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

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Words count:3619

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 micrometres (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 1999-2001 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 31.3µg/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 5µg/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.

KEYWORDS: cohort, dementia, incidence, elderly, air pollution, fine particulate matter, nitrogen dioxide, black carbon.

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) [1]. With nearly 10 million new cases per year [2], 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 [3], 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 [4,5]. Moreover, epidemiological studies indicate that ambient air pollution might have a detrimental effect on cognitive function in aging populations [6–8]. 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 micrometres; PM2.5) [9–15], and even fewer studies have investigated the effects of air pollution exposure on the risk of AD or VaD [9,13,15]. 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 [12–15]. The rare longitudinal population-based studies with active search of dementia cases and validated diagnosis concerned only women [11] and small samples [9,10].

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.

METHODS

Study population

The Three-City Study (3C Study) is a longitudinal, population-based prospective cohort study of community-dwelling older adults [16]. 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 (Figure 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).

Diagnosis of dementia

Dementia was diagnosed following a 3-step procedure [16]. 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.

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 [17] 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) [18].

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 [19] and the Danish Eulerian Hemispheric Model [20]), and satellite-derived PM2.5 and NO_2 measurements. The final models, described in detail by de Hoogh et al [17] 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 [17].

Then, the 2010 model estimates were extrapolated for the 1990–2012 period according to the method used in the ELAPSE study [17]. 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 x 26km Danish Eulerian Hemispheric Model, previously downscaled from the original 50 x 50km resolution using bilinear interpolation [21].

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 <36g per day, or heavy if ≥36g).

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 [22] at the IRIS level (Ilots Regroupés pour l'Information Statistique), the finest spatial census unit (2000 residents per unit).

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 5µg/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).

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 [23]. 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 [24]. 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.

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).

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. Figure 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) $x10^{-5}/m$ 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 5µg/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, S4 and 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 5µg/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).

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 5µg/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 µg/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) [25]. 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 [26]. 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 [27], where it triggers inflammation and oxidative stress directly in the cerebral tissues [4]. Alternatively, increased levels of circulating cytokines, due to particulate matter-related systemic inflammation in the lungs, might have a peripheral impact on the brain [27]. Finally, as exposure to PM2.5 has been associated with endothelial dysfunction [28] 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 μg/m^3 increase in PM2.5 levels [13]. In the UK (n ≥130 000 inner and borough London residents), a 1μg/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 [15]. 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 5μg/m^3 increase in PM2.5 levels [12].

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 μg/m^3), the risk of dementia increased by 92% [11]. In the second 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 [9].

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 [12,13,15]. However, dementia is poorly documented in medical records and death certificates [29], 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 [13] assigned averaged concentrations from the air quality routine monitoring measures, whereas the other studies, including ours, used predictions based on

different statistical modelling approaches [9,11,12,15]. 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 [25], but they were lower than those of the study in Taiwan [13] and higher than those of the Swedish study [9], which both reported larger effect size than ours.

Finally, most studies generated estimates of exposure averaged over 3 to 5 years before the year of dementia diagnosis [9,11,12], while another work considered exposure at baseline [13]. As AD clinical manifestations represent the final stage of a long preclinical neuropathological process [30], 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 [9,12,15]. 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 [9,15]. This is in line with the hypothesis that PM2.5 could be the most deleterious air pollutant for the brain [26]. 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. However, the observed dementia incidence (1.22 dementia cases per 100 person-years) is comparable to what reported for Europe and North America from the data of seven population-based cohorts [31]. Therefore, we can assume that the risk of selection bias is probably low, or at least not higher than in any other population-based cohort of older adults.

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.

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.

ACKNOWLEDGMENTS

We thank Elisabetta Andermarcher for English editing.

FUNDINGS

Marion Mortamais is supported by a post-doctoral fellowship from the Fondation de France (Allocation Postdoctorale n°engagement 00089836).

The 3C Study is carried out under a partnership agreement between the Institut National de la Santé et de la Recherche Medicale (INSERM), Victor-Segalen Bordeaux-2 University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale supported the preparation and initiation of the study. The 3C

The study was also supported by the Caisse Nationale Maladie des Travailleurs Salaries; Direction Générale de la Santé; MGEN; the Institut de la Longevité; Agence Nationale de la Recherche ANR PNRA 2006 (06-01-01) and Longvie 2007 (LVIE-003- 01); Agence Française de Sécurité Sanitaire des Produits de Santé; the Regional Governments of Aquitaine, Bourgogne, and Languedoc-Roussillon; the Fondation de France; the Ministry of Research-INSERM Programme Cohorts and collection of biological material; Fondation Plan Alzheimer" (FCS 2009-2012); the Caisse Nationale de Solidarité pour l'Autonomie (CNSA); Novartis ; and the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses, grant N° 2019/1/116).

The funders had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

DECLARATION OF INTEREST

The authors do not have any conflict of interest to declare**.**

REFERENCES

[1] Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4-9.

[2] World Health Organization. Dementia n.d. https://www.who.int/news-room/fact-sheets/detail/dementia (accessed July 24, 2020).

[3] Amieva H, Le Goff M, Millet X, Orgogozo JM, Pérès K, Barberger-Gateau P, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol 2008;64:492–8. https://doi.org/10.1002/ana.21509.

[4] Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci 2009;32:506–16. https://doi.org/10.1016/j.tins.2009.05.009.

[5] Calderón-Garcidueñas L, Azzarelli B, Acuna H, Garcia R, Gambling TM, Osnaya N, et al. Air pollution and brain damage. Toxicol Pathol 2002;30:373–89. https://doi.org/10.1080/01926230252929954.

[6] Kulick ER, Elkind MSV, Boehme AK, Joyce NR, Schupf N, Kaufman JD, et al. Long-term exposure to ambient air pollution, APOE-ε4 status, and cognitive decline in a cohort of older adults in northern Manhattan. Environ Int 2020;136:105440. https://doi.org/10.1016/j.envint.2019.105440.

[7] Tzivian L, Jokisch M, Winkler A, Weimar C, Hennig F, Sugiri D, et al. Associations of long-term exposure to air pollution and road traffic noise with cognitive function-An analysis of effect measure modification. Environ Int 2017;103:30–8. https://doi.org/10.1016/j.envint.2017.03.018.

[8] Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. Neurotoxicology 2016;56:235–53. https://doi.org/10.1016/j.neuro.2016.06.004.

[9] Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. JAMA Neurol 2020. https://doi.org/10.1001/jamaneurol.2019.4914.

[10] Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. Environ Health Perspect 2016;124:306–12. https://doi.org/10.1289/ehp.1408322.

[11] Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women

and to amyloidogenesis in experimental models. Transl Psychiatry 2017;7:e1022. https://doi.org/10.1038/tp.2016.280.

[12] Chen H, Kwong JC, Copes R, Hystad P, van Donkelaar A, Tu K, et al. Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study. Environ Int 2017;108:271–7. https://doi.org/10.1016/j.envint.2017.08.020.

[13] Jung C-R, Lin Y-T, Hwang B-F. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. J Alzheimers Dis JAD 2015;44:573–84. https://doi.org/10.3233/JAD-140855.

[14] Chang K-H, Chang M-Y, Muo C-H, Wu T-N, Chen C-Y, Kao C-H. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. PloS One 2014;9:e103078. https://doi.org/10.1371/journal.pone.0103078.

[15] Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open 2018;8:e022404. https://doi.org/10.1136/bmjopen-2018-022404.

[16] 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22:316–25. https://doi.org/10.1159/000072920.

[17] de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, et al. Spatial PM2.5, NO2, O3 and BC models for Western Europe - Evaluation of spatiotemporal stability. Environ Int 2018;120:81–92. https://doi.org/10.1016/j.envint.2018.07.036.

[18] Eeftens M, Tsai M-Y, Ampe C, Anwander B, Beelen R, Bellander T, et al. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 – Results of the ESCAPE project. Atmos Environ 2012;62:303–17. https://doi.org/10.1016/j.atmosenv.2012.08.038.

[19] Inness A, Baier F, Benedetti A, Bouarar I, Chabrillat S, Clark H, et al. The MACC reanalysis: an 8 yr data set of atmospheric composition. Atmospheric Chem Phys 2013;13:4073–109. https://doi.org/10.5194/acp-13-4073-2013.

[20] Brandt J, Silver JD, Frohn LM, Geels C, Gross A, Hansen AB, et al. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos Environ 2012;53:156–76. https://doi.org/10.1016/j.atmosenv.2012.01.011.

[21] Brandt J, Silver JD, Frohn LM, Geels C, Gross A, Hansen AB, et al. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos Environ 2012;53:156–76. https://doi.org/10.1016/j.atmosenv.2012.01.011.

[22] Letellier N, Gutierrez L-A, Carrière I, Gabelle A, Dartigues J-F, Dufouil C, et al. Sex-specific association between neighborhood characteristics and dementia: The Three-City cohort. Alzheimers Dement J Alzheimers Assoc 2018;14:473–82. https://doi.org/10.1016/j.jalz.2017.09.015.

[23] Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. Int J Epidemiol 2019. https://doi.org/10.1093/ije/dyz154.

[24] Liu Y, De A. Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. Int J Stat Med Res 2015;4:287–95. https://doi.org/10.6000/1929-6029.2015.04.03.7.

[25] European Environment Agency. Air quality in Europe: 2011 report. 2011.

[26] González-Maciel A, Reynoso-Robles R, Torres-Jardón R, Mukherjee PS, Calderón-Garcidueñas L. Combustion-Derived Nanoparticles in Key Brain Target Cells and Organelles in Young Urbanites: Culprit Hidden in Plain Sight in Alzheimer's Disease Development. J Alzheimers Dis JAD 2017;59:189–208. https://doi.org/10.3233/JAD-170012.

[27] Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. J Toxicol 2012;2012:782462. https://doi.org/10.1155/2012/782462.

[28] Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, et al. Vascular responses to long- and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). J Am Coll Cardiol 2012;60:2158–66. https://doi.org/10.1016/j.jacc.2012.08.973.

[29] Taylor DH, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. J Alzheimers Dis JAD 2009;17:807–15. https://doi.org/10.3233/JAD-2009-1099.

[30] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16. https://doi.org/10.1016/S1474-4422(12)70291-0.

[31] Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. Neurology 2020;95:e519–31. https://doi.org/10.1212/WNL.0000000000010022.

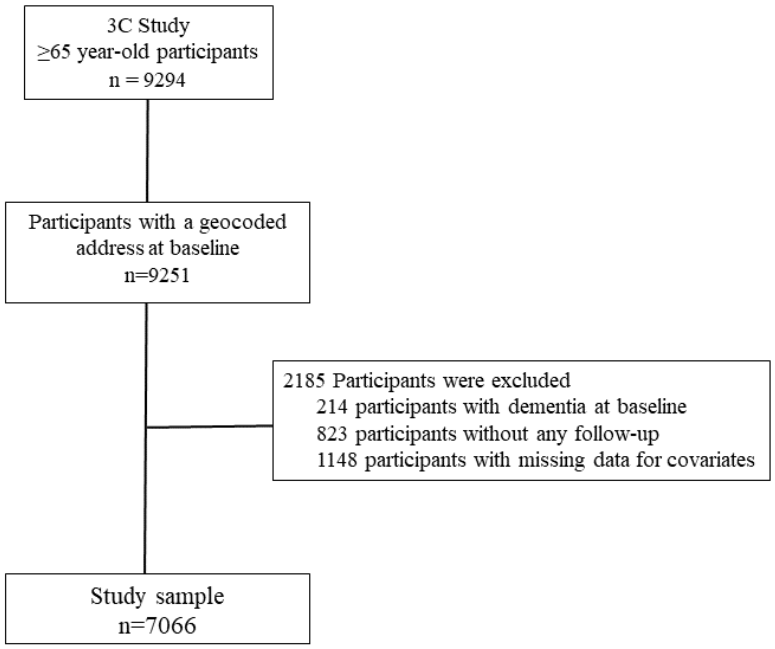

Figure 1. Flowchart of the Three-City study with a 12-year follow-up.

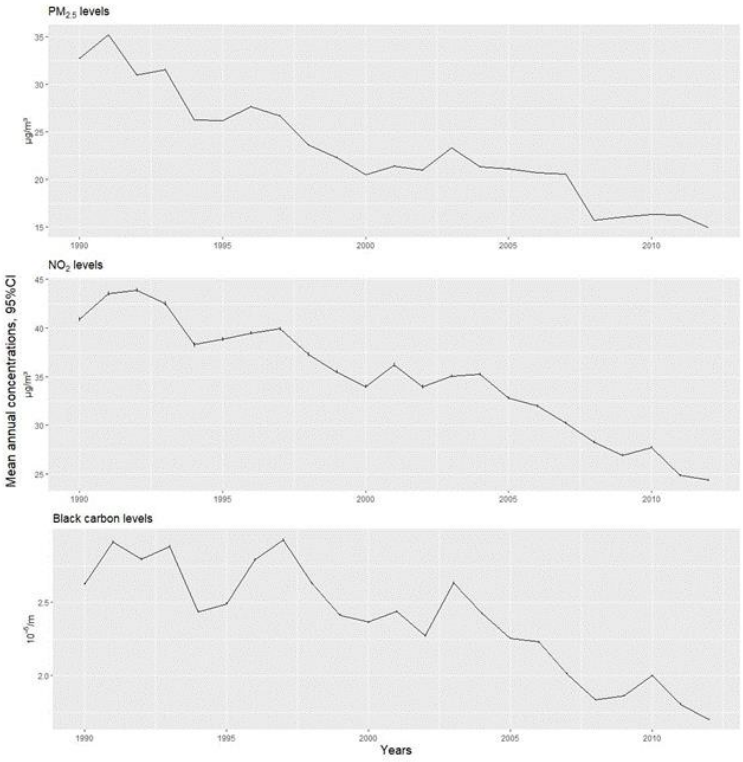

Figure 2. Estimated annual PM2.5, black carbon and NO_2 concentrations at the participants' residential address for the 1990-2012 period.

Table 1. Participants' characteristics at baseline

	All Participants	All-cause dementia cases over the 12-year follow-up		
	Total, n=7066	**Non-cases, n=6275**	**Cases, n=791**	**p-value[a]**
	n (%) or median (IQR)			
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%)	

[a] Wilcoxon test for quantitative variables, and Chi2 test for qualitative variables.

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 >36g per day.

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

Air pollutants	Mean (SD)	Median	Range
$PM_{2.5}$ (μg/m3)	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 (μg/m3)	34.2 (7.5)	32.8	12.8 – 91.8

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

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

			M0		M1	
	N_{total}	N_{cases}	HR (CI 95%)	p	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.

[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 5μg/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

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.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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

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Marion Mortamais: Conceptualization, Methodology, Writing-Original draft**. Laure-Anne Gutierrez**: Data curation, statistical analyses. **Kees de Hoogh, Jie Chen, and Danielle Vienneau** : Exposure estimation, Validation, Reviewing and editing. **Isabelle Carrière**: statistical analyses, reviewing and editing. **Noémie Letellier, Catherine Helmer, Audrey Gabelle, and Thibault Mura:** methodology, reviewing &editing. **Tarik Benmarhnia**: methodology, reviewing and editing**. Bénédicte Jacquemin**: conceptualization, methodology and Reviewing and editing. **Claudine Berr:** Supervision, Reviewing and Editing.