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**Air quality improvement and incident dementia: effects of observed and hypothetical reductions in air pollutant using parametric g-computation**

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## **ABSTRACT**

**INTRODUCTION:** No evidence exists about the impact of air pollution reduction on incidence of dementia. The aim was to quantify how air quality improvement leads to dementia-incidence benefits.

**METHODS:** Among the French Three-City Cohort (12 years of follow-up), we used parametric g-computation to quantify the expected number of prevented dementia cases under different hypothetical interventions with PM<sub>2.5</sub> reductions.

**RESULTS:** Among 7051 participants, 789 participants developed dementia. The median PM<sub>2.5</sub> reduction between 1990 and 2000 was 12.2 (µg/m<sup>3</sup>). Such reduction reduced the risk of all-type of dementia (hazard ratio (HR), 0.85; 95% confidence interval (CI), 0.76-0.95). If all study participants were enjoying a hypothetical reduction of more than 13.10 µg/m<sup>3</sup> (median reduction observed in the city of Montpellier), the rate difference was -0.37 (95%CI, -0.57- -0.17) and the rate ratio was 0.67 (95%CI, 0.50-0.84).

**DISCUSSION:** These findings highlight the possible substantial benefits of reducing air pollution in the prevention of dementia.

**Key words:** Air pollution, dementia, particulate matter, causal inference, g formula

## **BACKGROUND**

Air pollution represents a considerable global health threat (1,2). Ambient air pollution is a major cause of death and disease including heart disease, chronic respiratory disease, lung infections and cancer (1,3,4). More recently, studies have suggested air pollution may play a role in neurodegenerative processes, through increased oxidative stress and neuroinflammation (5). In this context, evidence of potentially harmful effects of inhaled air pollutants on the brain is rising (6,7). In parallel, some epidemiological studies have identified a positive association between exposure to air pollution and risk of developing dementia in different geographical contexts and populations (8–12). For example, a recent study found that, long-term PM<sub>2.5</sub> exposure (particulate matter measuring less than 2.5µm) was associated with increased dementia risk in the French 3C Study (13).

The 2020 Lancet commission on dementia prevention, intervention and care included, for the first time, air pollution in a list of major modifiable risk factors for dementia (14). Given that neurodegenerative process may begin at least 10 years before the onset of clinical symptoms (15), air pollution interventions during this lengthy critical period could be beneficial in delaying the onset of dementia. However, to the best of our knowledge, no empirical evidence exists about the impact of air pollution reduction on incidence of dementia. In this study, we assessed the effect of different scenarios of air pollution change. We used the parametric g-formula (also known as g-computation), a method that allowed us to estimate the risk of dementia that would have been observed had exposure been different from what cohort individuals had actually experienced. The g-formula methods are a class of causal inference methods based on standardization that can simulate different hypothetical dynamic

interventions on the exposure of interest (16–18). Previous studies have used these approaches to simulate complex interventions (19–21) for various settings including blood-pressure-lowering interventions and dementia (22,23).

In a context where more than 90% of people worldwide live in areas exceeding the WHO Guideline for healthy air and where the number of people living with dementia is projected to triple in the upcoming 30 years with ageing populations (24), it is crucial to take a multi-pronged approach to improve population health. Alongside developments in individual-level prevention strategies, population-level interventions such as regulations in air quality can offer longstanding benefits for a wide population. Quantifying the hypothetical change in dementia incidence given specific air pollution interventions can inform policy makers deciding between environmental regulations. The aim of this study is to quantify how observed reduction in PM<sub>2.5</sub> concentration leads to dementia-incidence benefits and simulate the benefits of hypothetical air quality improvement interventions on the reduction of dementia incidence, in a large French cohort.

## **METHODS**

### **Study population**

We used data from the 3C Study, a prospective cohort including 9294 noninstitutionalized participants aged 65 or older enrolled from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001. The main objective of the 3C Study was to assess the risk of dementia and cognitive impairment related to vascular factors (25). During the baseline assessment and at follow-up visits (performed 2, 4, 7, 10, and 12 years after baseline), standardized questionnaires, clinical examinations, and neuropsychological testing were conducted. All participants provided written consent, and the study protocol was approved by The Ethics Committees of the Hospital of Kremlin-Bicêtre and Sud-Méditerranée III.

## **Ascertainment of air pollution**

Exposure to PM<sub>2.5</sub> (µg/m<sup>3</sup>) was estimated at the geocoded baseline residential address of each participant using hybrid Land Use Regression (LUR) models (26). These models were developed for Western Europe within the framework of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) study (26). Models were applied to 100 × 100 m surfaces across Western Europe to allow for exposure assignment based on AirBase routine monitoring data, and incorporated satellite observations, dispersion model estimates, land use and traffic data. Details of evaluation has been described previously (26).

Briefly, West-European LUR models estimating annual mean PM<sub>2.5</sub> concentration for the year 2010 were derived from the European Environment Agency AirBase network that collects data recorded at routine monitoring stations (including traffic, industrial and underground sites). Then, the 2010 model estimates were extrapolated for the 1990–2012 period according to the method used in ELAPSE (26). Extrapolations were applied at the regional level to derive the exposures for the other years from the Danish Eulerian Hemispheric Model (27).

## **Diagnosis of dementia**

The protocol to diagnose dementia at baseline and during follow-up has been previously described (25). Briefly, at baseline and at each follow-up visit, cognitive function was assessed by a trained psychologist using neuropsychological tests (Mini-Mental State Examination, the Isaacs Set Test and the Benton Visual Retention Test). At each follow-up visit, based on neuropsychological performances, neurologists examined participants with suspected dementia to establish a provisional diagnosis (25). Diagnosis of dementia was then reviewed and validated according to the *DSM-IV* criteria by an independent committee of neurologists. Alzheimer disease (AD) cases were classified as possible or probable using the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and

Related Disorders Association criteria (28). Vascular/mixed dementia (VaD) cases were classified according to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences. For the present analyses, we considered all incident cases of all-cause dementia, and AD and VaD subtypes, over the 12-year follow-up.

### **Statistical analyses**

The baseline characteristics of the study population were described with median (interquartile range) and frequencies (%).

### ***Observed air pollution change***

In our main analysis, observed air pollution change was defined by subtracting the annual PM<sub>2.5</sub> concentrations in the baseline cohort (in 2000) from the annual PM<sub>2.5</sub> at 10 years before the inclusion (in 1990). To estimate the effect of this observed air pollution change on incident dementia, we fit a Cox proportional hazards model and an Aalen additive hazards model, with age as the time scale, estimating hazard ratios (HR), parameter estimates and 95% confidence intervals (CI) for every 1µg/m<sup>3</sup> decrease in PM<sub>2.5</sub> (29,30). Participants who died or were lost to follow-up without dementia were censored at the last cognitive examination. We included the following covariates in the models: sex; education level (primary education [ $\leq 5$  years], short secondary education [5-9 years], or upper secondary education [ $> 9$  years]); apolipoprotein E $\epsilon$ 4 (APOE $\epsilon$ 4) carrier status; deprivation index (previously calculated at the iris level, the finest French spatial census unit (31)); alcohol intake (none, moderate if  $< 36$ g per day, or heavy if  $\geq 36$ g (32)); and smoking habit (never/ex or current smoker). We considered spatial clustering by incorporating census iris level as a random effect for the intercept. We tested the proportional hazards assumption of Cox regressions based on the distribution of Schoenfeld residuals.

### ***Hypothetical interventions: G formula***



G formula (or g-computation) is part of Robins' generalized methods and has been previously described (33). Application of the G formula contrasts potential outcomes (difference or ratio) by modeling the joint density of the observed data to generate potential outcomes under different exposure scenarios (34). The method is an extension of standardization to a time-varying framework and allows estimation of population average risk under hypothetical exposure scenarios that may differ from what is observed. Counterfactual risk (on both absolute and relative scales) was estimated under a series of hypothetical scenarios (see details below).

We considered three types of interventions with more dramatic PM<sub>2.5</sub> reductions that could have been implemented during the 10 years prior to enrollment (Figure 1). First, we considered a hypothetical intervention with limits set at the values corresponding to the 10<sup>th</sup> (11.52 µg/m<sup>3</sup>), 25<sup>th</sup> (11.91 µg/m<sup>3</sup>), 50<sup>th</sup> (12.17 µg/m<sup>3</sup>) and 75<sup>th</sup> (12.61 µg/m<sup>3</sup>) percentiles of the observed distribution of PM<sub>2.5</sub> change between 1990 and 2000. Second, we considered a hypothetical intervention where PM<sub>2.5</sub> reduction would be at the level of what has been observed in the city of Montpellier (where the PM<sub>2.5</sub> reduction was the highest). In Montpellier, the median change in PM<sub>2.5</sub> concentration between 1990-2000 was 13.10 µg/m<sup>3</sup>. Third, we considered the limits of intervention based on the difference between the PM<sub>2.5</sub> European Union (EU) air quality standard (set at 20 µg/m<sup>3</sup>) and the observed PM<sub>2.5</sub> level in 2000. The limits of intervention corresponded to the quartiles of the distribution of this difference (0.42 to 0.68 µg/m<sup>3</sup> under 20 µg/m<sup>3</sup>, 0.69 to 0.84 under 20 µg/m<sup>3</sup>, 0.84 to 3.84 under 20 µg/m<sup>3</sup>). We applied the parametric g-formula to assess the effects that each of these hypothetical interventions to reduce long term PM<sub>2.5</sub> exposure would have on dementia risk.

We fit parametric models for the outcome (Cox proportional hazard model with age as the scale time), adjusted for sex, education level, APOE genotype, deprivation index, alcohol intake, and smoking habit. Following steps for the parametric g-formula described elsewhere (16), we then simulated dementia risk under each of the three specific interventions. Predicted dementia risk

under these interventions were compared with the category with the lower change in order to assess any potential reduction of dementia incidence. We estimated the rate difference (RD) by subtracting the dementia incidence under each hypothetical intervention from the category with the lower change and the rate ratio (RR) by dividing the dementia incidence under each hypothetical intervention from the category with the lower change. We repeated this analysis for each intervention of interest. We used bootstrap (200 iterations) to generate percentile-based 95% confidence intervals (CIs) for the rate differences and ratios.

We also considered PM<sub>2.5</sub> reduction as time-varying exposure and calculated adjusted survival curves using the parametric G formula (18). Such approach allows us to consider a moving average to PM<sub>2.5</sub> based on the timing on the diagnosis of dementia (as opposed to the cohort start date as done in the main analysis) and estimate effect estimates for each time point, as opposed to a traditional approach with Cox PH models for which Hazard Ratios represent an aggregated effect estimate across the study period (35).

We used a pooled logistic regression model for the outcome with similar covariates as in the model previously defined (and applying similar IPCW to consider censoring and death as a competing risk; see details below) and calculated the survival probability for each year according to the following potential intervention: what we would have observed had PM<sub>2.5</sub> reduction been set at the value 10.44 (75th of the observed reduction) in the 9 years before dementia onset. Such approach allowed us to estimate the cumulative dementia risk at each follow-up year standardizing on the identified confounders while allowing the natural course exposure to PM<sub>2.5</sub> to vary with time. We used the R package gfoRmula and the different steps required for this analysis are previously explained in details (36).

One of the co-authors (JD) independently replicated all the results. All analyses were carried out in SAS (version 9.4) and R (version 3.6.0).

### *Supplementary analyses*

In supplementary analyses, we assessed the observed change of PM<sub>2.5</sub> in three other ways. We considered PM<sub>2.5</sub> reduction as a categorical variable, using the categories defined for the hypothetical interventions. We calculated the PM<sub>2.5</sub> reduction by subtracting the average level of PM<sub>2.5</sub> concentration for the first two years (1990 and 1991) from the last two years (1999 and 2000). Then, we evaluated PM<sub>2.5</sub> reduction during the five years before the inclusion (between 1995 and 2000).

Additional analyses were performed to consider potential differential informed censoring at baseline and during follow-up. First, we calculated an inverse probability of censoring weights (IPCW) to consider informed attrition (including death, withdrawal, and lost to follow-up) (37). Specifically, a propensity score for the probability of being censored was calculated using logistic regression with age, sex, centre, education level, APOE genotype, deprivation index, alcohol intake, smoking habits, diabetes, history of vascular pathology, history of respiratory pathology as predictors. Second, participants excluded from the analytical sample at baseline were older, more often men, more often APOE ε4 allele carriers, with a lower level of education, and living in poorer neighborhoods (Table S1). To minimize the possibility of selection bias, we estimated the inverse of the probability of an individual being excluded from the analytical sample at baseline conditional on covariates listed above. These two complementary weights allowed to give a proportionally higher weight to individuals who are under-represented and proportionally lower weights to the most represented ones.

## **RESULTS**

### **Study Population**

A total of 7051 people without dementia at baseline, followed at least one time for dementia and with complete data for exposure and covariates was included in this analysis (4350 [62%])

women; median age, 73.4 years) (Figure S1). Among them, 789 (11.2%) developed dementia during the 12-year period (including 539 AD and 155 VD). Baseline characteristics of participants are detailed in Table 1.

### **Observed PM<sub>2.5</sub> change**

We observed a decreasing trend of PM<sub>2.5</sub> levels for each study center (Figure S2). In 1990, the median PM<sub>2.5</sub> concentration was 32.4 µg/m<sup>3</sup> (IQR range, 31.4-34.2) which declined to 19.9 µg/m<sup>3</sup> (IQR range, 19.3-21.6) in 2000. The median PM<sub>2.5</sub> reduction between 1990 and 2000, i.e. the 10 years prior to inclusion, was 12.2 (µg/m<sup>3</sup>). The highest PM<sub>2.5</sub> reduction among the study sites was observed in Montpellier where the median PM<sub>2.5</sub> reduction was 13.1 (µg/m<sup>3</sup>). This observed reduction was associated with a decreased risk of all-type of dementia (hazard ratio (HR) for every 1µg/m<sup>3</sup> decrease, 0.85; 95% confidence interval (CI), 0.76-0.95) and Alzheimer's disease (HR, 0.83; 95%CI, 0.72-0.94) after adjusting for identified confounders (Table 2). Approximately 197 less cases of all type of dementia and 164 of AD per 100 000 persons and year could be attributed to observed PM<sub>2.5</sub> reduction. No association was observed for VaD (HR, 0.94; 95%CI, 0.74-1.18).

The findings obtained using different PM<sub>2.5</sub> reduction definition are in line with the previous findings. Regarding the exposure assessment as a categorical variable, a PM<sub>2.5</sub> reduction equal or higher than 13.10 µg/m<sup>3</sup> between 1990 and 2000, as observed in the city of Montpellier, was associated with a decreased risk of all-type of dementia (HR, 0.66; 95%CI, 0.51-0.87) (Table S2). Although we did not identify any association for the other categories, we observed a reduction of the HR according to percentile of PM<sub>2.5</sub> reduction with a HR (95%CI) of 1.06 (0.82, 1.38) for a PM<sub>2.5</sub> reduction lower than 11.52 µg/m<sup>3</sup> (corresponding to the 10<sup>th</sup> percentile) and a HR (95%CI) of 0.82 (0.63, 1.07) for a PM<sub>2.5</sub> reduction equal or higher than 12.61 µg/m<sup>3</sup> (corresponding to the 75<sup>th</sup> percentile). When we assessed the PM<sub>2.5</sub> reduction by subtracting the average level of PM<sub>2.5</sub> concentration for the first two years (1990 and 1991) from the last two

years (1999 and 2000), we found that such reduction was associated with dementia risk (HR, 0.88; 95%CI, 0.79-0.97) (data not shown). Moreover, we found that the observed PM<sub>2.5</sub> reduction during the five years prior the inclusion (between 1995 and 2000) was also associated with a decreased risk of all-type of dementia (HR, 0.93; 95%CI, 0.87-0.99) and approximately 96 less cases of all type of dementia could be attributed to this PM<sub>2.5</sub> reduction (Table S3).

### **Hypothetical PM<sub>2.5</sub> change**

Using g-formula, even if the contrast were not significant for the first counterfactual scenario, it seems that dementia incidence would have been lower had PM<sub>2.5</sub> reduction been higher than what it was observed to be (Table 3). The counterfactual change in dementia risk after 12 years under a hypothetical intervention setting a reduction of over 12.61 µg/m<sup>3</sup> (corresponding to the 75th percentile of the exposure distribution) compared with a reduction lower than 11.52 µg/m<sup>3</sup> (10th of the exposure distribution) corresponded to a rate difference of -0.21 (95%CI, -0.50-0.07) and a rate ratio of 0.82 (95%CI, 0.60-1.03). The greatest risk reduction for dementia was achieved for compliance with a hypothetical reduction of more than 13.10 µg/m<sup>3</sup> (median reduction observed in the city of Montpellier), the rate difference was -0.37 (95%CI, -0.57- -0.17) and the rate ratio was 0.67 (95%CI, 0.50-0.84). The rate ratios and rate differences comparing the dementia risk under hypothetical exposure scenarios that were less dramatic, such as the difference between PM<sub>2.5</sub> at baseline and EU air quality standard, were not significant.

In supplementary analyses, the effect of PM<sub>2.5</sub> reduction on risk of all-type of dementia and AD were similar using IPCW to consider potential selection bias at baseline and attrition bias (Table S4). Even if for the first counterfactual intervention, the results were imprecise and weaker, the contrasts were globally consistent to sensitivity analyses and a clear benefit for the second hypothetical intervention was again highlighted (Montpellier scenario) (Table S5).

Based on adjusted survival curves accounting for time-varying PM<sub>2.5</sub> reduction (Figure S3), we found a benefit under a hypothetical intervention that set PM<sub>2.5</sub> reduction of 10 in the 9 years before dementia onset. Interestingly, the survival probability under this potential high PM<sub>2.5</sub> reduction was consistently higher than what we observed under the natural course (no change in exposure).

## **DISCUSSION**

In this large prospective cohort in older participants, reduction in levels of particulate matter measuring less than 2.5µm was associated with a decrease in dementia incidence. Observed reduction of PM<sub>2.5</sub> concentration between 1990-2000, during the 10 years prior to enrollment, was associated with reduced risk of all-type of dementia and Alzheimer's disease, on multiplicative and additive scales. We also estimated counterfactual risk under realistic hypothetical exposure reduction scenarios and compared it to the risk under lower exposure change on the ratio and difference scales. We found a clear benefit for the second scenario with the most dramatic reduction in PM<sub>2.5</sub>. Had the PM<sub>2.5</sub> reduction been higher than reduction observed in the city of Montpellier (13.10 µg/m<sup>3</sup>), dementia incidence would have been markedly lower. These results were consistent even when exposure was assessed differently and globally persistent to sensitivity analyses when considering censoring. Considering PM<sub>2.5</sub> reduction as time-varying exposure, the survival probability under a potential high PM<sub>2.5</sub> reduction was consistently higher than what we observed under the natural course (no change in exposure).

The observed PM<sub>2.5</sub> reduction was associated with a decreased risk of all-type of dementia and AD, but no association was observed for VaD. This can be due to the lower number of VaD cases (155 VaD cases vs. 539 AD cases). Moreover, although the association of PM<sub>2.5</sub> reduction and VaD was non-statistically significant, the HR seems to indicate a minor reduction of VaD. As cardiovascular disease could be an underlying mechanism between air pollution and

dementia (38,39), it could be particularly interesting to explore such association in cohort with higher number of VaD cases.

There is mounting evidence that exposure to air pollution may cause dementia (9,11,13,40–46), but to the best of our knowledge, this study quantifies for the first time the benefit of air quality improvement on dementia incidence using both observed and hypothetical changes in PM<sub>2.5</sub>. These results highlight that improvement of ambient air quality may be one intervention to reduce dementia incidence. Epidemiologists often wish to estimate the effects of realistic interventions on health to inform policy and clinical decisions. Using causal inference methods, under stated identification assumptions, can be helpful to emulate a target trial when using observational data (47). G-computation method is very useful to simulate hypothetical scenario to provide information for potential recommendations and inform policy decisions. G-computation was previously used to evaluate chemical neurotoxic effects in early life (48), the effects of lifestyle interventions on cognitive impairment and dementia risk in older adults (22,23) or to look at the positive public health impact of air quality improvements especially on childhood lung-function development and asthma incidence (49,50). In this study, we show that such analytical approach can be particularly useful to compare different air pollution mitigation strategies and quantify the expected benefits in the context of longitudinal settings.

The potential underlying mechanisms how air pollution affects brain are not well understood, yet several biological mechanisms are possible including oxidative stress, neuroinflammation and cardiovascular disease (5,38,51,52). Ultrafine particles may contribute to neurodegeneration through circulation and systemic inflammation, damaging the blood-brain barrier and activating the microglia (5,51,53). Postmortem studies indicate that particulates can be found in the olfactory bulb neurons and the frontal cortical areas of brain, and even nanoparticles were found associated with abnormal proteins (e.g. hallmarks of Alzheimer's disease), in children and young adults (53,54). Recent neuroimaging studies shows that ambient

air pollution may lead to structural changes in the brain such as reduced gray matter, cortical thinning and reduced subcortical volume (7,55,56).

This study has several strengths. First, we used data from a large and long-term prospective study. Second, the diagnosis of dementia was actively evaluated with standardized clinical assessment and a consensus-based clinical diagnosis. Third, we used both multiplicative and additive methods to evaluate the impact of observed PM<sub>2.5</sub> reduction on dementia risk to triangulate evidence and account for potential violations in either model assumptions. Finally, we utilized g-computation to estimate dementia incidence under counterfactual air pollution reduction scenarios, allowing to answer the question, “How would the incidence of dementia change if we could modify participant’s exposure to PM<sub>2.5</sub> between 1990-2000?”. We have relied on realistic air pollution reduction scenarios to inform policy decisions surrounding air quality. We considered informed attrition at follow-up and at baseline by coupling IPCW with our g-estimation models and we also considered time-varying exposure by providing adjusted survival curves.

Our study also has limitations. Exposure was assessed by LUR models that interpolated air pollution estimates at earlier dates. Yet, air pollution data was not as thoroughly available in the 90s as in most recent years. Furthermore, these findings are specific to this population because PM<sub>2.5</sub> change was evaluated only in 3 French cities. Thus, our conclusions may not extrapolate to the target population (i.e. the French population at risk for dementia).

In a context of climate change, massive urbanization and worldwide aging of the population, it is crucial to determine what can be done to support healthy ageing. Knowledge of the effects of air pollution change on dementia is essential to informing actions to reduce pollution in ways that have the greatest potential to benefit cognitive ageing. By modeling both the effect of observed reduction to PM<sub>2.5</sub> and simulated hypothetical reduction to PM<sub>2.5</sub> in incident dementia in a large prospective cohort, we provide evidence that PM<sub>2.5</sub> reduction may reduce the risk of



dementia. Whether confirmed in different populations, these findings are encouraging because it may involve that reducing PM<sub>2.5</sub> levels today (e.g., through vehicle emissions, coal-burning power plants, industrial emissions) could yield to important implications for prevention of dementia and provide new argument to reinforce the need for appropriately set air quality standards.

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## **CONFLICT OF INTEREST DISCLOSURES**

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

## REFERENCES

1. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*. 2017;389(10082):1907-18.
2. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A*. 2018;115(38):9592-7.
3. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of Cause-Specific Mortality Associated With PM<sub>2.5</sub> Air Pollution in the United States. *JAMA Netw Open*. 2019;2(11):e1915834.
4. Health Effects Institute. 2019. State of Global Air 2019. Special Report. Boston, MA:Health Effects Institut
5. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*. 2009;32(9):506-16.
6. de Prado Bert P, Mercader EMH, Pujol J, Sunyer J, Mortamais M. The Effects of Air Pollution on the Brain: a Review of Studies Interfacing Environmental Epidemiology and Neuroimaging. *Curr Environ Health Rep*. 2018;5(3):351-64.
7. Cho Jaelim, Noh Young, Kim Sun Young, Sohn Jungwoo, Noh Juhwan, Kim Woojin, et al. Long-Term Ambient Air Pollution Exposures and Brain Imaging Markers in Korean Adults: The Environmental Pollution-Induced Neurological Effects (EPINEF) Study. *Environ Health Perspect*. 2020;128(11):117006.

8. 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.
9. 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.
10. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air Pollution and Dementia: A Systematic Review. *J Alzheimers Dis.* 70(Suppl 1):S145-63.
11. Shi L, Wu X, Yazdi MD, Braun D, Awad YA, Wei Y, et al. Long-term effects of PM<sub>2.5</sub> on neurological disorders in the American Medicare population: a longitudinal cohort study. *Lancet Planet Health.* 2020; (20)30227-8
12. Weuve J, Bennett EE, Ranker L, Gianattasio KZ, Pedde M, Adar SD, et al. Exposure to Air Pollution in Relation to Risk of Dementia and Related Outcomes: An Updated Systematic Review of the Epidemiological Literature. *Environ Health Perspect.* 2021;129(9):096001.
13. Mortamais M, Gutierrez L-A, de Hoogh K, Chen J, Vienneau D, Carrière I, et al. Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study. *Environ Int.* 2021;148:106376.
14. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet.* 2020;396(10248):413-46.

15. 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(5):492-8.
16. Breskin A, Edmonds A, Cole SR, Westreich D, Cocohoba J, Cohen MH, et al. G-computation for policy-relevant effects of interventions on time-to-event outcomes. *Int J Epidemiol*. 2020;49(6):2021-9.
17. Snowden JM, Rose S, Mortimer KM. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. *Am J Epidemiol*. 2011;173(7):731-8.
18. Keil AP, Edwards JK, Richardson DB, Naimi AI, Cole SR. The parametric g-formula for time-to-event data: intuition and a worked example. *Epidemiol Camb Mass*. 2014;25(6):889-97.
19. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *Int J Epidemiol*. 2009;38(6):1599-611.
20. Edwards JK, McGrath LJ, Buckley JP, Schubauer-Berigan MK, Cole SR, Richardson DB. Occupational radon exposure and lung cancer mortality: estimating intervention effects using the parametric g-formula. *Epidemiol Camb Mass*. 2014;25(6):829-34.
21. Mokhayeri Yaser, Hashemi-Nazari Seyed Saeed, Khodakarim Soheila, Safiri Saeid, Mansournia Nasrin, Mansournia Mohammad Ali, et al. Effects of Hypothetical Interventions on Ischemic Stroke Using Parametric G-Formula. *Stroke*. 2019;50(11):3286-8.

22. Rojas-Saunero LP, Hilal S, Murray EJ, Logan RW, Ikram MA, Swanson SA. Hypothetical blood-pressure-lowering interventions and risk of stroke and dementia. *Eur J Epidemiol.* 2021;36(1):69-79.
23. Zhou Z, Cai L, Fu J, Han Y, Fang Y. Hypothetical Interventions on Risk Factors for Cognitive Impairment among Chinese Older Adults: An Application of the Parametric G-Formula. *Int J Environ Res Public Health.* 2020;17(3):1021.
24. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol.* 2016;15(5):455-532.
25. 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(6):316-25.
26. de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzler M, et al. Spatial PM2.5, NO2, O3 and BC models for Western Europe - Evaluation of spatiotemporal stability. *Environ Int.* 2018;120:81-92.
27. 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.
28. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34(7):939-44.

29. Lange T, Hansen JV. Direct and indirect effects in a survival context. *Epidemiol Camb Mass*. 2011;22(4):575-81.
30. Aalen O. A Model for Nonparametric Regression Analysis of Counting Processes. In: Klonecki W, Kozek A, Rosiński J, éditeurs. *Mathematical Statistics and Probability Theory*. New York, NY: Springer; 1980. p. 1-25.
31. 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*. 2018;14(4):473-82.
32. Zureik M, Gariépy J, Courbon D, Dartigues J-F, Ritchie K, Tzourio C, et al. Alcohol consumption and carotid artery structure in older French adults: the Three-City Study. *Stroke*. 2004;35(12):2770-5.
33. Hernán MA, Robins JM (2020). *Causal Inference: What If*. Boca Raton: Chapman & Hall/CRC.
34. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol*. 2017;46(2):756-62.
35. Hernán MA. The Hazards of Hazard Ratios. *Epidemiol Camb Mass*. janv 2010;21(1):13-5.
36. McGrath S, Lin V, Zhang Z, Petite LC, Logan RW, Hernán MA, et al. gfoRmula: An R Package for Estimating the Effects of Sustained Treatment Strategies via the Parametric g-formula. *Patterns N Y N*. 2020;1(3):100008.
37. Oakes JM, Kaufman JS. *Methods in Social Epidemiology*. John Wiley & Sons; 2017

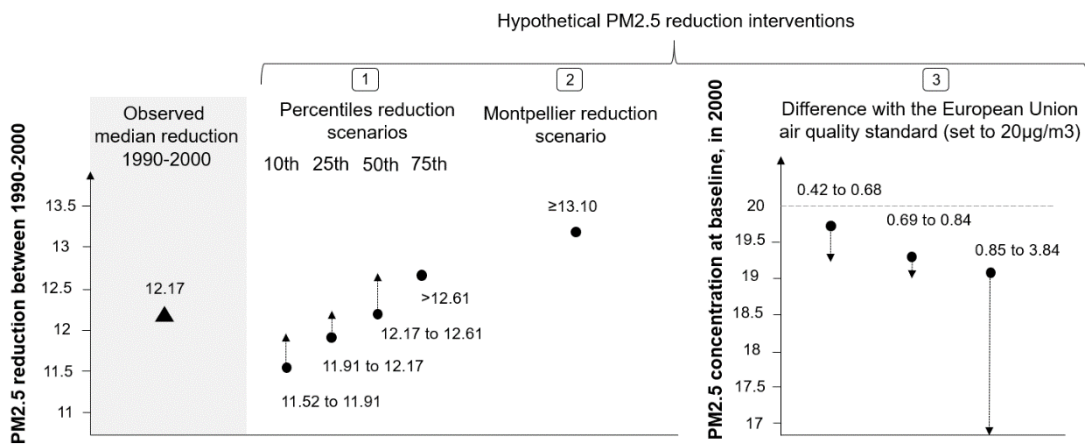
38. Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *Int J Epidemiol.* 2020; 49(1):36-44.
39. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. *JAMA Neurol.* 2020;77(7):801-9.
40. Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet.* 2017;389(10070):718-26.
41. Oudin Anna, Forsberg Bertil, Adolfsson Annelie Nordin, Lind Nina, Modig Lars, Nordin Maria, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. *Environ Health Perspect.* 2016;124(3):306-12.
42. 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(2):573-84.
43. 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(8):e103078.
44. 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(9):e022404.

45. Nunez Yanelli, Boehme Amelia K., Weisskopf Marc G., Re Diane B., Navas-Acien Ana, van Donkelaar Aaron, et al. Fine Particle Exposure and Clinical Aggravation in Neurodegenerative Diseases in New York State. *Environ Health Perspect.* 2021;129(2):027003.
46. Calderón-Garcidueñas L, Villarreal-Ríos R. Living close to heavy traffic roads, air pollution, and dementia. *Lancet.* 2017;389(10070):675-7.
47. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol.* 2016;183(8):758-64.
48. Oulhote Y, Coull B, Bind M-A, Debes F, Nielsen F, Tamayo I, et al. Joint and independent neurotoxic effects of early life exposures to a chemical mixture: A multi-pollutant approach combining ensemble learning and G-computation. *Environ Epidemiol.* 2019;3(5):e063.
49. Garcia E, Berhane KT, Islam T, McConnell R, Urman R, Chen Z, et al. Association of Changes in Air Quality With Incident Asthma in Children in California, 1993-2014. *JAMA.* 2019;321(19):1906-15.
50. Urman R, Garcia E, Berhane K, McConnell R, Gauderman WJ, Gilliland F. The Potential Effects of Policy-driven Air Pollution Interventions on Childhood Lung Development. *Am J Respir Crit Care Med.* 2019;201(4):438-44.
51. Jayaraj RL, Rodriguez EA, Wang Y, Block ML. Outdoor Ambient Air Pollution and Neurodegenerative Diseases: the Neuroinflammation Hypothesis. *Curr Environ Health Rep.* 2017;4(2):166-79.



52. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease – Evidence from epidemiological and animal studies. *Biomed J.* 2018;41(3):141-62.
53. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, et al. Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid  $\beta$ -42 and  $\alpha$ -Synuclein in Children and Young Adults. *Toxicol Pathol.* 2008;36(2):289-310.
54. Calderón-Garcidueñas L, González-Maciel A, Reynoso-Robles R, Hammond J, Kulesza R, Lachmann I, et al. Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles (and engineered Ti-rich nanorods). The substantia nigrae is a very early target in young urbanites and the gastrointestinal tract a key brainstem portal. *Environ Res.* 2020;191:110139.
55. Cserbik D, Chen J-C, McConnell R, Berhane K, Sowell ER, Schwartz J, et al. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environ Int.* 2020;143:105933.
56. Beckwith T, Cecil K, Altaye M, Severs R, Wolfe C, Percy Z, et al. Reduced gray matter volume and cortical thickness associated with traffic-related air pollution in a longitudinally studied pediatric cohort. *PLOS ONE.* 2020;15(1):e0228092.

Figure 1. Reduction of PM<sub>2.5</sub> between 1990-2000 under the observed course of exposure and different hypothetical exposure interventions



- 1 First counterfactual scenario limits based on the 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentile of the observed exposure reduction between 1990-2000
- 2 Second counterfactual scenario based on the reduction observed in the city of Montpellier, where the PM<sub>2.5</sub> reduction was the highest (≥13.10 µg/m<sup>3</sup>)
- 3 Third counterfactual scenario limits based on the 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentile of the difference between the EU air quality standard and the observed exposure in 2000

Table 1. Distribution of Characteristics of selected participants from the 3C Study (N=7051)

Characteristics, n (%)	Non-demented	Incident Demented	Overall,
	N = 6,262	N = 789	N = 7,051
Age*	73.0 (69.4-77.2)	77.1 (73.2-80.3)	73.4 (69.7-77.7)
Female	3,833 (61.2)	517 (65.5)	4,350 (61.7)
Study centre			
Bordeaux	1,328 (21.2)	276 (34.9)	1,604 (22.7)
Dijon	3,644 (58.2)	387 (49.0)	4,031 (57.2)
Montpellier	1,290 (20.6)	126 (16.0)	1,416 (20.1)
Education			
Primary	1,420 (22.7)	280 (35.5)	1,700 (24.1)
Short secondary	2,333 (37.3)	233 (29.5)	2,566 (36.4)
Upper secondary	2,509 (40.1)	276 (35.0)	2,785 (39.5)
Geographical deprivation index*	-0.29 (-1.32-0.66)	-0.16 (-1.14-0.89)	-0.27 (-1.32-1.70)
Alcohol consumption†			
None	1,251 (20.0)	180 (22.8)	1,431 (20.3)
Moderate	4,505 (71.9)	556 (70.5)	5,061 (71.8)

Characteristics, n (%)	Non-demented	Incident Demented	Overall, N = 7,051
	N = 6,262	N = 789	
High	506 (8.1)	53 (6.7)	559 (7.9)
Smoking habits			
Never	3,839 (61.3)	523 (66.3)	4,362 (61.9)
Ex or current	2,423 (38.7)	266 (33.7)	2,689 (38.1)
APOE ε4 allele carriers	1,184 (18.9)	211 (26.7)	1,395 (19.8)

\*Median (interquartile range)

†Alcohol consumption (none, moderate if <36g per day, or heavy if ≥36g)

	Cox model*		Aalen model*	
	HR <sup>†</sup>	(95% CI)	Estimate <sup>†</sup>	(95% CI)
<b>All-cause of dementia (N= 789 / 7051)</b>				
PM <sub>2.5</sub> reduction 1990-2000	0.85	(0.76,0.95)	-197x10 <sup>-5</sup>	(-327x10 <sup>-5</sup> , -67x10 <sup>-5</sup> )
<b>Alzheimer's disease (N= 539 / 6801)</b>				
PM <sub>2.5</sub> reduction 1990-2000	0.83	(0.72,0.94)	-168x10 <sup>-5</sup>	(-276x10 <sup>-5</sup> , -60x10 <sup>-5</sup> )
<b>Vascular or mixed dementia (N= 155 / 6417)</b>				
PM <sub>2.5</sub> reduction 1990-2000	0.94	(0.74,1.18)	-12x10 <sup>-5</sup>	(-64x10 <sup>-5</sup> , 41x10 <sup>-5</sup> )

Table 2. Effect of observed PM<sub>2.5</sub> concentrations reduction between 1990-2000 on dementia risk (Cox proportional hazards model and Aalen model)

\*Models are adjusted for sex, education, APOE4, smoking habits, alcohol intake and geographical deprivation index

<sup>†</sup>For each 1µg/m<sup>3</sup> decrease

Table 3. All-cause of dementia risk under different hypothetical PM<sub>2.5</sub> reduction interventions

	Rate Ratio	95% CI	Rate Difference	95% CI
<b><i>PM<sub>2.5</sub> reduction scenarios*</i></b>				
PM <sub>2.5</sub> reduction < 11.52 µg/m <sup>3</sup>	Ref.		Ref.	
PM <sub>2.5</sub> reduction 11.52 to 11.91 µg/m <sup>3</sup>	1.07	(0.79, 1.35)	0.08	(-0.22, 0.38)
PM <sub>2.5</sub> reduction 11.91 to 12.17 µg/m <sup>3</sup>	0.89	(0.66, 1.13)	-0.12	(-0.41, 0.16)
PM <sub>2.5</sub> reduction 12.17 to 12.61 µg/m <sup>3</sup>	0.96	(0.71, 1.21)	-0.05	(-0.34, 0.24)
PM <sub>2.5</sub> reduction ≥ 12.61 µg/m <sup>3</sup>	0.82	(0.60, 1.03)	-0.21	(-0.50, 0.07)
<b><i>PM<sub>2.5</sub> Montpellier scenario</i></b>				
PM <sub>2.5</sub> reduction < 13.10 µg/m <sup>3</sup>	Ref.		Ref.	
PM <sub>2.5</sub> reduction ≥ 13.10 µg/m <sup>3</sup>	0.67	(0.50, 0.84)	-0.37	(-0.57, -0.17)
<b><i>Difference between PM<sub>2.5</sub> at baseline and EU air quality standard<sup>†</sup></i></b>				
1 <sup>th</sup> quartile (0.00-0.41)	Ref.		Ref.	
2 <sup>nd</sup> quartile (0.42-0.68)	0.96	(0.87, 1.05)	-0.05	(-0.16, 0.07)
3 <sup>rd</sup> quartile (0.69-0.84)	0.92	(0.74, 1.10)	-0.10	(-0.32, 0.13)
4 <sup>th</sup> quartile (0.85-3.84)	0.88	(0.62-1.14)	-0.14	(-0.46, 0.18)

\*Limits corresponding to the 10th, 25th, 50th and 75th percentile of the observed exposure distribution

†Limits corresponding to the quartile of the difference between the PM<sub>2.5</sub> UE air quality standard (set at 20 µg/m<sup>3</sup>) and the observed PM<sub>2.5</sub> level in 2000

