the result heterogeneity could be that co-exposure to multiple pollutants is usually not considered, although people are generally exposed to a mixture of different pollutants.

The present study has many strengths. Data were from a large cohort (the Three-City study) with a substantial follow-up duration (12 years). The regular assessment of cognitive performance by trained psychologists, using different and complementary cognitive tests, ensured a qualitative evaluation of both global cognition and specific cognitive functions over time. The participants' exposure could be estimated at their residential address using fine-scale LUR models with good performance. When modeling cognitive decline, time-by-covariate interactions were taken into account. As highlighted previously (Power et al., 2016), it is important to add these terms when covariates can influence cognitive decline.

Some limitations of our study should also be considered. Selection bias cannot be ruled out because people excluded from the analysis had worse cognitive test performance at baseline. Moreover, sensitivity analyses after multiple imputation did not corroborate the statistical significance of our main result. Therefore, we cannot exclude that our main result might be biased because of selection at inclusion in the study. How selection could have influenced that result is difficult to determine: we probably excluded mainly individuals from deprived neighborhoods but we cannot predict if deprived neighborhoods were more or less exposed to air pollution. However, despite attenuation of the effect after imputation, the direction of the association remained the same. On the contrary, sensitivity analyses accounting for attrition bias did not invalidate the significant association found in the main analyses between $PM_{2.5}$ and MMSE performance decline.

As no information on anterior address(es) was available, the 5 years before the baseline visit was defined as the exposure window.

Participants who had moved during the 5 years before the baseline visit were excluded, and the others had a stable residence because they had lived at their baseline address for 27 years, on average. Therefore, older exposures should be correlated with our exposure window. However, we cannot be sure that exposure to the three pollutants did not change during the follow-up, as we had not enough data on residence change after the baseline visit. This could have led to information bias via differential exposure misclassification, especially if participants moved to care homes because of worsened cognitive health. As NO_2 and BC are related to traffic, their levels could be more variable in an urban environment; if someone move away from a traffic area for instance. Thus, differential exposure misclassification related to change in residence could have been more pronounced for NO_2 and BC, but it remains difficult for us to predict in what direction it could have influenced our results. Combined with the lower performance of the NO_2 and BC LUR models, which could have resulted in non-differential misclassification and therefore associations tending towards the null, this could partly explain our weaker results for these two pollutants.

Finally, the back extrapolation could have led to exposure misclassification for our exposure period, because extrapolation coefficients were available at the regional level but not at the individual level. However, it is likely that misclassification would be non-differential, leading estimations toward the null.

5. Conclusions

This study in a French cohort of older adults showed that exposure to $PM_{2.5}$, but not to NO_2 and BC, may be associated with accelerated decline in global cognition, but not in specific cognitive domains. This study adds to a growing literature on $PM_{2.5}$ potential effects on cognition, but more research is needed on other ambient air pollutants.

CRediT authorship contribution statement

Jeanne Duchesne: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Laure-Anne Gutierrez:** Methodology, Writing – review & editing. **Isabelle Carrière:** Methodology, Writing – review & editing. **Thibault Mura:** Methodology, Writing – review & editing. **Jie Chen:** Methodology, Writing – review & editing. **Danielle Vienneau:** Methodology, Writing – review & editing. **Kees de Hoogh:** Methodology, Writing – review & editing. **Catherine Helmer:** Investigation, Writing – review & editing. **Bénédicte Jacquemin:** Funding acquisition, Investigation, Methodology, Writing – review & editing. **Claudine Berr:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing, Supervision. **Marion Mortamais:** Conceptualization, Funding acquisition, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107118.

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