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Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study

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ABSTRACT

Introduction: Emerging studies have implicated air pollution in the neurodegenerative processes. Less is known about the influence of air pollution, especially at the relatively low levels, on developing dementia. We conducted a population-based cohort study in Ontario, Canada, where the concentrations of pollutants are among the lowest in the world, to assess whether air pollution exposure is associated with incident dementia.

Methods: The study population comprised all Ontario residents who, on 1 April 2001, were 55–85 years old, Canadian-born, and free of physician-diagnosed dementia (~2.1 million individuals). Follow-up extended until 2013. We used population-based health administrative databases with a validated algorithm to ascertain incident diagnosis of dementia as well as prevalent cases. Using satellite observations, land-use regression model, and an optimal interpolation method, we derived long-term average exposure to fine particulate matter (≤ 2.5 μm in diameter) ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3), respectively at the subjects' historical residences based on a population-based registry. We used multilevel spatial random-effects Cox proportional hazards models, adjusting for individual and contextual factors, such as diabetes, brain injury, and neighborhood income. We conducted various sensitivity analyses, such as lagging exposure up to 10 years and considering a negative control outcome for which no (or weaker) association with air pollution is expected.

Results: We identified 257,816 incident cases of dementia in 2001–2013. We found a positive association between $PM_{2.5}$ and dementia incidence, with a hazard ratio (HR) of 1.04 (95% confidence interval (CI): 1.03–1.05) for every interquartile-range increase in exposure to $PM_{2.5}$. Similarly, NO_2 was associated with increased incidence of dementia (HR = 1.10; 95% CI: 1.08–1.12). No association was found for O_3. These associations were robust to all sensitivity analyses examined. These estimates translate to 6.1% of dementia cases (or 15,813 cases) attributable to $PM_{2.5}$ and NO_2, based on the observed distribution of exposure relative to the lowest quartile in concentrations in this cohort.

Discussion: In this large cohort, exposure to air pollution, even at the relative low levels, was associated with higher dementia incidence.

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Abbreviations and acronyms

CI	confidence interval
HR	hazard ratio
IQR	interquartile-range
NO_2	nitrogen dioxides
O_3	ozone
ONPHEC	Ontario Population Health and Environment Cohort
$PM_{2.5}$, PM_{10}	particulate matter ≤ 2.5-μm (or < 10-μm) in diameter
Ppb	parts per billion
SES	socioeconomic status

1. Introduction

Once people develop dementia, their memory, cognition, and daily functioning become severely impaired, resulting in significantly deteriorated quality of life and survival (World Health Organization, 2016). With 47 million people living with dementia worldwide and the number expected to triple by 2050 (Prince et al., 2015), the need for curbing its impacts becomes more pressing than ever. However, the risk factors of dementia that are amenable to intervention and control have remained largely elusive (Baumgart et al., 2015).

Over the past decade, a small number of epidemiologic studies have reported that exposure to ambient air pollution was associated with cognitive decline (Chen and Schwartz, 2009; Power et al., 2011; Ranft et al., 2009; Tonne et al., 2014; Weuve et al., 2012), pathological changes in the brain (Chen et al., 2015; Wilker et al., 2015), and neurological hospital admissions (Kioumourtzoglou et al., 2016). Experimental and animal studies also observed that inhalation of particulate matter and diesel exhaust enhanced reactive oxygen species and inflammatory responses in the brain (Calderon-Garciduenas et al., 2008a; Levesque et al., 2011), which were accompanied by neuropathological changes including microglial activation (Block et al., 2004) and disruption of the blood-brain barrier (Calderon-Garciduenas et al., 2008b; Genc et al., 2012). As well, cerebrovascular dysfunction and stroke, which may precipitate neurodegeneration (Baumgart et al., 2015), were linked to air pollution (Shah et al., 2015; Shin et al., 2014a; Wellenius et al., 2013). Furthermore, living near major roadways was associated with higher incidence of dementia (Chen et al., 2017).

While converging lines of evidence imply that air pollution could adversely affect the neurodegenerative processes, direct evidence linking air pollution and dementia incidence remains sparse. To date, a small number of studies have evaluated this association (Cacciottolo et al., 2017; Chang et al., 2014; Jung et al., 2015; Oudin et al., 2016; Wu et al., 2015), but these previous studies comprised few dementia cases, relied on limited residential history in exposure assessment, and almost all considered exposure windows within two years prior to or concurrent with outcome assessment (Power et al., 2016). In addition, little is known whether exposure to relatively low levels of air pollution may adversely affect dementia risk.

Given the ubiquity of air pollution exposure and the enormous public health burden of dementia, we conducted a large population-based cohort study in Ontario, Canada, where the concentrations of pollutants are among the lowest in the world, to investigate whether exposure to common air pollutants, especially fine particulate matter (≤ 2.5 μm in diameter or $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) is associated with the incident diagnosis of dementia.

2. Methods

2.1. Study population

We conducted the analysis using the Ontario Population Health and Environment Cohort (ONPHEC), a large population-based cohort in Ontario (Chen et al., 2016a). This cohort comprised all Ontario adults who, on 1 April 1996 onwards, were registered with provincial health insurance, resided in Ontario for > five years, and were Canadian-born. The ONPHEC was constructed through record linkage of population-based health administrative databases using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES) (Chen et al., 2016a). Hospital, laboratory, and physician services in Ontario are funded by the provincial government through a single-payer universal medicare system that covers all residents (Chen et al., 2013).

We restricted the cohort to individuals who, on 1 April 2001, were 55–85 years old, and according to Medicare data (since 1991), did not have physician-diagnosed dementia. This yielded a total of 2,066,639 subjects. Follow-up extended until 31 March 2013.

The Research Ethics Board of Sunnybrook Health Sciences Center, Toronto, approved the study.

2.2. Outcomes

We ascertained incident diagnoses of dementia by applying a validated algorithm to health administrative data (Jaakkimainen et al., 2016); cases of dementia were defined as any individual having ≥ one hospital admission with a diagnosis of dementia or three physician claims over a two-year period or a prescription relating to dementia (*International Classification of Diseases* codes are listed in Supplementary Material). Based on a validation against patient charts, this algorithm identifies individuals aged ≥ 20 years with dementia with a sensitivity of 75% (or 79% for those ≥ 65 years) and specificity of ~100% (Jaakkimainen et al., 2016).

To detect possible bias due to unmeasured confounding and other errors that may lead to spurious causal inference, we also considered deaths from accidental causes as a negative control outcome (Lipsitch et al., 2010) (see "Online Methods" in Supplementary material).

2.3. Assessment of ambient concentrations of $PM_{2.5}$, NO_2, and O_3

Estimates of exposure to $PM_{2.5}$ were derived from satellite observations in combination with outputs from a global atmospheric chemistry transport model (GEOS-Chem CTM) (see "Online Methods" in Supplementary Material) (van Donkelaar et al., 2013). The $PM_{2.5}$ estimates were calibrated using information on land cover, elevation, and aerosol composition using a geographically-weighted regression, producing annual mean concentration of $PM_{2.5}$ (1 × 1 km) yearly between 1998 and 2012 (van Donkelaar et al., 2015). Covering all of North America, these annual estimates of $PM_{2.5}$ closely agree with ground-level measurements at fixed-site monitors across North America (R^2 = 0.82, n = 1440) (van Donkelaar et al., 2015).

To derive exposure to NO_2, we used a national land-use regression model developed using NO_2 observations at fixed-site monitors from National Air Pollution Surveillance Network (Environment Canada, 2016). This model included an array of predictors (*e.g.*, satellite estimates of NO_2, industrial land use, road length) in conjunction with spatially-varying multipliers representing a distance-decay gradient in NO_2 to capture background, regional, and local-scale variations of NO_2 (Hystad et al., 2011). The final model explained 73% of the variability in annual 2006 measurements of NO_2 (Hystad et al., 2011).

To estimate exposure to O_3, we used a long-term average O_3 surface derived using optimal interpolation technique (Robichaud and Menard, 2013). This approach combines the true observations of O_3 with the benefits of physically-based air quality prediction models that account for meteorological and chemical patterns of O_3. Using this approach, Environment and Climate Change Canada has produced a long-term annual mean warm-season exposure surface of O_3 (21 × 21 km) covering Canada between 2002 and 2009 (Robichaud and Menard, 2013).

Because our exposure surfaces were derived at certain periods in