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Air pollution in the week prior to delivery and preterm birth in 24 Canadian cities: a time to event analysis

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Abstract

Background: Numerous studies have examined the association between air pollution and preterm birth (<37 weeks gestation) but findings have been inconsistent. These associations may be more difficult to detect than associations with other adverse birth outcomes because of the different duration of exposure in preterm vs. term births, and the existence of seasonal cycles in incidence of preterm birth.

Methods: We analyzed data pertaining to 1,001,700 singleton births occurring between 1999 and 2008 in 24 Canadian cities where daily air pollution data were available from government monitoring sites. In the first stage, data were analyzed in each city employing Cox proportional hazards models using gestational age in days as the time scale, obtaining city-specific hazard ratios (HRs) with their 95% confidence intervals (CIs) expressed per interquartile range (IQR) of each air pollutant. Effects were examined using distributed lag functions for lags of 0–6 days prior to delivery, as well as cumulative lags from two to six days. We accounted for the potential nonlinear effect of daily mean ambient temperature using a cubic B-spline with three internal knots. In the second stage, we pooled the estimated city-specific hazard ratios using a random effects model.

Results: Pooled estimates across 24 cities indicated that an IQR increase in ozone (O₃, 13.3 ppb) 0–3 days prior to delivery was associated with a hazard ratio of 1.036 (95% CI 1.005, 1.067) for preterm birth, adjusting for infant sex, maternal age, marital status and country of birth, neighbourhood socioeconomic status (SES) and visible minority, temperature, year and season of birth, and a natural spline function of day of year. There was some evidence of effect modification by gestational age and season. Associations with carbon monoxide, nitrogen dioxide, particulate matter, and sulphur dioxide were inconsistent.

Conclusions: We observed associations between daily O₃ in the week before delivery and preterm birth in an analysis of approximately 1 million births in 24 Canadian cities between 1999 and 2008. Our analysis is one of a limited number which have examined these short term associations employing Cox proportional hazards models to account for the different exposure durations of preterm vs. term births.

Keywords: Preterm birth, Air pollution, Time-to-event
Introduction
Preterm birth is a key determinant of infant mortality and morbidity, and of health status in childhood and even adulthood [1–3]. Numerous studies conducted worldwide have examined the association between air pollution and preterm birth [4–10]. Many studies have found that air pollution exposure increases the risk of preterm birth and it has been estimated that 23% or 3.4 million preterm births globally were attributable to PM2.5 in 2010 [1]. However, there has been some inconsistency in findings, including in Canada, where in some instances we observed significant associations [11], while in others we did not [12, 13]. Most studies have employed cohort or case-control designs, characterizing exposure over the entire pregnancy, trimester or birth month [8], while a smaller number have examined short term exposure, employing time-series [14–20], case-crossover [21] or time to event analysis [22–26]. It has been hypothesized that the association between air pollution and preterm birth may be more difficult to detect than associations with other outcomes such as term low birth weight or small for gestational age because of the different duration of exposure over the entire pregnancy or third trimester in preterm vs. term births, and the existence of seasonal cycles in incidence of preterm birth [15, 21, 27, 28]. To address these issues and to examine the influence of short-term exposure, here we employ a time to event analysis, using Cox models examining exposures in the week prior to birth.

Methods
We employed data from the Canadian births database. Live birth events are reported to Statistics Canada by the provincial and territorial Vital Statistics Registries in Canada. For this study, singleton live births between 1999 and 2008 in 24 cities with daily air pollution data were eligible. Data include more than one birth to the same mother, but these could not be identified due to data limitations. Preterm births were those occurring at less than 37 weeks gestation, which were further categorized as 20–27, 28–31, 32–33 and 34–36 weeks gestation [29]. Information on maternal behaviours including smoking and alcohol consumption, and individual-level data on socioeconomic status (SES) and ethno-cultural origins were not available in this dataset. Area-level socioeconomic status characteristics were assigned to singleton births by geocoding birth records using the six character maternal postal code from the births database and the Postal Code Conversion File Plus (PCCF+) version 5 k in order to obtain Statistics Canada standard geographic identifiers [30]. Using geocoded birth records, neighbourhood-level SES variables were calculated at the Dissemination Area (DA) level using census data, including the proportion of individuals aged 15 years and over who were unemployed, or in the lowest income quintile, and the proportion of females aged 25 years and over with post-secondary education [31, 32]. Proportion of individuals in a DA who were classified as visible minority was also calculated. Visible minority groups are defined by the Canadian Employment Equity Act and classification of individuals is based on response to census questions pertaining to self-identified population group [33]. Neighbourhood-level variables were calculated based on the census year closest to the date of birth (2001 or 2006). There were 52,993 and 54,626 DAs in the 2001 and 2006 censuses respectively. Based on the 2006 census, the median and 70th percentile of DA population and land area were 513, 598, 0.26 km² and 1.27 km² respectively.

Daily air pollution data were obtained from the National Air Pollution Surveillance (NAPS) monitoring network for particulate matter of median aerodynamic diameter less than 2.5 μm (PM2.5) as well as carbon monoxide (CO), nitrogen dioxide (NO₂), ozone (O₃), and sulfur dioxide (SO₂). Daily temperature data were obtained from Environment and Climate Change Canada’s meteorology data archive. Where data were available from multiple monitors, they were averaged.

Statistical analysis was conducted in two stages. In the first stage, data were analyzed in each city employing Cox proportional hazards models using gestational age in days as the time scale, obtaining city-specific hazard ratios (HRs) with their 95% confidence intervals (CIs) expressed per interquartile range (IQR) of each air pollutant. We tested the proportional hazards assumption using the cox.zph function in R, which evaluates the significance of the interaction between the scaled Schoenfeld residuals for the air pollution term(s) and time, and found no evidence of violation of the proportional hazards assumption. Effects of air pollution were examined using distributed lag functions [34, 35] for lags of 0–6 days prior to delivery, as well as cumulative lags from two to six days. Specification of the lag structure for air pollution and temperature was based on natural spline functions employing three to five degrees of freedom, optimality of which was evaluated based on model Akaike Information Criterion (AIC). We evaluated the optimal lag response specification for O₃ and temperature in three cities representing diverse climates: Toronto (central Canada), Edmonton (north) and Vancouver (coastal). Three degrees of freedom in the natural spline of both O₃ and temperature exhibited the lowest AIC for all three cities. We therefore employed this lag structure specification in all 24 cities. Potential non-linearity in associations with air pollution was assessed by specifying air pollution as a natural spline with 3 degrees of freedom. We accounted for the potential nonlinear effect of daily mean ambient temperature using a cubic B-spline with 3 internal knots, placement of which was
evaluated based on model AIC and guided by recent literature [36]. We compared cubic B-splines with 3 internal knots placed at the 10th, 50th and 90th vs. 10th, 75th, and 90th percentiles of city-specific temperature distributions, and found that the AIC was lowest for the latter. Infant sex, maternal age (19 years or less, 20–39, 30–39, 40+ years), maternal marital status (single, married, separated, divorced, widowed), maternal country of birth (Canada, elsewhere), tertile of neighbourhood percent unemployed, low income, visible minority, and with post-secondary education, indicator variables for year and season of birth and a natural spline function of day of year with 3 degrees of freedom were included as covariates in each city specific model. Subgroup analyses were conducted by infant sex, gestational age category (20–27, 28–31, 32–33, 34–36 weeks), tertile of neighbourhood percent low income and season. In the second stage, we pooled the estimated city-specific hazard ratios using a random effects model. Associations with p-values < 0.05 were considered statistically significant. Analyses were performed with R version 3.4, using dlmnm package, version 2.3.2 and metafor, version 2.0.

**Results**

During the study period there were 1,248,240 singleton births in the 24 cities. Frequency and prevalence of preterm and term birth by maternal and infant characteristics, city, season and year are shown in Table 1. Maternal age 19 years and under or 40 years and over, and maternal marital status of single, divorced and separated were associated with a higher prevalence of preterm birth. St. John’s, Winnipeg, Calgary and Edmonton had the highest prevalence of preterm birth. There was no apparent trend by year or season. After exclusion of births with missing covariate data, 1,001,700 births were included in the analysis including 63,400 preterm births, resulting in an overall prevalence of preterm birth of 6.34%. (Note that in accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. Statistical analyses employed unrounded data.)

The combined population of the 24 cities was 11,522,776 in 2006. A descriptive summary of air pollution and temperature data is shown in Table 2. Mean PM$_{2.5}$ concentrations were highest in Montreal, Hamilton and Windsor, reflecting local industrial activity, and CO concentrations were uniformly low. Mean temperatures were generally mildest and exhibited the narrowest ranges in the coastal British Columbia cities of Richmond, Vancouver, Victoria and Nanaimo.

Pooled estimates of associations with O$_3$ by lag day from distributed lag models are shown in Fig. 1. The lag 0, 1 and 6 day Hazard Ratios (HR) were positive and significant, while lags 3 and 4 days were negative and significant. $I^2$, Cochrane’s Q and p-values of Q are shown in Table 3. There was significant heterogeneity between cities only for lag 2 days. The cumulative lag HRs for 0–1, 0–2 and 0–3 days were significant. Results for individual cities at lag 0 days are shown in Additional file 1: Figure S1. Significant positive associations were observed in Toronto (HR 1.038 95% CI 1.009, 1.067), Mississauga (HR 1.057 95% CI 1.005, 1.111), Quebec City (HR 1.075 95% CI 1.004, 1.151), Edmonton (HR 1.096 95% CI 1.040, 1.156) and Windsor (HR 1.131 95% CI 1.035, 1.236) (all are expressed per 13.3 ppb O$_3$). As a sensitivity analysis, we specified O$_3$ as a natural spline function with 3 degrees of freedom in four cities of varying sizes and climates (Vancouver, Edmonton, Winnipeg and Toronto) and found that in all cases models employing a linear O$_3$ term had a lower AIC, indicating better fit.

Analyses by subgroups revealed similar results by lag day for male and female infants (Fig. 2). Significant positive associations were observed of O$_3$ with preterm birth at lags 0 and 1 days in the 1st tertile, lag 0 days in the 2nd tertile and lag 6 days in the 3rd tertile of neighbourhood percent low income (Fig. 3). Significant positive associations at lag 0 days were observed for births at 34–36 weeks, while no significant positive associations were observed for births at 20–27, 28–31 or 32–33 weeks (Fig. 4). Significant positive associations were observed at multiple lags in spring, summer and fall, and only at lag 0 in winter (Fig. 5).

Associations with other pollutants were mixed (Additional file 1: Figures S2-S5). CO and NO$_2$ exhibited significant negative associations with preterm birth at lag 0, 1, 5 and 6 days and 0, 1 and 6 days respectively. PM$_{2.5}$ exhibited no significant associations, and SO$_2$ exhibited significant negative associations at lag 0 and 1 day.

**Discussion**

We observed associations between daily O$_3$ in the week prior to delivery and preterm birth in an analysis of approximately 1 million births in 24 Canadian cities between 1999 and 2008. Our findings for PM$_{2.5}$ and NO$_2$ were similar to our earlier analysis where we found null or negative associations of preterm birth with PM$_{2.5}$ or NO$_2$ averaged over gestational month, trimester or the entire pregnancy [12, 13]. Associations were similar for
male and female infants but differed by gestational age and season. Our observation of significant associations only at longer gestational ages may result from greater statistical power afforded by the larger number of pregnancies in these categories of gestational age. Greater time spent outdoors and/or increased indoor penetration
| City          | 2006 population | PM$_{2.5}$ (μg/m³) | NO₂ (ppb) | O₃ (ppb) | SO₂ (ppb) | CO (ppm) | T (°C) |
|--------------|-----------------|---------------------|-----------|----------|----------|----------|--------|
|              | N mean min max  | N mean min max      | n mean min max | n mean min max | n mean min max | n mean min max |       |
| St John's    | 100,646         | 3470 46 0 0 49.0    | 3040 7.8 0.1| 57.8     | 3620 25.0| 2.1 575 3105 2.5| 0 19.7 3605 0.4| 0 1.9 3655 6.2| −15.3 24.6 |
| Saint John   | 68,043          | 3350 68 0 0 109.1   | 3575 7.4 0.0| 59.4     | 3655 25.0| 3.0 727 3645 4.4| 0 0 3510 0.5| 0 0 3655 5.6| −23.4 23.6 |
| Fredericton  | 50,535          | 3365 59 0 0 42.0    | 3190 4.9 0.0| 0 34.8   | 3460 24.6| 2.4 561 0 0 3470 0.3| 0 0 3655 6.7| −23.8 28.2 |
| Quebec       | 491,142         | 3360 10.1 0 0 111.9  | 3465 12.8 0.4| 56.9    | 3655 21.1| 1.0 572 3440 2.1| 0 0 3604 0.4| 0 0 3655 5.3| −28.2 28.5 |
| Trois Rivières | 126,323      | 3540 97 0 0 66.3    | 0 0 0 0 3460 21.2 0.7| 585 0 0 3600 3.0| 0 0 3655 6.0| −27.3 28.5 |
| Montreal     | 1,620,693       | 3650 11.4 0 0 83.4   | 3655 18.3 3.8| 57.9    | 3655 19.1| 0.9 680 3640 4.4| 0 0 3655 6.7| −26.4 29.2 |
| Ottawa       | 812,129         | 3435 85 0 0 70.0    | 3575 14.7 0.0| 57.0    | 3655 22.8| 0.8 662 3640 2.4| 0 0 3655 7.0| −26.7 30.4 |
| Oshawa       | 141,590         | 3610 98 0 0 63.5    | 3180 15.3 0.3| 52.9    | 3610 25.1| 2.5 665 3650 3.3| 0 0 3655 8.6| −21.0 29.0 |
| Hamilton     | 504,559         | 3655 106 0 0 64.9    | 3650 21.9 4.8| 62.3    | 3650 21.7| 2.4 656 3650 3.2| 0 0 3655 8.3| −20.5 30.8 |
| Mississauga  | 668,549         | 3580 10.1 0 0 67.8   | 1855 19.8 3.2| 58.9    | 3590 22.6| 0.7 756 2670 3.4| 0 0 3655 8.9| −20.3 31.5 |
| Brampton     | 433,806         | 3070 99 0 0 69.2    | 3035 16.2 1.8| 58.1    | 3085 25.6| 0.5 785 2365 2.1| 0 0 3655 8.6| −21.0 29.0 |
| Hamilton     | 504,559         | 3595 115 0 0 64.2    | 3575 17.7 1.0| 62.6    | 3595 23.8| 0.0 846 3580 5.1| 0 0 3655 8.3| −20.5 30.8 |
| St. Catharines | 131,989       | 3555 102 0 0 63.5    | 2515 13.9 2.1| 77.6    | 3555 24.3| 0.0 810 1705 2.9| 0 0 3655 9.7| −15.0 30.0 |
| Kitchener    | 204,668         | 3360 98 0 0 67.8    | 3305 12.2 0.8| 53.2    | 3350 26.4| 0.8 827 2080 2.9| 0 0 3650 7.3| −22.0 30.0 |
| Windsor      | 216,473         | 3475 119 0 0 68.0    | 3490 18.4 2.9| 55.7    | 3590 22.7| 0.5 769 3590 5.9| 0 0 3655 10.6| −16.8 31.5 |
| Winnipeg     | 633,451         | 3650 71 0 0 63.8    | 3650 11.8 1.1| 39.3    | 3655 19.9| 1.2 510 0 0 3645 4.0| 0 0 3640 4.6| −33.0 30.0 |
| Calgary      | 988,193         | 3635 91 0 0 90.7    | 3655 21.3 4.9| 63.7    | 3655 18.9| 0.6 511 3625 2.1| 0 0 3655 4.9| −31.6 24.7 |
| Edmonton     | 730,372         | 3655 93 0 0 74.0    | 3650 20.8 3.2| 62.9    | 3650 18.4| 0.5 486 0 0 3655 0.5| 0 0 3655 4.9| −34.7 26.5 |
| Richmond     | 174,461         | 3570 68 0 0 44.0    | 3655 16.7 3.6| 40.5    | 3655 15.2| 0.3 449 3580 1.0| 0 0 3655 0.5| 0 1.9 3655 10.6| −8.6 24.2 |
| Vancouver    | 578,041         | 3565 69 1 1 36.3    | 3655 22.5 4.7| 43.2    | 3655 10.0| 0.0 375 3655 3.3| 0 0 3655 11.1| −7.0 25.0 |
| Victoria     | 78,057          | 3160 73 0 0 37.9    | 2770 11.1 0.5| 30.9    | 3215 17.9| 0.2 464 2945 1.3| 0 0 3650 10.2| −7.2 26.7 |
| Nanaimo      | 786,922         | 3620 55 0 0 24.5    | 865 8.4 1.1| 20.1    | 3600 19.2| 0.1 450 1055 1.0| 0 0 3655 11.1| −11.0 27.0 |
| Kamloops     | 80,376          | 3595 69 0 0 140.0   | 3545 10.6 0.1| 38.2    | 3600 20.9| 0.0 524 3645 0.5| 0 0 3655 9.4| −24.2 29.8 |
| Kelowna      | 106,707         | 3590 69 0 0 186.0   | 3345 9.0 0.2| 35.3    | 3615 21.0| 0.0 51.1 2915 0.2| 0 0 3650 8.9| −24.2 28.5 |

*24 h average values*
of outdoor pollutants in spring, summer and autumn could explain our observation of significant positive associations over multiple lags during these seasons, but only for a single lag in winter. Associations with other pollutants were inconsistent.

Our analysis is one of a limited number which have examined these short term associations employing Cox proportional hazards models to account for the different exposure durations of preterm vs. term births (in contrast to studies based on exposure during the entire pregnancy or third trimester). O₃ exposure in particular has received relatively little attention in previous studies.

In their analysis of 13 birth cohorts comprising 71,493 births from the European Study of Cohorts for Air Pollution Effects (ESCAPE), Giorgis-Allemand et al. found no association of preterm birth with NO₂, nitrogen oxides (NOₓ), PM₂.₅ and PM₁₀ exposures over durations ranging from one week to the entire pregnancy [22]. In an analysis of 78,633 births in Rome and 27,255 in Barcelona, Schifano et al. found that PM₁₀ and NO₂ in the week prior to delivery were positively associated with preterm birth in Barcelona and negatively associated with preterm birth in Rome, while ozone was positively associated with preterm birth in both cities [23]. The hazard ratios for O₃ were comparable in magnitude to what we observed: 1.010 (95% CI 1.001, 1.020) per 9.2

### Table 3

| Lag | Hazard Ratio | 95% confidence interval | p   | I² | Q    | p(Q)  |
|-----|--------------|-------------------------|-----|----|------|-------|
| 0   | 1.032        | 1.017, 1.048            | <.0001 | 12.83% | 26.3945 | 0.2831 |
| 1   | 1.010        | 1.001, 1.020            | 0.0327 | 26.81% | 31.4232 | 0.1127 |
| 2   | 0.994        | 0.984, 1.005            | 0.2897 | 38.81% | 37.5859 | 0.0282 |
| 3   | 0.985        | 0.973, 0.997            | 0.0171 | 33.68% | 34.6821 | 0.0559 |
| 4   | 0.987        | 0.978, 0.996            | 0.0066 | 23.55% | 30.0833 | 0.147  |
| 5   | 1.000        | 0.993, 1.007            | 0.9832 | 0.00%  | 18.9691 | 0.703  |
| 6   | 1.019        | 1.006, 1.032            | 0.005  | 0.00%  | 22.7601 | 0.4749 |
| 0–1 | 1.032        | 1.016, 1.049            | <.0001 | 16.81% | 27.649  | 0.2293 |
| 0–2 | 1.042        | 1.016, 1.068            | 0.0012 | 23.37% | 30.0158 | 0.1489 |
| 0–3 | 1.036        | 1.005, 1.067            | 0.0209 | 29.10% | 32.4378 | 0.0914 |
| 0–4 | 1.022        | 0.987, 1.057            | 0.227  | 33.94% | 34.8155 | 0.0543 |
| 0–5 | 1.009        | 0.971, 1.049            | 0.6396 | 34.61% | 35.1717 | 0.05   |
| 0–6 | 1.006        | 0.971, 1.042            | 0.7587 | 20.63% | 28.9787 | 0.181  |

*Per 13.3 ppb O₃ (interquartile range)
ppb in Barcelona and 1.025 (95% CI 1.009, 1.042) per 15.3 ppb in Rome [23]. In contrast to our findings, they observed larger associations at shorter pregnancy durations [23]. An earlier study by the same authors examining preterm birth in Rome using time-series methods found that PM$_{10}$, O$_3$ and NO$_2$ lagged 0–2 days were not associated with preterm birth in the warm or cold season; only PM$_{10}$ lagged 12–22 days in the warm season was significantly associated with preterm birth [19]. In a study of nearly 500,000 births in Guangzhou, significant associations were observed between preterm birth and PM$_{10}$, NO$_2$ and O$_3$, with the peak magnitude of effect at 25 weeks (HR = 1.048, 95% CI 1.034–1.062 per IQR, 37.0 μg/m$^3$), 26 weeks (HR = 1.060, 95% CI 1.028–1.094 per IQR, 15.4 ppb) and 28

![Fig. 2](image1.png)

**Fig. 2** Pooled hazard ratios, 95% confidence intervals by infant sex, single day lag, distributed lag models. Expressed per 13.3 ppb O$_3$ (interquartile range)

![Fig. 3](image2.png)

**Fig. 3** Pooled hazard ratios, 95% confidence intervals by tertile neighbourhood percent low income, single day lag, distributed lag models. Expressed per 13.3 ppb O$_3$ (interquartile range)
weeks (HR = 1.063, 95% CI 1.046–1.081 per IQR, 45.8 ppb) gestation respectively [26]. We recently reported that PM$_{2.5}$ on the day of delivery was associated with preterm birth only among women assigned to the highest quartile of PM$_{2.5}$ glutathione-related oxidative potential based on approximately 200,000 births among 31 cities in the province of Ontario, Canada [25]. Johnson et al. found no association between cumulative third trimester PM$_{2.5}$ or NO$_2$ and preterm birth in a discrete time survival analysis of 258,294 births in New York City [24]. Sagiv et al. conducted a time-series analysis of 187,997 births in Pennsylvania and found that preterm birth was associated with PM$_{10}$ 2 days and 5 days before birth (relative risk (RR) = 1.10; 95% CI, 1.00–1.21 per 50 μg/m$^3$ and RR = 1.07; 95% CI, 0.98–1.18 per 50 μg/m$^3$ respectively) [14]. Associations with O$_3$ were not reported. In another time series analysis of 476,489 births in Atlanta, Darrow et al. observed mostly null

| Season | Lag (days) | Pooled Hazard Ratio (95% Confidence Interval) |
|--------|------------|-----------------------------------------------|
| Spring | 1          | 1.02 (0.98, 1.06) |
|        | 10         | 1.03 (0.99, 1.07) |
|        | 30         | 1.01 (0.97, 1.04) |
|        | 60         | 1.00 (0.96, 1.04) |
|        | 90         | 1.00 (0.95, 1.05) |
|        | 120        | 1.00 (0.95, 1.05) |
|        | 150        | 1.00 (0.95, 1.05) |
|        | 180        | 1.00 (0.95, 1.05) |
|        | 210        | 1.00 (0.95, 1.05) |
|        | 240        | 1.00 (0.95, 1.05) |
|        | 270        | 1.00 (0.95, 1.05) |
|        | 300        | 1.00 (0.95, 1.05) |
|        | 330        | 1.00 (0.95, 1.05) |
|        | 360        | 1.00 (0.95, 1.05) |
|        | 390        | 1.00 (0.95, 1.05) |
|        | 420        | 1.00 (0.95, 1.05) |
|        | 450        | 1.00 (0.95, 1.05) |
|        | 480        | 1.00 (0.95, 1.05) |
|        | 510        | 1.00 (0.95, 1.05) |
|        | 540        | 1.00 (0.95, 1.05) |
|        | 570        | 1.00 (0.95, 1.05) |
|        | 600        | 1.00 (0.95, 1.05) |
|        | 630        | 1.00 (0.95, 1.05) |
|        | 660        | 1.00 (0.95, 1.05) |
|        | 690        | 1.00 (0.95, 1.05) |
|        | 720        | 1.00 (0.95, 1.05) |
|        | 750        | 1.00 (0.95, 1.05) |
|        | 780        | 1.00 (0.95, 1.05) |
|        | 810        | 1.00 (0.95, 1.05) |
|        | 840        | 1.00 (0.95, 1.05) |
|        | 870        | 1.00 (0.95, 1.05) |
|        | 900        | 1.00 (0.95, 1.05) |
|        | 930        | 1.00 (0.95, 1.05) |
|        | 960        | 1.00 (0.95, 1.05) |
|        | 990        | 1.00 (0.95, 1.05) |
|        | 1020       | 1.00 (0.95, 1.05) |
|        | 1050       | 1.00 (0.95, 1.05) |
|        | 1080       | 1.00 (0.95, 1.05) |
|        | 1110       | 1.00 (0.95, 1.05) |
|        | 1140       | 1.00 (0.95, 1.05) |
|        | 1170       | 1.00 (0.95, 1.05) |
|        | 1200       | 1.00 (0.95, 1.05) |
|        | 1230       | 1.00 (0.95, 1.05) |
|        | 1260       | 1.00 (0.95, 1.05) |
|        | 1290       | 1.00 (0.95, 1.05) |
|        | 1320       | 1.00 (0.95, 1.05) |
|        | 1350       | 1.00 (0.95, 1.05) |
|        | 1380       | 1.00 (0.95, 1.05) |
|        | 1410       | 1.00 (0.95, 1.05) |
|        | 1440       | 1.00 (0.95, 1.05) |
|        | 1470       | 1.00 (0.95, 1.05) |
|        | 1500       | 1.00 (0.95, 1.05) |
|        | 1530       | 1.00 (0.95, 1.05) |
|        | 1560       | 1.00 (0.95, 1.05) |
|        | 1590       | 1.00 (0.95, 1.05) |
|        | 1620       | 1.00 (0.95, 1.05) |
|        | 1650       | 1.00 (0.95, 1.05) |
|        | 1680       | 1.00 (0.95, 1.05) |
|        | 1710       | 1.00 (0.95, 1.05) |
|        | 1740       | 1.00 (0.95, 1.05) |
|        | 1770       | 1.00 (0.95, 1.05) |
|        | 1800       | 1.00 (0.95, 1.05) |

Fig. 4 Pooled hazard ratios, 95% confidence intervals by gestational age, single day lag, distributed lag models. Expressed per 13.3 ppb O$_3$ (interquartile range)

Fig. 5 Pooled hazard ratios, 95% confidence intervals by season, single day lag, distributed lag models. Expressed per 13.3 ppb O$_3$ (interquartile range)
associations with air pollution (including O₃), but reported that preterm birth was associated with PM₂.₅ sulfate and PM₂.₅ water-soluble metal concentrations in the week preceding delivery [15]. Rappazzo et al. also reported that PM₂.₅ lagged 0–2 weeks before birth was associated with an increased risk of preterm birth in an analysis of nearly 1.8 million births in Ohio, Pennsylvania, and New Jersey [17]. O₃ was included as a covariate but associations of preterm birth with O₃ were not reported. A time series study in Ahvaz, Iran found no association between O₃ in the two weeks prior to birth and preterm birth, although significant associations with CO, NO₂ and PM₁₀ were observed [20]. Lee et al. reported no associations of O₃, PM₁₀ or meteorological variables with preterm birth in a time series analysis in London examining exposures in the week prior to birth [16]. Arroyo et al. found an association between O₃ in the twelfth week of gestation and preterm birth in a time-series analysis in Madrid [18]. Finally, employing a novel hierarchical spatiotemporal model, Warren et al. found that O₃ in weeks 1–5 and PM₂.₅ in weeks 4–22 were associated with increased risk of preterm birth in a study in eastern Texas [37]. In their analysis of air pollution attributable preterm births worldwide, Malley et al. [1] employed an odds ratio of 1.13 (95% CI 1.03, 1.24) per 10 μg/m³ PM₂.₅ based on the meta-analysis by Sun et al. [9], considerably larger than what Sagiv et al. [14] or Schifano et al. [23] observed. It should be noted that there may be substantial differences in other factors that could contribute to preterm birth among these studies, including prenatal care, employment rights of pregnant women, and obstetrical decision-making (e.g. decision to induce labour).

Mechanisms through which exposures in the days prior to delivery might trigger preterm birth are unknown, but may include non-specific processes such as inflammation or oxidative stress, which are known to be associated with both preterm birth [38–41] and air pollution exposure [42]. PM₂.₅ could also trigger preterm birth through cardiovascular mechanisms or effects on endothelial function [42].

Strengths of our study include the large sample size distributed over multiple cities and utilization of Cox models which account for the differing length of exposure in preterm and term births, and distributed lag models which parsimoniously evaluate effects over multiple lags. We also assessed the shape of the exposure response relationship, examined effect modification by infant, maternal and other factors, and considered the effects of other pollutants. Limitations of our study include the lack of data on maternal behavioural risk factors and possible exposure measurement error owing to the limited number of monitors within each city. Since our analysis deals by design with short term temporal variability in air pollution exposure, observed associations are unlikely to be confounded by short-term time invariant risk factors such as smoking.

In the only other study employing the same design which included data on maternal smoking, Giorgis-Allemand et al. found that results were not sensitive to inclusion of smoking and other individual characteristics as covariates [22]. Exposure measurement error would be expected to be non-differential, biasing observed associations towards the null [43], and as a secondary pollutant, O₃ concentrations would be expected to be relatively homogeneous over larger areas compared to pollutants such as NO₂. Of four other studies with the same design, two with the same limitations with respect to relatively sparse fixed site monitoring data found consistent associations with O₃ and inconsistent associations with NO₂ and PM₁₀ [23], while two others employing temporally adjusted land use regression models for NO₂, NOₓ, PM₂.₅ and PM₁₀ [22] and NO₂ and PM₂.₅ [24], potentially reducing exposure measurement error, found no significant associations with preterm birth [22, 24]. Data were missing for at least one covariate for approximately 20% of births in our study. Marital status was the most common missing covariate, and births for which this was missing had a higher prevalence of preterm birth. This suggests that these births differed from those where all covariate data were available which could have biased our results. Results from individual cities were pooled using a random effects model, which treats estimates from individual cities as originating from separate underlying distributions rather than a single common distribution [44]. Differences between cities may stem from differences in the exposure mix, impact of confounders such as weather, or population characteristics. The random effects model is conservative relative to a fixed effects model in that it assigns greater variance to the overall (pooled) measure of effect by incorporating both within and between study variance [44].

Conclusions

In this study, one of a small number employing time to event analysis, we observed significant associations between O₃ in the week prior to delivery and preterm birth, based on an analysis of approximately 1 million births over a ten year period. Given the mixed findings in other studies of this kind, additional studies are needed to determine whether the weight of evidence supports the existence of a causal association between preterm birth and air pollution exposure in the days preceding delivery.

Additional file

**Additional file 1:** Figure S1. Hazard Ratio by City per 13.3 ppb O₃ lag 0 days. Figure S2. Pooled Hazard Ratio by Lag per 0.36 ppm CO. Figure S3. Pooled Hazard Ratio by Lag per 10.3 ppb NO₂. Figure S4. Pooled Hazard Ratio by Lag per 7.4 μg/m³ PM₂.₅. Figure S5. Pooled Hazard Ratio by Lag per 2.9 ppm SO₂. (PDF 119 kb)
Abbreviations
AIC: Akaike Information Criterion; CI: Confidence intervals; CO: Carbon monoxide; DA: Dissemination Area; ESCAPE: European Study of Cohorts for Air Pollution Effects; HR: Hazard ratio; IQR: Interquartile range; NO2: Nitrogen dioxide; O3: Ozone; PCF+: Postal Code Conversion File Plus; PM2.5: Particulate matter of median aerodynamic diameter ≤2.5 μm; SES: Socioeconomic status; SO2: Sulfur dioxide

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Availability of data and materials
Supporting data are available to bona fide researchers, subject to availability of data and materials

Consent for publication
Consent to participate is not applicable since the study was based on de-identified vital statistics data.

Consent to participate
The study was approved by Health Canada’s Research Ethics Board (2011–0046).

Ethics approval and consent to participate
The study was approved by Health Canada’s Research Ethics Board (2011–0046). Consent to participate is not applicable since the study was based on de-identified vital statistics data.

Competing interests
The authors declare that they have no competing interests.

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