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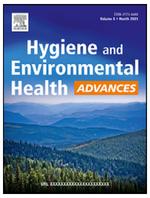

Industrial air pollutant emissions and mortality from Alzheimer's disease in Canada

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ABSTRACT

Background: There is increasing interest in the health effects of source-specific air pollution. However, the relationship between industrial air pollutants and Alzheimer's disease has received limited investigation.
Objectives: To assess associations of industrial fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) exposures with mortality from Alzheimer's disease.
Methods: Approximately 3.2 million adults involved in the 2006 Canadian Census Health and Environment Cohort (CanCHEC) were followed from Census day (May 16, 2006) until death or December 31, 2016. Three-year moving-average industrial emissions with a one-year lag were assigned to the participants based on their residential postal codes. The neighborhood emission of each of the three industrial air pollutants for a postal code was estimated by considering weights of the air pollutant emissions from all industries within a 15 km buffer area, distances between the postal code area and the emitters, and percentages of time per year that the postal code area was downwind of the industrial emitters. Cox proportional hazards models were used to compute hazard ratios (HRs) for deaths from Alzheimer's, adjusting for 15 socio-demographic and contextual covariates. Sensitivity analyses were conducted by adjusting for other industrial emissions, greenness, and comorbidity index, individually.
Results: We identified 4500 deaths due to Alzheimer's disease from 2006 to 2016 for a total of 32,909,200 person-years across the follow-up period. The adjusted HR for mortality from Alzheimer's related to one interquartile range increase in industrial $PM_{2.5}$, NO_2, and SO_2 tonnes/meter per year are 1.006 (95% confidence intervals: 1.000-1.011), 0.994 (0.978-1.011), and 0.998 (0.996-1.001), respectively. Similar positive associations between industrial $PM_{2.5}$ and mortality from Alzheimer's disease were observed, but there were no clear associations for NO_2 and SO_2 in sensitivity analyses.
Conclusions: Exposure to industrial $PM_{2.5}$ increases the risk of mortality from Alzheimer's disease.

1. Introduction

Air pollution is recognized as a global public health issue and particularly a risk factor for cardiovascular and respiratory diseases (Dominici et al., 2006; Kampa and Castanas, 2008; Mills et al., 2009; Cakmak et al., 2018). Recent toxicological studies found that exposure to air pollution can lead to inflammatory and oxidative reactions in lungs, trigger biochemical changes in brain tissues, and cause injury to the central nervous systems of humans (Babadjouni et al., 2017; González-Guevara et al., 2014; Thomson, 2019). Thus, adverse effects of air pollution on neurological health outcomes including Parkinson's disease, stroke, dementia, mild cognitive impairment, and total cerebral brain volume have been well documented (e.g. Béjot et al., 2018; Chen et al., 2017a; Chen et al., 2017b; Zhao et al., 2021).

Dementia is the second largest neurological cause of disability (Carroll, 2019) and Alzheimer's disease is the most common form of dementia (Moulton and Yang, 2012). In 2016, Alzheimer's disease affected 43.8 million people worldwide (Nichols et al., 2019), and this prevalence is constantly increasing (Brookmeyer et al., 2007). Alzheimer's disease was officially listed as the sixth-leading cause of death in the United States in 2019 and the seventh-leading cause of death in 2020 and 2021 (Alzheimer's Association, 2022). A few studies, conducted in

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several countries including Canada, have demonstrated significant positive associations between Alzheimer's disease (or dementia) and exposures to air pollutants (e.g. fine particulate matter less than 2.5 micrometers in diameter – $PM_{2.5}$ and nitrogen dioxide – NO_2); however, nearly all focused on ambient air pollution (Moulton and Yang, 2012; Shi et al., 2020; Shou et al., 2019; Zhao et al., 2021). Therefore, there is limited information on the associations of mortality from Alzhemier's disease with industrial air pollution.

Specific sources of air pollution may differentially influence health (Oberdörster, 2000; Zhao et al., 2020), and the characteristics of pollutants can vary significantly by source (EEA, 2022). In Canada, positive relationships of neurological disease incidence with traffic-related air pollution have been found by a few studies (e.g. Finkelstein and Jerrett, 2007; Cakmak et al., 2019; Yuchi et al., 2020), but evaluations of mortality from neurological diseases and industrial air pollution are absent. Finkelstein and Jerrett (2007) found an association between the risk of Parkinson's disease and ambient levels of manganese in total suspended particles in the city of Hamilton, Ontario, a city with a large steelmaking sector. Yuchi et al. (2020) found that road proximity was associated with incidence of non-Alzheimer's dementia, Parkinson's disease, Alzheimer's disease and multiple sclerosis. It is thus important to know of the public health consequences of exposure to specific sources of air pollutants and whether industrial sources of air pollutants may pose higher risks than the overall $PM_{2.5}$, NO_2 and SO_2. If industrial source air pollutants generate higher risks relative to their IQRs than total $PM_{2.5}$, NO_2 and SO_2, this suggests that analyses using total $PM_{2.5}$, NO_2 and SO_2 may fail to identify important public health implications of exposure to air pollutants. Therefore, in this study we investigated the associations between emissions of three major industrial air pollutants (i.e. $PM_{2.5}$, NO_2, and sulfur dioxide – SO_2) and mortality attributable to Alzheimer's disease using a large, nationally-representative cohort from Canada.

2. Method

2.1. Study cohorts

Our analyses were based on the 2006 Canadian Census Health and Environment Cohort (CanCHEC) that was assembled by linking the 2006 Census long-form questionnaire to tax and mortality databases (Tjepkema et al., 2019). The 2006 Census long-form questionnaire is distributed to 20% of Canadian households (approximately 3.2 million adults aged 25 or older), with nearly 100% of households in remote areas and enumerated Indian reserves. At baseline, the Census contained a wide range of socio-demographic variables such as age, sex, educational attainment, employment status, occupational level, visible minority, immigration status, and marital status. The annual geographically-adjusted income for 2006 to 2016 obtained from the annual tax records was also included in the CanCHEC.

The respondents who completed the 2006 Census long-form questionnaire were linked to income tax files to obtain annual postal code history through standard deterministic and probabilistic linkage techniques using sex, date of birth, postal code, and marital status (Tjepkema et al., 2019). Subsequently, tax-linked Census respondents were deterministically linked to the Amalgamated Mortality Database (AMDB) using social insurance numbers. The AMDB is a dataset that includes death records from both the Canadian Mortality Database which compiles provincial and territorial hospital death registries beginning in 1950, and deaths recorded in tax files. Deaths that occurred between census day (May 16, 2006) and December 31, 2016 were eligible for linkage. Follow-up extended from entry in the cohort (i.e., May 16, 2006) until the date of death, reaching age 90, or the end of the study (i.e., December 31, 2016). The postal code (as derived from tax files) has an increasingly low correspondence to where someone lives (because the taxes are filed by a third party and their postal code is used and not that of the person) as Canadians get into older age, especially over age of 90. Thus, we censored at age 90 in addition to being consistent with many other CanCHEC air pollution studies (Zhao et al., 2021). Deaths from Alzheimer's disease were identified by the ICD-10 code of G30. Since the purpose of this analysis was to evaluate the long-term effects of air pollution exposure, the study population was restricted to adults aged 25 to 90 years at enrollment.

2.2. Industrial air pollution emissions

The wind and inverse-distance weighted (WIDW) industrial $PM_{2.5}$ emission was estimated as per Buteau et al. (2018), and we improved their estimates by including all (not only the closest major) emitters within a large geographic area. Specifically, we computed distances between the participant's residence and the nearby industries using the centroid of the six-digit residential postal code and the complete address of the industries as given in the National Population Release Inventory (NPRI). The NPRI includes industrial emission data as well as addresses of industries that release $PM_{2.5}$, NO_2 and SO_2. We then estimated annual industrial $PM_{2.5}$ emissions by multiplying tons of the pollutant emitted from all industrial emitters located within a 15 km radius (doubling the original 7.5 km radius) of a centroid of a postal code area by the inverse of the distance between the centroid to the emitters, and by the percentages of time per year that the postal code area was downwind of the industrial emitters. That is, the industrial $PM_{2.5}$ exposure for the jth participant (E_j) for a specific year was estimated by the following equation:

$$E_j = \sum_{i=1}^{n} A_i \times P_i \div D_i$$

where E_j is the industrial $PM_{2.5}$ exposure for jth participant for a specific year with the unit of tons/meter, i represents an industrial source within 15 km to a postal code, A_i denotes the amount of an industrial pollutant (i.e. $PM_{2.5}$) emitted from the ith industrial source with the unit of tons for the year of interest, P_i represents the percentage of hours per year that the postal code was downwind of the source, and D_i is the distance from the ith industrial source to the postal code with the unit of meter. Using the same method, we estimated WIDW industrial NO_2 and SO_2 emissions for each postal code for each year. Hourly wind direction data were retrieved from the National Climatic Data Access Integration by the "weathercan" package (LaZerte and Albers, 2018) in the R statistical computing environment. Previous studies used radiuses of 2.5 km and 7.5 km from the residence to define the exposure (Labelle et al., 2015; Buteau et al., 2018). We extended it to 15 km to capture more industries since air pollution can travel further distances (National Research Council, 2010). The unit of the wind- and inverse-distance weighted industrial pollution to which a person is exposed yearly is defined as tons/meter per year.

Following guidance from the Canadian Council of Ministers of the Environment (2012), we created a three-year moving-average exposure window with a one-year lag for each of the follow-up years. These moving-averaged annual industrial air pollution emissions were assigned to each participant based on their six-digit residential postal codes (obtained from the Historical Tax Summary File).

2.3. Environmental, geographical, and contextual covariates

The presence of vegetation around people's homes has been associated with many benefits to health (Lee and Maheswaran, 2011). Normalized Difference Vegetation Index (NDVI) is the most widely used satellite-derived indicator of the quantity of vegetation on the ground. We assigned decadal mean NDVI values for 2001 to 2010 to each participant's postal code and adjusted for NDVI in our models, including potential effect modification. The red and near-infrared bands reflectance used to calculate NDVI was collected by Landsat 5 and Landsat 8 satellites during the vegetation growing season of May to August (Crouse et al., 2017; CANUE, 2018).

We included airshed as a geographic covariate in our analyses. An airshed is an area where the movement of air, and air pollutants, can be hindered by local geographical features, thus creating a region of relatively homogeneous air quality. These geographical features have been shown to correlate with regional differences in morbidity and mortality rates across Canada (Pappin et al., 2019). Canada is divided into six airshed regions (i.e., Western, Prairie, West Central, Southern Atlantic, East Central, and North) based on large-scale air masses and meteorological characteristics (Crouse et al., 2016).

The Canadian Marginalization Index (Can-Marg) is a census-based measure to reflect four dimensions of Canadian marginalization: residential instability, material deprivation, dependency, and ethnic concentration (Matheson et al., 2012). Previous studies showed that Can-Marg has been associated with differences in health outcomes (Matheson et al., 2012; Pappin et al., 2019). In this study, we used Can-Marg available at the dissemination area level. A dissemination area (DA) is the smallest standard geographic area (each DA includes about 400-700 people on average) for which all census data are disseminated in Canada.

Following Gordon and Janzen (2013), we developed an urban form variable to consider the possible effects of different built environments and neighborhoods within communities on health for the 2006 Census year and linked to individuals by their six-digit residential postal codes. The types of urban form were defined by population density and major transportation modes in census tracts. In this study, the categories of the urban form variable included urban core, transit-reliant suburb, auto-reliant suburb, exurban, and rural.

The Charlson Comorbidity Index (a measure of frailty) is a well-known summary comorbidity index which is based on 17 conditions from all annual episodes of hospitalizations (Austin et al., 2015). The index is created by assigning a weighted integer of “one” to the following ten conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease-rheumatic disease, peptic ulcer disease, mild liver disease, and diabetes without complications), “two” to the next four conditions (diabetes with complications, paraplegia and hemiplegia, renal disease, and cancer), “three” to moderate or severe liver disease, and “six” to metastatic carcinoma, and HIV/AIDS representing the most severe morbidity. The summation of the weighted comorbidity scores results in a summary score ranging from (0-33). We then assigned the 3-year lag index score to each participant yearly, to account for the lag-effect of those comorbidities in the survival model. We categorized the index score into no comorbidity (0 score), moderate comorbidity (1-3 score), and high comorbidity (4+ score). The Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD) was used to obtain records of hospitalization during the study period.

2.4. Statistical methods

Cox proportional hazards models were used to assess the associations between industrial $PM_{2.5}/NO_2/SO_2$ emissions and mortality from Alzheimer’s disease. The primary model was stratified by sex and age group (from 25 to 54 years in a 10-year increment, 55-69, and 70-90) and adjusted for educational attainment, employment status, income, occupational level, visible minority status, immigration status, marital status, Can-Marg variables, urban form, and airshed. The baseline hazard function was stratified by sex and age group (from 25 to 54 years in a 10-year increment, 55-69, and 70-90), and censored at 90 years of age. We evaluated the sensitivity of the primary model by adjusting for the other industrial air pollutants, greenness (i.e. NDVI), and comorbidity variables, individually. We further assessed possible effect modification across subgroups of sex, age group, urban form, frailty (i.e. Charlson Comorbidity Index), and airshed.

3. Results

We identified 4500 deaths, of which 3700 deaths had full industrial air pollution emissions and covariate information available, from Alzheimer’s disease, by following 3,184,500 adults (51.8% males) from May 16, 2006 to December 31, 2016 for a total of 32,909,200 person-years. Approximately 95.6% of Alzheimer’s disease deaths were in the 70+ age subgroup, while this subgroup only contained 25.6% participants. Additionally, 26.8% of the deaths were in the decile of the lowest income with only 6.5% participants. The number of deaths in each of the other subgroups was generally proportional to the population in the subgroups.

Neighborhood industrial $PM_{2.5}$ emissions are more closely correlated with industrial NO_2 emissions (Pearson’s correlation coefficient, r=0.58, p<0.01) than industrial SO_2 emissions (r=0.28, p<0.01). Industrial NO_2 emissions are also correlated with industrial SO_2 emissions (r=0.27, p<0.01). Detailed participant characteristics and industrial pollution emissions across subgroups of each covariate are shown in Table 1. There were no significant differences in air pollutants by outcome status (not shown).

We observed a significantly increased mortality risk of Alzheimer’s disease with every interquartile range (0.53 tonnes/meter per year) increment in industrial $PM_{2.5}$ emissions from the primary Cox model (hazard ratio, HR: 1.006; 95% confidence interval, CI: 1.000–1.011) (Table 2). The HR increased after additionally adjusting for industrial NO_2 and industrial SO_2 either in a two-pollutant or a three-pollutant model. The estimated risk remained consistent following the adjustment for greenness (NDVI) and decreased slightly with the addition of the Charlson Comorbidity Index to the primary model. The adjusted HRs and corresponding 95% CIs from primary and sensitivity analysis models did not suggest conclusive relationships between industrial NO_2/SO_2 emissions and mortality due to Alzheimer’s disease (Table 2). When included as potential confounders, there were no effects on the hazard ratios in Table 2 from normalized difference vegetation index (NDVI), income, education, employment, or occupation, individually. Furthermore, these confounders were not significant factors for the models in Table 2 and were thus not included in the stratified analysis.

Effect modification of industrial $PM_{2.5}$, NO_2, and SO_2 emissions with mortality of Alzheimer’s disease by many covariates is provided in Table 3. In the subgroup analyses, a significant positive association between industrial $PM_{2.5}$ emissions and Alzheimer’s disease mortality was observed in males but not in females. Similar significant associations between industrial $PM_{2.5}$ emissions and Alzheimer’s disease mortality were seen in the older age (70+ years), no comorbidities, and urban form subgroups, while the risks were relatively higher in auto-reliant suburbs and the East Central airshed (Ontario and Quebec) (Table 3).

By age group, HRs (95%CI) were 0.905 (0.740 – 1.106) for under 65s and 1.006 (1.000 – 1.013) for over 65s for $PM_{2.5}$. While the effect of industrial pollutants on AD were not statistically significant on age < 65, mostly due to a small number of AD deaths for this age group, the statistically significant associations were observed with $PM_{2.5}$ for the over 65 group. We found that none of the industrial pollutants have a significant impact on total non-accidental mortality ($PM_{2.5}$ = HR (95%CI): 1.001 (0.999 – 1.002); NO_2 = HR (95%CI: 0.995 (0.993 – 0.997); SO_2 (95%CI = HR: 0.999 (0.998 – 1.000)), suggesting that industrial sourced $PM_{2.5}$ may negatively impact AD and may be of significance in elderly populations given the widespread exposure, or in individuals exposed to very high levels of $PM_{2.5}$.

We observed a significant positive association between industrial NO_2 emissions and mortality only in the West Central airshed subgroup, with 100 deaths. However, in the other subgroups, industrial NO_2/SO_2 emissions were not significantly associated with mortality due to Alzheimer’s disease (Table 3).

Compared to other findings in the literature, the median and IQR for estimated exposure levels of industrial pollutants of $PM_{2.5}$ and SO_2 for the province of Quebec were compared between this study and those

Table 1
Distribution of Alzheimer's mortality and industrial pollutants across subgroups of covariates.

				Median (IQR) – tonnes/meter per year		
Covariate	Subgroup	Person-years	Number of deaths *	$PM_{2.5}$	NO_2	SO_2
Sex	Male	17,130,400	2,600	0.16 (0.53)	0.27 (3.79)	1.49 (5.31)
	Female	15,778,900	1,900	0.16 (0.53)	0.25 (3.67)	1.42 (5.25)
Age	<65	24,773,200	100	0.22 (0.59)	1.90 (6.11)	0.49 (4.92)
	≥65	8,136,000	4,400	0.20 (0.56)	1.80 (5.92)	0.42 (4.88)
Educational attainment	Not completed high school	6,476,700	2,000	0.12 (0.52)	0.12 (3.21)	1.03 (4.92)
	High school	9,008,747	1,200	0.15 (0.52)	0.22 (3.43)	1.33 (5.11)
	University	10,527,900	900	0.15 (0.51)	0.22 (3.43)	1.33 (5.12)
	Master or higher degree	6,895,700	400	0.23 (0.55)	0.47 (4.47)	2.18 (5.81)
Employment status	Employed	21,684,200	300	0.16 (0.52)	0.26 (3.62)	1.48 (5.20)
	Unemployed	1,212,700	<100	0.15 (0.55)	0.18 (3.57)	1.30 (5.19)
	Not in labor force	10,012,300	4,200	0.16 (0.55)	0.25 (4.04)	1.43 (5.46)
Income	1st decile - highest	3,625,900	500	0.15 (0.47)	0.23 (3.65)	1.39 (4.78)
	2nd decile	3,559,900	200	0.15 (0.48)	0.22 (3.58)	1.30 (4.88)
	3rd decile	3,489,500	200	0.15 (0.49)	0.22 (3.55)	1.31 (4.91)
	4th decile	3,390,000	200	0.15 (0.51)	0.23 (3.61)	1.33 (5.02)
	5th decile	3,293,300	300	0.16 (0.53)	0.25 (3.68)	1.39 (5.20)
	6th decile	3,187,700	300	0.16 (0.54)	0.26 (3.77)	1.45 (5.33)
	7th decile	3,070,300	400	0.17 (0.56)	0.28 (3.80)	1.51 (5.47)
	8th decile	2,869,000	400	0.18 (0.57)	0.29 (3.86)	1.57 (5.59)
	9th decile	2,592,100	500	0.19 (0.60)	0.33 (3.95)	1.73 (5.91)
	10th decile - lowest	2,355,800	1,100	0.19 (0.61)	0.33 (4.19)	1.76 (6.05)
Occupational level	Management	2,641,700	<100	0.16 (0.49)	0.24 (3.42)	1.50 (5.00)
	Professional	4,518,000	<100	0.20 (0.51)	0.37 (4.21)	1.86 (5.43)
	Skilled, technical & supervisor	7,458,300	100	0.13 (0.49)	0.19 (3.35)	1.22 (4.82)
	Semi-skilled	7,206,200	100	0.16 (0.54)	0.25 (3.45)	1.42 (5.26)
	Unskilled	2,394,000	<100	0.16 (0.57)	0.25 (3.63)	1.43 (5.58)
	No occupation	8,691,100	4,200	0.17 (0.57)	0.27 (4.26)	1.47 (5.56)
Visible minority	Not visible minority	27,271,600	4,300	0.14 (0.48)	0.23 (4.00)	1.20 (4.90)
	Visible minority	5,637,600	200	0.32 (0.68)	0.44 (2.94)	2.55 (6.46)
Immigration status	Non-immigrant	25,520,200	3,600	0.11 (0.44)	0.17 (3.63)	0.99 (4.54)
	Immigrant	7,389,000	900	0.36 (0.68)	0.70 (4.01)	2.89 (6.54)
Marital status	Single, never married	4,694,500	300	0.27 (0.63)	0.61 (5.55)	2.15 (6.58)
	Common - law	3,942,500	100	0.12 (0.48)	0.26 (4.71)	1.03 (4.82)
	Married	19,672,000	2,600	0.15 (0.50)	0.18 (2.97)	1.33 (4.86)
	Separated	914,600	<100	0.19 (0.59)	0.35 (4.18)	1.73 (5.86)
	Divorced	2,075,300	200	0.20 (0.59)	0.48 (5.21)	1.82 (6.12)
	Widowed	1,610,400	1,200	0.18 (0.58)	0.30 (4.38)	1.56 (5.68)
Can-Marg: Residential instability	Q1 - lowest	7,737,800	700	0.10 (0.41)	0.08 (1.67)	0.92 (3.80)
	Q2	8,714,000	1,100	0.08 (0.36)	0.04 (2.19)	0.62 (3.55)
	Q3	6,541,500	900	0.17 (0.57)	0.27 (3.78)	1.53 (5.38)
	Q4	5,687,900	1,000	0.25 (0.63)	0.71 (5.90)	2.20 (6.11)
	Q5 - highest	4,228,000	900	0.38 (0.72)	1.80 (9.62)	3.67 (8.20)
Can-Marg: Dependency	Q1 - lowest	6,119,300	500	0.20 (0.51)	0.56 (4.39)	2.18 (5.66)
	Q2	5,480,400	500	0.19 (0.56)	0.37 (3.79)	1.72 (5.76)
	Q3	5,218,100	600	0.24 (0.62)	0.31 (4.14)	1.85 (5.90)
	Q4	6,549,600	1,000	0.16 (0.53)	0.28 (3.64)	1.36 (5.38)
	Q5 - highest	9,541,839	2,000	0.10 (0.43)	0.04 (3.05)	0.59 (3.95)
Can-Marg: Material deprivation	Q1 - lowest	7,040,200	800	0.14 (0.39)	0.22 (3.13)	1.43 (4.34)
	Q2	6,316,000	800	0.16 (0.46)	0.25 (3.00)	1.62 (5.07)
	Q3	6,509,800	900	0.14 (0.52)	0.16 (2.70)	1.25 (4.81)
	Q4	5,572,700	800	0.25 (0.67)	0.59 (5.17)	1.93 (6.64)
	Q5 - highest	7,470,400	1,200	0.15 (0.66)	0.24 (5.41)	1.10 (5.78)
Can-Marg: Ethnic concentration	Q1 - lowest	10,170,500	1,400	0.03 (0.22)	0.01 (1.78)	0.17 (2.23)
	Q2	8,085,800	1,400	0.11 (0.39)	0.12 (3.56)	0.74 (3.81)
	Q3	5,742,800	800	0.18 (0.49)	0.42 (4.41)	1.71 (5.00)
	Q4	4,529,900	500	0.33 (0.63)	1.09 (7.09)	2.95 (6.95)
	Q5 - highest	4,380,100	400	0.54 (0.68)	1.27 (5.87)	4.46 (6.99)
Urban form	Active urban core	2,796,000	500	0.39 (0.60)	1.77 (7.80)	4.20 (7.33)
	Transit-reliant suburb	2,287,700	300	0.51 (0.73)	1.85 (9.76)	4.22 (8.17)
	Car-reliant suburb	14,430,900	1,800	0.25 (0.59)	0.70 (5.61)	2.26 (6.28)
	Exurban	1,873,700	200	0.05 (0.22)	0.02 (1.84)	0.39 (2.19)
	Rural	11,520,900	1,600	0.01 (0.15)	0.01 (0.47)	0.07 (1.36)
Airshed	Western	4,109,600	600	0.16 (0.57)	0.11 (1.69)	1.07 (6.29)
	Prairie	4,431,700	400	0.12 (0.40)	0.22 (5.17)	1.97 (5.39)
	West Central	1,817,500	200	0.07 (0.19)	0.10 (1.41)	0.14 (0.56)
	Southern Atlantic	2,943,900	500	0.02 (0.29)	0.12 (4.72)	0.10 (2.72)
	East Central	19,317,500	2900	0.22 (0.59)	0.37 (5.34)	1.93 (5.53)
	Northern	289,000	<100	0.01 (0.25)	0.01 (0.08)	0.38 (2.33)

IQR: interquartile range, Can-Marg: the Canadian Marginalization Index.

* Numbers of deaths were rounded up to the nearest 100 due to confidentiality and may not add up to the total.

Table 2
Hazard ratios (HRs) and 95% confidence intervals (CIs) from different Cox proportional hazards models for time to deaths due to Alzheimer's, per interquartile range increase in industrial $PM_{2.5}$ (0.53 tonnes/meter per year), NO_2 (5.28 tonnes/meter per year), and SO_2 (3.73 tonnes/meter per year) emissions respectively.

Model[**]	HR (95% CI)		
	$PM_{2.5}$	NO_2	SO_2
Primary model[**]	**1.006 (1.000-1.011)**	0.994 (0.978-1.010)	0.998 (0.996-1.001)
Primary model + $PM_{2.5}$	-	0.984 (0.966-1.002)	0.997 (0.995-1.001)
Primary model + NO_2	**1.009 (1.004-1.015)**	-	0.998 (0.995-1.001)
Primary model + SO_2	**1.008 (1.003-1.012)**	0.999 (0.982-1.017)	-
Primary model + $PM_{2.5}$+NO_2	-	-	0.998 (0.995-1.001)
Primary model + $PM_{2.5}$ + SO_2	-	0.990 (0.971-1.009)	-
Primary model + NO_2 + SO_2	**1.009 (1.004-1.015)**	-	-
Primary model + NDVI (greenness)	**1.006 (1.000-1.011)**	0.993 (0.976-1.008)	0.998 (0.996-1.001)
Primary model + Charlson Comorbidity Index	**1.005 (1.000-1.011)**	0.992 (0.976-1.008)	0.998 (0.995-1.001)

Note: Values in bold are statistically significant at $p < 0.05$.

[**] The primary model is stratified by sex, age, and adjusted for educational attainment, income adequacy quintile, employment status, occupational group, visible minority status, immigration status, marital status, Can-Marg variables (instability, ethnic concentration, material deprivation, and dependency), urban form, and airshed.

Table 3
Effect modification of hazard ratios (HRs) and 95% confidence intervals (CIs) for industrial $PM_{2.5}$, NO_2, and SO_2 emissions with mortality of Alzheimer's disease.

Subgroup	The number of deaths[+]	HR (95% CIs)		
		$PM_{2.5}$	NO_2	SO_2
Sex				
Male	2100	**1.014 (1.004-1.023)**	0.993 (0.972-1.014)	0.998 (0.995-1.001)
Female	1600	1.003 (0.992-1.013)	0.996 (0.973-1.019)	0.998 (0.995-1.002)
Age group				
<65	100	0.905 (0.740-1.106)	0.777 (0.585-1.031)	0.934 (0.845-1.031)
≥65	3600	**1.006 (1.000-1.013)**	0.990 (0.974-1.006)	0.997 (0.995-1.000)
Urban form				
Urban core	400	1.001 (0.971-1.032)	0.962 (0.900-1.029)	0.988 (0.976-1.001)
Transit-reliant suburb	300	0.925 (0.853-1.002)	0.951 (0.894-1.013)	0.990 (0.974-1.007)
Auto-reliant suburb	1600	**1.018 (1.005-1.030)**	1.006 (0.980-1.032)	0.997 (0.993-1.002)
Exurban	200	1.023 (0.982-1.067)	1.033 (0.981-1.088)	0.994 (0.977-1.012)
Rural	1300	**1.006 (1.000-1.012)**	1.002 (0.978-1.026)	1.000 (0.999-1.002)
Frailty (Charlson Comorbidity Index)				
No comorbidities (0 index)	2400	**1.006 (1.000-1.012)**	0.989 (0.968-1.010)	0.999 (0.996-1.001)
Moderate (1-3 index)	1200	0.999 (0.975-1.024)	1.001 (0.977-1.025)	0.996 (0.992-1.001)
High (4+ index)	100	0.989 (0.906-1.080)	0.946 (0.851-1.051)	0.959 (0.911-1.008)
Airshed				
Western	400	1.006 (0.960-1.005)	0.935 (0.839-1.042)	0.998 (0.996-1.001)
Prairie	300	0.979 (0.981-1.076)	1.021 (0.973-1.072)	1.001 (0.995-1.008)
West Central	100	1.032 (0.981-1.086)	**1.059 (1.000-1.121)**	1.000 (0.995-1.002)
Southern Atlantic	400	1.004 (0.994-1.015)	0.996 (0.961-1.032)	1.000 (0.991-1.009)
East Central	2400	**1.008 (1.000-1.016)**	0.988 (0.967-1.009)	0.997 (0.993-1.001)
Northern	<100	-	-	-

Notes: Values in bold are statistically significant at $p < 0.05$.

[+] Numbers of deaths were rounded up to the nearest 100 for the demonstration purpose due to confidentiality and may not add up to the total, while we used precise values of the deaths for the modelling analyses. The analysis was not performed if the number of deaths in the subgroup is less than 100. Frailty represents the Charleston Comorbidity Index.

calculated by Buteau et al. (2018) (Table 4). Our weighted estimates for median and IQR for $PM_{2.5}$ and SO_2 are larger than Buteau's weighted estimates. Similarly, our weighted estimate for the median and IQR of SO_2 is larger than Buteau's unweighted estimate. However, Buteau's unweighted estimate for the median of $PM_{2.5}$ is larger than ours. In addition, the IQRs for our estimates were larger.

4. Discussion

In this study, we observed significant positive associations between industrial $PM_{2.5}$ emissions and mortality from Alzheimer's disease, while the association between industrial NO_2/SO_2 emissions and mortality was not clear.

We used time-varying emission estimates to consider residential mobility of participants and potential calendar-year trends in the emissions (Zhao et al., 2021). Compared with Buteau et al.'s (2018) study, we comprehensively estimated industrial air pollutant emissions by considering all, not only the closest major, emitters in a larger buffer area (15 km vs. 7.5 km). These factors contributed to the higher emission level estimates in this study compared to Buteau et al. (2018).

Oxidative stress can be regarded as one factor that plays an important role in the development of Alzheimer's disease (Moulton and Yang, 2012) and the appearance of senile plaques is the preceding hallmark of the disease (Markesbery, 1997). Increasing toxicological evidence shows that exposure to $PM_{2.5}$ is likely to induce respiratory and systemic inflammation, resulting in chronic oxidative stress (Migliore and Coppede, 2009; Ranft et al., 2009; Tsai et al., 2019). Additionally, exposure to $PM_{2.5}$ intensifies generation of reactive oxygen species that impairs the blood-brain barrier and increases the production of amyloid-beta peptides, the principal component of senile plaques (Mark, et al., 1996; Ranft et al., 2009). Thus, exposure to ambient $PM_{2.5}$ is treated as a risk factor for Alzheimer's disease. The above toxicological plausibility is demonstrated by epidemiological studies, in which significant associations between ambient $PM_{2.5}$ exposure and morbidity/mortality from Alzheimer's disease were observed (Shi et al., 2020;

Table 4

Median and IQR for estimated $PM_{2.5}$ and SO_2 emissions in this study compared to Buteau et al. (2018).

Pollutant	Estimated emissions in this study				Estimated emissions in Buteau et al. (2018)			
	Weighted (tons) [1]		Weighted (tons) [2]		Weighted (tons) [2]		Unweighted (tons) [3]	
	median	IQR	median	IQR	median	IQR	Median	IQR
$PM_{2.5}$	0.16	0.53	160	530	36	97	177	96
SO_2	1.45	3.73	1450	3730	71	255	299	1075

Note: Pollutants in this study are reported in tons/meter/year but are converted to tons/km/year here for comparison purposes (km = meter*1000).

[1] Weighted by wind and inverse distance in meters (m).

[2] Weighted by wind and inverse distance in kilometers (km).

[3] Emissions by the nearest major emitter within 7.5 km of the residence (unweighted).

Thiankhaw et al., 2022) in different age groups. Differing from the previous epidemiological studies that focused on ambient $PM_{2.5}$, this is the first study to observe an association between industrial $PM_{2.5}$ exposure and mortality due to Alzheimer's disease.

In contrast to studies on $PM_{2.5}$ and alzheimer's disease, there are fewer studies focusing on the associations between ambient NO_2/SO_2 and alzheimer's disease, and findings in those studies do not show consistent positive associations (Fu and Yung, 2020). Ku et al. (2016) observed injuries of neurobehavior induced by co-exposure (inhalation) to ambient $PM_{2.5}$, NO_2 and SO_2 in mice brains. Similarly, deterioration of spatial learning and memory, as well as the accumulation of amyloid proteins, pathological abnormalities, and cognitive defects related to alzheimer's disease, were observed in mice following exposure to NO_2 inhalation (Yan et al., 2016). In addition, levels of rat synaptophysin, a crutial synaptic vesicle membrane protein involved in synaptic vesicle trafficking and neurotransmitter release, were decreased in rat hippocampus after SO_2 inhalation (Yun et al., 2013). These results suggested that SO_2 exposure may lead to synaptic depression and contribute to cognitive decline (Yun et al., 2013). Although injuries of neurobehavior induced by ambient NO_2/SO_2 inhalation have been found in these studies (Ku et al., 2016; Yun et al., 2013), a clear association between industrial NO_2/SO_2 emission and deaths from AD was not observed in our study. Relatively low neighborhood industrial NO_2/SO_2 emissions (i.e., for many participants of this study, no industrial NO_2/SO_2 emitters within the 15 km buffer of their residences) may have contributed to the null association.

Significant associations were found for the East Central airshed. This region contains the urbanized areas of Quebec and southwestern Ontario and high levels of industrial pollution, while other airsheds may have had low statistical power due to lower populations and lower levels of pollutants. It has been previously shown that airshed can significantly impact health (Zhao et al., 2018; Sheridan and Kalkstein, 2004) and is specifically a modifier for the effect of air polluants on neurological health (Zhao et al., 2021). Additionally, we found a significant effect of age in those greater than 65. Neuro- inflammation is increasingly prevalent in aged tissues (Mumaw et al., 2016), which may explain why those >65 years of age are more vulnerable to its effects.

Although hospital visits due to dementia has been used as one of the factors in computing the Charlson comorbidity index and was used as a measure to adjust for frailty in the study, we still cannot readily discern whether industrial $PM_{2.5}$ emissions led to an increased incidence of Alzheimer's disease and consequently caused more deaths, or if the emission caused more mortality in people who already had the disease. In the future, we will integrate administrative health data such as the Discharge Abstract Database (DAD) from the Canadian Institute of Health Information (CIHI) with the CanCHEC to better understand the associations with Alzheimer's disease as an underlying vs. contributing cause of death.

It is important to understand the public health consequences of exposure to specific sources of air pollutants. If industrial-source air pollutants generate higher risks relative to their IQRs than total $PM_{2.5}$, NO_2 and SO_2, this would suggest that analyses using total $PM_{2.5}$, NO_2 and SO_2 may underestimate important public health implications of air pollutant exposure. Our study suggests that controlling emissions of $PM_{2.5}$ from those industrial sources may curb the mortality burden of Alzheimer's disease by controlling the overall environmental burden of $PM_{2.5}$.

The effect sizes observed in this study are small. However, the estimated contributions of industry sources to total PM in Canada is also small (14.2%) (Meng et al., 2019). If this effect is calculated/interpolated as a result of an increase equivalent to the IQR of total $PM_{2.5}$, we would expect an IQR increase in total $PM_{2.5}$ to be associated with a 7% increase in AD mortality, which is similar in size to what Chen et al. (2017b) found between total $PM_{2.5}$ and dementia incidence, with an HR of 1.06 (95% CI: 1.05–1.07) per IQR increase in $PM_{2.5}$ exposure after adjusting for age, sex, and region in Ontario, Canada.

Observational studies such as this one do not infer causality, but rather suggest and support hypotheses and suggest areas of further research. Causality is judged on several factors such as repeatability, strength of association, and biological plausibility. Multiple comparisons increase the risk of false positives but the results need to be interpreted based on other relevant evidence. Based on previous literature, the comparisons we made were reasonable and they could have either been made in one study or as part of several separate studies and the risk of false positives would be the same overall. Results from observational studies are strengthened by similar findings from different populations in different countries done by different investigators.

4.1. Strengths and limitations

Approximately 3.2 million participants living in not only urban but also rural and remote, northern regions of Canada were included, and this large representative population is the principal strength of this study. Another noticeable strength is a relatively comprehensive adjustment for demographic, socioeconomic, environmental, and geographic factors. In particular, we included the Charlson Comorbidity Index to assess the possible influence of frailty of individuals on the association between the exposures and Alzheimer's disease mortality, since people with comorbidities are likely dying from other causes but not Alzheimer's disease. This potential confounder was not considered in most previous studies using the CanCHEC Cohort (e.g. Pappin et al., 2019; Zhao et al., 2021). Additionally, we used a dynamic annual geographically-adjusted income to replace stationary unadjusted income at the baseline. The dynamic annual income may reduce the potential error generated by ascertaining employment status as of baseline because we found a strong association between reported employment status as of census date and annual income through the follow-up period.

Despite the improved estimation on industrial air pollution emissions, we acknowledge that diffusion of air pollutants is affected by additional meteorological and geographic factors (e.g. air humidity, terrain and mixing height) besides wind (Liu et al., 2017, 2018). In the future, we will consider using a complex atmospheric dispersion model (e.g. the California Puff) to estimate the industrial air pollutant emissions (Exponent, 2018; Zhao et al., 2020), though at present, the computing time cost of using the atmospheric dispersion model to estimate the emissions at a relatively fine spatial resolution for the whole Canada is nearly unaffordable.

Despite the adjustment for 15 covariates in our primary Cox model, some potential confounders, typically smoking habits, were not collected in our cohort. However, based on our previous study using the lung-cancer mortality rate to indirectly adjust for smoking, the effects of smoking on HRs of mortality of neurological diseases are limited (Zhao et al., 2021).

It is important to note that emissions of the three industrial pollutants are correlated in space. Thus, the issue of collinearity may confound our findings when two or more emission variables were included in information loss (Bennette and Vickers, 2012). Moreover, supposing a linear and additive combination of exposures and covariates may also generate errors (Bobb et al., 2015), though most existing studies used the same supposition. Developing an efficient non-parametric machine learning method may be helpful to solve the above issues.

Even though we did not observe significant associations between non-accidental mortality and air pollutants, we still can not ignore the possibility of underestimating the true risk. Since AD is developed mostly at later age there is a chance that the true effect of $PM_{2.5}$ on AD risk might be underestimated due to possibility that participants are dying from other causes before they can develop dementia.

5. Conclusion

We identified a positive association between industrial $PM_{2.5}$ emissions and mortality from Alzheimer's disease. However, we did not observe a clear association of mortality with industrial NO_2/SO_2 emissions. Additional work is needed by using more accurate estimates of industrial pollution emissions, better understanding of the disease course using hospital records, and adopting novel statistical methods to more flexibly model health effects of multiple exposures and covariates.

Ethics

Data were analyzed and maintained according to the principles of disclosure and confidentiality as per the Canadian Statistics Act.

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Declaration of Competing 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.

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