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Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study

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ABSTRACT

Background: Emerging epidemiological evidence suggests a relationship between exposure to air pollution and dementia. However, most of the existing studies relied on health administrative databases for the diagnosis of dementia. In a large French population-based cohort (the 3C Study), we assessed the effects of particulate matter ≤2.5 μm (PM2.5), nitrogen dioxide (NO_2) and black carbon (BC) on the risk of dementia diagnosed with reliable tools.

Methods: Participants aged ≥65 years were recruited between 1999 and 2001 and followed for 12 years. At baseline and every 2 years, dementia was suspected on the basis of the neuropsychological and neurological examination and confirmed by an independent committee of clinicians. Exposure to NO_2, BC and PM2.5 at the participants' residential address was estimated using land use regression models. For each pollutant and year of follow-up, the 10-year moving average of past exposure was estimated. Multilevel spatial random-effects Cox proportional hazards models were used in which exposure was included as a time-varying variable. Analyses were adjusted for individual (age, sex, education, APOE4 genotype, health behaviours) and contextual (neighbourhood deprivation index) confounders.

Results: At baseline, the median age of the 7066 participants was 73.4 years, and 62% were women. The median follow-up duration was 10.0 years during which 791 participants developed dementia (n = 541 Alzheimer's disease (AD) and n = 155 vascular/mixed dementia (VaD)). The 10-year moving average of PM2.5 concentrations ranged from 14.6 to 31.3 μg/m^3.

PM2.5 concentration was positively associated with dementia risk: HR = 1.20, 95% CI (1.08–1.32) for all-cause dementia, 1.20 (1.09–1.32) for AD, and 1.33 (1.05–1.68) for VaD per 5 μg/m^3 PM2.5 increase. No association was detected between NO_2 or BC exposure and dementia risk.

Conclusion: In this large cohort of older adults, long-term PM2.5 exposure was associated with increased dementia incidence. Reducing PM2.5 emissions might lessen the burden of dementia in aging populations.

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1. Introduction

Dementia defines a group of neurological disorders in which deterioration of memory, thinking, behaviour and ability to perform everyday activities leads to disability and dependency. In older adults, the most common form of dementia is Alzheimer's disease (AD, 70% of cases), followed by mixed or vascular dementia (VaD) (Lobo et al., 2000). With nearly 10 million new cases per year (World Health Organization, 2020), dementia is a huge burden worldwide. As no effective treatment exists yet, the identification of modifiable risk factors that could be targeted by prevention strategies is an important public health challenge. This is particularly important for AD, in which the neurodegenerative process may begin at least 10 years before the onset of clinical symptoms (Amieva et al., 2008), thus potentially offering a wide temporal window to delay disease onset.

Emerging evidence suggests that air pollutants might contribute to the neurodegenerative pathology through oxidative stress, microglia overactivation, and neuroinflammation (Block and Calderón-Garcidueñas, 2009; Calderón-Garcidueñas et al., 2002). Moreover, epidemiological studies indicate that ambient air pollution might have a detrimental effect on cognitive function in aging populations (Kulick et al., 2020; Tzivian et al., 2017; Power et al., 2016). However, only few studies have assessed the link between dementia incidence and air pollutants, such as nitrogen oxides (NO_x, NO_2) and fine particulate matter (airborne solid and liquid particles smaller than 2.5 μm; PM2.5) (Grande et al., 2020; Oudin et al., 2016; Cacciottolo et al., 2017; Chen et al., 2017; Jung et al., 2015; Chang et al., 2014; Carey et al., 2018), and even fewer studies have investigated the effects of air pollution exposure on the risk of AD or VaD (Grande et al., 2020; Jung et al., 2015; Carey et al., 2018). Moreover, these studies present important methodological limitations. Indeed, most of them relied on population-based health administrative databases for the diagnosis of dementia, a method that is prone to classification bias (Chen et al., 2017; Jung et al., 2015; Chang et al., 2014; Carey et al., 2018). The rare longitudinal population-based studies with active search of dementia cases and validated diagnosis concerned only women (Cacciottolo et al., 2017) and small samples (Grande et al., 2020; Oudin et al., 2016).

As air pollution levels can be modified by public policies with benefits at the population level, it is important to precisely characterize the magnitude of the air pollution effects on dementia. In this study, we investigated the association between long-term exposure to air pollutants and incidence of dementia in older adults using reliable diagnostic tools in a large population-based cohort in France.

2. Methods

2.1. Study population

The Three-City Study (3C Study) is a longitudinal, population-based prospective cohort study of community-dwelling older adults (3C Study Group, 2003). Between March 1999 and March 2001, non-institutionalized, ≥65-year-old adults, registered in the electoral rolls of selected districts in Dijon, Bordeaux, and Montpellier (France) were invited to participate through a personal letter (acceptance rate = 37%). In total, 9294 participants were included. The baseline assessment and the following extensive follow-up visits performed every two years included standardized questionnaires, clinical examinations, and detailed cognitive evaluations.

Among the 9294 participants originally included, 9251 had a baseline residential address that could be geocoded. Among them, 214 participants with prevalent dementia at baseline and 823 participants who did not have any follow-up visit (at 2, 4, 7, 10, and 12 years after baseline) were excluded. Therefore, the present analyses were carried out on 7066 participants for whom complete and validated data on exposure to air pollution, dementia diagnosis, and covariates were available (Fig. 1).

The study protocol was approved by the Ethics Committee of the Hospital of Kremlin-Bicêtre and Sud-Méditerranée III. A written informed consent was obtained from all participants (consent for research).

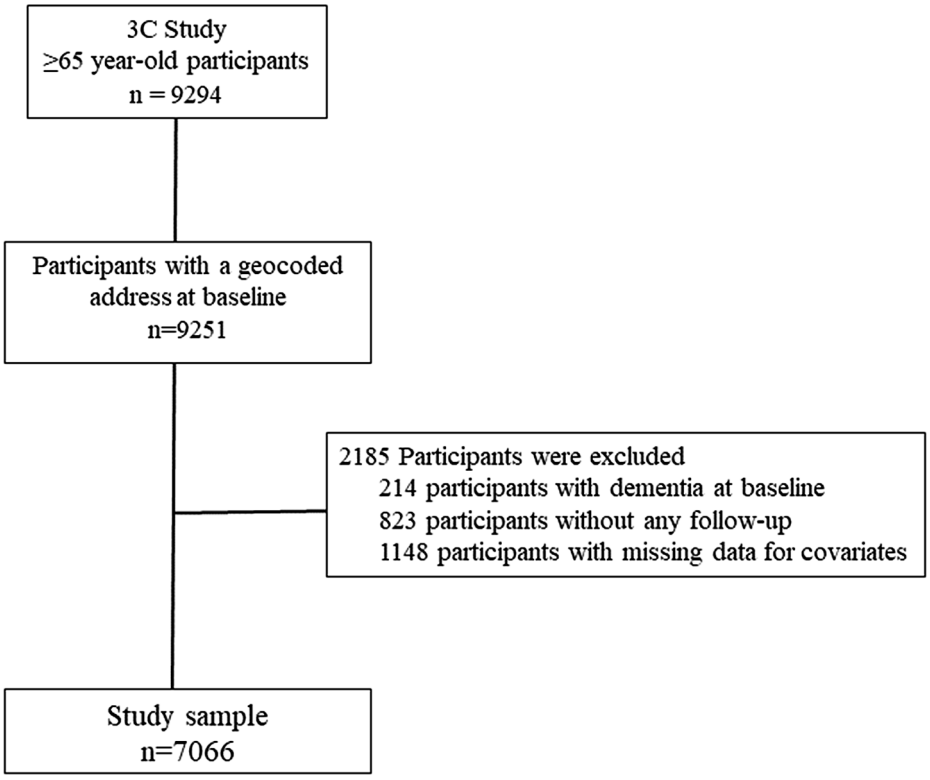

Fig. 1. Flowchart of the Three-City study with a 12-year follow-up.

2.2. Diagnosis of dementia

Dementia was diagnosed following a 3-step procedure (3C Study Group, 2003). First, at baseline and at each follow-up visit, a careful neuropsychological evaluation was carried out by trained psychologists. Second, all participants in Bordeaux and Montpellier were examined by a neurologist at baseline. Conversely, in Dijon, due to the larger number of participants, only those with suspected dementia, based on their neuropsychological performances, underwent neurological examination. During the follow-up visits, only participants with suspected dementia based on their extensive neuropsychological examination were seen by a neurologist, with the exception of the Montpellier centre where everybody had a neurological examination at each follow-up visit. Third, an independent committee of neurologists reviewed all potential cases of dementia to confirm the diagnosis and aetiology, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatry Association, 2000).

Cases of AD were classified according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association, and cases of mixed/vascular dementia according to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

In this study, all incident cases of all-cause dementia, AD, and vascular/mixed dementia (VaD) during the 12-year follow-up were considered.

2.3. Exposure to air pollution

Exposure to PM2.5, black carbon (BC), and NO_2 was estimated at the geocoded baseline residential address of each participant using hybrid land use regression (LUR) models (de Hoogh et al., 2018) that were developed for Western Europe within the framework of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE). Briefly, PM2.5 and NO_2 concentration data for the year 2010 derived from the European Environment Agency AirBase network that collects data recorded at routine monitoring stations (including traffic, industrial and underground sites). The annual mean BC concentrations (measured as PM2.5 absorbance based on reflectance measurement of the filters) for the 2009–2010 period were derived 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, distance to the sea, 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 PM2.5 and NO_2 measurements. The final models, described in detail by de Hoogh et al. (2018) explained 72%, 54% and 59% of the spatial variation in the measured concentrations of PM2.5, BC and NO_2, respectively. Models were for 100x100m grid cells across Western Europe (de Hoogh et al., 2018).

Then, the 2010 model estimates were extrapolated for the 1990–2012 period according to the method used in the ELAPSE study (de Hoogh et al., 2018). Backward and forward extrapolations were applied at the regional level (*i.e.* European Classification of Territorial Units for Statistics) to derive the exposures for the other years. This extrapolation was based on the annual mean estimates from the 26 × 26 km Danish Eulerian Hemispheric Model, previously downscaled from the original 50 × 50 km resolution using bilinear interpolation (Brandt et al., 2012).

2.4. Individual and contextual covariates at baseline

The covariates that could be potential confounders were pre-selected based on the review of literature data.

Socio-demographic variables included sex, age, study centre, and education level (primary education: ≤5 years; lower secondary education: up to 9 years; and higher secondary education: >9 years). Health behaviour variables included smoking habits (never/past or current smoker), 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 neighbourhood socioeconomic status was defined using a deprivation index based on the proportion of households without car, of tenants and single parents, unemployment rate, settlement index, and tax household income (Letellier et al., 2018) at the IRIS level (Ilots Regroupés pour l'Information Statistique), the finest spatial census unit (2000 residents per unit).

2.5. Statistical analysis

The relationships between dementia incidence and PM2.5, NO_2, and BC exposure levels were assessed using Cox proportional hazards models that included a marginal intra-municipality correlation, delayed entry, and age as the basic timescale. These models, which used a robust sandwich variance estimator, allow taking into account the correlations between individuals in the same municipality (n = 3 in Dijon and Montpellier, and n = 6 in Bordeaux). Participants without dementia who died or were lost to follow-up were censored at the last cognitive examination. The date of dementia onset was set as the midpoint between the last follow-up visit without dementia and the first one with dementia.

Exposure to air pollution was included as a time-varying variable. For each year of follow-up, the 10-year moving average of the past exposure to each pollutant was estimated for each participant. All models were single-pollutant models.

First, the crude association between air pollution exposure and risk of dementia (model 0) was investigated. Then, model 1 was adjusted for sex, education level, centre, APOE genotype, deprivation index, alcohol intake, and smoking habit. The proportional hazards assumption was verified by adding the cross-product of each variable with the logarithm of the time variable.

In an additional analysis, the potential effect modification (on the multiplicative scale) by sex, centre, education, APOE genotype, and deprivation index was assessed by including an interaction term with air pollutant.

The assumption of log-linearity for each pollutant was verified using restricted cubic spline functions with three to five knots. As no strong evidence of departure from linearity for the relation of any of the three pollutants was observed, the results of the proportional-hazards regression analyses were expressed as hazard ratios (HR) with 95% confidence intervals (CI) for every 5 $\mu g/m^3$ increase in PM2.5 or NO_2 levels, and for every 10^{-5}/m increase in BC level.

Analyses were performed with the SAS software, version 9.4 (SAS Institute).

2.6. Sensitivity analyses

Additional analyses were performed after adjusting for household income, family history of dementia (models 1a and 1b), and then for vascular risk factors (diabetes and history of vascular pathology, model 2), considered as mediators in the pathway between air pollution exposure and risk of dementia (Ilango et al., 2019). Model 2 was then adjusted for depressive symptomatology and physical activity (model 3). Analyses were also restricted to non-movers (by excluding participants who moved during the 10 years before baseline).

As more than 10% of the entire study population was excluded due to missing data, additional analyses were performed after imputing missing data using the fully conditional specification multiple imputation method (Liu and De, 2015). Finally, inverse probability weighting (IPW) was implemented to account for the potential attrition bias.

The multiple imputation and IPW procedures and the obtained

results are described in Supplemental Material.

3. Results

Among the 7066 participants at baseline, 791 incident cases of dementia were diagnosed during the 12 years of follow-up (incidence = 1.22 dementia cases per 100 person-years): 541 cases of AD (68%), 155 cases of VaD (20%), and 95 cases of other dementia types. During the study period, 1543 participants died (22%), and 1911 (27%) were lost to follow-up or refused to continue the study.

Table 1 describes the baseline characteristics of the 7066 participants in function of their dementia status. In the whole sample, the median (IQR) age was 73.4 (8.0) years, 62% were women, and 37% had more than 9 years of education. The median follow-up duration was 10.0 (6.9) years. Compared with participants without dementia, participants who developed dementia were significantly older, more frequently women, and with lower education level. They were also more likely to live in a deprived neighbourhood.

Compared with the study population, participants who were excluded from the initial sample were significantly older and more frequently men (Table S1).

Table 1
Participants' characteristics at baseline.

	All Participants	All-cause dementia cases over the 12-year follow-up		
	Total, n = 7066 n (%) or median (IQR)	Non-cases, n = 6275	Cases, n = 791	p-value[a]
Age at baseline, years	73.4 (8.0)	72. 9 (7.8)	77.1 (7.1)	<0.001
Duration of follow-up, years	10.0 (6.9)	10.5 (7.1)	6.7 (4.8)	<0.001
Sex, women	4359 (61.7%)	3842 (61.2%)	517 (65.4%)	0.024
Study centre				
Bordeaux	1616 (23.0%)	1338 (21.3%)	278 (35.2%)	<0.001
Dijon	4034 (57.0%)	3647 (58.1%)	387 (48.9%)	
Montpellier	1416 (20.0%)	1290 (20.6%)	126 (15.9%)	
Education				
Primary (≤5 years)	2323 (32.9%)	1971 (31.4%)	352 (44.5%)	<0.001
Lower secondary (5–9 years)	2108 (29.8%)	1925 (30.7%)	183 (23.1%)	
Higher secondary (>9 years)	2635 (37.3%)	2379 (37.9%)	256 (32.4%)	
Deprivation index	−0.27 (2.02)	−0.29 (1.99)	−0.16 (2.02)	0.006
APOE ε4 allele carriers	1397 (19.8%)	1185 (18.9%)	212 (26.8%)	<0.001
Smoking habits				
Never	4374 (61.9%)	3850 (61.3%)	524 (66.3%)	0.008
Past or current	2692 (38.1%)	2425 (38.7%)	267 (33.7%)	
Alcohol intake				
None	1438 (20.4%)	1257 (20.0%)	181 (22.9%)	0.094
Moderate	5067 (71.7%)	4510 (71.9%)	557 (70.4%)	
High	561 (7.9%)	508 (8.1%)	53 (6.7%)	

Abbreviations: APOE, apolipoprotein E; IQR, Interquartile Range.
The deprivation index was based on the proportion of households without car, tenants and single parents, unemployment rate, settlement index, and tax household income at the IRIS level (Ilots Regroupés pour l'Information Statistique), the finest spatial census unit (2000 residents per unit). Higher scores indicate more deprived neighbourhood areas (scores ranged from −4.19 to 10.75 in our study).
High alcohol intake was defined by an intake >36 g per day.
[a] Wilcoxon test for quantitative variables, and Chi2 test for qualitative variables.

All baseline home addresses were located in urban areas, as defined by the French National Statistics Institute (INSEE, https://www.insee.fr/en/metadonnees/definition/c1501), and 80% of participants had lived at that address for at least 10 years before enrolment. Fig. 2 shows the estimated annual mean concentrations of PM2.5, BC and NO_2 for the study participants during the 1990–2012 period. The mean individual exposures estimated at the participants' residential address for the 10 years before dementia onset for participants with incident dementia or before the date of censoring for participants who did not develop dementia were 21.9 (2.6) $\mu g/m^3$ for PM2.5, 2.4 (0.3) $\times 10^{-5}$/m for BC, and 34.2 (7.5) $\mu g/m^3$ for NO_2 (Table 2). PM2.5 exposure level was modestly correlated with NO_2 and BC levels (Pearson's correlations: 0.36 and 0.60). The exposure levels of BC and NO_2, two markers of vehicle exhaust, were strongly correlated (Pearson's correlation: 0.80).

The associations between air pollutant exposure and incidence of dementia are presented in Table 3. PM2.5 exposure level was positively associated with dementia risk in the crude (models 0) and adjusted models (models 1). Adjustment for sex, centre, education, deprivation index, APOE genotype and health behaviours (model 1) substantially decreased the effect size for all-cause dementia and AD. In model 1, a 5 $\mu g/m^3$ increase in PM2.5 level was associated with an increase by 20% of the risk of all-cause dementia [HR = 1.20, 95%CI (1.08–1.32)], by 20% for AD [HR = 1.20 (1.09–1.32)], and by 33% for VaD [HR = 1.33 (1.05–1.68)].

The effect of PM2.5 was not modified by sex, centre, education, APOE genotype, and deprivation index. No relationship was observed between NO_2 or BC exposure and risk of dementia (all causes), AD or VaD.

Sensitivity analyses showed that adjustment for household income, family dementia history (Table S2) or vascular risk factors (Table S3) did not change the results, but for the association between PM2.5 exposure and VaD risk that was no longer significant (Table S3).

Additional adjustments in model 3 (*i.e.* history of respiratory pathology, depressive symptomatology, and physical activity), exclusion of movers from the study population, and multiple imputation of missing data did not substantially change the results (Tables S3–S6).

The HR values obtained from the IPW analyses were slightly higher than those of the main analyses (HR = 1.42, 95%CI [1.30–1.56] per 5 $\mu g/m^3$ increase in PM2.5 levels for all-cause dementia), but NO_2 and BC were again not associated with the risk of dementia (Table S7).

4. Discussion

In this large population-based study of older adults living in urban areas, long-term exposure to PM2.5 was associated with increased risk of dementia incidence during the 12 years of follow-up. A 5 $\mu g/m^3$ increase in the mean exposure to PM2.5 in the last 10 years was associated with an increased risk of all-cause dementia by 20%, of AD by 20%, and of VaD by 33%, independently of socio-demographic and health behaviour variables, and APOE genotype. These long-term effects were observed for a chronic exposure to mean levels of PM2.5 that did not exceed the limit target value of 25 $\mu g/m^3$ established by the European Union in 2015 (Directive, 2008/50/EC). No significant NO_2 or BC effect on the risk of all-cause dementia, AD, or VaD was observed.

PM2.5 is of natural origin (*e.g.* wildfire smoke, pollen, volcanic ash) or from anthropogenic sources, mainly from fuel combustion (*e.g.* thermal power generation, incineration, domestic heating, and vehicles) (European Environment Agency, 2011). Our findings are in line with the hypothesis that among all air pollutants, PM2.5 is the most important inhaled toxicant in urban air, particularly for brain (González-Maciel et al., 2017). Experimental and animal studies reported that after inhalation, PM2.5 can directly reach the brain through the nasal pathway or through the systemic circulation by crossing the blood brain barrier (Genc et al., 2012), where it triggers inflammation and oxidative

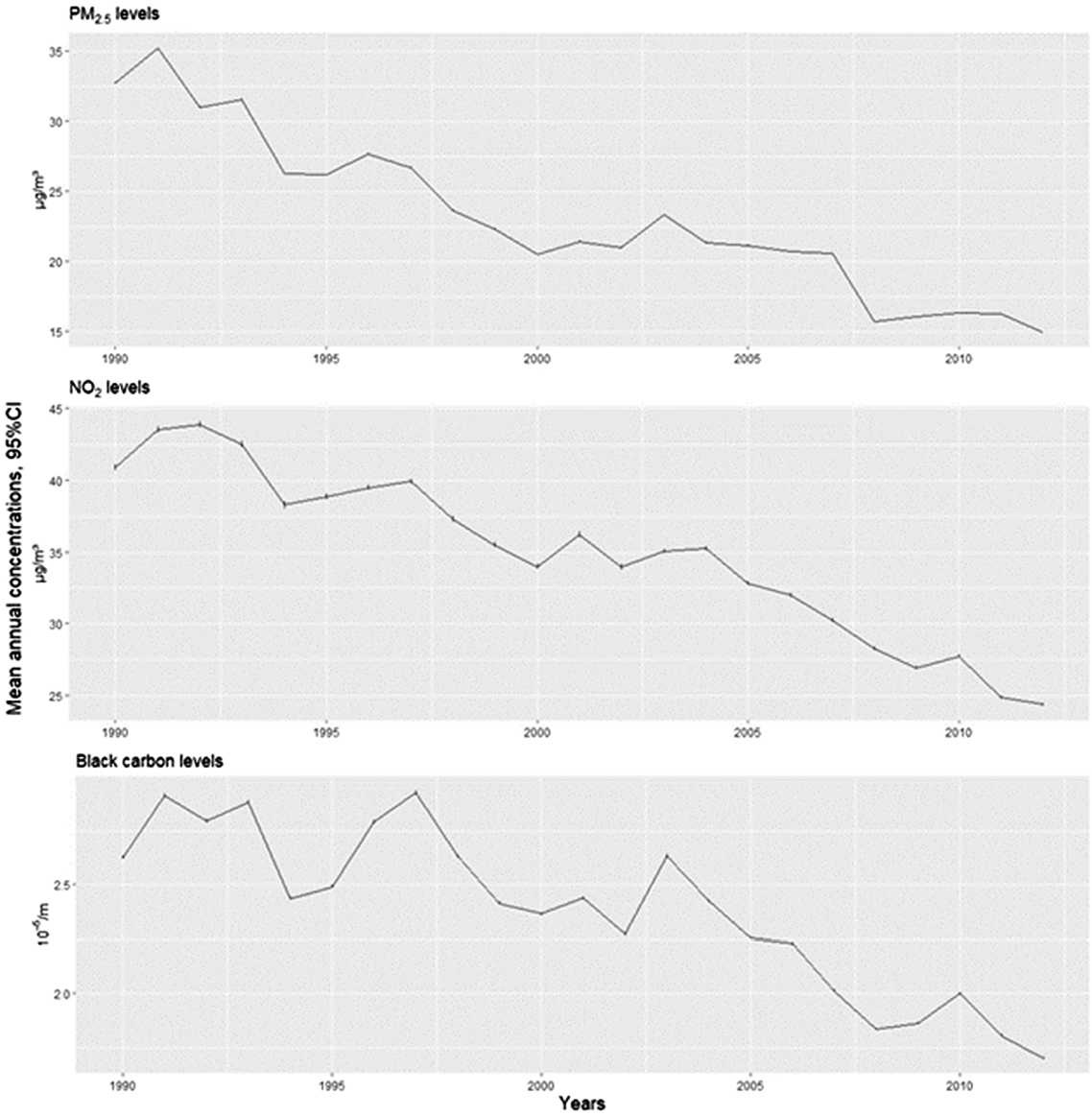

Fig. 2. Estimated annual PM2.5, black carbon and NO_2 concentrations at the participants' residential address for the 1990–2012 period.

Table 2
Participants' mean exposure levels to air pollutants during the 10 years before the event or censoring.

Air pollutants	Mean (SD)	Median	Range
$PM_{2.5}$ ($\mu g/m^3$)	21.9 (2.6)	21.3	14.6–31.3
BC ($10^{-5}/m$)	2.4 (0.3)	2.3	1.4–4.6
NO_2 ($\mu g/m^3$)	34.2 (7.5)	32.8	12.8–91.8

Abbreviations: PM, Particulate Matter; BC, Black Carbon; SD, Standard Deviation

stress directly in the cerebral tissues (Block and Calderón-Garcidueñas, 2009). Alternatively, increased levels of circulating cytokines, due to particulate matter-related systemic inflammation in the lungs, might have a peripheral impact on the brain (Genc et al., 2012). Finally, as exposure to PM2.5 has been associated with endothelial dysfunction (Krishnan et al., 2012) that may precipitate neurodegeneration, PM2.5 might impair cognition indirectly, even without reaching the brain parenchyma. In our study, vascular risk factors differently influenced the association between PM2.5 and dementia type, suggesting that the mechanisms that underlie the effects of this air pollutant may be distinct for AD and VaD.

The few previous epidemiological works, which relied on population-based health administrative databases, showed associations between exposure to PM2.5 and dementia risk. First, a cohort study (n = 96 000 older adults) in Taiwan observed a substantial increase of AD incidence (HR = 2.38) for each 4 $\mu g/m^3$ increase in PM2.5 levels (Jung et al., 2015). In the UK (n ≥ 130 000 inner and borough London residents), a 1 $\mu g/m^3$ increase in PM2.5 levels was associated with a 6% increase in all-cause dementia risk and a 10% increase in AD risk (Carey et al., 2018). In Ontario (Canada), where air pollutant concentrations are much lower than in Taiwan and London, a large population-based study that included all ≥55-year-old residents showed a 4% increase in dementia incidence per 5 $\mu g/m^3$ increase in PM2.5 levels (Chen et al., 2017).

Before the present analysis, only two longitudinal population-based studies investigated the relationship between PM2.5 exposure estimates and risk of dementia with repeated clinical evaluations to identify incident cases. Specifically, Cacciottolo et al. observed that in 3647 women residing in US areas with PM2.5 exposure exceeding the US Environmental Protection Agency standards (>12 $\mu g/m^3$), the risk of dementia increased by 92% (Cacciottolo et al., 2017). In the second

Table 3
Hazard ratios (95% CI) for the association between air pollutants[a] and dementia risk during the 12-year period of follow-up.

	N_{total}	N_{cases}	M0 HR (CI 95%)	p	M1 HR (CI 95%)	p
All-cause dementia						
$PM_{2.5}$[b]	7066	791	1.33 (1.17–1.50)	<0.001	1.20 (1.08–1.32)	<0.001
BC[c]	7066	791	0.91 (0.58–1.42)	0.677	1.10 (0.84–1.43)	0.503
NO_2[b]	7066	791	0.96 (0.88–1.04)	0.292	1.01 (0.95–1.08)	0.703
Alzheimer's disease						
$PM_{2.5}$[b]	6816[d]	541	1.33 (1.14–1.56)	<0.001	1.20 (1.09–1.32)	<0.001
BC[c]	6816[d]	541	0.82 (0.53–1.27)	0.378	1.00 (0.80–1.25)	0.991
NO_2[b]	6816[d]	541	0.94 (0.87–1.01)	0.076	1.01 (0.96–1.05)	0.777
Vascular or mixed dementia						
$PM_{2.5}$[b]	6430[e]	155	1.35 (1.03–1.77)	0.029	1.33 (1.05–1.68)	0.019
BC[c]	6430[e]	155	1.29 (0.65–2.55)	0.462	1.47 (0.80–2.68)	0.213
NO_2[b]	6430[e]	155	0.99 (0.87–1.13)	0.915	1.01 (0.88–1.17)	0.854

Abbreviations: APOE, apolipoprotein E; BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.
M0: Cox Proportional Hazards model with delayed entry with age as the basic timescale and birth as the time origin.
M1: M0 adjusted for sex, centre, education, APOE genotype, deprivation index, alcohol intake, and smoking habits.
[a] for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.
[b] for each 5 μg/m^3 increase.
[c] for each 10^{-5}/m increase.
[d] after exclusion of all incident cases of dementia other than AD.
[e] after exclusion of all incident cases of dementia other than vascular or mixed dementia.

study (n = 2927 older adults living in a district in central Stockholm, Sweden), an interquartile range increase of PM2.5 levels (0.88 μg/m^3) was associated with 50% and 66% increase in the risk of all-cause dementia and VaD, respectively (Grande et al., 2020).

Overall, the magnitude of the effect observed in the 3C study is relatively small compared with the previous studies. This can be explained by different reasons. First, population characteristics and methods of dementia diagnosis were heterogeneous among studies. Longitudinal population-based studies included small numbers of healthy volunteers. Conversely, studies that relied on health administrative databases had access to extremely large samples, probably more representative of the target population (Chen et al., 2017; Jung et al., 2015; Carey et al., 2018). However, dementia is poorly documented in medical records and death certificates (Taylor et al., 2009), and aetiological diagnoses are less reliable. Therefore, such methods of passive surveillance of the dementia status might underestimate the incident cases, leading to differential or non-differential misclassifications.

Another reason of heterogeneity is the difference in the exposure assessment methods across studies. The study in Taiwan (Jung et al., 2015) assigned averaged concentrations from the air quality routine monitoring measures, whereas the other studies, including ours, used predictions based on different statistical modelling approaches (Grande et al., 2020; Cacciottolo et al., 2017; Chen et al., 2017; Carey et al., 2018). Studies relying on health administrative databases exploited aggregated exposure estimates at the postcode level. On the other hand, the estimates of PM2.5 levels were at a finer spatial resolution level (almost the individual level) in our study and in the other two longitudinal population-based studies. Besides these exposure assessment issues that can lead to biased estimates, PM2.5 composition and levels vary among regions, and the intensity of the relationship between PM2.5 exposure and risk of dementia might change in a non-linear manner along a wide range of concentrations. The levels observed in the three French cities were close to those reported for Europe (European Environment Agency, 2011), but they were lower than those of the study in Taiwan (Jung et al., 2015) and higher than those of the Swedish study (Grande et al., 2020), which both reported larger effect size than ours.

Finally, most studies generated estimates of exposure averaged over 3–5 years before the year of dementia diagnosis (Grande et al., 2020; Cacciottolo et al., 2017; Chen et al., 2017), while another work considered exposure at baseline (Jung et al., 2015). As AD clinical manifestations represent the final stage of a long preclinical neuropathological process (Jack et al., 2013), our study used a more relevant 10-year exposure model that should overlap with the probable beginning of pathology accumulation and cognitive decline.

Our analysis did not highlight any significant relationship between dementia and long-term exposure to NO_2 and BC, while previous studies consistently reported associations between NO_2 and increased risk of dementia (Grande et al., 2020; Chen et al., 2017; Carey et al., 2018). This discrepancy cannot be explained by differences in exposure levels because the range of NO_2 concentration estimates was similar among studies. However, the correlation between NO_2 and PM2.5 observed in our study was weaker than what previously reported (Grande et al., 2020; Carey et al., 2018). This is in line with the hypothesis that PM2.5 could be the most deleterious air pollutant for the brain (González-Maciel et al., 2017). Moreover, our observations question NO_2 role in the risk of dementia independently of PM2.5. On the other hand, as the LUR models explained 59% and 72% of the spatial variation for NO_2 and PM2.5 concentrations, respectively, we cannot rule out a higher possibility of non-differential misclassification for NO_2 exposure. Consequently, the results for NO_2 might be more biased towards the null than those for PM2.5.

This study has several strengths. To date, this is the largest cohort study with repeated clinical evaluations that investigated the effect of air pollution exposure on the risk of dementia. The sample size and the follow-up length provided sufficient power to estimate precisely the magnitude of this effect on the main forms of dementia (*i.e.* AD and VaD). The dementia aetiological diagnoses were validated by an independent committee, thus limiting the classification bias.

The PM2.5 exposure estimates were provided by a fine-scale LUR model with a good predictive power.

Our study has some limitations. First, the 3C cohort participation acceptance rate was low and a risk of selection bias cannot be excluded.

Then, it was assumed that the participants' baseline residence address did not change during the entire follow-up period, based on the fact that participants seemed to be unwilling to move because, on average, they had lived at their baseline address for 24 years before enrolment. This assumption could have led to exposure misclassifications. As the probability of residential mobility might have been similar for most participants, this misclassification should be mostly of the non-differential type, thus giving HR values closer to the null value that they probably are. However, we cannot rule out that higher levels of air pollution exposure might be associated with higher frequency of chronic comorbid conditions that could motivate residential mobility. The influence of this potential differential misclassification on the results is difficult to predict.

Finally, participants who were excluded from the analysis were older, less educated and at higher risk of dementia than those included. The IPW analyses also revealed that the attrition bias probably led to an underestimation of the reported association between air pollution exposure and risk of dementia.

5. Conclusion

This study provides evidence that long-term exposure to PM2.5 is associated with all-cause dementia, AD, and VaD incidence. By suggesting that exposure to PM2.5 might be a modifiable risk factor of the

main forms of dementia in older adults, these results add to the emerging evidences highlighting the urgent need to re-evaluate public policies on PM2.5 emissions. Reducing anthropogenic PM2.5 emissions might have a preventive effect on dementia incidence at the population level.

CRediT authorship contribution statement

Marion Mortamais: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - original draft. **Laure-Anne Gutierrez:** Data curation, Formal analysis, Methodology, Writing - review & editing. **Kees de Hoogh:** Methodology, Writing - review & editing. **Jie Chen:** Methodology. **Danielle Vienneau:** Methodology, Writing - review & editing. **Isabelle Carrière:** Methodology, Writing - review & editing. **Noémie Letellier:** Methodology. **Catherine Hemer:** Investigation, Writing - review & editing. **Audrey Gabelle:** Methodology. **Thibault Mura:** Methodology. **Jordi Sunyer:** Writing - review & editing. **Tarik Benmarhnia:** Methodology, Writing - review & editing. **Bénédicte Jacquemin:** Funding acquisition, Investigation, Methodology, Writing - review & editing. **Claudine Berr:** Conceptualization, Funding acquisition, Investigation, 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.2020.106376.

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