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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  $\leq 2.5$  micrometres (PM<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>) and black carbon (BC) on the risk of dementia diagnosed with reliable tools.

### Methods

Participants aged  $\geq 65$  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<sub>2</sub>, BC and PM<sub>2.5</sub> 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 PM<sub>2.5</sub> concentrations ranged from 14.6 to 31.3  $\mu\text{g}/\text{m}^3$ .

PM<sub>2.5</sub> 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  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> increase. No association was detected between NO<sub>2</sub> or BC exposure and dementia risk.

### Conclusion

In this large cohort of older adults, long-term PM<sub>2.5</sub> exposure was associated with increased dementia incidence. Reducing PM<sub>2.5</sub> emissions might lessen the burden of dementia in aging populations.

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

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## 1 INTRODUCTION

2 Dementia defines a group of neurological disorders in which deterioration of memory, thinking,  
3 behaviour and ability to perform everyday activities leads to disability and dependency. In older  
4 adults, the most common form of dementia is Alzheimer's disease (AD, 70% of cases), followed  
5 by mixed or vascular dementia (VaD) [1]. With nearly 10 million new cases per year [2], dementia  
6 is a huge burden worldwide. As no effective treatment exists yet, the identification of modifiable  
7 risk factors that could be targeted by prevention strategies is an important public health challenge.  
8 This is particularly important for AD, in which the neurodegenerative process may begin at least  
9 10 years before the onset of clinical symptoms [3], thus potentially offering a wide temporal  
10 window to delay disease onset.

11 Emerging evidence suggests that air pollutants might contribute to the neurodegenerative  
12 pathology through oxidative stress, microglia overactivation, and neuroinflammation [4,5].  
13 Moreover, epidemiological studies indicate that ambient air pollution might have a detrimental  
14 effect on cognitive function in aging populations [6–8]. However, only few studies have assessed  
15 the link between dementia incidence and air pollutants, such as nitrogen oxides (NO<sub>x</sub>, NO<sub>2</sub>) and  
16 fine particulate matter (airborne solid and liquid particles smaller than 2.5 micrometres; PM<sub>2.5</sub>)  
17 [9–15], and even fewer studies have investigated the effects of air pollution exposure on the risk  
18 of AD or VaD [9,13,15]. Moreover, these studies present important methodological limitations.  
19 Indeed, most of them relied on population-based health administrative databases for the diagnosis  
20 of dementia, a method that is prone to classification bias [12–15]. The rare longitudinal  
21 population-based studies with active search of dementia cases and validated diagnosis concerned  
22 only women [11] and small samples [9,10].

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

## 29 **METHODS**

### 30 **Study population**

31 The Three-City Study (3C Study) is a longitudinal, population-based prospective cohort study of  
32 community-dwelling older adults [16]. Between March 1999 and March 2001, non-  
33 institutionalized,  $\geq 65$ -year-old adults, registered in the electoral rolls of selected districts in  
34 Dijon, Bordeaux, and Montpellier (France) were invited to participate through a personal letter  
35 (acceptance rate = 37%). In total, 9294 participants were included. The baseline assessment and  
36 the following extensive follow-up visits performed every two years included standardized  
37 questionnaires, clinical examinations, and detailed cognitive evaluations.

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

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

### 48 **Diagnosis of dementia**

49 Dementia was diagnosed following a 3-step procedure [16]. First, at baseline and at each follow-  
50 up visit, a careful neuropsychological evaluation was carried out by trained psychologists.  
51 Second, all participants in Bordeaux and Montpellier were examined by a neurologist at baseline.  
52 Conversely, in Dijon, due to the larger number of participants, only those with suspected  
53 dementia, based on their neuropsychological performances, underwent neurological examination.  
54 During the follow-up visits, only participants with suspected dementia based on their extensive  
55 neuropsychological examination were seen by a neurologist, with the exception of the Montpellier

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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 PM<sub>2.5</sub>, black carbon (BC), and NO<sub>2</sub> 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, PM<sub>2.5</sub> and NO<sub>2</sub> 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 PM<sub>2.5</sub> 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 PM<sub>2.5</sub> and NO<sub>2</sub> 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

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2 83 concentrations of PM<sub>2.5</sub>, BC and NO<sub>2</sub>, respectively. Models were for 100x100m grid cells across  
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4 84 Western Europe [17].

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7 86 Then, the 2010 model estimates were extrapolated for the 1990–2012 period according to the  
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9 87 method used in the ELAPSE study [17]. Backward and forward extrapolations were applied at  
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11 88 the regional level (*i.e.* European Classification of Territorial Units for Statistics) to derive the  
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13 89 exposures for the other years. This extrapolation was based on the annual mean estimates from  
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15 90 the 26 x 26km Danish Eulerian Hemispheric Model, previously downscaled from the original 50  
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17 91 x 50km resolution using bilinear interpolation [21].  
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### 23 92 24 93 **Individual and contextual covariates at baseline**

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27 94 The covariates that could be potential confounders were pre-selected based on the review of  
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29 95 literature data.

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31 96 Socio-demographic variables included sex, age, study centre, and education level (primary  
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33 97 education: ≤5 years; lower secondary education: up to 9 years; and higher secondary education:  
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35 98 >9 years). Health behaviour variables included smoking habits (never/past or current smoker),  
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37 99 alcohol intake (none, moderate if <36g per day, or heavy if ≥36g).

40 100 APOEε4 carrier was defined as the presence of at least one ε4 allele.

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42 101 For each participant, the contextual neighbourhood socioeconomic status was defined using a  
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44 102 deprivation index based on the proportion of households without car, of tenants and single parents,  
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46 103 unemployment rate, settlement index, and tax household income [22] at the IRIS level (Ilots  
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48 104 Regroupés pour l'Information Statistique), the finest spatial census unit (2000 residents per unit).

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### 52 106 **Statistical analysis**

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57 107 The relationships between dementia incidence and PM<sub>2.5</sub>, NO<sub>2</sub>, and BC exposure levels were  
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59 108 assessed using Cox proportional hazards models that included a marginal intra-municipality  
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109 correlation, delayed entry, and age as the basic timescale. These models, which used a robust  
110 sandwich variance estimator, allow taking into account the correlations between individuals in  
111 the same municipality (n=3 in Dijon and Montpellier, and n=6 in Bordeaux). Participants without  
112 dementia who died or were lost to follow-up were censored at the last cognitive examination. The  
113 date of dementia onset was set as the midpoint between the last follow-up visit without dementia  
114 and the first one with dementia.

115 Exposure to air pollution was included as a time-varying variable. For each year of follow-up, the  
116 10-year moving average of the past exposure to each pollutant was estimated for each participant.  
117 All models were single-pollutant models.

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

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

125 The assumption of log-linearity for each pollutant was verified using restricted cubic spline  
126 functions with three to five knots. As no strong evidence of departure from linearity for the  
127 relation of any of the three pollutants was observed, the results of the proportional-hazards  
128 regression analyses were expressed as hazard ratios (HR) with 95% confidence intervals (CI) for  
129 every 5 $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> or NO<sub>2</sub> levels, and for every 10<sup>-5</sup>/m increase in BC level.

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

131

132 Sensitivity analyses

133 Additional analyses were performed after adjusting for household income, family history of  
134 dementia (models 1a and 1b), and then for vascular risk factors (diabetes and history of vascular  
135 pathology, model 2), considered as mediators in the pathway between air pollution exposure and

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136 risk of dementia [23]. Model 2 was then adjusted for depressive symptomatology and physical  
137 activity (model 3). Analyses were also restricted to non-movers (by excluding participants who  
138 moved during the 10 years before baseline).

139 As more than 10% of the entire study population was excluded due to missing data, additional  
140 analyses were performed after imputing missing data using the fully conditional specification  
141 multiple imputation method [24]. Finally, inverse probability weighting (IPW) was implemented  
142 to account for the potential attrition bias.

143 The multiple imputation and IPW procedures and the obtained results are described in  
144 Supplemental Material.

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146 **RESULTS**

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3 147 Among the 7066 participants at baseline, 791 incident cases of dementia were diagnosed during  
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5 148 the 12 years of follow-up (incidence = 1.22 dementia cases per 100 person-years): 541 cases of  
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7 149 AD (68%), 155 cases of VaD (20%), and 95 cases of other dementia types. During the study  
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9 150 period, 1543 participants died (22%), and 1911 (27%) were lost to follow-up or refused to  
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11 151 continue the study.

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15 152 Table 1 describes the baseline characteristics of the 7066 participants in function of their dementia  
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17 153 status. In the whole sample, the median (IQR) age was 73.4 (8.0) years, 62% were women, and  
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19 154 37% had more than 9 years of education. The median follow-up duration was 10.0 (6.9) years.

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21 155 Compared with participants without dementia, participants who developed dementia were  
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23 156 significantly older, more frequently women, and with lower education level. They were also more  
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25 157 likely to live in a deprived neighbourhood.

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28 158 Compared with the study population, participants who were excluded from the initial sample were  
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30 159 significantly older and more frequently men (Table S1).

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35 161 All baseline home addresses were located in urban areas, as defined by the French National  
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37 162 Statistics Institute (INSEE, <https://www.insee.fr/en/metadonnees/definition/c1501>), and 80% of  
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39 163 participants had lived at that address for at least 10 years before enrolment. Figure 2 shows the  
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41 164 estimated annual mean concentrations of PM<sub>2.5</sub>, BC and NO<sub>2</sub> for the study participants during  
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43 165 the 1990-2012 period. The mean individual exposures estimated at the participants' residential  
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45 166 address for the 10 years before dementia onset for participants with incident dementia or before  
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47 167 the date of censoring for participants who did not develop dementia were 21.9 (2.6) µg/m<sup>3</sup> for  
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49 168 PM<sub>2.5</sub>, 2.4 (0.3) x10<sup>-5</sup>/m for BC, and 34.2 (7.5) µg/m<sup>3</sup> for NO<sub>2</sub> (Table 2). PM<sub>2.5</sub> exposure level  
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51 169 was modestly correlated with NO<sub>2</sub> and BC levels (Pearson's correlations: 0.36 and 0.60). The  
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53 170 exposure levels of BC and NO<sub>2</sub>, two markers of vehicle exhaust, were strongly correlated  
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55 171 (Pearson's correlation: 0.80).

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2 174 The associations between air pollutant exposure and incidence of dementia are presented in Table  
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4 175 3. PM<sub>2.5</sub> exposure level was positively associated with dementia risk in the crude (models 0) and  
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6 176 adjusted models (models 1). Adjustment for sex, centre, education, deprivation index, APOE  
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8 177 genotype and health behaviours (model 1) substantially decreased the effect size for all-cause  
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10 178 dementia and AD. In model 1, a 5µg/m<sup>3</sup> increase in PM<sub>2.5</sub> level was associated with an increase  
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12 179 by 20% of the risk of all-cause dementia [HR=1.20, 95%CI (1.08-1.32)], by 20% for AD  
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14 180 [HR=1.20 (1.09-1.32)], and by 33% for VaD [HR=1.33 (1.05 – 1.68)].

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17 181 The effect of PM<sub>2.5</sub> was not modified by sex, centre, education, APOE genotype, and deprivation  
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19 182 index. No relationship was observed between NO<sub>2</sub> or BC exposure and risk of dementia (all  
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21 183 causes), AD or VaD.

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24 184 Sensitivity analyses showed that adjustment for household income, family dementia history  
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26 185 (Table S2) or vascular risk factors (Table S3) did not change the results, but for the association  
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28 186 between PM<sub>2.5</sub> exposure and VaD risk that was no longer significant (Table S3).

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31 187 Additional adjustments in model 3 (*i.e.* history of respiratory pathology, depressive  
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33 188 symptomatology, and physical activity), exclusion of movers from the study population, and  
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35 189 multiple imputation of missing data did not substantially change the results (Tables S3, S4 and  
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37 190 S6).

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41 191 The HR values obtained from the IPW analyses were slightly higher than those of the main  
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43 192 analyses (HR=1.42, 95%CI [1.30-1.56] per 5µg/m<sup>3</sup> increase in PM<sub>2.5</sub> levels for all-cause  
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45 193 dementia), but NO<sub>2</sub> and BC were again not associated with the risk of dementia (Table S7).

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195 **DISCUSSION**

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3 196 In this large population-based study of older adults living in urban areas, long-term exposure to  
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5 197 PM2.5 was associated with increased risk of dementia incidence during the 12 years of follow-  
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7 198 up. A 5µg/m<sup>3</sup> increase in the mean exposure to PM2.5 in the last 10 years was associated with an  
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9 199 increased risk of all-cause dementia by 20%, of AD by 20%, and of VaD by 33%, independently  
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11 200 of socio-demographic and health behaviour variables, and APOE genotype. These long-term  
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13 201 effects were observed for a chronic exposure to mean levels of PM2.5 that did not exceed the  
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15 202 limit target value of 25 µg/m<sup>3</sup> established by the European Union in 2015 (Directive,  
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17 203 2008/50/EC). No significant NO<sub>2</sub> or BC effect on the risk of all-cause dementia, AD, or VaD was  
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19 204 observed.  
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25 206 PM2.5 is of natural origin (*e.g.* wildfire smoke, pollen, volcanic ash) or from anthropogenic  
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27 207 sources, mainly from fuel combustion (*e.g.* thermal power generation, incineration, domestic  
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29 208 heating, and vehicles) [25]. Our findings are in line with the hypothesis that among all air  
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31 209 pollutants, PM2.5 is the most important inhaled toxicant in urban air, particularly for brain [26].  
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33 210 Experimental and animal studies reported that after inhalation, PM2.5 can directly reach the brain  
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35 211 through the nasal pathway or through the systemic circulation by crossing the blood brain barrier  
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37 212 [27], where it triggers inflammation and oxidative stress directly in the cerebral tissues [4].  
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39 213 Alternatively, increased levels of circulating cytokines, due to particulate matter-related systemic  
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41 214 inflammation in the lungs, might have a peripheral impact on the brain [27]. Finally, as exposure  
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43 215 to PM2.5 has been associated with endothelial dysfunction [28] that may precipitate  
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45 216 neurodegeneration, PM2.5 might impair cognition indirectly, even without reaching the brain  
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47 217 parenchyma. In our study, vascular risk factors differently influenced the association between  
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49 218 PM2.5 and dementia type, suggesting that the mechanisms that underlie the effects of this air  
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51 219 pollutant may be distinct for AD and VaD.  
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56 220 The few previous epidemiological works, which relied on population-based health administrative  
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58 221 databases, showed associations between exposure to PM2.5 and dementia risk. First, a cohort  
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222 study (n=96 000 older adults) in Taiwan observed a substantial increase of AD incidence  
223 (HR=2.38) for each 4  $\mu\text{g}/\text{m}^3$  increase in PM2.5 levels [13]. In the UK (n  $\geq$ 130 000 inner and  
224 borough London residents), a 1 $\mu\text{g}/\text{m}^3$  increase in PM2.5 levels was associated with a 6% increase  
225 in all-cause dementia risk and a 10% increase in AD risk [15]. In Ontario (Canada), where air  
226 pollutant concentrations are much lower than in Taiwan and London, a large population-based  
227 study that included all  $\geq$ 55-year-old residents showed a 4% increase in dementia incidence per  
228 5 $\mu\text{g}/\text{m}^3$  increase in PM2.5 levels [12].

229 Before the present analysis, only two longitudinal population-based studies investigated the  
230 relationship between PM2.5 exposure estimates and risk of dementia with repeated clinical  
231 evaluations to identify incident cases. Specifically, Cacciottolo et al. observed that in 3647 women  
232 residing in US areas with PM2.5 exposure exceeding the US Environmental Protection Agency  
233 standards ( $>12 \mu\text{g}/\text{m}^3$ ), the risk of dementia increased by 92% [11]. In the second study (n = 2927  
234 older adults living in a district in central Stockholm, Sweden), an interquartile range increase of  
235 PM2.5 levels (0.88  $\mu\text{g}/\text{m}^3$ ) was associated with 50% and 66% increase in the risk of all-cause  
236 dementia and VaD, respectively [9].

237 Overall, the magnitude of the effect observed in the 3C study is relatively small compared with  
238 the previous studies. This can be explained by different reasons. First, population characteristics  
239 and methods of dementia diagnosis were heterogeneous among studies. Longitudinal population-  
240 based studies included small numbers of healthy volunteers. Conversely, studies that relied on  
241 health administrative databases had access to extremely large samples, probably more  
242 representative of the target population [12,13,15]. However, dementia is poorly documented in  
243 medical records and death certificates [29], and aetiological diagnoses are less reliable. Therefore,  
244 such methods of passive surveillance of the dementia status might underestimate the incident  
245 cases, leading to differential or non-differential misclassifications.

246 Another reason of heterogeneity is the difference in the exposure assessment methods across  
247 studies. The study in Taiwan [13] assigned averaged concentrations from the air quality routine  
248 monitoring measures, whereas the other studies, including ours, used predictions based on

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249 different statistical modelling approaches [9,11,12,15]. Studies relying on health administrative  
250 databases exploited aggregated exposure estimates at the postcode level. On the other hand, the  
251 estimates of PM<sub>2.5</sub> levels were at a finer spatial resolution level (almost the individual level) in  
252 our study and in the other two longitudinal population-based studies. Besides these exposure  
253 assessment issues that can lead to biased estimates, PM<sub>2.5</sub> composition and levels vary among  
254 regions, and the intensity of the relationship between PM<sub>2.5</sub> exposure and risk of dementia might  
255 change in a non-linear manner along a wide range of concentrations. The levels observed in the  
256 three French cities were close to those reported for Europe [25], but they were lower than those  
257 of the study in Taiwan [13] and higher than those of the Swedish study [9], which both reported  
258 larger effect size than ours.

259 Finally, most studies generated estimates of exposure averaged over 3 to 5 years before the year  
260 of dementia diagnosis [9,11,12], while another work considered exposure at baseline [13]. As AD  
261 clinical manifestations represent the final stage of a long preclinical neuropathological process  
262 [30], our study used a more relevant 10-year exposure model that should overlap with the probable  
263 beginning of pathology accumulation and cognitive decline.

264

265 Our analysis did not highlight any significant relationship between dementia and long-term  
266 exposure to NO<sub>2</sub> and BC, while previous studies consistently reported associations between NO<sub>2</sub>  
267 and increased risk of dementia [9,12,15]. This discrepancy cannot be explained by differences in  
268 exposure levels because the range of NO<sub>2</sub> concentration estimates was similar among studies.

269 However, the correlation between NO<sub>2</sub> and PM<sub>2.5</sub> observed in our study was weaker than what  
270 previously reported [9,15]. This is in line with the hypothesis that PM<sub>2.5</sub> could be the most  
271 deleterious air pollutant for the brain [26]. Moreover, our observations question NO<sub>2</sub> role in the  
272 risk of dementia independently of PM<sub>2.5</sub>. On the other hand, as the LUR models explained 59%  
273 and 72% of the spatial variation for NO<sub>2</sub> and PM<sub>2.5</sub> concentrations, respectively, we cannot rule  
274 out a higher possibility of non-differential misclassification for NO<sub>2</sub> exposure. Consequently, the  
275 results for NO<sub>2</sub> might be more biased towards the null than those for PM<sub>2.5</sub>.

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

283 The PM<sub>2.5</sub> exposure estimates were provided by a fine-scale LUR model with a good predictive  
284 power.

285  
286 Our study has some limitations. First, the 3C cohort participation acceptance rate was low.  
287 However, the observed dementia incidence (1.22 dementia cases per 100 person-years) is  
288 comparable to what reported for Europe and North America from the data of seven population-  
289 based cohorts [31]. Therefore, we can assume that the risk of selection bias is probably low, or at  
290 least not higher than in any other population-based cohort of older adults.

291 Then, it was assumed that the participants' baseline residence address did not change during the  
292 entire follow-up period, based on the fact that participants seemed to be unwilling to move  
293 because, on average, they had lived at their baseline address for 24 years before enrolment. This  
294 assumption could have led to exposure misclassifications. As the probability of residential  
295 mobility might have been similar for most participants, this misclassification should be mostly of  
296 the non-differential type, thus giving HR values closer to the null value that they probably are.

297 However, we cannot rule out that higher levels of air pollution exposure might be associated with  
298 higher frequency of chronic comorbid conditions that could motivate residential mobility. The  
299 influence of this potential differential misclassification on the results is difficult to predict.

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

304



305 **CONCLUSION**

1  
2 306 This study provides evidence that long-term exposure to PM2.5 is associated with all-cause  
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4 307 dementia, AD, and VaD incidence. By suggesting that exposure to PM2.5 might be a modifiable  
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6 308 risk factor of the main forms of dementia in older adults, these results add to the emerging  
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8 309 evidences highlighting the urgent need to re-evaluate public policies on PM2.5 emissions.  
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10 310 Reducing anthropogenic PM2.5 emissions might have a preventive effect on dementia incidence  
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12 311 at the population level.  
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## DECLARATION OF INTEREST

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

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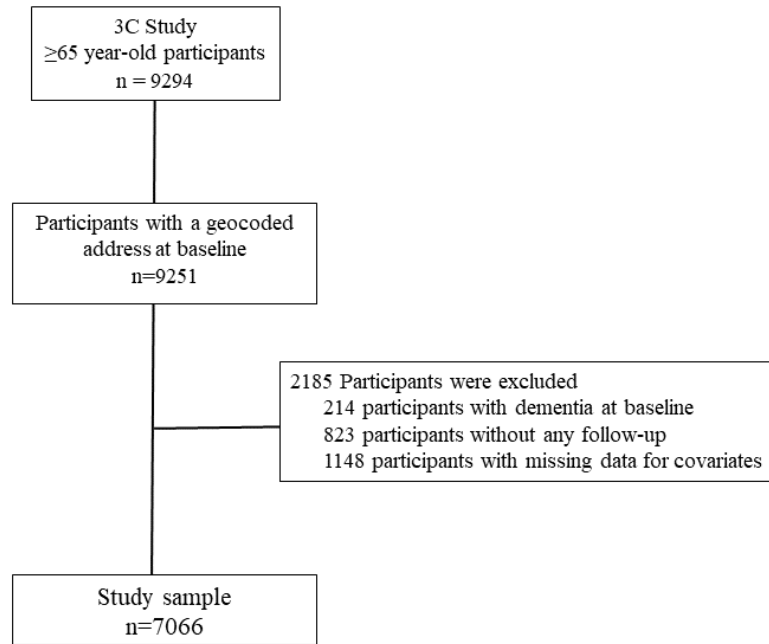


Figure 1. Flowchart of the Three-City study with a 12-year follow-up.

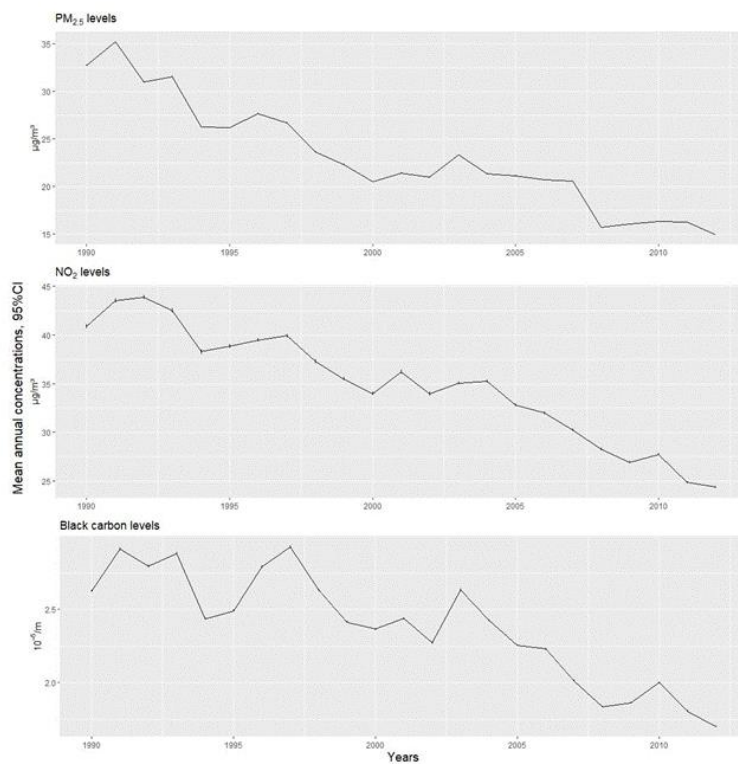


Figure 2. Estimated annual PM<sub>2.5</sub>, black carbon and NO<sub>2</sub> concentrations at the participants' residential address for the 1990-2012 period.

Table 1. Participants' characteristics at baseline

	All Participants		All-cause dementia cases over the 12-year follow-up		p-value <sup>a</sup>
	Total, n=7066	Non-cases, n=6275	Cases, n=791		
	n (%) or median ( IQR)				
<b>Age at baseline, years</b>	73.4 (8.0)	72.9 (7.8)	77.1 (7.1)	<0.001	
<b>Duration of follow-up, years</b>	10.0 (6.9)	10.5 (7.1)	6.7 (4.8)	<0.001	
<b>Sex, women</b>	4359 (61.7%)	3842 (61.2%)	517 (65.4%)	0.024	
<b>Study centre</b>					
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%)		
<b>Education</b>					
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%)		
<b>Deprivation index</b>	-0.27 (2.02)	-0.29 (1.99)	-0.16 (2.02)	0.006	
<b>APOE ε4 allele carriers</b>	1397 (19.8%)	1185 (18.9%)	212 (26.8%)	<0.001	
<b>Smoking habits</b>					
Never	4374 (61.9%)	3850 (61.3%)	524 (66.3%)	0.008	
Past or current	2692 (38.1%)	2425 (38.7%)	267 (33.7%)		
<b>Alcohol intake</b>					
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%)		

<sup>a</sup> 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.

<b>Air pollutants</b>	<b>Mean (SD)</b>	<b>Median</b>	<b>Range</b>
<b>PM<sub>2.5</sub></b> (µg/m <sup>3</sup> )	21.9 (2.6)	21.3	14.6 – 31.3
<b>BC</b> (10 <sup>-5</sup> /m)	2.4 (0.3)	2.3	1.4 – 4.6
<b>NO<sub>2</sub></b> (µg/m <sup>3</sup> )	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<sup>a</sup> and dementia risk during the 12-year period of follow-up

	<b>M0</b>				<b>M1</b>	
	<b>N<sub>total</sub></b>	<b>N<sub>cases</sub></b>	<b>HR (CI 95%)</b>	<b>p</b>	<b>HR (CI 95%)</b>	<b>p</b>
<b>All-cause dementia</b>						
PM <sub>2.5</sub> <sup>b</sup>	7066	791	1.33 (1.17-1.50)	<0.001	1.20 (1.08-1.32)	<0.001
BC <sup>c</sup>	7066	791	0.91 (0.58-1.42)	0.677	1.10 (0.84-1.43)	0.503
NO <sub>2</sub> <sup>b</sup>	7066	791	0.96 (0.88-1.04)	0.292	1.01 (0.95-1.08)	0.703
<b>Alzheimer's disease</b>						
PM <sub>2.5</sub> <sup>b</sup>	6816 <sup>d</sup>	541	1.33 (1.14 – 1.56)	<0.001	1.20 (1.09 – 1.32)	<0.001
BC <sup>c</sup>	6816 <sup>d</sup>	541	0.82 (0.53 – 1.27)	0.378	1.00 (0.80 – 1.25)	0.991
NO <sub>2</sub> <sup>b</sup>	6816 <sup>d</sup>	541	0.94 (0.87 – 1.01)	0.076	1.01 (0.96 – 1.05)	0.777
<b>Vascular or mixed dementia</b>						
PM <sub>2.5</sub> <sup>b</sup>	6430 <sup>e</sup>	155	1.35 (1.03 – 1.77)	0.029	1.33 (1.05 – 1.68)	0.019
BC <sup>c</sup>	6430 <sup>e</sup>	155	1.29 (0.65 – 2.55)	0.462	1.47 (0.80 – 2.68)	0.213
NO <sub>2</sub> <sup>b</sup>	6430 <sup>e</sup>	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.

<sup>a</sup> for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.

<sup>b</sup> for each 5µg/m<sup>3</sup> increase

<sup>c</sup> for each 10<sup>-5</sup>/m increase

<sup>d</sup> after exclusion of all incident cases of dementia other than AD

<sup>e</sup> 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.

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**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.



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