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Ozone exposure and cardiovascular-related mortality in the Canadian Census Health and Environment Cohort (CANCHEC) by spatial synoptic classification zone☆

Sabit Cakmak [a, *], Chris Hebbern [a], Jennifer Vanos [b], Dan L. Crouse [c], Rick Burnett [a]

[a] Population Studies Division, Environmental Health Science & Research Bureau, Health Canada, 50 Columbine Driveway, Ottawa, ON K1A 0K9, Canada
[b] Department of Geosciences, Texas Tech University, Box 41053, Lubbock, TX 79409-1053, USA
[c] Department of Sociology, University of New Brunswick, PO Box 4400, Fredericton, NB E3B 5A3, Canada

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A B S T R A C T

Our objective is to analyse the association between long term ozone exposure and cardiovascular related mortality while accounting for climate, location, and socioeconomic factors. We assigned subjects with 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC) to one of seven regions based on spatial synoptic classification (SSC) weather types and examined the interaction of exposure to both fine particulate matter ($PM_{2.5}$) and ground level ozone and cause of death using survival analysis, while adjusting for socioeconomic characteristics and individual confounders. Correlations between ozone and $PM_{2.5}$ varied across SSC zones from −0.02 to 0.7. Comparing zones using the most populated SSC zone as a reference, a 10 ppb increase in ozone exposure was associated with increases in hazard ratios (HRs) that ranged from 1.007 (95% CI 0.99, 1.015) to 1.03 (95% CI 1.02, 1.041) for cardiovascular disease, 1.013 (95% CI 0.996, 1.03) to 1.058 (95% CI 1.034, 1.082) for cerebrovascular disease, and 1.02 (95% CI 1.006, 1.034) for ischemic heart disease. HRs remained significant after adjustment for $PM_{2.5}$. Long term exposure to ozone is related to an increased risk of mortality from cardiovascular and cerebrovascular diseases; the risk varies by location across Canada and is not attenuated by adjustment for $PM_{2.5}$. This research shows that the SSC can be used to define geographic regions and it demonstrates the importance of accounting for that spatial variability when studying the long term health effects of air pollution.

1. Introduction

Elevated exposure to ambient outdoor air pollution has been shown to contribute to acute and chronic health effects in the Canadian population (Cakmak et al., 2014, 2011; Crouse et al., 2012, 2015). The association between long-term exposure to fine particulate matter (particles measuring <2.5 μm in aerodynamic diameter [$PM_{2.5}$]) and cardiovascular mortality has been well documented (Brook et al., 2010; Crouse et al., 2015, 2012; Goldberg et al., 2006; Krewski et al., 2009) while the association between long-term exposure to ozone and mortality has been less studied. Bell et al. (2004) did find a 10 ppb increase in short term ozone was associated with a 0.64% increase in cardiovascular and respiratory mortality in a study of 95 large urban communities in the United States (Bell et al., 2004). In contrast, a UK-based cohort study found no positive association between ozone exposure and cardiovascular or respiratory causes of mortality (Carey et al., 2013). However, an independent effect of ozone exposure has been difficult to discern as ozone and $PM_{2.5}$ share common point sources of emissions or chemical precursors, such as traffic and industrial pollution, and tend to be spatially correlated (Crouse et al., 2015). For example, a study of mortality from ischemic heart disease and lung cancer deaths in Los Angeles found relative risks of mortality from $PM_{2.5}$ ranging from 1.24 to 1.6, after adjustments for ozone and expressway exposure (Jerrett et al., 2005). A later study in California using individualised exposure assessments found positive associations between $PM_{2.5}$, ozone, and NO_2 with the incidence of ischemic heart disease (Jerrett et al., 2013); the inclusion of ozone with $PM_{2.5}$ in the same all-cause mortality model raised the risk estimate for $PM_{2.5}$, whereas NO_2 attenuated the risk from $PM_{2.5}$.

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* Corresponding author.
E-mail address: sabit.cakmak@canada.ca (S. Cakmak).

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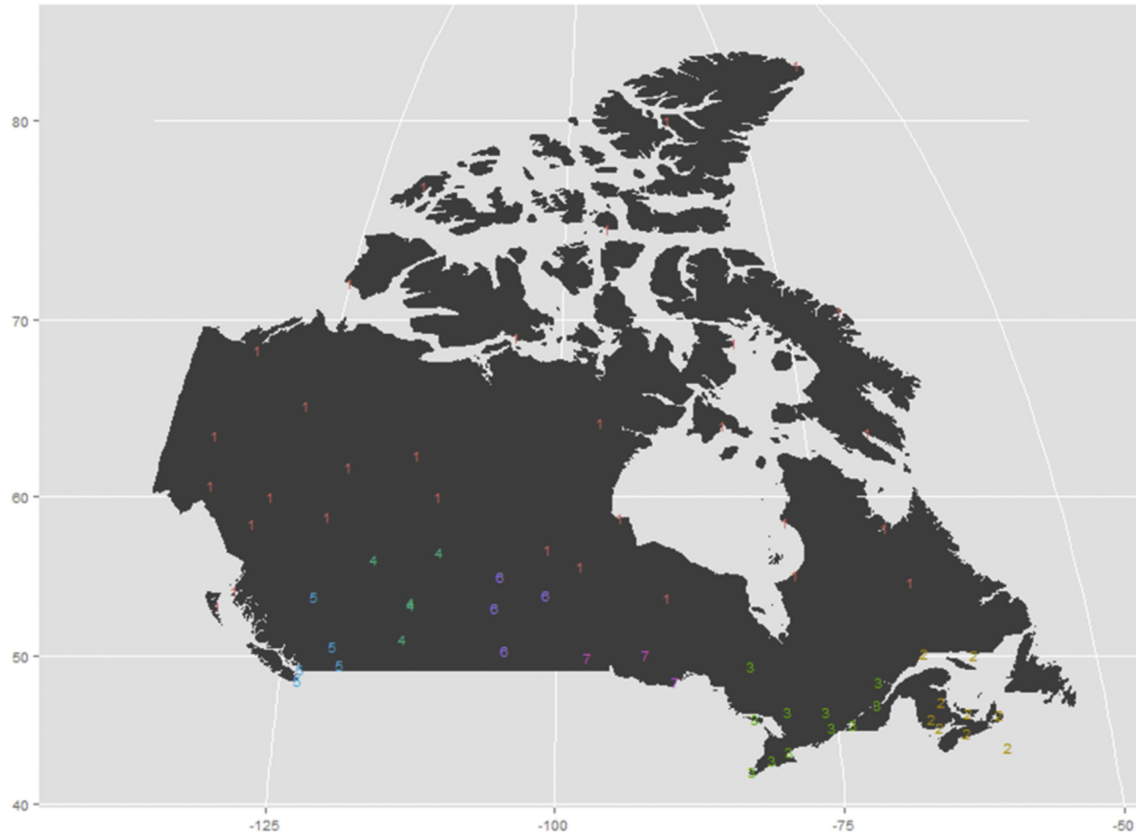

Fig. 1. SSC zones derived from cluster analysis of daily SSC time series for 1991 to 2006 across Canada. 1: Polar; 2 East coast; 3: Great Lakes/St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central.

The spatial synoptic classification (SSC) is a daily weather-type classification scheme that has become widely used in climatological and epidemiological investigations (Hondula et al., 2013). The SSC is a relative, rather than an absolute classification system, and can therefore account for differences in local responses to stressful meteorological conditions (Sheridan, 2002). Temperature has been widely studied as a predictor for morbidity and mortality (Gasparrini et al., 2015; Martin et al., 2012; O'Neill and Ebi, 2009), but the modifying effect of temperature on the relationship between health outcomes and air pollution is complex. . Daily weather is classified into one of six types: (Dry Polar [DP], Dry Moderate [DM], Dry Tropical [DT], Moist Polar [MP], Moist Moderate [MM], Moist Tropical [MT]), or an additional Transition category (TR), based on six-hourly meteorological parameters (air temperature, dew point, wind velocity, pressure, and cloud cover). Research has found associations between SSC weather types and human mortality, inspired the use of empirically based heat health warning systems, and has been used to illustrate the rising frequency of the warm air masses through the year in Canada at the expense of cool air masses (Vanos and Cakmak, 2014). While many epidemiological studies have examined merely temperature as a main cause for specific health outcomes, the SSC provides a complementary and holistic approach to understanding relationships between numerous environmental parameters, air pollution levels linked to such parameters, and human health outcomes (Kalkstein, 1991; Rainham et al., 2005).

As a secondary pollutant, ozone is formed by photochemical reactions that can occur in homogenous manner in air masses over large spatial scales. These scales, and the conditions that may be more or less favourable for ozone formation, can be captured by the spatial synoptic classification (Hanna et al., 2011). In a previous study covering ten Canadian cities, the relative risk of mortality in the elderly was not modified by weather type for CO, NO_2, or SO_2; however, the modifying effect of weather type was significant for ozone (Vanos et al., 2014). The atmospheric conditions that favour ozone formation may also differ across spatial scales, and are more common in the Great Lakes/St. Lawrence cities such as Toronto, Montreal, and Ottawa (Vanos et al., 2014).

Previous research has found that warmer air masses in the summer months can result in increased health care burdens and hospital utilisation; on oppressively hot days, ambulance calls increased by 4% over a four year period in Toronto (Dolney and Sheridan, 2006), and extreme high temperatures in New York were found to increase hospital admissions for cardiovascular disorders (Wu et al., 2013). DT and MT+ weather types have been implicated in heat-related mortality events (Sheridan et al., 2009) in the short term. DT weather types produce conditions associated with photoreactive air pollutants such as ozone (Hanna et al., 2011), and it is likely that cities that experience more of these weather type days may be at greater risk of mortality due to these pollutants. For example, analysis of the National Morbidity and Mortality Air Pollution Study data found that high temperatures positively modified the effects of ozone on cardiovascular mortality (Ren et al., 2009, 2008).

The Canadian Census Health and Environment Cohort (CanCHEC) is a study of 2.7 million Canadians enrolled in 1991 and followed through until 2009, with a geographic range, level of detail in the long-form census, link to the Canadian Mortality Database, and population size providing a significant opportunity in understanding longterm influences of weather and climate on human health. A previous study of the CanCHEC cohort suggested that spatial clustering of diabetes deaths occurs across Canada and

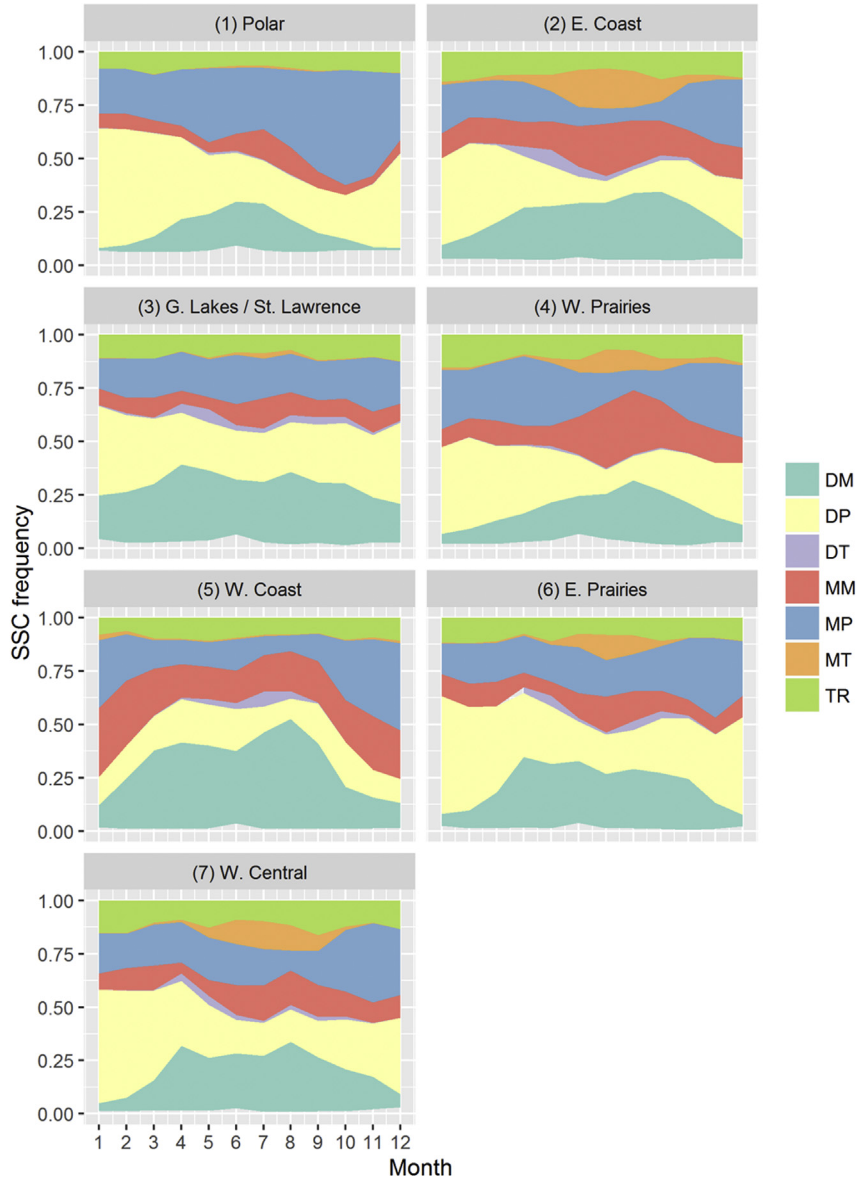

Fig. 2. Annual frequency of spatial synoptic classification weather types by SSC zone for the period (1991–2006) for a full year. Each color represents a portion of the frequency of each weather type, where the highest values representing the most frequent weather types for the climate zone. Dry Polar [DP], Dry Moderate [DM], Dry Tropical [DT], Moist Polar [MP], Moist Moderate [MM], Moist Tropical [MT], or an additional Transition category (TR).

could not be accounted for by the covariates included in the model (Brook et al., 2013); similarly, Crouse et al. (2012) found unexplained spatial variation in the association between $PM_{2.5}$ exposure and cardiovascular mortality. We hypothesize that some of the spatial clustering may be due to regional differences in weather type exposures. Jerrett et al. (2009) also reported that temperature and region of the US modified the effect of ozone on risk of death from respiratory diseases in the American Cancer Society Cancer Prevention Study II, a similarly long term national cohort study. However, In Canada broad geographic census definitions that can be used to capture geographic pollution exposures are not available, so we attempted to create such a spatial differentiation by defining regional zones using the spatial synoptic classification.

Accordingly, the current study seeks to create such a regional spatial differentiation of climate zones using the SSC based on prevailing weather type days through statistical clustering, and account for these zones and socioeconomic factors in analysing the association between long term ozone exposure and cardiovascular related mortality. The inclusion of the climate zones as strata in the overall model, we are able to account for regional differences in the association between exposure to air pollution and health outcomes, we included those zones as strata in survival models. We then compared models: one which did not take into account spatial (regional) variability, to one that takes spatial variability into account by using zones as strata, and adjusted models for the effect of $PM_{2.5}$ to identify an independent long term effect of ozone on cardiovascular mortality.

2. Data and methods

2.1. Weather data

The Spatial Synoptic Classification is a semi-automated daily weather type classification system that categorises daily surface

Table 1
Cohort population by climate zone and individual level risk factors. 1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central.

Variable	Zone 1	2	3	4	5	6	7
Full cohort							
	73,880 (3.3%)	192,630 (8.5%)	1,401,090 (62%)	188,585 (8.3%)	236,875 (10.5%)	74,230 (3.3%)	91,845 (4.1%)
Visible minority							
No	99%	99%	95%	95%	90%	99%	96%
Yes	1%	1%	5%	5%	10%	1%	4%
Immigrant status							
Non-immigrant	4%	4%	19%	16%	26%	7%	14%
Immigrant/permanent resident	96%	96%	81%	84%	74%	93%	86%
Sex							
Female	51%	51%	50%	52%	51%	51%	51%
Male	49%	49%	50%	48%	49%	49%	49%
Aboriginal status							
Yes	77%	3%	2%	4%	3%	8%	7%
No	%	97%	98%	96%	97%	92%	93%
Marital Status							
Single	10%	12%	13%	9%	11%	11%	11%
Married/common law	13%	11%	13%	10%	10%	9%	10%
Separated/divorced/widowed	77%	77%	75%	81%	79%	80%	78%
Education level							
Post-secondary, non-university degree	13%	14%	16%	18%	18%	15%	15%
High School with or without certificate	34%	36%	37%	39%	41%	34%	35%
Did not complete high school	45%	40%	33%	28%	26%	39%	37%
University degree	8%	10%	14%	15%	15%	11%	13%
Labour force status							
Employed	11%	11%	6%	5%	6%	4%	5%
Unemployed	28%	29%	27%	19%	25%	25%	26%
Not in labour force	61%	60%	67%	75%	69%	71%	70%
Occupational group							
Management	7%	9%	3%	10%	10%	7%	8%
Professional (all)	25%	31%	7%	30%	26%	30%	26%
Skilled/technical/supervisor	25%	32%	76%	25%	25%	24%	26%
Semi-skilled	11%	12%	2%	7%	7%	7%	7%
Unskilled	22%	3%	7%	15%	21%	20%	21%
NA	10%	13%	4%	14%	13%	11%	12%
Socioeconomic status							
Lowest	12%	16%	13%	1%	1%	0.2%	2%
2	22%	19%	20%	22%	22%	23%	22%
3	23%	21%	22%	25%	25%	25%	25%
4	22%	22%	23%	26%	26%	26%	26%
Highest	20%	22%	23%	27%	27%	26%	26%

weather variables into one of six weather types and an additional Transition type (TR), where the weather type shifts from one to another. The data used for classification are obtained from the Meteorological Service of Canada from airport and other weather stations and the daily SSC classifications for each station are available at the SSC archive (http://sheridan.geog.kent.edu/ssc.html).

Sixty-one weather stations across Canada which covered large areas of the country and including all major cities and for which data were available from 1991 to 2006, were used as a source of data for analysis. Using the individual daily station SSC data from these stations, days categorised as one of seven spatial synoptic classification weather types were entered into a hierarchical agglomerative clustering analysis to determine a small number of spatially differentiated weather type zones. The number of clusters was determined based on satisfying the Akaike's Information Criteria (Akaike, 1974). Missing data were Each zone was categorised by similarities in the frequency of the proportion of SSC weather types (as displayed in Fig. 2), and subsequently each station was assigned a value corresponding to the SSC zone. Missing data was imputed using seasonal median values for each station; stations with greater than 10% missing data were excluded from the cluster analysis. This clustering resulted in seven SSC zones across Canada (see Figs. 1 and 2): Polar, East coast, Great Lakes St. Lawrence, West Prairies, West coast, East Prairies, West Central. The climate zones were then connected to the cohort health outcomes data through assigning each cohort member a value corresponding to the SSC zone for each year based on the nearest SSC station to their postal code. The clustering analysis was completed in R (version 3.1.3, package hclust). Although SSC climate zones have been created for North America through a similar analysis and can be found on the SSC website, there are very few zones (3 large zones) in the SSC climate types; thus we felt it necessary to determine climate zones specifically within Canada at a higher number for statistical purposes. Herein, the Canadian SSC climate zones will be termed as climate zone for the given study.

2.2. Study cohort

The CanCHEC is a population-based cohort of subjects who were

Table 2
Cause of death by cohort population (percentage by zone over 16 year study follow up period).by climate zone (1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central).

	Climate zones						
	1	2	3	4	5	6	7
Cerobravscular disease	0.5	0.7	0.8	0.6	0.8	1.0	1.0
Cardiovascular disease	2.4	3.7	4.0	3.1	3.6	4.6	4.5
Ischemic heart disease	1.4	2.3	2.6	1.9	2.0	2.7	6.0

Table 3
Exposure means by climate zone (1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central).

Climate zone	Ozone (ppb)	SD	Min	Max	$PM_{2.5}$ (mg/m^3)	SD	Min	Max
1	14.3	3.1	9.3	20.1	2	0.5	1	3
2	31.3	3.6	26.5	36.5	4.8	1.1	3.1	6.5
3	40.9	7.1	28.2	53	8.8	3.3	3.7	15.1
4	32.5	5.4	25.8	38	5.9	2.3	3.2	8.3
5	33.2	3.7	29.9	37.6	4.3	1.2	2.6	5.7
6	28.9	7.9	22.5	39.6	5.3	2.5	3.3	8.9
7	33.2	4.3	30.3	38.2	5.4	2.2	3.3	7.6

at least 25 years old at baseline and among the 20% of Canadian households selected to complete the mandatory long-form census questionnaire in 1991. Date of death and cause of death were linked to the cohort from the Canadian Mortality Database using deterministic and probabilistic linkage methods with follow-up to 2006 (Peters et al., 2013). The cohort has also been linked to annual income tax filings beginning in 1984 (i.e., preceding baseline by eight years) for the purposes of assigning annual residential postal codes for each year of follow-up. ICD-9 codes were used for deaths before 2000 and ICD-10 for deaths after that time. Cerebrovascular disease causes were identified with ICD-9: 430–438; ICD-10: I60–I69; cardiovascular disease (CVD) causes with ICD-9: 410–417, 420–438, 440–449; ICD-10: I20–I28, I30– I52, I60–I79; and ischemic heart disease (IHD) causes with ICD-9: 410–414; ICD-10: I20– I25 (all reported counts have been rounded to the nearest five for confidentiality reasons). Individual-level risk factors for mortality were obtained from the long form census (Table 1). Time-varying contextual variables from the closest census year, for the proportion of adults that had not completed high school, the proportion of visible minorities, and the proportion of individuals in the lowest income quintile were also included and were reassigned each year according to the subject's location (Crouse et al., 2015).

2.3. Exposure data

Estimates of annual average ozone exposure were obtained from a model representing average daily 8-hr maximum concentrations from 1 May to 31 October for years 2002–2009 across Canada at a 21 km horizontal resolution (Robichaud and Ménard, 2014), and assigned to cohort subjects by residential postal code (Crouse et al., 2015). The ozone model uses an interpolation technique adapted to air pollutants, which linearly combines hourly modelled ozone estimates from air quality forecast models with ground-based observations. This model was restricted to warm seasons due to the fact that, for the most part, ozone is less of an environmental threat in colder seasons across Canada. $PM_{2.5}$ exposures represent median concentrations for the period 1998–2006 based on satellite-derived measurements determined on a 10 km by 10 km grid surface (van Donkelaar et al., 2010). Temporal variation in $PM_{2.5}$ between 1998 and 2006 was inferred from two radiometrically stable satellite instruments (MISR and SeaWiFS) (Boys et al., 2014). Subject exposures were coded as missing if no residential postal code was available, which could indicate that the subject had left Canada, moved to an institution, or that they had not filed an income

Table 4
Ozone, ppb (and standard deviation) by climate zone (1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central).

Variables	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7
Visible minority							
Yes	34.8 (2.8)	36.1 (8.1)	44.5 (4.5)	35.4 (3.9)	32.7 (2.8)	33.8 (4.4)	33.8 (4)
No	35.2 (2.9)	35.9 (6.4)	42.7 (6.5)	35.7 (3.8)	33.1 (3.3)	34.8 (4.3)	33.9 (4.2)
Immigrant status							
Non-immigrant	35.2 (2.9)	36.9 (6.4)	42.2 (6.5)	35.7 (3.8)	33.1 (3.4)	34.8 (4.3)	33.9 (4.2)
Immigrant/permanent resident	35 (2.8)	38.2 (7.4)	45.2 (5.2)	35.7 (3.9)	32.8 (3.1)	34.5 (4.4)	33.9 (4.2)
Sex							
Female	35.2 (2.9)	36.9 (6.4)	42.7 (6.5)	35.7 (3.8)	33 (3.3)	34.8 (4.3)	33.9 (4.2)
Male	35.2 (2.9)	37 (6.4)	42.8 (6.4)	35.7 (3.9)	33 (3.3)	34.8 (4.3)	33.9 (4.2)
Aboriginal status							
Yes	34.3 (2)	37.1 (6.2)	41.7 (7)	34.8 (3.4)	33.5 (3.5)	35 (3.6)	34.2 (4.1)
No	35.5 (3)	36.9 (6.4)	42.8 (6.4)	35.7 (3.9)	33 (3.3)	34.8 (4.4)	33.9 (4.2)
Marital Status							
Single	35.4 (3)	37.4 (6.5)	42.6 (6.3)	35.8 (3.9)	33 (3.3)	34.8 (4.4)	34.2 (4.4)
Married/common law	35.1 (2.8)	37.1 (6.4)	42 (5.9)	35.8 (3.8)	32.8 (3.1)	37.4 (4.3)	34.1 (4.4)
Separated/divorced/widowed	35.2 (2.9)	36.8 (6.4)	42.9 (6.5)	35.6 (3.8)	33.1 (3.3)	34.8 (4.3)	33.8 (4.2)
Education level							
Post-secondary, non-university degree	35.2 (2.9)	37 (6.6)	43.1 (6.4)	35.7 (3.9)	32.9 (3.3)	34.6 (4.3)	34 (4.2)
High School with or without certificate	35.2 (2.9)	36.8 (6.4)	42.8 (1.5)	35.6 (3.8)	33.1 (3.3)	34.8 (4.3)	33.9 (4.2)
Did not complete high school	35.1 (2.9)	36.8 (6.2)	42.5 (6.6)	35.6 (3.8)	33.2 (3.4)	35 (4.3)	33.7 (4.1)
University degree	35.4 (2.9)	37.4 (7)	43.2 (5.8)	35.8 (3.9)	32.7 (3.1)	34.5 (4.4)	34.3 (4.5)
Lab force status							
Employed	35.2 (2.8)	36.2 (5.6)	42 (6.4)	35.6 (3.8)	33.2 (3.4)	35.1 (4.1)	33.9 (4.1)
Unemployed	35.2 (2.9)	37.1 (6.4)	42.5 (6.4)	35.8 (3.9)	33 (3.3)	34.8 (4.3)	34 (4.3)
Not in labour force	35.2 (2.9)	37.1 (6.4)	42.5 (6.4)	35.8 (3.9)	33 (3.3)	34.8 (4.3)	34 (4.3)
Occupational group							
Management	35.2 (2.8)	36.9 (6.7)	43.2 (6.2)	35.7 (3.9)	32.9 (3.3)	34.6 (4.4)	34 (4.3)
Professional (all)	35.1 (2.8)	36.8 (6.4)	42.8 (6.5)	35.7 (3.8)	33.1 (3.3)	34.9 (4.3)	33.7 (4.1)
Skilled/technical/supervisor	35.3 (2.9)	36.8 (6.4)	43 (6.5)	35.6 (3.8)	33.1 (3.3)	34.8 (4.3)	33.8 (4.2)
Semi-skilled	35.1 (2.8)	36.7 (6.1)	42.6 (6.7)	35.6 (3.7)	33.2 (3.3)	34.9 (4.3)	33.7 (4)
Unskilled	35.2 (3)	37.2 (6.3)	42.4 (6.4)	35.8 (4)	33 (3.3)	34.8 (4.3)	34 (4.3)
NA	35.1 (2.8)	37.1 (6.6)	43 (6)	35.7 (3.9)	32.8 (3.2)	34.5 (4.4)	34.2 (4.3)
Socioeconomic status							
Lowest	35.5 (3.1)	37 (6.3)	42 (6.3)	35.7 (4.8)	33.8 (4.9)	35.7 (6.1)	33.3 (4.1)
2	35.1 (2.8)	36.9 (6.4)	42.8 (6.4)	35.7 (3.3)	33.1 (3.3)	34.8 (4.3)	34 (4.2)
3	35.1 (2.8)	36.9 (6.4)	42.8 (6.4)	35.7 (3.3)	33.1 (3.3)	34.9 (4.3)	33.8 (4.1)
4	35.2 (2.9)	36.9 (6.4)	42.9 (6.4)	35.7 (3.3)	33 (3.3)	34.8 (4.3)	33.9 (4.2)
Highest	35.3 (2.9)	36.9 (6.5)	43 (6.4)	35.6 (3.9)	32.9 (3.3)	34.7 (4.3)	33.9 (4.3)

Table 5
$PM_{2.5}$, mg/m^3 (and standard deviation) by climate zones (1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central).

Variables	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7
Visible minority							
Yes	7.5 (1.5)	7.3 (2.3)	11.3 (2.3)	6.6 (1.4)	5.1 (1.1)	6.3 (1.4)	5.4 (1.8)
No	6.7 (1.9)	6.9 (2.3)	9.6 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
Immigrant status							
Non-immigrant	6.7 (1.9)	6.9 (2.3)	9.3 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.2 (1.7)
Immigrant/permanent resident	7.4 (1.5)	7.3 (2.3)	11.1 (2.3)	6.6 (1.4)	5 (1.3)	6.2 (1.3)	5.3 (1.7)
Sex							
Female	6.7 (1.9)	6.9 (2.3)	9.6 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
Male	6.7 (1.9)	6.9 (2.3)	9.7 (2.8)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
Aboriginal status							
Yes	7.4 (1.3)	6.8 (2.2)	8.8 (3)	6.8 (1.3)	5.5 (1.5)	6.6 (1.2)	5.5 (1.7)
No	6.5 (2)	6.9 (2.3)	9.7 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.2 (1.7)
Marital Status							
Single	6.5 (1.9)	7 (2.4)	9.7 (2.8)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.4 (1.7)
Married/common law	6.6 (1.9)	6.9 (2.3)	9.6 (2.9)	6.6 (1.4)	5.1 (1.3)	6.2 (1.3)	5.3 (1.7)
Separated/divorced/widowed	6.7 (1.9)	6.9 (2.3)	9.7 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.2 (1.7)
Education level							
Post-secondary, non-university degree	6.8 (1.9)	7 (2.3)	9.7 (2.8)	6.5 (1.4)	5 (1.4)	6.2 (1.3)	5.2 (1.7)
High School with or without certificate	6.8 (1.9)	6.9 (2.3)	9.6 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
Did not complete high school	6.6 (1.9)	6.9 (2.4)	9.6 (2.9)	6.6 (1.3)	5.1 (1.4)	6.2 (1.3)	5.4 (1.7)
University degree	6.9 (1.8)	7 (2.2)	10 (2.7)	6.5 (1.5)	5 (1.3)	6.2 (1.3)	5 (1.7)
Lab force status							
Employed	6.5 (1.9)	6.6 (2.3)	9.4 (3)	6.6 (1.4)	5.2 (1.5)	6.3 (1.2)	5.3 (1.7)
Unemployed	6.5 (1)	6.9 (2.4)	9.6 (2.9)	6.6 (1.4)	5 (1.4)	6.9 (1.3)	5.3 (1.7)
Not in labour force	6.8 (1.8)	6.9 (2.3)	9.7 (2.8)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.2 (1.7)
Occupational group							
Management	7 (1.8)	6.9 (2.3)	9.8 (2.7)	6.5 (1.5)	5 (1.4)	6.2 (1.3)	5.2 (1.7)
Professional (all)	6.7 (1.8)	6.9 (2.3)	9.6 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.2 (1.7)
Skilled/technical/supervisor	6.7 (1.9)	6.9 (2.3)	9.7 (2.8)	6.6 (1.4)	5.1 (1.4)	6.3 (1.3)	5.3 (1.7)
Semi-skilled	6.7 (1.8)	6.8 (2.3)	9.6 (2.9)	6.6 (1.3)	5.2 (1.4)	6.2 (1.3)	5.3 (1.7)
Unskilled	6.4 (1.9)	7 (2.4)	9.5 (2.9)	6.6 (1.4)	5 (1.4)	6.2 (1.3)	5.3 (1.7)
NA	6.9 (1.9)	6.9 (2.2)	9.8 (2.8)	6.5 (1.4)	5 (1.3)	6.2 (1.3)	5.1 (1.7)
Socioeconomic status							
Lowest	6 (1.9)	6.9 (2.3)	9.4 (2.9)	6.8 (1.8)	5.4 (2)	6.6 (1.9)	5.1 (1.7)
2	6.9 (1.8)	6.9 (2.3)	9.7 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
3	6.8 (1.8)	6.9 (2.3)	9.7 (2.9)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
4	6.8 (1.9)	6.9 (2.3)	9.7 (2.8)	6.6 (1.4)	5.1 (1.4)	6.2 (1.3)	5.3 (1.7)
Highest	6.7 (1.9)	6.9 (2.3)	9.7 (2.8)	6.5 (1.4)	5 (1.4)	6.2 (1.3)	5.2 (1.7)

tax return that year. For each year of follow-up, a 7-year moving window of past exposures to each pollutant, incorporating a single year lag, was estimated for each subject beginning with data from 1984 (i.e., the earliest year of postal code data available to us, and thus the largest window of exposure available). The moving window of exposure was assigned where postal codes were available for at least 4 out of the seven years, allowing the retention of subjects with partial postal code histories and to incorporate into our models the variability in exposures associated with annual residential mobility patterns (Crouse et al., 2015).

2.4. Statistical methods

We used the Cox proportional hazards model to relate exposure to date of death. Follow-up time was from 4 June 1991 to 21 December 2006. The baseline hazard function was stratified by sex and age from 25 years old to 90 in 5 year increments and censored at 90 years of age. The following covariates were included in our survival models: aboriginal status, visible minority status, marital status, education level, occupational group, immigrant status and income quintile (covariate category definitions given in Table 1). In order to examine the sensitivity of the association between air pollution and mortality for adjustment to climate zone, we calculated estimates of the overall effect of ozone or $PM_{2.5}$ on mortality by including/excluding SSC zones (adjusting/not adjusting respectively for climate zone) from the baseline hazard function as strata in the model. We also examined the effect modification of climate zone on the air pollution-mortality association by including in the survival model an interaction between air pollution and a categorical variable for climate zone, using the most populated zone (#3) as the reference category as it was the largest subject size, provided the most stable estimate for the reference group and had the most even distribution of the weather types. We used this method to examine effect modification as subjects can move among zones throughout the follow-up period, and examining by zone separately would remove person-years of follow-up from the analysis if a subject moved out of or into a zone. In other words, this method allowed us to include the entire cohort at once so subjects can move between zones and within zones; if we examined each zone separately then subjects who moved out of a zone would have been lost to follow up. Hazard ratios for each of the causes of death were estimated for long term exposure to ozone, $PM_{2.5}$, and ozone adjusted for $PM_{2.5}$ as a model covariate, using zone 3 as a reference.

Table 6
Pearson Correlations between mean ozone and $PM_{2.5}$ concentrations by SSC zone (1: Polar; 2 East coast; 3: Great Lakes St. Lawrence; 4: West Prairies; 5: West coast; 6: East Prairies; 7: West Central).

Climate zone	Correlation coefficient
1	0.35
2	0.7
3	0.65
4	0.09
5	0.24
6	−0.02
7	0.21

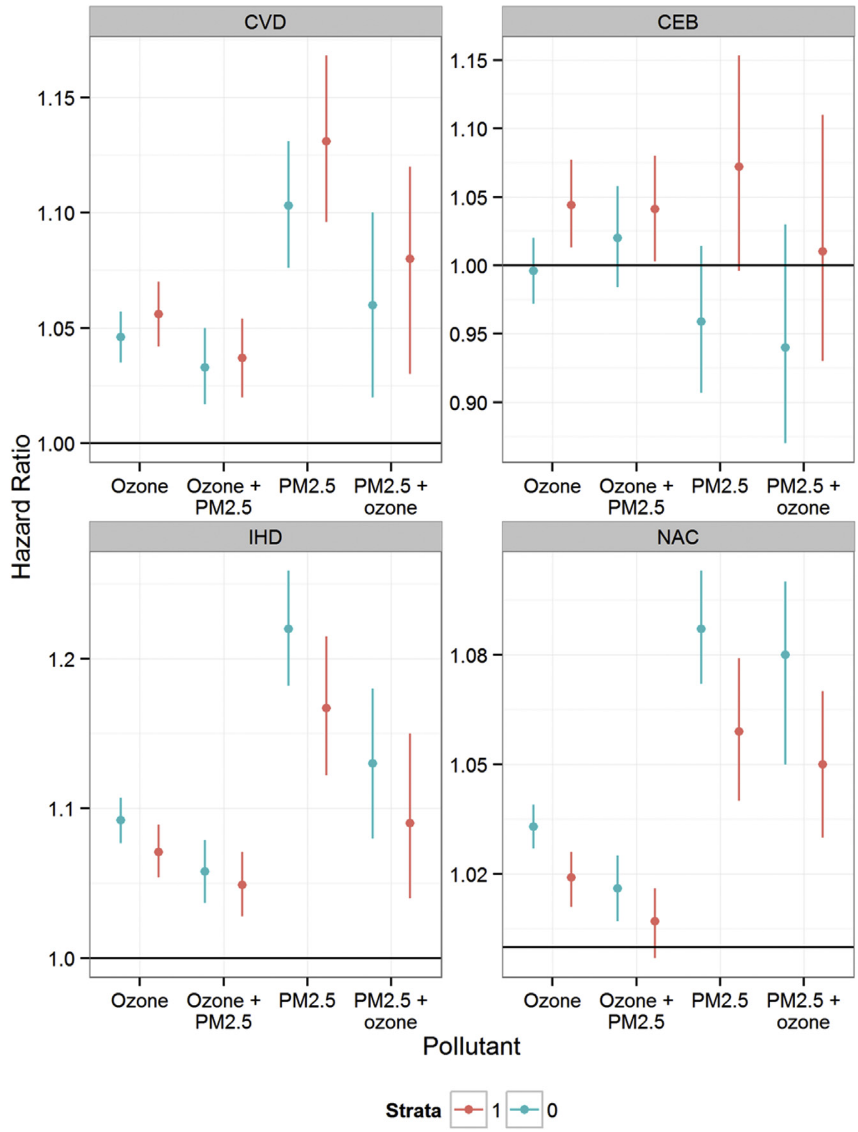

Fig. 3. Hazard ratios and 95% confidence intervals for non-accidental causes (NAC), cardiovascular disease (CVD), cerebrovascular disease (CEB) and ischemic heart disease (IHD) for ozone, and ozone adjusted for $PM_{2.5}$ exposure, $PM_{2.5}$, $PM_{2.5}$ adjusted for ozone exposure. Analysis completed for the full cohort, with estimates shown for SSC zone included in the model as a stratum (orange line), and climate zone excluded (green line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Hazard ratios were calculated for increments of 10 ppb for ozone and 10 μg/m^3 for $PM_{2.5}$. Likelihood ratio tests were used to assess the improvement in mortality prediction of the zone-air pollution interaction.

3. Results

The cluster analysis identified seven zones (Fig. 1) across Canada. Polar stations (zone 1) experience primarily dry polar and moist polar weather types with a seasonal summer increase in dry moderate days. West coast stations (zone 5) experience very few dry tropical days, the majority of the days being dry moderate or moist moderate, with an increase in moist polar days during the winter. The two prairie zones, 4 and 6, are broadly similar to each other: zone 4 is closer to the Rockies and experiences fewer dry polar days compared to zone 6, which has a greater number of dry polar days during the winter with cold air coming from the arctic. For both zones, dry moderate, dry polar and moist polar days are most common. The distribution of different weather types is more even in the Great Lakes/St Lawrence (zone 3) and West Central (zone 7), where moist tropical and dry tropical weather occurs in the summer months with large increases in winter dry polar days. In the east coast (zone 2), seasonal differences are less pronounced: in summer, there is an increase in moist moderate and moist tropical days while the rest of the year is characterised by moist polar and dry polar weather types, as a result of the coastal location.

The population of the cohort was greatest in zone 3 (Table 1), the Great Lakes/St Lawrence region, an area that includes three of Canada's largest urban cities, Toronto, Montreal, and Ottawa. Sixty-two percent of the total population lived in this zone over the study period. The second largest population was found in zone 5, the west coast, with 10.5% of the total.

The cohort consisted of 2,415,505 subjects for whom an SSC zone could be assigned, with 17,565 subjects dying of a cause coded as cerebrovascular disease; 86,590 from cardiovascular disease; and 57,310 from ischemic heart disease. Based on the zone at time

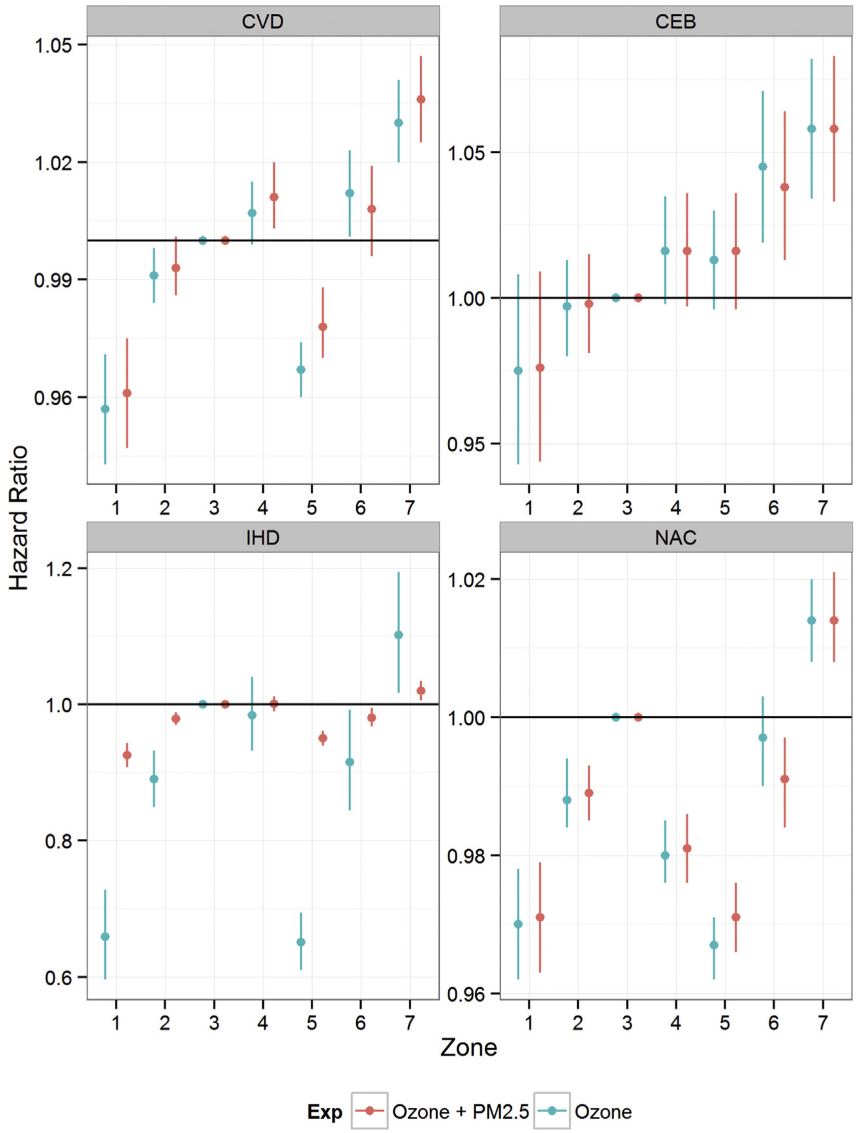

Fig. 4. Hazard ratios and 95% confidence intervals for non-accidental causes (NAC), cardiovascular disease (CVD), cerebrovascular disease (CEB) and ischemic heart disease (IHD) for ozone, and ozone adjusted for $PM_{2.5}$ exposure, by SSC zone, using climate zone 3 as baseline reference.

of death, the percentages of deaths were broadly similar for all three causes (Table 2): mortality from IHD was highest in zone 7, west central Canada, at 6%, and lowest in zone 1, the polar region, at 1.4%. CEB ranged from 0.5% of all non-accidental deaths in zone 1 to 1% in zones 6 and 7. CVD was highest in zone 6 at 4.6% and lowest in zone 1 at 1.4%.

Ozone exposures (Table 3) ranged from 14.1 (SD 3.1) ppm in zone 1 to 40.9 (SD 7.1) ppm in zone 3, the difference in part due to colder arctic air in zone 1 being less favourable for the formation of ozone, while in zone 3, industry, traffic pollution and warmer weather contribute to favourable conditions for ozone formation. $PM_{2.5}$ exposures ranged from 2 (SD 0.5) ppm in zone 1 to 8.8 (SD 3.3) ppm in zone 3. By demographic group (Table 4), ozone exposures were highest in the visible minority (44.5, SD 4.5) and new immigrant groups (45.2, SD 5.2) in zone 3, but the difference was not significant between groups. Similarly for $PM_{2.5}$ (Table 5), exposures varied more greatly by zone than by demographic group.

3.1. Association between ozone and $PM_{2.5}$ exposure and cardiovascular and related disease mortality

Exposure correlations: Correlations between mean levels of ozone and $PM_{2.5}$ ranged from −0.02 in zone 6, 0.04 in zone 4 to 0.7 in zone 2 (Table 6). The difference between the subject-weighted average of the correlation coefficients by zone (0.515) and the correlation determined without stratifying by zone overall (0.73), was significant at $P < 0.001$ using Fisher's Test (Fisher, 1921). Stratifying by zone reduced the correlation between ozone and $PM_{2.5}$, thus reducing the potential for confounding between the two pollutants.

Beta correlations: Correlations between parameter estimates for ozone and $PM_{2.5}$ were reduced by including zone as a stratum in the model. For all causes of death, the correlations reduced from approximately −0.73 without zone as a stratum to −0.57 when zone was included as a stratum in the model.

SSC zone as a model stratum: When zone was not included as a model stratum, ozone was associated with increased cardiovascular mortality (Fig. 3): HR 1.046 (95% CI 1.035, 1.057). Including zone as a

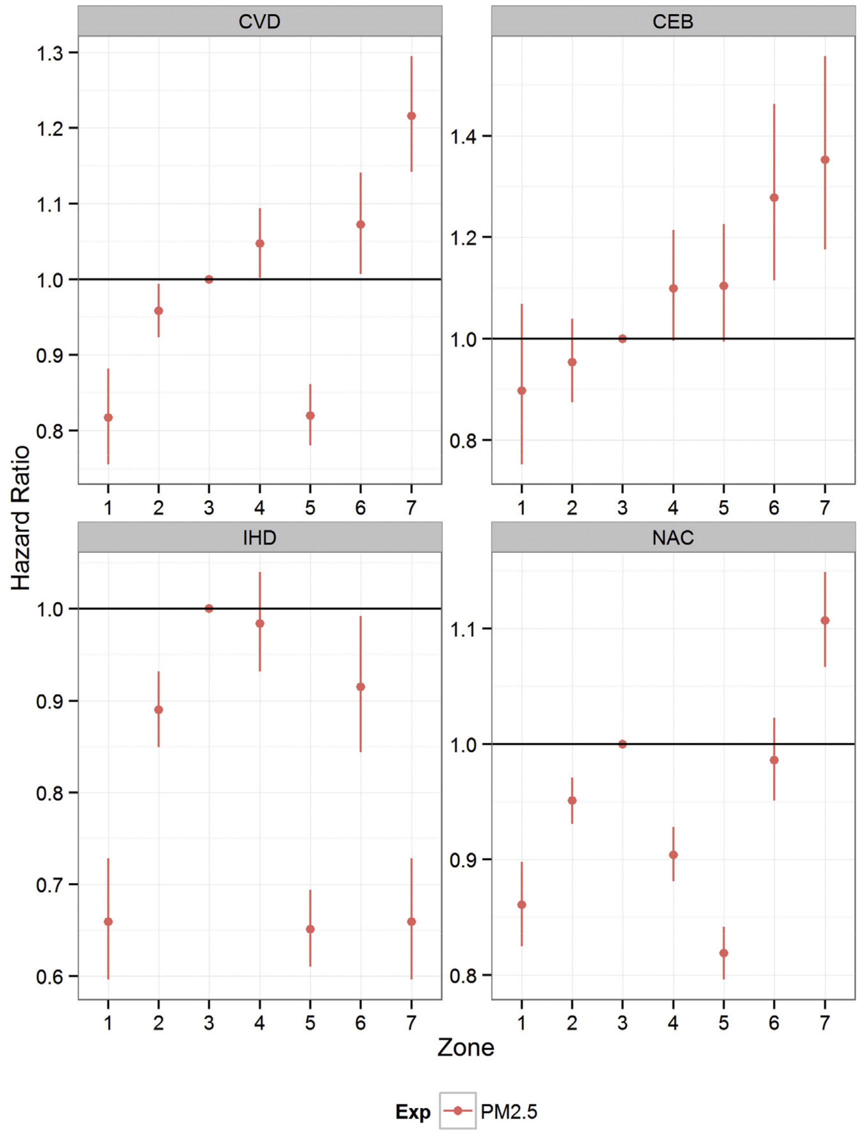

Fig. 5. Hazard ratios and 95% confidence intervals for non-accidental causes (NAC), cardiovascular disease (CVD), cerebrovascular disease (CEB) and ischemic heart disease (IHD) for $PM_{2.5}$ by SSC zone, using climate zone 3 as baseline reference.

stratum changed the HR only slightly and increased the 95% confidence intervals, to HR 1.056 (95% CI 1.042, 1.07). Adjustment for the effect of $PM_{2.5}$ reduced the risk estimate slightly to HR 1.033 (95% CI 1.017, 1.05) and little difference was observed when zone was included as a model stratum. HRs for the effect of $PM_{2.5}$ on cardiovascular mortality were higher than the effect of ozone, at HR 1.131 (95% CI 1.096, 1.168), and this dropped to HR 1.08 (95% CI 1.03, 1.12) when $PM_{2.5}$ was adjusted for the effect of ozone.

For IHD as cause of death, for ozone and ozone adjusted for $PM_{2.5}$, the HRs were slightly reduced after including zone as a model stratum, for example, in the case of ozone falling from 1.092 (95% CI 1.077, 1.107) to 1.071 (95% CI 1.054, 1.089). The differences were greatest for the relationship between $PM_{2.5}$ exposure and IHD: from 1.22 (95% CI 1.182, 1.259) to 1.167 (95% CI 1.122, 1.215).

The effect of including zone as a stratum in the model for CEB mortality was an increase in HRs, for ozone and $PM_{2.5}$ in both adjusted and unadjusted models. For example, for ozone, the HRs increased from 0.996 (0.972, 1.02) to 1.044 (1.013, 1.077), becoming significant.

Considering all non-accidental causes of death, the pattern was similar to that seen with CVD and IHD. Including zone in the model as a strata reduced the hazard ratios, with a larger difference for $PM_{2.5}$ than for ozone. Adjustment for the effect of either $PM_{2.5}$ or ozone reduced the initial risk estimate.

SSC zone as a model interaction term Log likelihood ratio tests showed that including zone as an interaction term improved model fit ($p < 0.0001$) for all pollutant and cause of death models.

HRs by SSC zone: ozone effect and adjusted for $PM_{2.5}$: When we estimated mortality risk by SSC zone, ozone was positively associated with cardiovascular disease mortality in the Cox survival model but the results were unevenly distributed across Canada (Fig. 4). The association was positive in zones 4 (HR 1.007, 95% CI 0.99, 1.015), 6 (HR 1.012, 95% CI 1.001, 1.023) and 7 (HR 1.03, 95% CI 1.02, 1.041), when compared to zone 3 as a reference zone. After adjustment for the effect of $PM_{2.5}$, the hazard ratios increased slightly for all zones except zone 6.

Similarly, ozone was positively associated with increased CEB related mortality in zone 4 (HR 1.016, 95% CI 0.998, 1.035), 5 (HR 1.013, 95% CI 0.996, 1.03), 6 (HR 1.045, 95% CI 1.019, 1.071), and 7 (HR 1.058, 95% CI 1.034, 1.082).

For IHD mortality and ozone, HRs were not significantly different between zone 3 and zone 4; all other zones except 7 presented a lower mortality risk than for zone 3. After adjustment for the effect of $PM_{2.5}$ (Fig. 4), the hazard ratios increased, except in zone 7 where a decreased HR was observed (HR 1.02, 95% CI 1.006, 1.034).

For mortality due to all non-accidental causes and ozone, and using zone 3 as reference, the only mortality risk significantly greater than zone 3 was in zone 7 (HR 1.014, 95% CI 1.008, 1.02).

HRs by SSC zone, $PM_{2.5}$ effect: The effect of $PM_{2.5}$ on mortality (Fig. 5) showed a stronger positive association with CVD in zone 4 (HR 1.047, 95% CI 1.002, 1.094), 6 (HR 1.072, 95% CI 1.007, 1.141) and zone 7 (HR 1.216, 95% CI 1.142, 1.295) when compared to zone 3. Similarly more positive association of $PM_{2.5}$ and death from CEB were observed in zones 4 (HR 1.099, 95% CI 0.996, 1.214), 5 (HR 1.104, 95% CI 0.994, 1.226), 6 (HR 1.278, 95% CI 1.115, 1.463) and 7 (HR 1.353, 95% CI 1.176, 1.557) when compared to the reference zone 3. For all non-accidental mortality causes, the relationship was greater than in zone 3 only in zone 7 (HR 1.107, 95% CI 1.067, 1.149).

4. Discussion

The spatial synoptic classification provided a means to identify different regions across Canada with similar frequencies of exposures to weather types, although we cannot directly test for the effect of different weather types on the long term pollutant-mortality relationship. Pollution exposures can have very distinctive geographic patterns, and we undertook this study as we are interested in understanding the broader and finer spatial concordance between air pollution and health.

When we included zone as a stratum, the model fits for ozone and $PM_{2.5}$ were improved, indicating that the baseline hazard differs by zone for the three causes of death examined. Further including an interaction term for SSC zone and pollutant in the model demonstrated significant differences in risk by zone, suggesting a potential difference in population reactivity to pollutant exposure in each zone. Correlations between pollutants were higher overall, that is, when estimated across Canada. Correlations between pollutants were reduced significantly on a per zone basis, reducing the potential for confounding between ozone and $PM_{2.5}$. Additionally, including zone as strata in the model, the correlations between parameter estimates were reduced; by including zone as a strata and accounting for spatial variability, the standard errors were increased for the mortality risk estimates (Fig. 3), suggesting they had been previously underestimated.

Correlations between ozone and $PM_{2.5}$ varied across the country by SSC zone, and were highest in zone 2 and 3, regions that include the more heavily populated cities. $PM_{2.5}$ is produced from a range of sources, including traffic and industry (Lee et al., 2003), and source apportionment of $PM_{2.5}$ in Canadian cities has found that secondary sulfate, nitrate, and elemental carbon associated with trans-boundary emissions from the north-eastern US states contributed to $PM_{2.5}$ in the Windsor – Toronto – Montreal area with a large contribution from traffic and road dust; in Halifax, sea salt contributed 18%. In less densely populated cities such as Edmonton (zone 4 in this study) local industrial sources and biomass burning were found to be major contributors, and there the correlation between ozone and $PM_{2.5}$ was only 0.09, reflecting the lower amount of industry, traffic and trans-boundary pollution compared to zone 3, the Great Lakes/St. Lawrence region. Compared to zone 3, we found similar or higher mortality from cardiovascular disease causes in zones 4, 6 and 7 and markedly lower mortality in zone 1 and 5, where mean levels of ozone were also lower than in zone 3. After adjustment for $PM_{2.5}$ the differences were reduced, and even more so for IHD, suggesting that an effect of ozone is modified by $PM_{2.5}$ and this differs by region.

Previous studies, such as from the American Cancer Society Cancer Prevention Study II (Jerrett et al., 2009) found long term ozone exposure to be associated with increased mortality from cardiopulmonary causes, although the effect was not significant when $PM_{2.5}$ was taken into account. The colinearity of ozone and $PM_{2.5}$ is related to their common point sources such as vehicular traffic, making it difficult to disentangle an independent effect of ozone on mortality. Recent work with the CanCHEC cohort identified overall mortality risks for long term ozone exposure in multi-pollutant models including $PM_{2.5}$ and NO_2, and cardiovascular and cerebrovascular disease-related mortality (Crouse et al., 2015); the authors also suggest that the estimates of ozone could be better indicators of regional variation in air pollution whereas $PM_{2.5}$ represents regional and local scale variation.

Independently, $PM_{2.5}$ has been studied for its role in cardiovascular disease related conditions including acute ischemic stroke; O'Donnell et al. (2011) found a slight negative association between short term increases in $PM_{2.5}$ and ischemic stroke risk in eight cities in Ontario, Canada, in agreement with our own findings. We also observed an increase in risk of IHD –related mortality for ozone after adjustment for the effect of $PM_{2.5}$. A recent meta-analysis suggested that long term exposure to $PM_{2.5}$ is a risk factor for stroke, although the association is less clear in Asia compared to North America and Europe (Scheers et al., 2015).

Strengths and limitations: While we are unable to directly examine the relationship between short term SSC weather types and pollutant-mortality relationships in a long term study of this kind, differentiating the large geographic area covered by the cohort based on differences in weather types does provide a novel and meaningful context for understanding spatial differences. Previous work using this cohort had identified structures in the survival model that were not captured by the covariates, suggesting spatial differences that had not been fully elucidated (Crouse et al., 2012); Brook et al. (2013), also noted a spatial clustering of diabetes mortality that was not accounted for by the covariates in the model. Our approach may provide more insight into broad geographic differences in the pollution-mortality relationship that have been previously unidentified. Further work including time series studies may be better able to explore the modifying effect of weather types on mortality by looking at acute effects of pollutant exposures on short time scales.

5. Conclusion

Long term exposure to ozone was associated with a significant increase in cardiovascular-related mortality that persisted after adjustment for the effect of $PM_{2.5}$. This relationship varied across Canada. Our findings suggest that an additional location-specific factor may be a modifier of the relationship between ozone exposure and cardiovascular mortality, and spatial synoptic classification can be used to provide a meaningful way to differentiate geographic regions for the investigation of air pollution and long term health effects.

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