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Scientific Research

Short-Term Effects of Ozone and $PM_{2.5}$ on Mortality in 12 Canadian Cities*

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ABSTRACT

Numerous recent epidemiological studies have linked health effects with short-term exposure to air pollution levels commonly found in North America. The association between two key pollutants—ozone and fine particulate matter—and mortality in 12 Canadian cities was explored in a time-series study. City-specific estimates were obtained using Poisson regression models, adjusting for the effects of seasonality and temperature. Estimates were then pooled across cities using the inverse variance method. For a 10 ppb increase in 1-hr daily maximum ozone levels, significant associations were in the range of 0.56% - 2.47% increase in mortality. For a 10 μg/m^3 increase in the 24-hr average $PM_{2.5}$ concentration of, significant associations varied between 0.91% and 3.17% increase in mortality. Generally, stronger associations were found among the elderly. Effects estimates were robust to adjustment for seasonality, but were sensitive to lag structures. There was no evidence for effect modification of the mortality-exposure association by city-level ecologic covariates.

Keywords: Air Pollution; Ozone; Particulate Matter; Mortality; Canada

1. Introduction

Health effects of air pollution have become a major public health concern in North America, Europe and other developed regions in the past several years. The World Health Organization estimated 1.34 million premature deaths (2.4% of total deaths) were attributable to outdoor air pollution in 2008 [1]. Further, using satellite imaging data to predict tropospheric $PM_{2.5}$ concentrations globally, Evans *et al.* [2] recently estimated that 7% of global mortality may be attributable to particulate air pollution.

In Canada, the Canadian Medical Association's (CMA) report No Breathing Room—National Illness Costs of Air Pollution published in 2008, stated that air pollution results in considerable health and economic damages that will only increase over time. It was estimated that 21,000 deaths and 92,000 emergency department visits in Canada could be attributed to short- and long-term exposure to air pollution in year 2008. Associated economic costs for the year, including worker absenteeism, higher health care costs, loss of life, and other factors were expected to exceed $10 billion [3].

Numerous studies have shown positive and significant associations between adverse health effects and short-term exposure to ozone (O_3) and particulate matter (PM), both of which are major components of smog in Canada [4-16]. Both pollutants have been linked to various health effects including premature mortality, deaths, and hospital admissions due to respiratory or cardiovascular diseases. Other effects reported include decreases in lung

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function and the exacerbation of existing chronic respiratory and cardiovascular diseases. The elderly [6,17-20] and children [21-25] have been reported to be at greater risk than the general population. Exposure to high levels of air pollution during pregnancy has also been linked to low birth weight in Canada and other countries [26].

Health effects of short term exposure to air pollution are typically assessed using time-series studies, where associations between daily variations in air pollution levels and daily counts of deaths in a given area are estimated by Poisson regression models. One of the central issues in statistical modeling of time-series studies is adequate control for potential confounding. Confounders typically controlled for are those that change over relatively short periods such as seasonality, day of the week, and weather variables that are associated with both pollution levels and health outcomes. Control for confounding is usually achieved using smooth functions for time and temperature variables in the Poisson regression models [27]. For calendar time, penalized splines (PS) or natural cubic splines (NS) are commonly used as the smoothing functions. The degree of smoothing is determined by the degrees of freedom (df) allowed in the smoothing functions [28]. This must be selected carefully to ensure that there is neither over-fitting (too many df), which would fit the "noise", nor under-fitting (too few df), which would not remove the confounding effects of potential confounders in order to avoid bias in the effect estimate. Typically, 3 - 12 df per year have been used. Another important consideration in time-series models is the lag structure, which refers to the period between exposure to the pollutant and the event (health outcome). Lag periods used can be described using single-day lag models, which allow for a lag period of a number of days, or combined lag models. In combined models, the pollution exposure levels are averages of multiple single-day lags. Distributed lag models look at the effect of cumulative exposure to pollution over the course of several days, thus allowing each day to have an effect on health outcomes.

There have been many advances in time-series models since they were first used to study short-term effects of exposure to air pollution in the 1980s [28]. Early statistical approaches included standard regression models, which have now been replaced by semi-parametric models. The two main statistical models currently used are based on Generalized Linear Models (GLM) with parametric splines or Generalized Additive Models (GAM) with non-parametric splines. GAMs offer increased flexibility in estimating the smooth component of the model relative to GLM, and had been preferred over GLMs until 2002. It was then discovered that these methods underestimated the standard errors of linear terms in the model (the air pollution regression coefficients) and overestimated the effect of air pollution on health outcomes [28-30]. The discovery of these methodological and computational issues came at the time when the United States Environmental Protection Agency (EPA) was finalizing its most recent review of the epidemiologic evidence on particulate matter air pollution. As a result, all of the findings from time-series studies that had been based on GAMs were re-evaluated using alternative methods. Approximately 40 original studies from the US, Canada and Europe were reanalyzed and then peer reviewed by a panel appointed by the Health Effects Institute (HEI) [31]. The HEI re-analysis report stated that no optimal analytic method could be recommended to estimate the air pollution health effects. Studies that have compared different approaches have found that, although there may be some sensitivities in the results, the effects remain statistically significant with the common approaches used [11].

The purpose of the present paper is to quantitatively assess the impact of fine particulate matter ($PM_{2.5}$) and ozone on mortality (total, cardiovascular and respiratory) in Canada, and explore the sensitivity of the air pollution effects estimates to different model specifications. A secondary objective is to explore potential effect modification of socioeconomic and demographic variables on the effect of air pollution and health.

2. Materials and Methods

2.1. Data

2.1.1. Location, Exposure and Outcome

Air pollution and mortality data were analyzed for the following 12 Canadian cities: Calgary, Edmonton, Halifax, Hamilton, Montreal, Ottawa, Toronto, Quebec City, St John, Vancouver, Windsor and Winnipeg. Data sets were previously assembled and provided by Health Canada. The air pollution data were obtained through the National Air Pollution Surveillance (NAPS) program administered by Environment Canada, which is subject to an extensive quality assurance program. A single daily measurement for each pollutant was available and represented the average of the measurements of all monitors in that city. On days when one or more monitors were not functioning, daily measurements were derived from the remaining monitors. Daily ozone concentrations collected include the 1-hour (1-hr) and the 8-hour (8-hr) maximum concentrations. The 1-hr maximum, available on a daily basis from 1980-2001, was used in the analyses to facilitate comparison of results with previous findings. Particulate matter measurements represent the 24-hour average cumulative mass measurements from all the monitors in one city. $PM_{2.5}$ was measured once every six days. However, the data had occasional random periods with missing data in many of the cities. In general, the time

period with data available for each city varied between 6 - 16 years since 1984. Records of the daily mean temperature for the time-series were also available.

Health outcome data for this study were obtained from the Canadian Institute for Health Information (CIHI). To ensure the quality of data collected, CIHI regularly performs quality checks of its databases. Deaths were classified using the ICD-9 (International Statistical Classification of Diseases) codes. Records that had been classified using the ICD-10-CA scheme were converted to the ICD-9 classification scheme by CIHI and were then subject to a quality assurance program. Mortality data for the 12 Canadian cities were available for the 20-year period 1981-2001. The databases included information on residence (city), age, date of death, and single underlying cause of death.

2.1.2. Potential Effect Modifiers

Data on 29 ecologic covariates representing city-level demographic, socioeconomic, health care, and lifestyle determinants were used to explore effect modification. The data were initially compiled for use in the international study, Air Pollution and Health: A combined European and North American Approach (APHENA) [32], but was of limited use due to the lack of uniform data of variables in the US and Europe. To explore effect modification, city-specific risk coefficients, βs, were regressed on the city-level covariates, by weighted linear regression with weights inversely proportional to the variance of each city's β. Twenty-nine variables that might modify the exposure-mortality association were considered by including them in the time series models individually.

2.1.3. Analyses

1) First stage (city-specific estimates)

Poisson regression models allowing for over dispersion were used to estimate the associations of ozone and $PM_{2.5}$ with mortality. The city-specific model is presented in Equation (1):

$$\log E(\mu_t) = s_1(time, df) + s_2(temp_t, 3df) + \beta P_t + (DOW) + (holiday) \quad (1)$$

where $E(\mu_t)$ is the expected value of the Poisson distributed variable μ_t, which represents the daily counts of events (deaths) on day t. The term $s_1(time, df)$ controls for seasonality, where s_1 is a smooth function with natural cubic splines as basis functions for the time variable and df is the degrees of freedom that allows s_1 to take various functional forms. The function s_1 models the non-linear association between time-varying covariates, calendar time, and daily mortality. To control for weather, the term $s_2(temp, 3)$ was included, where s_2 is a smoothing function of temperature on day t with 3 df. P is the pollutant concentration (ozone in ppb or $PM_{2.5}$ in $\mu g/m^3$) on day t; DOW and holiday are dummy variables included in the model representing the day of week and holidays. The regression coefficient β represents the log relative increase (if β is positive) in the number of events in the target population per unit increase in pollutant concentration. Time-series studies generally report results as percent change in mortality per 10 units change in pollutant concentration (This value is simply obtained by multiplying the regression coefficient β by a factor of 1000).

Three mortality outcomes for each age group were considered based on the ICD-9 codes: <800 for total mortality corresponding to all non-accidental causes of death, 390 - 459 for cardiovascular causes of death, and 460 - 519 for respiratory causes of death.

Sensitivity analyses exploring the effect of degrees of freedom allowed for seasonality control in the smooth function of calendar time and the effect of varying the lag period were conducted. These analyses were limited to ozone, which had daily data. Effects estimates for ozone on all outcomes across all ages were determined with models allowing for 1 - 20 df for the time variable per year of data available. For temperature, three df were allowed in all analyses, based on previous findings that indicate that results are robust to varying degrees df used for temperature. Models included the same lagged term for temperature variable as was used for the pollutant under consideration.

To compare the effect of natural splines and penalized splines, a sensitivity analyses on the risk estimates was carried out on the Toronto data set. After the results of the df and lag period analyses were examined, three values of the df (4, 8 and 12 per year) and three lag periods (for ozone: lag1, lag02 and dist02) were selected for analyses of the data for the remaining cities. Combined lag structures could not be applied to $PM_{2.5}$ since data were available for every sixth day; thus, three single-day lag periods were selected for this pollutant (lag0, lag1, lag2).

2) Second stage (pooled estimates)

City-specific estimates were combined to arrive at pooled estimates by applying fixed effects (FEM) and random effects (REM) regression models. In the fixed effects approach, effects estimates (β's) were assumed to be normally distributed around an overall estimate and were pooled using inverse variance weighting, with weights proportional to the inverse variance of each city's β. In the random effects regression approach, the city-specific βs were assumed to form a sample of independent observations from a normal distribution with the same mean and with variance equal to the sum of the between-city variance and the variance of β. The between-city variance is added to the city-specific variance

and is estimated using the maximum likelihood estimation (MLE) method [33].

2.2. Effect Modification

Heterogeneity between city specific estimates was assessed by the I^2 index, which is a measure of the total variability among effect sizes that can be attributed to true heterogeneity (between-city variability) [34]. In general, an I2 less than 25% suggests low heterogeneity between cities. To explore potential effect modification, weighted linear regression of the city-specific estimates was performed onto each ecologic covariate. Weights were inversely proportional to the variance of each city specific risk estimate (β). Models where the data showed a significant linear association at the 95% confidence level between the potential effect modifier and the risk estimates were assumed to potentially modify the pollutant-health outcome relationship.

All analyses were completed using R statistical software for Windows version 2.6.1 [35].

3. Results

Descriptive statistics for the mortality data are provided **Tables 1** and **2**. There were a total of approximately 1.6 million deaths among all age groups between 1981 and 2000 across the 12 Canadian cities considered. The total exposed population was approximately 9.1 million. Individual city population ranged from 100,000 in St John to 2.3 million in Toronto, based on the 1991 Census. Mean daily death counts varied between 0 (respiratory mortality) and 48 deaths (total mortality), depending on the size of the city.

Descriptive statistics of the exposure database are presented in **Table 3**. Mean annual temperatures for the 12 cities ranged from 2.4˚C (Edmonton) to 10.6˚C (Vancouver). Ozone measurements were available on a daily basis during the period 1981-2000, with few missing data (except for Halifax). The mean measurements of the 1-hr maximum ozone levels were in the range 27 - 37 ppb. For $PM_{2.5}$, the mean 24-hour levels varied between 9 $\mu g/m^3$ and 16 $\mu g/m^3$. The time periods during which $PM_{2.5}$ data was available were not uniform across cites. $PM_{2.5}$ was generally measured every sixth day for most cities, with occasional intermittent missing data across longer periods. Ozone and $PM_{2.5}$ levels were not strongly correlated, with the highest correlation coefficients being 0.46 and 0.41 for Windsor and St John, respectively.

The city level socio-demographic, health services, and lifestyle ecological variables were assessed for potential effect modification of the association between air pollution and mortality. Several of the variables listed were highly correlated.

Table 1. Total number of death counts in the 12 Canadian cities in the 1981-2000 period.

Outcome/Age group	Total counts
All-cause mortality	
all ages	1,564,583
75 and over	748,498
under 75	815,978
Cardiovascular mortality	
all ages	641,072
75 and over	369,177
under 75	271,855
Respiratory mortality	
all ages	134,663
75 and over	85,971
under 75	48,683

Table 2. Summary of the population size and mean number of daily mortality counts by cause and age group in the 12 Canadian cities.

City	Population (×1000)	All-cause mortality			Cardiovascular mortality			Respiratory mortality		
		All ages	*75 and over*	*Under 75*	*All ages*	*75 and over*	*Under 75*	*All ages*	*75 and over*	*Under 75*
Calgary	711	10	5	5	4	2	2	1	1	0
Edmonton	617	11	5	6	5	3	2	1	1	0
Halifax	231	6	3	3	2	1	1	1	0	0
Hamilton	319	10	4	5	4	2	2	1	0	0
Montreal	1776	48	22	26	19	10	9	4	2	2
Ottawa	880	15	7	8	6	4	3	1	1	0
Quebec City	540	17	8	9	7	4	3	1	1	1
St John	103	3	1	1	1	1	1	0	0	0
Toronto	2276	47	22	24	18	11	8	4	3	1
Vancouver	1832	29	15	14	12	8	4	3	2	1
Windsor	191	6	3	3	3	2	1	0	0	0
Winnipeg	615	14	7	7	6	4	2	1	1	0

Table 3. Descriptive statistics for the study period, air pollutants and temperature data used in the analyses of mortality outcomes.

City	Calgary	Edmonton	Halifax	Hamilton.	Montreal	Ottawa	Quebec City	St John	Toronto	Vancouver	Windsor	Winnipeg
Temp (˚C)												
Mean	4.5	3.0	6.5	8.0	6.6	6.4	4.4	5.2	8.1	10.5	9.8	3.1
25th centile	−1.9	−5	-0.8	0.1	−2.1	−2.7	−4.6	−1.7	0.2	6.3	1.5	−7.4
Median	5.6	4.7	6.9	8.2	7.6	7.45	5.4	6.1	8.3	10.3	10.2	4.7
75th centile	13	13	14.6	17	16.7	17	14.8	13.7	17.2	15.3	19.1	15.4
Ozone (ppb)												
Time period (month/year)	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00	01/81-12/00
No. obs.[1]	7305	7302	5945	7290	7304	7303	7208	7144	7305	7292	7225	7159
No. missing[2]	0	3	1360	15	1	2	97	161	2	13	80	146
Mean (1 hr max)	33.1	31.2	29.0	34.8	28.7	28.8	28.8	34.5	34.2	27.0	36.9	30.0
Maximum (1 hr max)	94	110	100	129	115.7	105	135	160	144.1	104.6	159	99
25th centile	25	22	21	22.3	18.8	20	20	26	22.3	19.1	21	21.5
Median	33	30.5	28	31	26.2	27	28.5	32.3	30.5	26.6	31.5	29
75th centile	41	40	35	44	35.9	35.7	35.0	40.0	42.3	34	49	37.5
$PM_{2.5}$ (µg/m^3)												
Time period (month/year)	12/84-12/00	12/84-12/00	12/84-12/96	01/95-12/00	12/84-12/00	12/84-12/00	12/85-12/00	09/92-09/99	12/84-12/00	12/84-12/00	12/87-12/00	09/84-09/00
No. obs.	891	791	657	418	1180	807	524	1125	1537	1082	1031	816
No. missing	6414	6514	6648	6887	6125	6498	6781	6180	5770	6223	6274	6489
Mean	10.2	10.1	11.0	15.3	14.7	10.7	11.3	7.7	14.7	11.8	16.3	9.0
Maximum	66.1	64.0	45.5	74.1	72.0	53.8	50.4	53.2	71.0	67.0	85.6	71.3
25th centile	5.7	5.3	6.1	7.7	7.8	5.1	6.0	3.8	7.3	6.7	8.7	5.2
Median	8.3	8	9.15	12.5	12	8.32	9	6.3	12.34	9.8	13.7	7.3
75th centile	12.1	12	13.5	20.3	18.8	13.8	14.0	9.9	19.5	14.1	20.7	11.0

[1]Total number of observations; [2]Number of missing observations.

Figure 1 presents the pooled percent increase (random effects) in mortality outcomes across all ages associated with an increase of 10 ppb in the previous day's ozone concentrations (lag1). The number degrees of freedom allowed per year of data available was varied between 1 and 20 in the smooth function of time (natural splines) in the city-specific models. Estimates stabilized after allowing 4 - 5 df per year, displaying slight decreases as the degrees of freedom increased. In the absence of substantial heterogeneity among city specific estimates, fixed effects and random effects models gave comparable results across cities. Estimates were positive and statistically significant across all outcomes.

Results showing the effect of varying the lag period between exposure to ozone and day of death are presented in **Figure 2**. The figure represents the pooled results (random effects) for all ages at 4, 8 and 12 df per year of data. Higher estimates were observed for combined lag models relative to single day lags. Wider confidence intervals for respiratory mortality compared to other mortality outcomes were observed, a result of the low daily counts for this outcome. For total and cardiovascular mortality, effects estimates were significant at all lag structures and df examined.

The mortality effects estimates for ozone and $PM_{2.5}$ across all age groups with eight degrees of freedom for seasonality control and three lag structures are summarized in **Tables 4** and **5**, respectively. For ozone, results were statistically significant across all age groups, with higher estimates observed with the combined lags rela-

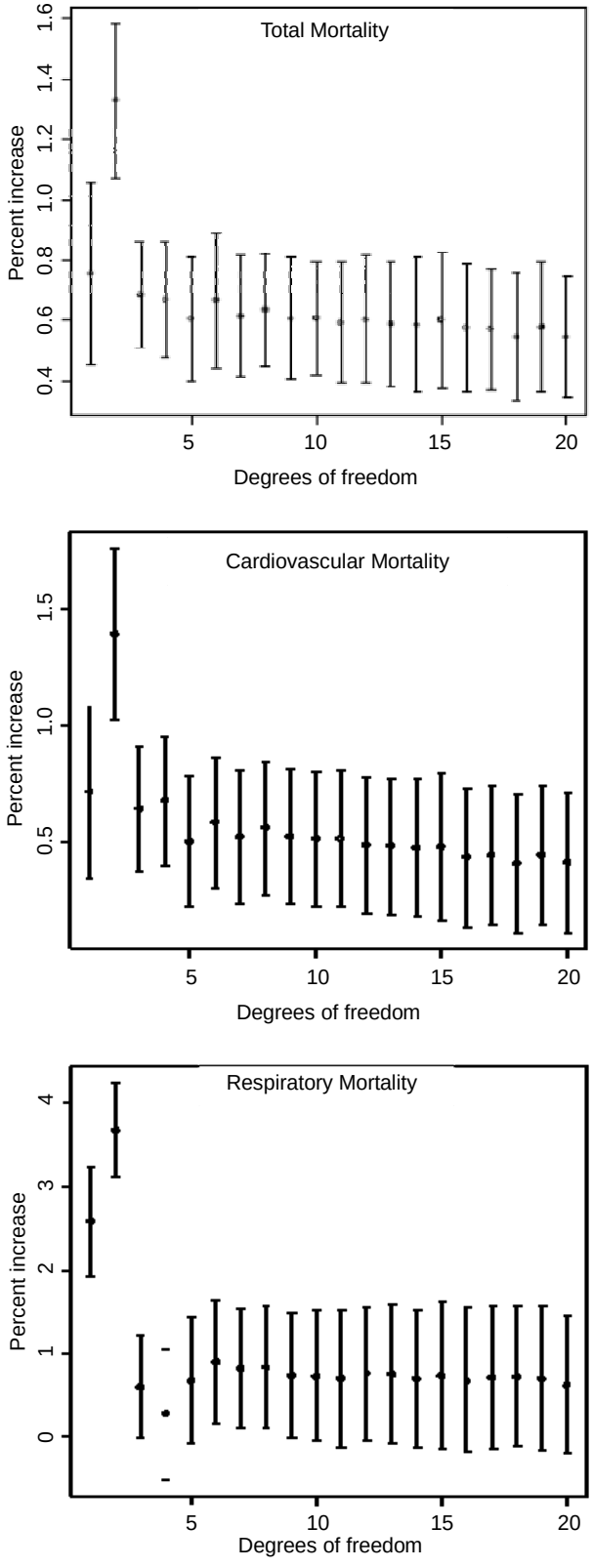

Figure 1. Pooled percent increase in mortality and 95% CI associated with a 10 ppb increase in the 1-hr maximum ozone levels in 12 Canadian cities with a 1-day lag with varying degrees of freedom per year for seasonality control.

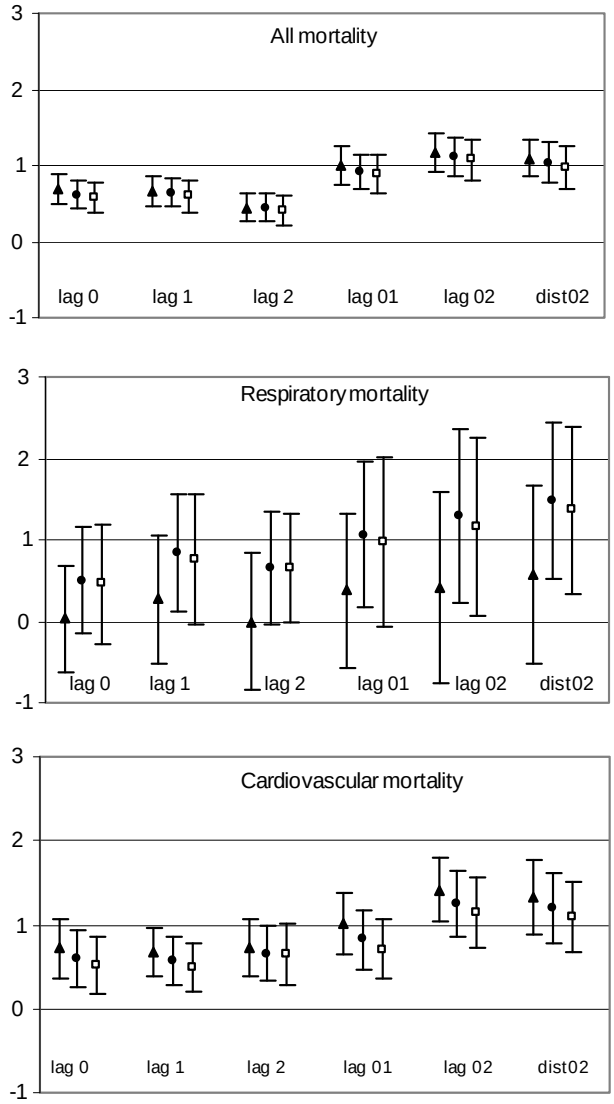

Figure 2. Pooled percent change in mortality (all ages) associated with an increase of 10 ppb in the 1-hr maximum ozone concentrations in 12 Canadian cities. Results are from random effects models with various df allowed for seasonality control. (Δ 4 df; ● 8 df; □ 12 df).

tive to the single day lag period. Effects estimates were generally stronger among the elderly. However, respiratory mortality estimates were stronger for the <75 age group compared to the ≥75 group, contrary to what might be expected.

For $PM_{2.5}$, three single-day lag structures were evaluated with exposure on the same day (lag0), the previous day (lag1) and two days prior (lag2). Effects represent the percent increase in the outcome associated with a 10 $\mu g/m^3$ increase in the 24-hour average $PM_{2.5}$ levels. Generally, fewer outcomes were statistically significant in relation to $PM_{2.5}$, compared to ozone. Estimates at 1- or 2-day lag periods were higher relative to effects at same day exposure, indicating that $PM_{2.5}$ may have a delayed

Table 4. Pooled percent increase in mortality outcomes associated with a 10 ppb increases in the 1-hour maximum ozone levels for three lag structures. Results are from fixed effects models with 8 df allowed for seasonality control.

Outcome/Age group	Percent increase (95% CI)		
	lag1	lag02	dist02
All mortality			
All ages	0.64 (0.45 - 0.82)	1.12 (0.87 - 1.38)	1.03 (0.77 - 1.30)
Under 75	0.59 (0.33 - 0.84)	1.01 (0.66 - 1.36)	0.95 (0.59 - 1.31)
75 and over	0.69 (0.42 - 0.96)	1.25 (0.87 - 1.62)	1.05 (0.66 - 1.45)
Cardiovascular mortality			
All ages	0.56 (0.27 - 0.84)	1.25 (0.85 - 1.65)	1.20 (0.79 - 1.61)
Under 75	0.07 (−0.36 - 0.51)	0.76 (0.16 - 1.37)	1.63 (0.01 - 1.25)
75 and over	0.93 (0.55 - 1.31)	1.62 (1.09 - 2.15)	1.40 (0.84 - 1.96)
Respiratory mortality			
All ages	0.86 (0.21 - 1.51)	1.34 (0.44 - 2.25)	1.49 (0.55 - 2.43)
Under 75	0.98 (−0.08 - 2.04)	2.14 (0.67 - 3.62)	2.47 (0.95 - 3.98)
75 and over	0.79 (−0.04 - 1.62)	0.86 (−0.29 - 2.01)	1.58 (0.33 - 2.84)

Table 5. Pooled percent increase in mortality outcomes associated with a 10 μg/m^3 increase in the 24-hr average $PM_{2.5}$ concentrations. Results are from fixed effects models with 8 df allowed for seasonality control.

Outcome/Age group	Percent increase (95% CI)		
	lag0	lag1	lag2
All mortality			
All ages	0.35 (−0.23 - 5.94)	1.43 (0.84 - 2.31)	0.98 (0.39 - 1.57)
Under 75	0.57 (−0.26 - 1.39)	0.91 (0.08 - 1.73)	0.14 (−0.68 - 4.97)
75 and over	0.12 (−0.72 - 5.96)	1.98 (1.14 - 2.81)	1.85 (1.01 - 2.68)
Cardiovascular mortality			
All ages	−0.23 (−1.18 - 0.72)	1.03 (0.09 - 1.97)	1.77 (0.83 - 2.71)
Under 75	0.11 (−1.37 - 1.68)	−1.44 (−4.84 - 1.96)	0.88 (−0.61 - 2.36)
75 and over	−0.45 (−1.68 - 0.78)	2.14 (0.92 - 3.35)	2.39 (1.17 - 3.61)
Respiratory mortality			
All ages	−1.12 (−3.19 - 1.95)	0.30 (−1.72 - 2.33)	1.31 (−0.75 - 3.36)
Under 75	0.04 (−3.80 - 3.99)	−0.27 (−3.87 - 3.33)	−1.77 (−5.53 - 2.88)
75 and over	−0.95 (−3.54 - 1.64)	0.73 (−1.74 - 3.21)	3.17 (0.61 - 5.72)

effect on health outcomes. Effects for mortality on the same day of exposure (lag0) were not statistically significant. Positive and significant effects were seen for total and cardiovascular mortality in 1- and 2-day lag models. Respiratory mortality effects were only significant at 2-day lag and among the elderly. Effects were consistently higher for older age groups.

There was no substantial heterogeneity between city-specific estimates in the majority of models applied. Two outcomes that displayed the highest heterogeneity based on the I^2 index were selected for effect modification analyses: cardiovascular mortality with ozone (assessed at lag02, 8 df for time, for <75 years, I^2 index 22%) and cardiovascular mortality with $PM_{2.5}$ (assessed at lag0, 8 df for time, for <75 years, I^2 index 16%). **Table 6** presents statistically significant results (at the 95% confidence level) of the effect modification analysis of $PM_{2.5}$ and ozone. Results represent the percent increases in daily number of deaths associated with an increase of 10 units in $PM_{2.5}$ or ozone at two different values for the effect modifier, corresponding to the 25th and the 75th percentiles of the city-specific distribution that variable.

Table 6. Percent change in mortality associated with a 10 μg/m^3 increase in $PM_{2.5}$ concentrations at the 25th and 75th percentile of the city-specific distributions of covariates that displayed significant effect modification.

Outcome/ Effect modifier	Percent change (95% CI)		p-value
	25th centile	75th centile	
Cardiovascular mortality and $PM_{2.5}$			
Area	−0.72 (−3.45, 2.02)	−0.17 (−2.79, 2.46)	0.05
Unemployment, males	1.72 (−1.32, 4.77)	0.16 (−2.44, 2.76)	0.05
Manufacturing	2.75 (−0.88, 6.38)	−0.24 (−2.85, 2.37)	0.04
Stress	1.6 (−0.89, 4.09)	0.47 (−1.8, 2.75)	0.01

Results can be seen as showing pollutant effects in a city characterized by a level of the effect modifier corresponding to the 25th or 75th percentile.

4. Discussion

This study presents results of the short-term effects of ozone and $PM_{2.5}$ exposure on mortality across 12 Canadian cities. Statistically significant associations were observed across the three mortality outcomes, with estimates being generally higher among the elderly. Risk estimates were robust to seasonality control when more than five degrees of freedom per year of data available were allowed. Sensitivity of risk estimates was observed to varying lag structures with higher estimates when using combined lag structures for ozone, and with 1 or 2 day lags for $PM_{2.5}$. Analyses of socio-demographic, health services and lifestyle covariates did not identify any potential effect modifiers that warrant further investigation.

4.1. Degrees of Freedom for Seasonality

Across the three mortality outcomes, effects estimates were found to stabilize beyond five degrees of freedom per year in the smoothing function of calendar time. Results obtained are in agreement with other studies that have explored the sensitivity of degrees of freedom for seasonality control. Peng *et al.* [20] conducted a simulation study that compared various methods commonly used to adjust for seasonal and long-term trends. By examining the variability of the regression coefficient, β, using 1 - 20 df per year, results indicated that the bias in β was only serious for df between 1 and 4 with natural splines (and between 1 and 6 df with penalized splines) and was stable afterwards. Another study in California found that effects estimates decreased with increasing df when evaluated at 4, 8 and 12 df per year with a greater reduction observed going from 4 to 8 df [13].

Although there is no preferred method to choose the optimal degrees of freedom, Touloumi *et al.* [36] suggest that the approach followed in NMMAPS (7 df per year) yields conservative air pollution effects estimates, since this value of df is large enough to ensure adequate control for seasonal and long-term trends. Many previous studies have selected a fixed value for df (generally between 4 - 12 df per year) to be used in analyses, based on sensitivity analyses or previous results [13,14,37,38]. The analyses in this study evaluated all the outcomes for different age groups at 4, 8 and 12 df per year to compare the effects across this range.

Natural cubic splines were used in all analyses presented. Penalized splines have also been used in time-series studies and both methods are believed to yield comparable results. Mortality risk estimates associated with ozone obtained from both approaches were compared in this study using the data set for one of the 12 cities (Toronto). Risk estimates varied between −4% and 6% when comparing both approaches at values of 6 - 14 df per year for time, confirming the comparability of risk estimates based on natural splines and penalized splines.

The effect of varying the df for the temperature variable was not explored in this study. It is generally accepted that the effects estimates are not as sensitive to the method used to control for temperature as they are to controlling for calendar time [39]. The approach followed in APHENA for controlling for temperature was adopted in this study, where three degrees of freedom were allowed in the smooth function of temperature in all models.

4.2. Effects Estimates

The use of the 1-hr maximum daily average for ozone facilitated the comparison of results with previous findings, as many of previous studies used this measure. The World Health Organization suggests that the 8-hour average may be a better indicator for respiratory function and lung inflammation [40]. However, correlation coefficients between the 1-hr and 8-hr maximum ozone levels were in the 0.94 - 0.97 range across the 12 Canadian cities. Thus, similar results are to be expected using either measurement. Results of both measures were compared

in the project Air Pollution and Health—A European Approach 2 (APHEA 2), and have been reported to give comparable results [11].

Pooled effects estimates across cities for ozone were positive and significant for total and cause specific mortality. Significant results observed were in the range of 0.56% to 2.47% increase in mortality for a 10 ppb increase in the 1-hr maximum ozone levels. In general, higher effects were obtained for the ≥75 age group. These results are comparable with previous studies [9,10,15,16,32]. A slightly stronger effect was detected for respiratory mortality, which is also consistent with other studies. In APHEA 2, a stronger association between ozone and respiratory mortality was found (2.26%) relative to other mortality outcomes (0.9% cardiovascular mortality and 0.66% for total mortality) per 10 ppb increase in the 1-hr maximum ozone levels [11]. In a study within NMMAPS that looked at 95 US urban communities, a positive and significant association (0.64% increase) per 10 ppb increase in the previous week's ozone levels was estimated for respiratory and cardiovascular mortality, slightly higher than the estimate for total mortality (0.52%). Further, in an Australian study of four cities, a significant association was obtained for respiretory mortality (2.2% increases per 10 ppb increase), but not for other outcomes (Simpson *et al.* 2005). The greatest effects estimates were observed with combined lag models in this study. The higher effects estimated with the 3-day average (lag02) and the distributed lag models (dist02) suggest that the effect of ozone may not only depend on same day exposure, but also on the exposure over the previous 2 days. This indicates that single day lag models may underestimate the cumulative effect of ozone on mortality due to repeated exposure to high levels of ozone. Hence, the combined and distributed lag models may be more appropriate for estimating ozone health effects. This is in agreement with previous findings that suggest multi-day exposure lags are higher than single day lags [9,10,32,41]. Studies that investigated lag models taking into account the previous week's ozone levels in 95 US cities and found that effects were consistently higher than those of single day lag models [9,10]. Meta-analyses that have looked at the health effects of ozone have found positive effects for both total and cardiovascular mortality [8] or only total mortality [16].

Estimates from this study are lower than the Canadian estimates from APHENA for all-cause mortality and cardiovascular mortality outcomes for ozone as the exposure pollutant. The data sets used in APHENA represent a subset of the data used in this study, covering a shorter time period (1987-1996). It is hypothesized that the use of a shorter time-series and the inclusion of additional covariates in the models (two terms for temperature control) in APHENA, may have led to different results. A sensitivity analysis exploring the effect of varying the number of temperature terms included in the time series was carried out. Results show that the use of one term (same day temperature (temp0)) or two terms (same day and previous day temperature (temp01)) for the temperature variable produced comparable risk estimates. Further investigation is needed to more fully explain the difference in results between this study and the Canadian APHENA results.

Fine particulate matter showed statistically significant effects estimates combined across cities. For total and cardiovascular mortality, significant estimates were in the range of 0.91% - 2.39% increase per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Results of this study are in agreement with previous study findings where estimates reported have generally been in the range of 0.8% - 2.4% increase [42]. A number of previous studies have reported comparable results [12-14], although others have found no significant effect on mortality [8,15]. The only significant estimate detected for respiratory mortality was a 3.17% increase for ≥65 at a 2-day lag. It is unusual to detect a relatively strong association for this age group when other groups considered did not show any significant effects. Compared to respiratory diseases, cardiovascular diseases are more prevalent which leads to increased power to detect weak associations [43]. It is possible that due to low number of respiratory related deaths, the models applied were not able to detect the weak association and that the 3.17% increase observed was obtained by chance.

Effects were consistently higher for older age groups, supporting the hypothesis that the elderly may be more susceptible to the effects of $PM_{2.5}$; this may be a result of exacerbation of pre-existing conditions that are more prevalent among individuals in this age group or due to reduced antioxidant defenses [44].

Effects of mortality on the same day of exposure (lag0) were not significant. Rather, across all mortality outcomes and two age groups (all ages and ≥75), the effect of $PM_{2.5}$ was strongest at 1-day lag (and sometimes at 2-day lag) compared to the effect of same day exposure, suggesting a delayed $PM_{2.5}$ effect. As with the case of ozone, findings for $PM_{2.5}$ reported in the literature have been inconsistent. For example, a study in Montreal found that cardiovascular mortality was more affected by exposure to $PM_{2.5}$ in previous days [18], whereas a study in 10 US cities found a stronger same-day exposure effect [41]. Results have also been inconsistent for respiretory deaths. Previous studies have reported stronger effects on day exposure levels [38] or exposure in the prior 1 or 2 days [45]. This inconsistency may be a result of the different chemical components of the $PM_{2.5}$ mixture with different chemicals responsible for immediate or delayed responses in individuals across the various study

locations. This may also be explained by the different population structures where certain subpopulations are more vulnerable to air pollution [46].

4.3. Effect Modification

City-specific results in general did not display significant heterogeneity across outcomes based on the I^2 index, which was generally in the range of 0% - 25%. The lack of heterogeneity between estimates of Canadian cities is supported by findings of APHENA [32]. Two mortality outcomes that showed some level of heterogeneity among cites were examined for effect modification by 29 ecological variables. None of the variables were found to modify the ozone-mortality relationship ($p > 0.05$). With $PM_{2.5}$, the association was statistically significant for four variables: area of city, percent of unemployed males, percent manufacturing and percent of population stressed. The PM-mortality association is not likely to be affected by the geographic area of city *per se*, but by other factors associated with it. The remaining city-level variables identified were found to modify the effect in the opposite sense of what would be expected. For example, mortality was seen to decrease with higher percentage of stress levels.

Previous findings on effect modification have been inconsistent, with several studies concluding that the effect of air pollution is not modified by city-level variables or reporting only geographical variations [11,12,16, 38]. However, Ostro *et al.* [13], reported that effect of $PM_{2.5}$ was higher among females, whites, diabetics, or persons with less than high school education. In addition, Bell and Dominici [10] looked at effect modification patterns in 98 US communities and reported that higher estimates were associated with higher unemployment, fraction of African American population, public transportation use, lower temperature and lower prevalence of central air conditioning. In APHEA 2, life expectancy was identified as an effect modifier.

The use of only 12 cities in this study may have limited the effect modification analyses. Although the $PM_{2.5}$ effect was found to be modified by several city-specific characteristics, results cannot be considered as providing strong evidence of effect modification. As several previous studies have reported, it is possible that effect modification with the covariates considered does not occur in the case of short-term exposure to air pollution. Repeating this analysis with a greater number of cities would give greater power to detect heterogeneity—if present—and allow stronger conclusions to be made regarding effect modification.

4.4. Biological Mechanisms

The exact biological mechanisms by which air pollution leads to morbidity and premature deaths remain under active investigation. However, much of the current evidence suggests that exposure to ozone and PM induces oxidative stress and inflammation in the lung tissue that lead to local and systemic events. The inflammatory response in the lungs has been demonstrated in animal and controlled human studies [47-49]. Inflammation in the lungs triggers the release of cytokines and chemokines that lead to sub-clinical systemic inflammation that may alter the vascular system [48,50,51].

Observed cardiovascular effects can be partially explained by activation of pulmonary neural reflexes that result from interactions between pollutants and lung receptors. Increases in fibrinogen levels and reductions in heart rate, two risk factors for cardiac diseases that lead to hospital admissions, have been associated with exposure to air pollution. Reductions in heart rate can lead to decreased parasympathetic input, which may in turn lead to arrhythmia and cardiovascular mortality [52,53]. Lung inflammation is also believed to exacerbate underlying lung diseases by weakening lung defense mechanisms. Animals with chronic obstructive pulmonary diseases (COPD) or chronic lung inflammation have been found to be more vulnerable to combustion particles compared to normal animals [52,53]. Influenza infections have also been shown to be exacerbated by air pollution in experiments [54,55]. Further, studies on mice and humans indicate that $PM_{2.5}$ may accelerate the development of atherosclerosis [48,56]. Other studies have detected PM in the heart muscle and brain cells indicating its ability to diffuse into the bloodstream which may lead to direct toxic effects [48,50].

4.5. Strengths and Limitations

This study examined the associations of two ambient air pollutants and health outcomes in 12 Canadian cities, with a total exposed population of 9 - 10 million Canadians. Statistical methods applied were uniform across all cities enabling the direct pooling of city-specific results.

The literature on the health effects of short-term exposure to $PM_{2.5}$ is somewhat limited [38], as its use in time series studies is relatively recent. Many previous studies have focused on larger particles rather than fine PM due to the availability of data, or have used conversion factors to convert between the two particle fractions. This study adds to the literature quantitative evidence of the significant effects of fine PM. This study was based on measurements of $PM_{2.5}$ as recorded by fixed monitors in each city; hence, errors inherent in conversion factors were not introduced into the measurements. Further, analyses in previous studies have sometimes been hindered by the different measurements methods that were used for each city [57]. However, air pollution and mor-

tality data were collected under a common framework and subject to the same quality assurance programs across the 12 Canadian cities included in this study.

Concentrations of ambient air pollution obtained from fixed outdoor monitors throughout each city were used as a surrogate measure for the population average personal exposure. This method assumes that exposure among all individuals in a given area is identical and does not take into account the differences in activity patterns (such as time spent outdoors) [58]. The feasibility of obtaining such data, usually collected for regulatory purposes, at low cost and no burden to study subjects, has made it convenient to use in time-series studies. As a result, time-series studies are believed to be subject to exposure misclassification, especially among subpopulations that are at a higher risk since their activity patterns may differ from that of the general population [58,59]. However, the use of fixed monitor measurements is supported by previous studies that have shown a strong correlation between outdoor, indoor and personal exposure to particulate matter [60,61]. It has also been reported that the presence of error in measurement of the exposure would lead to non-differential misclassification of exposure and hence underestimation of health effects [62-64]. Jerret *et al.* [63], showed that the health effects were three times higher when analyses were based on individual's proximity to high traffic regions compared to using community average concentrations. Models that correct for measurement error have also been developed [64].

Another limitation in this study was the systematically missing exposure data for $PM_{2.5}$. The incomplete exposure data may have resulted in an underestimation of the true effect estimates, based on the findings of a recent study by Samoli *et al.* [65] that showed systematically missing daily PM_{10} and ozone data gave considerably lower effect estimates. Having $PM_{2.5}$ measurements for every sixth day may have also led to effect estimates with greater uncertainty than those calculated for ozone (which had daily data). In Canada, $PM_{2.5}$ data have been collected on a daily basis since the late 1990s. The unavailability of daily PM data may have also contributed to greater heterogeneity between city estimates, thereby increasing the possibility of observing spurious associations as effect modifiers.

Confounding of co-pollutants in the $PM_{2.5}$ effect has been looked at in other studies. $PM_{2.5}$ is highly correlated with other co-pollutants, and it is often difficult to disentangle which component of the air pollution mixture is the one responsible for the observed health effects [66,67]. This study did not look at potential confounding by co-pollutants beyond ozone. Some previous studies have looked at the effect of seasonal variation in the levels of ozone, where higher effects were detected in the summer when ozone levels are typically higher [11,66,68]. This was not explored in this study.

Further, the power to detect heterogeneity between city estimates and consequently potential effect modifiers was limited by the low number of cities. It is recommended to repeat effect modification analyses with a larger number of cities to arrive at more conclusive results regarding potential effect modifiers.

Finally, the potential biases associated with the use of mortality data obtained from death certificates needs to be considered. A Canadian study by Stieb *et al.* [69], looked at the classification of cardio-respiratory diseases in emergency department visits. Findings found a fair degree of agreement in the diagnosis of seven independent assessments, with no evidence of diagnostic bias in relation to daily air pollution. The databases in this study have been subject to quality control by CIHI. Nevertheless, if errors were present in the management of data, this would result in non-differential misclassification bias, as such errors would not likely be related to variation in air pollution levels.

4.6. Public Health Implications

Results of this study indicate a substantial public health burden from ozone and $PM_{2.5}$ pollution. Further reductions in the levels of these two pollutants would bring considerable health and economic benefits to Canadians. For example, based on the calculated effects in this study, a 10 ppb increase in 1-hr maximum ozone levels would correspond to an additional 1,368 (95% CI, 985-759) premature deaths each year in the 12 cities considered in this study (based on lag02 model with 8 df and average annual mortality between 1980 and 2000). Similarly, a 10 $\mu g/m^3$ increase in daily average of $PM_{2.5}$ would correspond to 1148 (95% CI, 521-2319) premature deaths annually in these cities (based on lag2 model with 8 df and the average annual mortality between 1980 and 2000). These figures will be higher when considering the total Canadian population and the inclusion deaths associated with long-term exposure to these pollutants. Long-term effects related to ozone and $PM_{2.5}$ exposure have been reported to be much greater than short-term effects [3].

Previous studies have looked at the exposure-response relationship between air pollutants and mortality in an attempt to identify a threshold concentration, below which air pollution would not lead to increases in deaths [32,70,71]. However, recent epidemiologic findings have consistently detected associations at low ambient pollution levels, without clear evidence supporting the existence of a threshold concentration [32,66,71].

5. Conclusion

This study supports previous findings that have linked

short-term exposure to ozone and $PM_{2.5}$ with mortality. Effects estimates were robust to confounding adjustment of seasonality but sensitive to lag structures. Statistically significant central estimates of the increase in mortality associated with a 10 ppb increase the 1-hr maximum ozone ranged from 0.56% (95% CI 0.27-0.84) to 2.14% (95% CI 0.95-3.98). For $PM_{2.5}$, significant central estimates of the increases in mortality ranged from 0.91% (95% CI 0.08-1.73) to 3.17% (95% CI 0.61-5.72). Although estimated effects are relatively weak, they represent a substantial health burden given the size of the exposed population. Based on these results, it is reasonable to assume that reductions in air pollution would likely lead to health benefits by reducing premature mortality.

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