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Long-term exposure to air pollution and the incidence of multiple sclerosis: A population-based cohort study

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ABSTRACT

Background: Evidence of the adverse neurological effects of exposure to ambient air pollution is emerging, but little is known about its effect on the development of multiple sclerosis (MS), the most common autoimmune disease of the central nervous system.

Objectives: To investigate the associations between MS incidence and long-term exposures to fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3)

Methods: We conducted a population-based cohort study to investigate the associations between long-term exposures to $PM_{2.5}$, NO_2, and O_3 and the incidence of MS. Our study population included all Canadian-born residents aged 20–40 years who lived in the province of Ontario, Canada from 2001 to 2013. Incident MS was ascertained from a validated registry. We assigned estimates of annual concentrations of these pollutants to the residential postal codes of subjects for each year during the 13 years of follow-up. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for each pollutant separately using random-effects Cox proportional hazards models. We conducted various sensitivity analyses, such as lagging exposure up to 5 years and adjusting for access to neurological care, annual average temperature, and population density.

Results: Between 2001 and 2013, we identified 6203 incident cases of MS. The adjusted HR of incident MS was 0.96 (95% CI: 0.86–1.07) for $PM_{2.5}$, 0.91(95% CI: 0.81–1.02) for NO_2, and 1.09 (95% CI: 0.98–1.23) for O_3. These results were robust to various sensitivity analyses conducted.

Conclusions: In this large population-based cohort, we did not observe significant associations between MS incidence and long-term exposures to $PM_{2.5}$, NO_2, and O_3 in adults in Ontario, 2001–2013.

1. Introduction

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS) and usually diagnosed in young adults aged 20–40 years (Amankwah et al., 2017; MS Society of Canada, 2018). MS attacks myelin, the protective covering of the nerves, causing symptoms such as fatigue, lack of coordination, impaired sensation, vision problems, and cognitive impairment (Browne et al., 2014; MS Society of Canada, 2018). Approximately 2.3 million people have MS globally and the incidence of MS is on the rise (Browne et al., 2014). Furthermore, MS is three times as likely to occur in women as in men (Amankwah et al., 2017). The etiology of MS remains largely unknown,

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but there is some evidence suggesting that autoimmunity, genetic predisposition, geographic latitude, smoking, viral exposures, and vitamin D deficiency may play a role in its pathogenesis (O'Gorman et al., 2012; Browne et al., 2014).

Recently, it has been hypothesized that exposure to ambient air pollution may induce inflammation and oxidative stress, leading to blood-brain barrier breakdown, neuroinflammation, and neurodegeneration, which may, in turn, contribute to the development of MS (Xu et al., 2016; Mousavi et al., 2017). However, epidemiologic evidence supporting this hypothesis is limited. Previous epidemiologic studies of short-term health effects of air pollution have linked daily increases in PM_{10} and NO_2 to elevated daily rate of MS relapse (i.e., old symptoms become worse or new symptoms appear) (Oikonen et al., 2003; Heydarpour, 2014; Angelici, 2016; Laura et al., 2016; Roux, 2017; Jeanjean, 2018), but in two recent cohort studies no associations were found for MS incidence with long-term exposure to particulate air pollution (i.e., PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) (Palacios et al., 2017) or residential proximity to major roadways (a measure of exposure to traffic-related pollution) (Chen et al., 2017a).

Considering that North America and Europe have the world's highest prevalence of MS (140 and 108 per 100,000 respectively) (Browne et al., 2014) and the emerging evidence relating air pollution to adverse neurological outcomes (Xu et al., 2016), we sought to investigate the associations between incidence of MS and long-term exposures to $PM_{2.5}$, NO_2 and ozone (O_3) in a large population-based cohort in Ontario, Canada.

2. Material and methods

2.1. Study population and design

We conducted a population-based cohort study using the Ontario Population Health and Environment Cohort (ONPHEC). Details regarding this cohort have been published previously (Chen et al., 2016). Briefly, ONPHEC comprised all Canadian-born adults who resided in Ontario for 5 or more years and were registered with Ontario's provincial health insurance plan on April 1, 1996. The ONPHEC was created through record linkage of population-based administrative databases, with the goal of quantifying the environmental burden of chronic diseases.

We restricted our cohort to subjects who were 20–40 years old (Widdifield et al., 2015; MS Society of Canada, 2018) and free of physician-diagnosed MS at the time of entry (April 1, 2001). Subjects were followed from cohort entry until December 31, 2013 to determine incident cases of MS. Ontario has a universal publicly funded healthcare system for hospital, laboratory, and physician services that covers virtually all residents (Chen et al., 2016).

The Research Ethics Board of Sunnybrook Health Sciences Centre approved the study.

2.2. Ascertainment of multiple sclerosis

We ascertained incident diagnoses of MS by applying a validated algorithm to linked provincial health administrative data (Widdifield et al., 2015). This algorithm was developed using hospital discharge abstracts from the Canadian Institute for Health Information and physician service claims from the Ontario Health Insurance Plan. Incident cases of MS were defined as any individual having at least one hospital admission with a diagnosis of MS [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) diagnostic code 340 or ICD-10 code G35] or five physician claims (code 340) over a two-year period. Compared to patient charts, this algorithm has a sensitivity of 84.2%, specificity of 100.0%, positive predictive value of 86.0%, and negative predictive value of 99.9%. All datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Follow-up ended when participants died, became ineligible for provincial health insurance (i.e., moved out of Ontario), or reached the end of follow-up.

2.3. Exposure assessment

We derived estimates of ground-level $PM_{2.5}$ by relating satellite retrievals of aerosol optical depth, a measure of light extinction by aerosols in the total atmospheric column, to $PM_{2.5}$ using a global atmospheric chemistry transport model (GEOS-Chem CTM). Details about the model have been reported previously (van Donkelaar et al., 2015a, 2015b). Briefly, covering all of North America below 70°N, which includes all of Ontario, $PM_{2.5}$ estimates were available on a grid with a spatial resolution of approximately 1 km × 1 km for each year between 1998 and 2012. These annual estimates of $PM_{2.5}$ were strongly correlated with ground-level monitoring data across North America (R^2 = 0.82). These data have been used in recent cohort studies assessing the health effects of long-term $PM_{2.5}$ exposure (Crouse et al., 2015; Chen et al., 2017b).

Residential exposure to NO_2 was derived from a national land-use regression (LUR) model developed using measurements of NO_2 at the fixed-site stations of Environment Canada's National Air Pollution Surveillance Network (NAPS). Details about the model have been reported previously (Hystad et al., 2011). Briefly, this model includes 2005–2011 satellite NO_2 estimates, road length within 10 km, area of industrial land use within 2 km, and mean summer rainfall. This model explained 73% of the variability in NO_2 measurements at fixed-site monitors with a root mean square error of 2.9 parts per billion. The NO_2 estimates from this model have been applied previously to examine associations of traffic-related air pollution with mortality (Crouse et al., 2015).

We used an exposure surface of O_3 representing the average of the daily 8-hr maximum concentrations during the warm seasons (1 May to 31 October) from 2002 to 2009 across North America with 21-km horizontal resolution through multi-year objective analyses (Robichaud and Ménard, 2014). This surface is based on an optimal interpolation with capabilities for adaptive error statistics for ozone, using air quality model outputs from the CHRONOS model (Canadian and Hemispheric Regional Ozone and NOx System) for the period 2002–2009 (Pudykiewicz et al., 1997). This approach provides high precision of estimates of O_3 with an absolute annual averaged systematic error less than 0.6 ppbv (parts per billion by volume), and a random error generally less than 9 ppbv.

Since our exposure surfaces were available for certain periods of time ($PM_{2.5}$: 1998–2012; NO_2: 2006; O_3: 2002–2009) (Hystad et al., 2011; Robichaud et al., 2014; van Donkelaar et al., 2015), we conducted yearly calibration of these surfaces to relevant time periods during the study, similar to previous studies (Beelen et al., 2014; Oudin et al., 2016; Chen et al., 2017b) (see Supplementary Material for more details). Briefly, we extrapolated $PM_{2.5}$ estimates in 1998 annually to 1994–1997 by scaling the 1998 surface with a ratio between the average concentrations of $PM_{2.5}$ at all fixed-site monitors across Ontario in a given year in 1994–1997 and that in 1998. We also extrapolated $PM_{2.5}$ estimates in 2013 by scaling the data in 2012. Similarly, we created annual mean estimates of NO_2 and O_3 between 1994 and 2013 by scaling their respective exposure surfaces. These calibration approaches enabled us to assign annual estimates of exposure to the centroid of each subject's annual six-character residential postal code in that year, thereby accounting for residential mobility and long-term trends in exposure (a six-character postal code represents in urban areas a block face or a large building). The postal code information was obtained from the Registered Persons Database, a registry of all Ontario residents with health insurance.