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A national study of the association between traffic-related air pollution and adverse pregnancy outcomes in Canada, 1999–2008 ☆

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ABSTRACT

Numerous studies have examined the association of air pollution with preterm birth and birth weight outcomes. Traffic-related air pollution has also increasingly been identified as an important contributor to adverse health effects of air pollution. We employed a national nitrogen dioxide (NO_2) exposure model to examine the association between NO_2 and pregnancy outcomes in Canada between 1999 and 2008. National models for NO_2 (and particulate matter of median aerodynamic diameter <2.5 μm ($PM_{2.5}$) as a covariate) were developed using ground-based monitoring data, estimates from remote-sensing, land use variables and, for NO_2, deterministic gradients relative to road traffic sources. Generalized estimating equations were used to examine associations with preterm birth, term low birth weight (LBW), small for gestational age (SGA) and term birth weight, adjusting for covariates including infant sex, gestational age, maternal age and marital status, parity, urban/rural place of residence, maternal place of birth, season, year of birth and neighbourhood socioeconomic status and per cent visible minority. Associations were reduced considerably after adjustment for individual covariates and neighbourhood per cent visible minority, but remained significant for SGA (odds ratio 1.04, 95%CI 1.02–1.06 per 20 ppb NO_2) and term birth weight (16.2 g reduction, 95% CI 13.6–18.8 g per 20 ppb NO_2). Associations with NO_2 were of greater magnitude in a sensitivity analysis using monthly monitoring data, and among births to mothers born in Canada, and in neighbourhoods with higher incomes and a lower proportion of visible minorities. In two pollutant models, associations with NO_2 were less sensitive to adjustment for $PM_{2.5}$ than vice versa, and there was consistent evidence of a dose-response relationship for NO_2 but not $PM_{2.5}$. In this study of

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approximately 2.5 million Canadian births between 1999 and 2008, we found significant associations of NO_2 with SGA and term birth weight which remained significant after adjustment for $PM_{2.5}$, suggesting that traffic may be a particularly important source with respect to the role of air pollution as a risk factor for adverse pregnancy outcomes.

1. Introduction[1]

Numerous studies have examined the association of ambient air pollution with preterm birth and birth weight outcomes (Stieb et al., 2012). Traffic-related air pollution has also increasingly been identified as an important contributor to adverse health effects of air pollution (HEI, 2010), and it has been estimated that one third of Canadians live in areas with high levels of exposure to traffic-related air pollution (within 500 m of highways or 100 m of major roads) (Brauer et al., 2013). In some densely populated cities of Europe this proportion exceeds 90% (Su et al., 2015). Nitrogen dioxide (NO_2) has often served as a marker for traffic-related air pollution, and land use regression models in particular have frequently been used to model the fine scale spatial variability in NO_2 exposure (HEI, 2010). Many previous studies of air pollution and pregnancy outcomes, particularly earlier studies, have employed fixed site air pollution monitoring data to estimate maternal exposure (Stieb et al., 2012), but population coverage is generally low (Guay et al., 2011). Several studies have employed land use regression or other models to estimate maternal exposure (Brauer et al., 2008; Jackson et al., 2009; Slama et al., 2007; Wu et al., 2009; Madsen et al., 2010; Lepeule et al., 2010; Llop et al., 2010; Gehring et al., 2011a, 2011b; Ballester et al., 2010; Aguilera et al., 2009; Habermann et al., 2014; Gehring et al., 2014; Pedersen et al., 2013; Laurent et al., 2013; Ghosh et al., 2012; Pereira et al., 2011, 2012; Malmqvist et al., 2011; Wilhelm et al., 2011) but most have examined individual cities or communities. We previously reported results of a national Canadian study of fine particulate matter ($PM_{2.5}$) and pregnancy outcomes where we found that $PM_{2.5}$ was associated with reduced term birth weight and increased risk of small for gestational age (SGA) (Stieb et al., 2016). In the present study, we employ a national NO_2 exposure model to examine the association between NO_2 and preterm birth, term low birth weight, small for gestational age, and term birth weight as a continuous variable in Canada between 1999 and 2008.

2. Material and methods

2.1. Pregnancy Outcome Data

The Canadian Birth Database contains live birth events for the years 1985 up to the most recent year available and includes approximately 346,000 birth records each year. 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 were eligible. The following information was available: infant sex, date of birth, gestational age, birth weight, birth order, number of stillborn (if multiple birth), six-character postal code of maternal place of residence at the time of the child's birth, maternal age at child's birth, maternal marital status at child's birth, total number of liveborn and stillborn (ever), province and/or country of birth of the mother and father, and maternal education (Quebec only). Gestational age may be based on last menstrual period, ultrasound, physical examination or other method, but birth registration documents do not specify how the gestational age was calculated (Statistics Canada, 2014). Data may include more than one birth to the same mother, but these could not be identified. Pregnancy outcomes comprised preterm birth (gestational age < 37 weeks), term low birth weight (LBW, < 2500 g), small for gestational age (SGA, < 10 percentile of birth weight for gestational age) (Kramer et al., 2001), and term birth weight as a continuous variable. As a sensitivity analysis, we also examined associations by degree of prematurity as reported by Padula et al. (2014): 20–27 weeks, 28–31 weeks, 32–33 weeks and 34–36 weeks. Criteria for SGA were gender-specific but not race-specific. 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. Possible confounding by maternal smoking was examined using data from the Canadian Community Health Survey (see Section 2.5) and by individual-level SES using the 2006 Birth Census Cohort (see Section 2.3).

2.2. Geocoding and neighbourhood socioeconomic status

Area-level socioeconomic status characteristics were assigned to singleton births by geocoding birth records using the six character maternal postal code and the Postal Code Conversion File Plus (PCCF+) version 5k in order to obtain Statistics Canada standard geographic identifiers (Wilkins and Peters, 2012). In urban Canada (which represents about three-quarters of the population), postal codes generally refer to a small geographic area containing on average 30 total population. Each postal code is represented spatially by a representative point or points. In urban areas, it is most often located at the mid-point along a block-face portion, which generally corresponds to one side of a city block. For apartment buildings it is often the location of the building. For rural Canada, postal codes can cover a large geographic area with as many as 1100 total population, encompassing more than one census dissemination area. For these cases, postal code representative points are randomly allocated using a population-weighted file from Statistics Canada (Statistics Canada, 2013), such that the probability of a given dissemination area (DA) centroid being used reflects the spatial distribution of the underlying population. Postal codes were considered rural if the second character was zero. Using geocoded birth records, neighbourhood-level SES variables were calculated at the DA level using census data, including proportion of individuals aged 15 and over who were unemployed, proportion of individuals aged 15 and over in the lowest income quintile, and proportion of females aged 25 and over with post-secondary education (Crouse et al., 2012; Dadvand et al., 2013). Proportion of individuals in a DA who were 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 and aboriginal group (Statistics Canada,

[1] CI, confidence interval; CV, cross-validation; DA, dissemination area; DSA, deletion/substitution/addition; GEE, generalized estimating equations; ICAPPO, International Collaboration on Air Pollution and Pregnancy Outcome; IQR, interquartile range; IUGR, intrauterine growth restriction; LBW, low birth weight; LUR, land use regression; NAPS, national air pollution surveillance; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, particulate matter of median aerodynamic diameter < 2.5 μm; PM_{10}, particulate matter of median aerodynamic diameter < 10 μm; ppb, parts per billion; PCCF+, postal code conversion file plus; RMSE, root mean square error; SES, socioeconomic status; SGA, small for gestational age.

2015a). 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 km^2 and 1.27 km^2 respectively.

2.3. 2006 Birth Census Cohort

The 2006 Birth Census Cohort was created by linking birth events that occurred between May 16, 2004 and May 15, 2006 with the 2006 Census of Population. Using linkage keys such as date of birth of child, mother and father, postal code, sex and names, 90% of in-scope births were successfully linked to the 2006 Census. Only those births linked to a long-form census household were retained in the Birth Census Cohort. Data quality assessment indicated that linkage rates were slightly lower for births to younger mothers, to mothers born outside of Canada, and to births in the North. See Bushnik et al. (2016) for additional details. The 2006 Birth Census Cohort contains information on the socio-demographic, socio-economic and ethno-cultural characteristics of the child and its family. These data were used to examine the sensitivity of air pollution risk estimates to adjustment for mother visible minority, maternal education, maternal and paternal occupation and maternal income quintile in addition to neighbourhood (DA) level variables.

2.4. Exposure

Exposures were assigned by mapping the mother's six-character postal code to NO_2 and $PM_{2.5}$ surfaces, as described below. The NO_2 surface was available annually so that exposure during pregnancy was calculated as the weighted average of consecutive years, where weights were equal to the proportion of the pregnancy in each year. The $PM_{2.5}$ surface was available monthly so that a similar procedure was used for consecutive months.

2.4.1. NO_2 surface

A national NO_2 model for Canada was developed using ground-based monitoring data, estimates from remote-sensing, land use variables and deterministic gradients relative to road traffic sources. First, a national land use regression (LUR) model was created to estimate NO_2 concentrations across Canada, accounting for background, regional and local spatial variation. This model was developed from 2006 national air pollution surveillance (NAPS) monitoring data, following methods reported in Hystad et al. (2011). Background and regional components were estimated in the LUR using satellite-derived NO_2 estimates (Lamsal et al., 2008) and geographic variables, while local scale variation was modelled using deterministic gradients. The final LUR model included: road length within 10 km; 2005–2011 satellite NO_2 estimates; area of industrial land use within 2 km; and summer rainfall. This model explained 73% of the variation in NAPS measurements with a root mean square error (RMSE) of 2.9 ppb. Local scale variation was modelled using deterministic gradients as this fine-scale spatial variation in NO_2 from vehicle emissions was not captured in the LUR model due to siting of current NAPS monitors. Kernel density measures were used to apply these gradients and capture more complex patterns in potential roadway emissions (i.e. the influence of multiple roadways, intersections, off-ramps, etc.). The top 10th percentile of kernel density measures was given the highest NO_2 increases (65% for highways and 20% for major roads) with a decrease to no increase at 300 and 100 m respectively (Smargiassi et al., 2005; Su et al., 2009; Gilbert et al., 2003; Gilbert et al., 2007; Beckerman et al., 2008; Roorda-Knape et al., 1998). These gradients are multipliers that are applied to the LUR estimates, therefore roughly capturing differences in traffic volume. For example, a 30% increase applied to an LUR estimate of 20 ppb in Toronto adds 6 ppb compared to 3 ppb when applied to an LUR estimate of 10 ppb in Victoria. Yearly estimates of NO_2 from 1999 to 2008 were calculated by applying an adjustment to the 2006 estimates based on trends in historical NAPS monitoring data. While there was some heterogeneity between cities in the NO_2 decline during this period, all demonstrated a consistent decrease. Thus one country-wide adjustment was used. The best model fit ($R2=0.98$, $RMSE=0.48$) of the yearly NAPS NO_2 data was a cubic polynomial, which resulted in the equation:

$$y=0.\ 001057x^3-0.\ 063393x^2+1.\ 478513x+8.\ 626218$$

where x represents the number of years prior to 2012.

Because the national NO_2 surface only provided annual values, we also conducted a sensitivity analysis employing data from 11 cities where continuous monitoring data were available (Calgary, Edmonton, Hamilton, Kamloops, Montreal, Ottawa, Quebec, Richmond, Toronto, Vancouver, Winnipeg). This allowed us to map NO_2 values more precisely to gestational periods and to examine effects by trimester. We also generated temporally adjusted LUR NO_2 values. For each city and month over the ten year period, we calculated the monthly ratio of average NO_2 from all monitors in the city to annual values for 2006 from the LUR model averaged over the city, and then multiplied this ratio by the 2006 LUR NO_2 value for each 6 digit postal code in that city.

2.4.2. $PM_{2.5}$ surface

Derivation of exposure estimates for $PM_{2.5}$ has been described in detail elsewhere (Beckerman et al., 2013; Stieb et al., 2016). Briefly, $PM_{2.5}$ exposures were estimated from a monthly surface based on a North American land use regression model that incorporated observations from fixed-site monitoring stations and satellite-derived estimates of $PM_{2.5}$. During the first stage of modelling, a machine learning method, known as the Deletion/Substitution/Addition (DSA) algorithm, was implemented to create an LUR model as described in Beckerman et al. (2013). Variables describing square of open (undeveloped) space within 200 m of a location and $PM_{2.5}$ concentration estimated from remote sensing (squared and cubed) were chosen by the DSA algorithm for the LUR model as the most predictive variables using cross-validation (CV) selection techniques. Additionally, an indicator for the Canadian dataset was interacted with the remote sensing variable to provide a small marginal adjustment to the remote sensing contribution to the prediction. The LUR model described 59% of the observed variability in the mean as measured by the CV normalized pseudo-R2 based on v-fold cross-validated prediction error, where $v=10$ as in Beckerman et al. (2013). However, there was significant residual variability as the non-normalized CV pseudo-R2 was 26%. In the second stage, the Bayesian Maximum Entropy interpolation method (Christakos, 1990) was used to create a spatiotemporal prediction model of the space-time residuals from the LUR model that were added to the LUR prediction estimates. This method (described in more detail in Beckerman et al., 2013), produced a final model with a CV R2 of 0.36. CV estimates were based on 1436 (10%) randomly selected leave-out observations from 22 monitoring sites. This model appeared less predictive than the US model (CV $R2=0.79$), however the poor fit was partly driven by a small number of outlying observations, and removing them improved the model prediction (CV $R2=0.53$).

2.5. Statistical analysis

We used a similar approach to that employed in the recent International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO) multi centre analysis (Dadvand et al., 2013), reporting unadjusted results, and incrementally adding adjustments for SES and maternal and infant characteristics. Generalized estimating equations (GEE) were used to examine the association between air pollution and pregnancy outcomes, employing logistic regression for preterm birth, term LBW, and SGA, and linear regression for term birth weight. Models adjusted for covariates including infant sex, gestational age (weeks), maternal age (<18, 18–29, 30–39, 40+ years) and marital status (single, married, widowed, divorced, separated), parity (1st, 2nd, $\geq$3rd birth), urban/rural place of residence, maternal place of birth (within/outside Canada), season (winter (January to March), spring (April to June), summer (July to September) and fall (October to December)), year of birth (calendar year) and DA proportions of individuals aged 15 and over who were unemployed, of individuals aged 15 and over in the lowest income quintile, of females aged 25 and over with post-secondary education and of individuals who were visible minority. Because some provinces and territories had few births, we adjusted for location of mother's place of residence using an indicator for six regional airsheds to control for broad regional patterns in the outcomes and the exposure (Stieb et al., 2016). NO_2 and $PM_{2.5}$ were treated as linear terms and by quartile. Two pollutant models were constructed to examine the sensitivity of the effect of each pollutant to adjustment for the other. We accounted for clustering of observations by DA by treating births from the same DA as repeated subjects in the GEE analysis. Subgroup analyses were conducted based on parity, maternal place of birth (within vs. outside Canada), urban vs. rural place of residence, neighbourhood (DA) SES, and per cent visible minority, and season and year of birth.

In order to address possible confounding by maternal smoking during pregnancy, we examined the association between NO_2 exposure and smoking during pregnancy in participants in cycles 1.1 (2001), 2.1 (2003) and 3.1 (2005) of the Canadian Community Health Survey (CCHS), a nationally representative general health survey (Statistics Canada, 2015b). Women between 15 and 55 years of age who were pregnant within the five years prior to the survey were asked whether they smoked (yes vs. no in Cycle 1.1 and daily or occasionally or not at all in Cycles 2.1 and 3.1) during their last pregnancy. NO_2 exposures were assigned based on their six character postal codes using the national surface described in Section 2.4.1.

All analyses were conducted using SAS version 9.3.

3. Results

During the study period there were 3,104,090 live births. Of these, 3,046,675 (98.15%) could be mapped to NO_2 exposures, of which 2,956,050 were singletons (in accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five). Among these, 27,535 births were missing $PM_{2.5}$ exposure data. The overall prevalence of preterm birth was 6.23%, of term LBW, 1.57% and SGA, 8.33%. 9.60% of preterm births were SGA, 7.14% of SGA births were preterm, 96.29% of term LBW births were SGA and 18.33% of term SGA births were term LBW. After further excluding births with missing covariate data, analyses of preterm birth were based on 2,558,405 births (87.4% of those with NO_2 and $PM_{2.5}$ exposures), analyses of SGA were based on 2,557,460 births (87.3% of those with NO_2 and $PM_{2.5}$ exposures) and after excluding 155,860 preterm births, analyses of term LBW and birth weight were based on 2,402,545 births. Descriptive statistics for NO_2 and $PM_{2.5}$ concentrations are shown in Table 1. There was little difference in exposure between term and preterm births, but both NO_2 and $PM_{2.5}$ tended to be higher for term LBW and SGA births. NO_2 and $PM_{2.5}$ exhibited a moderate correlation (Spearman $R=0.61$, $p<0.0001$).

Maternal and infant characteristics are summarized in Table 2. Nearly all factors exhibited highly significant associations with the prevalence of adverse pregnancy outcomes ($p<0.0001$), with the exception of urban versus rural maternal place of residence and preterm birth ($p=0.14$), and year of birth and LBW ($p=0.017$). Several factors were associated with both prevalence of adverse pregnancy outcomes and pollutant concentrations, including maternal age, place of birth, and place of residence. Prevalence of adverse pregnancy outcomes and pollutant concentrations tended to increase across tertiles of per cent unemployed, per cent low income and per cent visible minority. Prevalences decreased across tertiles of per cent of women with postsecondary education, while pollutant concentrations increased. Gradients in neighbourhood SES variables were consistent with those in individual-level maternal education in Quebec (23% of births) where individual-level data on maternal education were available, i.e. compared to mothers with lower educational attainment, a larger percentage of mothers with higher educational attainment lived in DAs with: the highest percentage of females who had completed post-secondary education, the lowest percentage of individuals in

Table 1
Summary of estimated entire pregnancy NO_2 and $PM_{2.5}$ exposures.

Population	N[a]	Mean	Standard deviation	5th Percentile	Median	95th Percentile	Interquartile range
		NO_2 (ppb)					
All	2,928,515	13.4	7.8	3.7	11.9	27.8	11.5
Term	2,746,040	13.4	7.8	3.7	11.9	27.8	11.5
Preterm	182,475	13.5	7.8	3.6	12.1	27.8	11.7
Term normal BW[b]	2,700,620	13.4	7.8	3.7	11.9	27.8	11.5
Term LBW	43,080	14.5	8.1	3.8	13.5	29.0	12.6
Non SGA	2,681,055	13.3	7.7	3.6	11.8	27.7	11.4
SGA	243,620	14.5	8.1	3.8	13.4	28.9	12.5
		$PM_{2.5}$ ($\mu g/m^3$)					
All	2,928,515	8.5	2.4	4.6	8.5	12.4	3.6
Term	2,746,040	8.5	2.4	4.6	8.5	12.4	3.6
Preterm	182,475	8.4	2.4	4.6	8.4	12.5	3.6
Term normal BW	2,700,620	8.5	2.4	4.6	8.5	12.4	3.6
Term LBW	43,080	8.7	2.4	4.8	8.8	12.5	3.6
Non SGA	2,681,055	8.4	2.4	4.6	8.4	12.4	3.6
SGA	243,620	8.7	2.4	4.8	8.7	12.5	3.6

[a] In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. Statistical analyses employed unrounded data.
[b] Birth weight.

Table 2
Prevalence of pregnancy outcomes and mean NO_2 and $PM_{2.5}$ exposures by infant, maternal and neighbourhood characteristics.

Variable	Preterm birth n[a] (%)	Term low birth weight n (%)	Small for gestational age n (%)	Mean NO_2 (ppb)	Mean $PM_{2.5}$ (μg/m^3)
Sex					
Male	100,190 (6.67)	17,720 (1.26)	127,955 (8.52)	13.4	8.5
Female	82,285 (5.77)	25,360 (1.89)	115,665 (8.12)	13.4	8.5
Unknown	(0)	(0)	(0)	10.0	8.4
Maternal age					
< 18	3135 (8.15)	685 (1.94)	3760 (9.79)	11.3	7.6
18–29	103,685 (6.14)	25,500 (1.61)	147,695 (8.75)	12.7	8.3
30–39	71,435 (6.2)	15,875 (1.47)	87,590 (7.61)	14.4	8.7
40+	4200 (8.71)	1020 (2.32)	4555 (9.46)	15.5	8.7
Unknown	20 (11.76)	(0)	20 (11.76)	14.8	8.9
Marital status					
Single	53,020 (6.99)	12,925 (1.84)	70,560 (9.33)	11.7	8.3
Married	104,545 (5.7)	24,490 (1.42)	142,265 (7.76)	14.2	8.6
Widowed	185 (7.99)	35 (1.65)	215 (9.33)	14.8	8.8
Divorced	2470 (7.54)	565 (1.87)	2950 (9.03)	13.5	8.2
Separated	950 (8.47)	210 (2.05)	1030 (9.2)	12.2	7.0
Unknown	21,310 (7.37)	4855 (1.81)	26,600 (9.21)	12.9	8.4
Maternal place of birth					
Canadian born	134,540 (6.26)	27,975 (1.39)	158,780 (7.4)	11.4	8.1
Not Canadian born	44,790 (6.08)	14,335 (2.07)	80,610 (10.95)	18.7	9.4
Unknown	3145 (7.27)	770 (1.92)	4230 (9.81)	20.5	10.3
Maternal place of residence					
Urban	151,805 (6.25)	36,845 (1.62)	208,130 (8.57)	15.0	8.8
Rural	30,670 (6.16)	6235 (1.34)	35,490 (7.14)	5.5	6.6
Parity					
1st birth	90,225 (6.92)	23,550 (1.94)	137,550 (10.56)	13.9	8.6
2nd birth	53,745 (5.26)	11,730 (1.21)	66,160 (6.49)	13.3	8.5
3rd or greater birth	37,470 (6.39)	7575 (1.38)	38,630 (6.6)	12.8	8.3
Unknown	1035 (6.36)	230 (1.51)	1280 (7.89)	7.0	6.3
Maternal province of residence					
Newfoundland and Labrador	2615 (6.8)	465 (1.3)	2630 (6.85)	4.0	5.0
Prince Edward Island	590 (5.27)	135 (1.27)	760 (6.8)	5.1	5.3
Nova Scotia	4590 (6.18)	1110 (1.59)	6030 (8.12)	5.6	6.1
New Brunswick	3,830 (6.1)	790 (1.34)	4740 (7.55)	5.5	5.4
Quebec	42,170 (6.27)	9655 (1.54)	54,905 (8.2)	13.6	9.5
Ontario	67,290 (6.01)	18,010 (1.71)	98,160 (8.77)	15.1	9.6
Manitoba	8145 (6.62)	1575 (1.37)	9475 (7.71)	11.6	6.2
Saskatchewan	6075 (6.1)	1350 (1.44)	7455 (7.49)	9.8	6.2
Alberta	25,845 (7.05)	5465 (1.6)	31,740 (8.67)	13.6	8.0
British Columbia	21,270 (5.91)	4525 (1.34)	27,675 (7.69)	13.5	6.5
Yukon Territory	15 (11.54)	(0)	(0)	6.0	5.2
Northwest Territories	20 (6.56)	(0)	20 (6.45)	6.1	3.9
Nunavut	20 (11.11)	5 (3.13)	30 (16.67)	3.0	5.9
Unknown	(0)	(0)	5 (100)	18.2	9.8
Birth year					
1999	3025 (6.44)	700 (1.59)	4135 (8.82)	15.6	8.9
2000	18,840 (6.2)	4320 (1.52)	24,780 (8.16)	15.3	9.1
2001	18,630 (5.98)	4540 (1.55)	26,020 (8.36)	15.0	8.9
2002	18,515 (6.01)	4515 (1.56)	25,650 (8.35)	14.6	8.9
2003	17,005 (6.2)	4035 (1.57)	22,870 (8.37)	14.3	9.2
2004	20,155 (6.39)	4575 (1.56)	25,545 (8.13)	13.7	8.5
2005	20,495 (6.3)	4775 (1.57)	27,270 (8.39)	13.1	8.6
2006	21,415 (6.35)	5210 (1.65)	28,685 (8.52)	12.4	8.2
2007	21,560 (6.2)	5140 (1.58)	29,395 (8.46)	11.7	7.5
2008	22,835 (6.36)	5275 (1.57)	29,270 (8.15)	11.0	7.6
Season					
Spring	46,130 (6.19)	10,425 (1.49)	59,645 (8.01)	13.4	8.6
Summer	45,410 (6.02)	11,105 (1.57)	63,440 (8.42)	13.2	8.4
Fall	46,400 (6.35)	11,075 (1.62)	62,380 (8.54)	13.4	8.1
Winter	44,540 (6.39)	10,475 (1.61)	58,155 (8.35)	13.6	8.7

Table 2 (*continued*)

Variable	Preterm birth n[a] (%)	Term low birth weight n (%)	Small for gestational age n (%)	Mean NO_2 (ppb)	Mean $PM_{2.5}$ (µg/m^3)
Percent unemployed (age 15+)					
1st tertile (≤ 4.6%)	58,110 (5.98)	12,880 (1.41)	75,000 (7.72)	12.7	8.4
2nd tertile (4.61–8.22%)	59,640 (6.15)	14,070 (1.55)	80,130 (8.27)	13.4	8.5
3rd tertile (> 8.22%)	63,960 (6.56)	15,960 (1.75)	87,615 (9.00)	14.2	8.4
Unknown	765 (6.55)	170 (1.56)	875 (7.50)	8.8	7.9
Percent in lowest income quintile (age 15+)					
1st tertile (≤ 9.25%)	56,445 (5.81)	11,745 (1.29)	69,060 (7.12)	10.9	8.2
2nd tertile (9.26–20.18%)	59,285 (6.10)	13,810 (1.51)	79,390 (8.18)	12.6	8.3
3rd tertile (> 20.18%)	65,980 (6.77)	17,360 (1.91)	94,295 (9.69)	16.7	8.9
Unknown	765 (6.55)	170 (1.56)	875 (7.51)	8.8	7.9
Percent of females completed postsecondary education (age 25+)					
1st tertile (≤ 20.36%)	64,745 (6.67)	15,725 (1.74)	85,415 (8.81)	11.7	8.1
2nd tertile (20.37–28.47%)	60,445 (6.22)	14,450 (1.59)	81,940 (8.44)	13.3	8.5
3rd tertile (> 28.47%)	56,520 (5.8)	12,735 (1.39)	75,390 (7.75)	15.2	8.8
Unknown	765 (6.55)	170 (1.56)	875 (7.51)	8.8	7.9
Percent visible minority					
1st tertile (≤ 2.04%)	60,120 (6.21)	12,480 (1.38)	70,820 (7.33)	7.6	7.4
2nd tertile (2.05–16.13%)	58,545 (6.08)	12,530 (1.39)	73,335 (7.62)	13.2	8.6
3rd tertile (> 16.13%)	61,900 (6.39)	17,655 (1.95)	97,285 (10.05)	19.6	9.4
Missing	1910 (6.79)	415 (1.58)	2180 (7.76)	9.5	7.4
Total	182,475 (6.23)	43,085 (1.57)	243,620 (8.33)	13.4	8.5

[a] In accordance with Statistics Canada disclosure rules, case counts of less than five were suppressed, and all frequencies were randomly rounded to base five. As a result, there may be discrepancies between column totals and totals by infant/maternal characteristic. Statistical analyses employed unrounded data.

the lowest income quintile, and the lowest percentage of unemployed individuals. Conversely, compared to mothers with higher educational attainment, a larger percentage of mothers with lower educational attainment lived in DAs with: the lowest percentage of females who had completed post-secondary education, the highest percentage of individuals in the lowest income quintile, and the highest percentage of unemployed individuals (Stieb et al., 2016).

134,002 births between May 16, 2004 and May 15, 2006 were linked to a 2006 long form census questionnaire. Of these, 124,421 could be mapped to the NO_2 surface and 95,252 included complete data on the variables of interest. Descriptive data for these births are shown in Supplementary Table S1. The prevalence of pregnancy outcomes by individual characteristics was generally similar to that observed in the entire sample.

Associations of entire pregnancy NO_2 exposure with pregnancy outcome are shown in Table 3, by level of adjustment. Preterm birth was weakly associated with NO_2 in unadjusted models and in models adjusted for neighbourhood SES. It exhibited a weak negative association with NO_2 after addition of individual covariates and neighbourhood per cent visible minority. All covariates other than birth year exhibited significant associations with preterm birth in the fully adjusted model and sequential addition of place of residence (urban vs. rural) and parity to the model resulted in the greatest absolute reduction in the coefficient for NO_2 (see Supplementary Table S2). Term LBW, SGA and term birth weight exhibited strong associations with NO_2 in unadjusted models and after adjustment for neighbourhood SES. Associations were reduced considerably after adjustment for individual covariates and neighbourhood per cent visible minority, but remained significant for SGA and term birth weight. All covariates exhibited significant associations with term LBW, SGA and term birth weight in fully adjusted models, except neighbourhood percent low income and SGA (see Supplementary Tables S3–S5). When added sequentially to the model, neighbourhood per cent visible minority resulted in the greatest absolute reduction in the coefficient for NO_2 for term LBW, SGA and term birth weight (see Supplementary Tables S3–S5). Compared to the national analysis, associations were consistently of larger magnitude in an analysis of data from 11 cities where continuous monitoring data were available, regardless of the source of exposure data (Table 3). In particular, associations with LBW were statistically significant. Associations with all outcomes were of greatest magnitude based on the city average from monitoring data. Analysis by trimester using temporally adjusted LUR values revealed little difference in the magnitude of effect by trimester (Fig. 1). Exposures by trimester were moderately to highly correlated (Spearman correlation trimester 1 vs. 2, 0.73, 2 vs. 3, 0.74, 1 vs. 3, 0.50). Associations with pregnancy outcomes in the 2006 Birth Census Cohort were generally similar to those observed in the entire sample, except that the magnitude of the associations with preterm birth, SGA and term birth weight was larger (Table 3).

In our analysis of CCHS data to examine potential confounding by maternal smoking, we found that in a sample of 22,410 women aged 15–55 who indicated that they had been pregnant in the previous five years, 20.9% smoked during pregnancy (unweighted). In unadjusted linear regression models, NO_2 exhibited a significant ($p < 0.0001$) negative association with smoking during pregnancy (i.e. NO_2 exposures were significantly higher in non-smokers). After adjusting for neighbourhood SES and per cent visible minority, as well as urban vs. rural place of residence, maternal age group and marital status, province, and maternal place of birth, the association remained negative but was non-significant ($p = 0.31$).

Analysis of preterm births by degree of prematurity revealed that there was a significant positive association with births with gestation 20–27 weeks (OR 1.10, 95% CI 1.05, 1.15), null associations

Table 3
Associations between entire pregnancy NO_2 and pregnancy outcome by level of adjustment (effects per IQR[a]).

Model	Adjustments	Preterm birth Odds Ratio (95% confidence interval)	Term low birth weight Odds Ratio (95% confidence interval)	Small for gestational age Odds Ratio (95% confidence interval)	Term birth weight β (95% confidence interval)
		Entire Sample – Land Use Regression Surface (IQR=11.5 ppb)			
		n=155,860[b] cases, 2,558,405 births	n=36,990 cases, 2,402,545 births	n=210,215 cases, 2,557,460 births	n=2,402,545 births
1	Unadjusted	1.01 (1.00, 1.02)	1.24 (1.22, 1.26)	1.25 (1.24, 1.26)	−54.2 (−55.7, −52.6)
2	1+neighbourhood SES[c]	1.01 (1.00, 1.02)	1.21 (1.19, 1.23)	1.23 (1.22, 1.24)	−54.0 (−55.7, −52.2)
3	2+individual covariates,[d] neighbourhood percent visible minority	0.98 (0.97, 0.99)	1.01 (0.99, 1.04)	1.02 (1.01, 1.03)	−9.3 (−10.8, −7.8)
		11 Cities[e]			
		n=49,850 cases, 779,040 births	n=12,868 cases, 729,190 births	n=73,276 cases, 778,678 births	N=729,190 births
		Land Use Regression Surface (IQR=9.6 ppb)			
3		0.94 (0.93, 0.96)	1.05 (1.02, 1.09)	1.04 (1.03, 1.06)	−12.0 (−14.1, −9.8)
		Monthly Average Monitoring Data (IQR=6.4 ppb)			
3		0.91 (0.88, 0.93)	1.15 (1.10, 1.20)	1.09 (1.07, 1.11)	−15.9 (−18.5, −13.3)
		Temporally Adjusted Land Use Regression Surface (IQR=8.0 ppb)			
3		0.96 (0.94, 0.97)	1.09 (1.06, 1.12)	1.05 (1.04, 1.07)	−11.6 (−13.6, −9.6)
		2006 Birth Census Cohort – Land Use Regression Surface (IQR=11.5 ppb)			
		n=5,539 cases, 95,252 births	n=1,246 cases, 89,713 births	n=7,126 cases, 95,251 births	n=89,713 births
3		0.91 (0.85, 0.97)	1.00 (0.88, 1.14)	1.05 (1.00, 1.11)	−18.3 (−24.9, −11.7)
4	3+ individual covariates[f]	0.93 (0.87, 0.99)	1.00 (0.88, 1.15)	1.06 (1.00, 1.12)	−18.2 (−24.9, −11.6)

[a] Interquartile range.
[b] In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. Statistical analyses employed unrounded data.
[c] Socioeconomic status; census dissemination area proportion of individuals 15 and over who were unemployed (preterm birth model only), proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education.
[d] Maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority; infant sex was also included in preterm birth, LBW and birth weight models, and gestational age was also included in LBW and birth weight models.
[e] Calgary, Edmonton, Hamilton, Kamloops, Montreal, Ottawa, Quebec, Richmond, Toronto, Vancouver, Winnipeg.
[f] Mother visible minority, maternal education, maternal and paternal occupation, maternal income quintile).

with births with gestation 28–31 weeks (OR 1.00, 95% CI 0.96, 1.04) and 32–33 weeks (OR 1.00, 95% CI 0.97, 1.03), and a significant negative association with births with gestation 34–36 weeks (OR 0.97, 95% CI 0.96, 0.98). Subgroup analyses (Table 4) revealed a larger odds ratio for SGA, a larger reduction in term birth weight, and a significant positive association with preterm birth among 3rd or greater births compared to those with lower parity. Larger odds ratios were also observed for term LBW and SGA, and a larger reduction in term birth weight among births to mothers born in Canada compared to those born elsewhere. The negative association with preterm birth was somewhat larger in magnitude among births to women in rural areas compared to those in urban areas. In the lowest tertiles of neighbourhood per cent low income, there was a larger magnitude negative association with preterm birth and term birth weight, and a larger magnitude positive association with term LBW and SGA, compared to the highest tertile. There was also a larger magnitude positive association with SGA and negative association with term birth weight in the lowest tertiles of neighbourhood visible minority, compared to the highest tertile, and a larger magnitude negative association with preterm birth in the highest tertiles of neighbourhood per cent visible minority, compared to the lowest tertile. Subgroup analysis by season revealed a non-significant positive association with preterm birth in the fall and significant negative or null associations in the other seasons, while analysis by period indicated that the magnitude of all associations was greater in the 2006–2008 period compared to the 1999–2005 period.

Analyses of associations by quartile of NO_2 and $PM_{2.5}$ are shown in Fig. 2. The magnitude of the association of NO_2 with LBW, SGA and birth weight increased with increasing quartile of exposure, in the case of LBW and SGA levelling off at the highest quartile. An increase in magnitude of the association by quartile was not observed for $PM_{2.5}$. NO_2 was not significantly associated with preterm birth in any quartile, while $PM_{2.5}$ exhibited a significant negative association with preterm birth in all of quartiles two through four.

Associations of NO_2 and $PM_{2.5}$ with all outcomes were of similar magnitude in single pollutant models (Table 5). In two pollutant models for SGA and term birth weight, associations with NO_2 were less sensitive to adjustment for $PM_{2.5}$ than vice versa.

4. Discussion

In this study, we applied a national model of NO_2 to 2.5 million births in Canada between 1999 and 2008, and found significant associations with SGA and term birth weight, which remained significant in joint models with $PM_{2.5}$, while effects of $PM_{2.5}$ tended to be reduced. Expressed per 20 ppb increment in NO_2 in keeping with other literature, in fully adjusted models, which also included $PM_{2.5}$, we found an OR of 1.04 (95%CI 1.02, 1.06) for the association between NO_2 and SGA, and a decrease in term birth weight of 13.5 g (95% CI 10.7, 16.3 g).

Based on a systematic review and meta-analysis, we previously

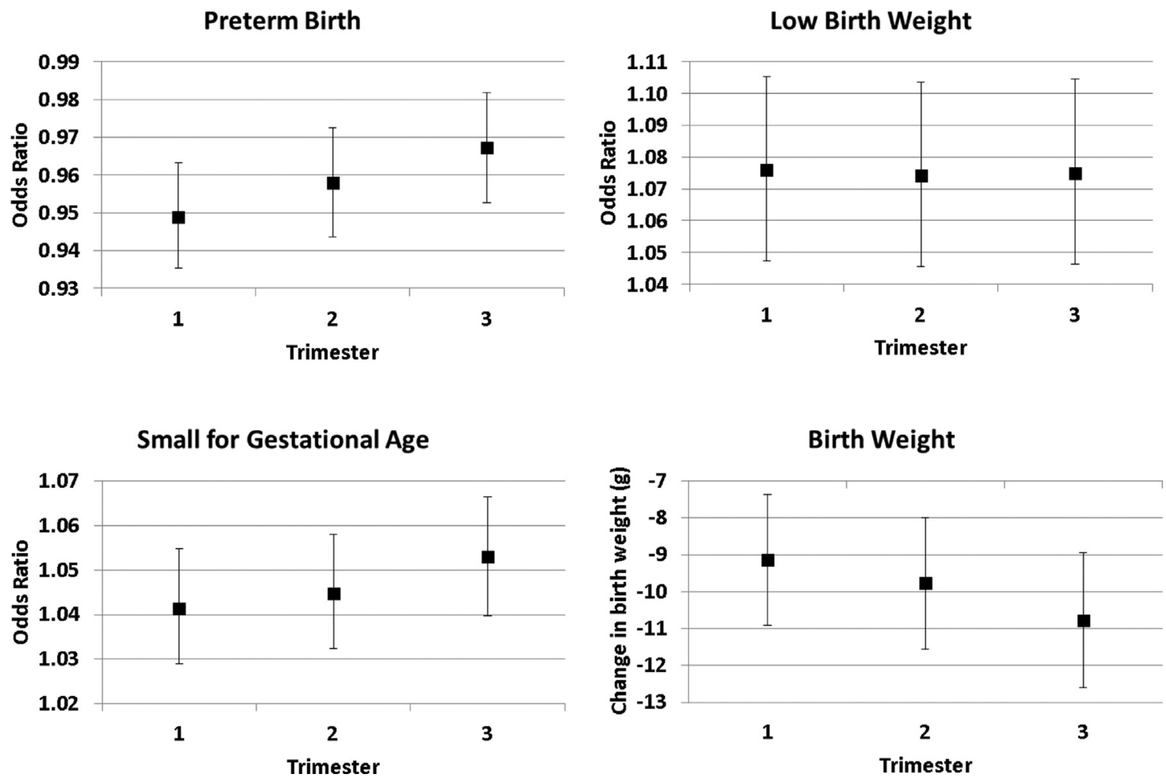

Fig. 1. Associations between NO_2 and pregnancy outcome by trimester based on temporally adjusted land use regression model, 11 cities (effects per interquartile range, 8.0 ppb). Point estimates and 95% confidence intervals are shown.

reported that NO_2 was associated with a 28.1 g reduction in birth weight per 20 ppb (95% CI 11.5, 44.8) based on 10 studies, and odds ratios of 1.05 (95% CI 1.00, 1.09) and 1.06 (95% CI 0.96, 1.18) per 20 ppb for low birth weight (based on 9 studies) and preterm birth (based on 6 studies), respectively. Results of individual studies employing monitoring data, land use regression or other models, or other measures of exposure to traffic have been mixed (Table 6). Mean NO_2 concentrations varied widely from slightly higher than that reported in the current study to nearly three fold higher in Los Angeles (Ghosh et al., 2012). Sample sizes were considerably smaller than the current study and varied widely, from small cohorts of as few as 570 (Aguilera et al., 2009) to a pooled analysis of multiple cohorts (total n=74,178) (Pedersen et al., 2013) to an administrative data based study of nearly 400,000 births (Ghosh et al., 2012). Increased risks of LBW, SGA and reduced birth weight were more consistently observed than increased risks of preterm birth. Several studies, particularly but not exclusively those based on small cohorts, reported no consistent associations with any outcome (Aguilera et al., 2009; Gehring et al., 2011a, 2011b; Habermann and Gouveia, 2014; Madsen et al., 2010); others have reported significant positive associations with LBW, SGA or reduced birth weight (Ballester et al., 2010; Malmqvist et al., 2011), including studies in Canada (Liu et al., 2003, 2007); and several reported differing results depending on whether exposures were measured or modelled (Brauer et al., 2008; Gehring et al., 2014; Ghosh et al., 2012; Laurent et al., 2013), but associations were not consistently of greater magnitude based on measured vs. modelled exposures or vice versa. With the exception of another large administrative data based study similar to ours (Ghosh et al., 2012), the magnitude of observed associations tended to be larger in previous studies compared to the present study.

We observed a negative association between NO_2 and preterm birth, similar to our earlier findings for $PM_{2.5}$ (Stieb et al., 2016). We do not consider it biologically plausible that air pollution exposure would have a protective effect with respect to preterm birth and hypothesize that this may reflect bias or residual confounding. The interpretation of our observation of a significant positive association with births with gestation 20–27 weeks, null associations with births with gestation 28–31 weeks and 32–33 weeks, and a significant negative association with births with gestation 34–36 weeks is also not straightforward. Padula et al. (2014) found that exposure to PAHs during the last 6 weeks of pregnancy was positively associated with preterm births with gestation 20–27 weeks, but entire pregnancy exposure exhibited a negative association. We also found that there was a significant positive association with preterm births among 3rd or greater births. Additional analyses are clearly warranted to better understand factors mediating the apparently complex association between air pollution and preterm birth. Analysis of associations with preterm birth may be confounded by temporal factors such as seasonality of conception and air pollution exposure, and differing exposure duration between preterm and term births (Chang et al., 2015; Darrow et al., 2009). Examination of effect modifiers and effects of exposure in the days or weeks preceding birth using time-series, case-crossover, or time to event methods may be informative.

Results of subgroup analyses in our study exhibited some similarities to our earlier findings for $PM_{2.5}$. In particular, we also observed a larger magnitude association of $PM_{2.5}$ with SGA and term birth weight (but not with term LBW) among births to mothers born in Canada (Stieb et al., 2016). There was also evidence of a trend of greater reduction in term birth weight in the lower tertiles of percent low income, but it was not significant. In the present analysis, we also found that the magnitude of associations with SGA and term birth weight were larger in neighbourhoods with a lower proportion of visible minority individuals. A “healthy immigrant effect” has been suggested where recent immigrants

Table 4
Associations between NO_2 and pregnancy outcome in entire sample, by parity, maternal place of birth, urban/rural place of residence, neighbourhood socioeconomic status, neighbourhood percent visible minority, season and period in models adjusted for neighbourhood socioeconomic status and individual covariates (effects per interquartile range = 11.5 ppb).

Subgroup	Preterm birth Odds Ratio (95% confidence interval)	Term low birth weight Odds Ratio (95% confidence interval)	Small for gestational age Odds Ratio (95% confidence interval)	Term birth weight β (95% confidence interval)
	n = 155,860[a] cases, 2,558,405 births	n = 36,990 cases, 2,402,545 births	n = 210,215 cases, 2,557,460 births	n = 2,402,545 births
Parity				
1st birth	0.95 (0.94, 0.97)	1.01 (0.98, 1.04)	1.01 (1.00, 1.02)	−6.0 (−7.9, −4.2)
2nd birth	0.99 (0.97, 1.02)	1.01 (0.97, 1.06)	1.03 (1.01, 1.05)	−8.0 (−10.2, −5.8)
3rd or greater birth	1.04 (1.02, 1.07)	1.04 (0.98, 1.10)	1.06 (1.03, 1.08)	−18.8, (−22.2, −15.4)
p-value (difference)	< 0.0001	0.6518	0.0111	< 0.0001
Maternal place of birth				
Canada	0.98 (0.96, 0.99)	1.04 (1.01, 1.08)	1.06 (1.04, 1.07)	−16.2 (−18.1, −14.3)
Elsewhere	0.98 (0.96, 1.00)	0.97 (0.94, 1.02)	0.99 (0.98, 1.01)	−5.3 (−7.8, −2.8)
p-value (difference)	0.7257	0.0066	< 0.0001	< 0.0001
Maternal place of residence				
Urban	0.98 (0.97, 1.00)	1.01 (0.99, 1.04)	1.02 (1.01, 1.03)	−8.3 (−9.8, −6.8)
Rural	0.87 (0.79, 0.96)	0.93 (0.76, 1.13)	1.00 (0.92, 1.09)	−1.6 (−14.4, 11.2)
p-value (difference)	0.0143	0.3918	0.6018	0.3081
Percent in lowest income quintile (age 15+)				
1st tertile (≤9.25%)	0.96 (0.93, 0.98)	1.04 (0.99, 1.09)	1.05 (1.03, 1.08)	−14.2 (−16.9, −11.4)
2nd tertile (9.26–20.18%)	0.97 (0.95, 0.99)	1.04 (1.00, 1.08)	1.02 (1.01, 1.04)	−6.8 (−9.2, −4.5)
3rd tertile (>20.18%)	1.00 (0.98, 1.02)	0.98 (0.95, 1.01)	0.99 (0.97, 1.00)	−1.9 (−4.4, 0.6)
p-value (difference)	0.0062	0.0509	< 0.0001	< 0.0001
Percent visible minority				
1st tertile (≤2.04%)	1.02 (0.99, 1.05)	1.05 (0.99, 1.12)	1.07 (1.04, 1.10)	−16.8 (−20.7, −12.9)
2nd tertile (2.05–16.13%)	0.98 (0.96, 1.00)	1.01 (0.96, 1.05)	1.05 (1.03, 1.07)	−19.0 (−21.4, −16.6)
3rd tertile (>16.13%)	0.96 (0.94, 0.98)	1.01 (0.98, 1.05)	1.02 (1.00, 1.03)	−10.6 (−13.3, −7.9)
p-value (difference)	0.0043	0.4843	0.0050	< 0.0001
Season				
Spring	0.97 (0.95, 0.99)	1.02 (0.97, 1.06)	1.03 (1.01, 1.05)	−10.0 (−12.5, −7.5)
Summer	0.95 (0.93, 0.97)	1.03 (0.98, 1.07)	1.02 (1.00, 1.04)	−9.9 (−12.4, −7.3)
Fall	1.02 (1.00, 1.05)	0.99 (0.95, 1.03)	1.02 (1.00, 1.04)	−8.0 (−10.6, −5.4)
Winter	0.99 (0.96, 1.01)	1.02 (0.98, 1.07)	1.01 (0.99, 1.03)	−9.2 (−11.8, −6.6)
p-value (difference)	< 0.0001	0.4217	0.4194	0.4753
Year				
1999–2005	0.99 (0.98, 1.01)	1.00 (0.98, 1.03)	1.02 (1.00, 1.03)	−7.8 (−9.5, −6.2)
2006–2008	0.94 (0.92, 0.97)	1.04 (1.00, 1.09)	1.04 (1.02, 1.06)	−14.5 (−17.1, −11.9)
p-value (difference)	0.000114	0.1819	0.0327	< 0.0001

[a] In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. Statistical analyses employed unrounded data.

experience better health and have better health behaviours (Ali et al., 2004). In our study, both NO_2 exposure and prevalence of term LBW and SGA were higher among non Canadian born mothers. It has been suggested that lower socioeconomic status confers a "double jeopardy" of increased stressors and increased exposure to environmental contaminants (Morello-Frosch et al., 2006). Woodruff et al. (2003) reported disparities in air pollution exposure during pregnancy based on a multi-pollutant index by race but not educational attainment in the US, while Buzzelli and Jerrett (2007) in a study in Toronto found higher NO_2 exposures among both those with lower incomes but also higher status occupations. We also found that NO_2 exposure increased across tertiles of both percent low income and percent of females who completed post-secondary education. Findings regarding effect modification by socioeconomic status in other studies have been mixed (Morello-Frosch et al., 2010; Ponce et al., 2005; Yi et al., 2010). Similar to our findings, in a study in Montreal, Généreux et al. (2008) found that associations between proximity to highways and pregnancy outcome were only observed among high socioeconomic status mothers. Shmool et al. (2015) reported that in New York City, NO_2 levels were highest in the least-deprived areas, and that NO_2 was associated with term birth weight in both the least- and most-deprived areas, but not in intermediate areas. Habermann and Gouveia (2014) found that mothers in Sao Paulo with higher education and neighbourhood level income were more highly exposed to traffic-related air pollution, but overall they observed a negative association between exposure and LBW.

We found that in a two pollutant model including NO_2 and

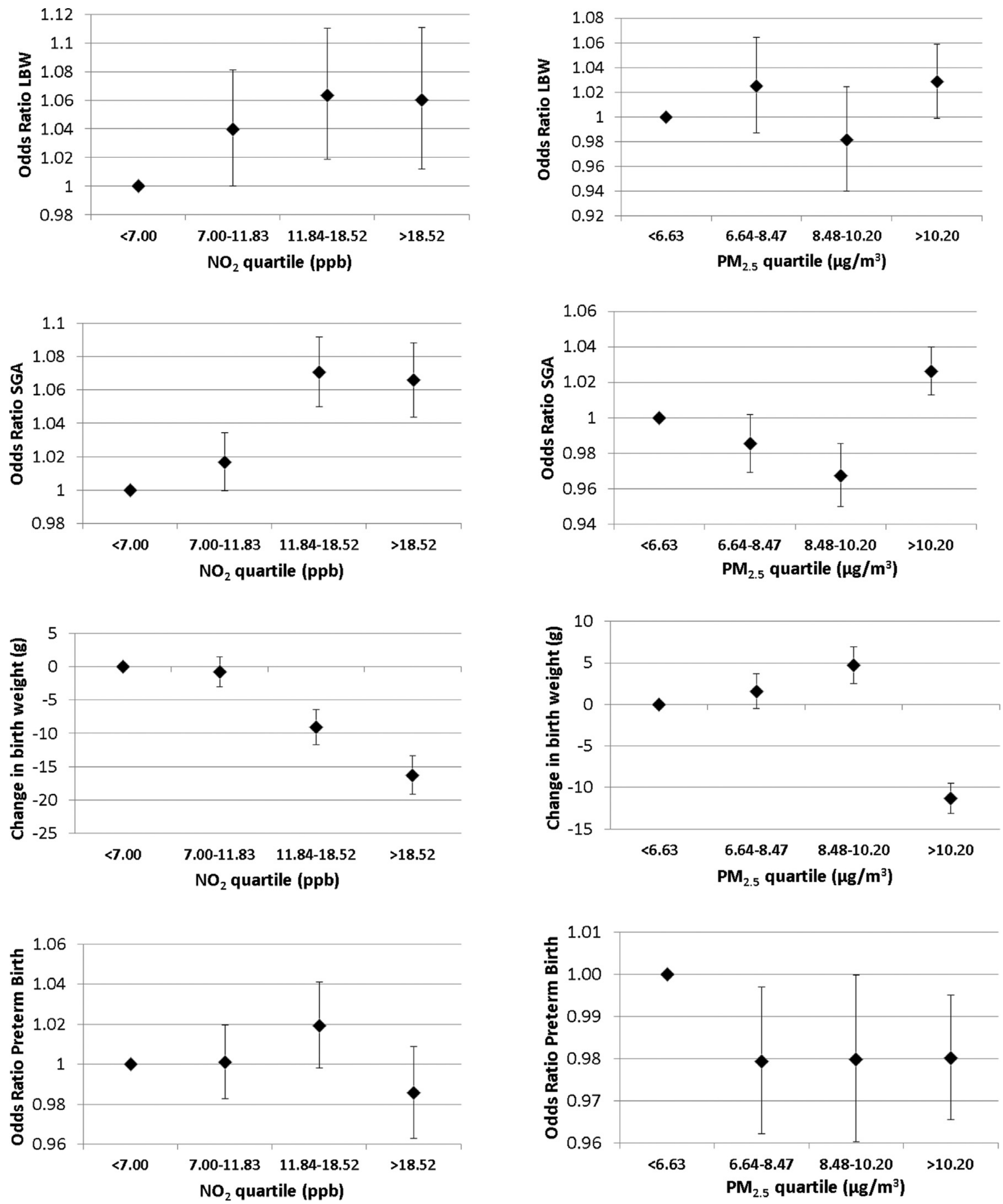

Fig. 2. Associations of entire pregnancy NO_2 and $PM_{2.5}$ with pregnancy outcome by quartile of exposure. Point estimates and 95% confidence intervals are shown.

$PM_{2.5}$, effects of $PM_{2.5}$ tended to be reduced in magnitude relative to a model with $PM_{2.5}$ alone, whereas the effect of NO_2 was relatively stable. One interpretation of this finding is that NO_2 is more strongly associated with pregnancy outcomes than $PM_{2.5}$. Indeed, analysis by quartile of exposure indicated that the magnitude of associations with LBW, SGA and birth weight generally increased with increased quartile of exposure for NO_2 but not $PM_{2.5}$. Alternatively, since the two pollutants exhibited a moderate correlation, it could reflect differences in the degree of measurement error of the two pollutants (Mauderly et al., 2010). In contrast, Pedersen et al. (2013) found that in models of term LBW, effects of NO_2 were reduced in magnitude relative to a model with NO_2 alone, whereas the effect of $PM_{2.5}$ was stable. In Canada, NO_2 appears to reflect local scale spatial variation in air pollution and fresh combustion, particularly traffic, whereas $PM_{2.5}$ reflects both local and regional variability (Crouse et al., 2015).

Strengths of our study include the large sample size, availability of exposure estimates for the entire country, including urban and rural areas, the ability to evaluate effects at comparatively low levels of exposure, and linkage to the individual census, permitting us to adjust for individual SES covariates. Limitations include the lack of data on individual risk factors such as maternal smoking, although smoking was strongly associated with maternal education in Quebec (Gilbert et al., 2014). Adjusting for SES may therefore at least partially account for confounding by smoking. In fact, we found that in a nationally representative general health survey,

Table 5
Associations of entire pregnancy NO_2 and $PM_{2.5}$ with pregnancy outcome in fully adjusted[a] one and two pollutant models (effects per interquartile range, 11.5 ppb NO_2, 3.5 μg/m³ $PM_{2.5}$) in entire sample.

Pollutant	Preterm birth Odds Ratio (95% confidence interval)	Term low birth weight Odds Ratio (95% confidence interval)	Small for gestational age Odds Ratio (95% confidence interval)	Term birth weight β (95% confidence interval)
NO_2	0.98 (0.97, 0.99)	1.01 (0.99, 1.04)	1.02 (1.01, 1.03)	−9.3 (−10.8, −7.8)
NO_2 (with $PM_{2.5}$)	0.99 (0.97, 1.00)	1.02 (0.99, 1.04)	1.02 (1.01, 1.03)	−7.7 (−9.4, −6.1)
$PM_{2.5}$	0.99 (0.97, 1.00)	1.00 (0.98, 1.03)	1.01 (1.00, 1.03)	−7.4 (−8.9, −5.9)
$PM_{2.5}$ (with NO_2)	0.99 (0.97, 1.01)	1.00 (0.97, 1.02)	1.00 (0.99, 1.02)	−4.0 (−5.6, −2.4)

[a] Adjusted for neighbourhood socioeconomic status: census dissemination area proportion of individuals 15 and over who were unemployed (preterm birth model only), proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education; and individual covariates: maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority; infant sex was also included in preterm birth, LBW and birth weight models, and gestational age was also included in LBW and birth weight models.

smoking during pregnancy was negatively associated with NO_2 exposure (i.e. higher exposures among non-smokers), which would tend to negatively confound the association between NO_2 and adverse pregnancy outcomes (i.e. drive observed associations which do not account for smoking towards the null). We also found that this association was reduced considerably in magnitude after adjusting for maternal characteristics and neighbourhood SES, which suggests that adjusting for these other factors would reduce residual confounding due to the lack of data on maternal smoking. This has also been reported regarding the effect of lack of smoking or other behavioural risk factor data in national cohort studies of air pollution and mortality (Villeneuve et al., 2011; Shin et al., 2014; Crouse et al., 2015). Others have reported that associations of air pollution with preterm birth (Ritz et al., 2007) and infant mortality (Darrow et al., 2006) were not sensitive to adjustment for behavioural risk factors including smoking and alcohol consumption. We also lacked data on maternal stature, exposure to traffic noise and residential mobility during pregnancy, and we could not identify multiple births to the same mother over the study period. Pre-pregnancy maternal height and weight are associated with birth weight outcomes and preterm birth in some studies (Aguilera et al., 2009; Gehring et al., 2011a, 2011b) and could act as confounders if also associated with air pollution exposure. To the extent this is mediated by factors such as ethnicity or SES, adjusting for these latter factors could reduce the impact of confounding when data on maternal stature are unavailable. While few studies have addressed the joint effects of noise and air pollution on pregnancy outcomes, Gehring et al. (2014) recently reported that in joint models, associations of noise with reduced birth weight were similar to effects observed in models with noise only, while associations with all air pollutants were reduced in magnitude relative to models without noise. In a recent analysis in Connecticut, accounting for residential mobility during pregnancy did not affect the association of pregnancy outcomes with particulate matter exposure (Pereira et al., 2016). Also, Pedersen et al. (2013) found that restricting their analysis to women with only one birth during the study, did not affect the magnitude of observed associations.

There are also a number of limitations of the NO_2 model employed here. First, the model was created from 2006 annual average NO_2 measurements at NAPS stations. One trend was used to adjust concentrations for the years 1999–2008, which does not account for any regional variation in the rate of change of NO_2 concentrations (although NAPS data suggest this is minimal). In a subgroup analysis by period (1999–2005 vs. 2006–2008), we found that the magnitude of all associations was greater in the 2006–2008 period. We found similar differences between the two periods using data from ground based monitoring (results not shown), which suggests that the difference between periods cannot be attributed to greater exposure measurement error in the earlier years due to back extrapolation from the year (2006) of the LUR model. Because NO_2 exposures were only available annually, in the national analysis we were unable to estimate exposures precisely to the gestational period and evaluate the effects of timing of exposure during pregnancy. Exposure misclassification is likely to be non-differential, resulting in biasing effects towards the null. Indeed, we observed that in a sensitivity analysis restricted to 11 cities where continuous monitoring data were available, the magnitude of associations was generally larger based on continuous monitoring data and temporally adjusted LUR values, which allowed us to map NO_2 values more precisely to gestational periods than simply using annual values from the LUR. This suggests that an important degree of measurement error may be introduced when monthly temporal variability is ignored. Additional research is needed to develop a full national monthly surface by spatially interpolating temporal scaling factors relating each monitor to the national LUR surface as described by Bechle et al. (2015). The lack of consistent differences in magnitude of effects by trimester is not surprising in that exposures by trimester were moderately to highly correlated, as has been previously reported (Brauer et al., 2008; Stieb et al., 2016). Finally, the large majority of NAPS monitors are located in metropolitan areas of Canada, and the model is therefore weighted towards these areas. This is appropriate for population exposure assessment, but this likely leads to overestimation of NO_2 concentrations in rural areas.

5. Conclusions

In this study of approximately 2.5 million Canadian births between 1999 and 2008, we found significant associations of NO_2 with SGA and term birth weight. Similar results were found in analyses of a subgroup of births where additional individual level data were available on education, occupation and income. Associations were of greater magnitude in a sensitivity analysis using monthly monitoring data, and among births to mothers born in Canada, and in neighbourhoods with higher incomes and a lower proportion of visible minorities. Associations remained significant after adjustment for $PM_{2.5}$, while effects of $PM_{2.5}$ were reduced in magnitude, and there was consistent evidence of a dose-response relationship for NO_2 but not $PM_{2.5}$, suggesting that traffic may be a particularly important source with respect to the role of air pollution as a risk factor for adverse pregnancy outcomes.

Table 6
Summary of Previous Literature.

Study	Location	Years	n	Outcomes	Exposure Characterization	Exposure	Results (per 20 ppb NO_2 unless otherwise noted)	Comment
Aguilera et al., 2009 (INMSA[a] cohort)	Sabadell, Spain	2004–2006	570	Birth weight	Temporally adjusted LUR	Mean 17.1 ppb	No consistent association	
Ballester et al., 2010 (INMA[b] cohort)	Valencia	2003–2005	785	SGA, birth weight	Temporally adjusted LUR	Mean 19.6 ppb	$NO_2 > 21$ ppb: −40.3 g (95% CI −15.6, −96.3) SGA: OR 3.3 (95% CI 1.04, 10.4)	
Brauer et al., 2008; Gehring et al., 2014	Vancouver	1999–2002	70,249	Term LBW, SGA, preterm birth	Inverse distance weighted (IDW) fixed site monitors, temporally adjusted LUR, proximity to highways	Mean 17.3 ppb (IDW)	LBW: OR 1.48 (95% CI 1.04, 2.16) SGA: OR 1.64 (95% CI 1.38, 1.86) Preterm birth (< 30 wks): 1.53 (95% CI 0.65, 3.54) (based on IDW)	Stronger associations based on IDW than LUR; LUR results sensitive to adjustment for traffic noise
Gehring et al., 2011a (ABCD[c] cohort)	Amsterdam	2003–2004	7,610	SGA Term birth weight	Temporally adjusted LUR	Median 20.6 ppb	No consistent associations	
Gehring et al., 2011b (PIAMA[d] cohort)	North, west, central Netherlands	1996–1997	3,853	Term birth weight, preterm birth	Temporally adjusted LUR	Mean 16.2 ppb	No association	
Ghosh et al., 2012	Los Angeles	1995–2006	379,103	Term LBW	Fixed monitoring stations, temporally adjusted LUR	Mean 34,8 ppb (monitor)	Monitors: OR 1.04 (95% CI 0.94, 1.14) LUR: OR 1.08 (95% CI 1.00, 1.17)	
Habermann and Gouveia, 2014	Sao Paolo	2006	11,586	Term LBW	Distance-weighted traffic density, distance to heavy traffic roads		Negative or inconsistent associations	
Laurent et al., 2013	Los Angeles	1997–2006	74,416	Term LBW, term birth weight	Fixed monitoring stations, temporally adjusted LUR, dispersion model, distance from roadways, traffic density	Mean 24.78 ppb (monitor)	LBW positively associated with traffic density and distance to major roadways, and negatively associated with NO_2 from monitoring stations	
Lepeule et al., 2010 (EDEN[e] cohort)	Poitier, Nancy, France	2003–2006	776	Birth weight	Fixed site monitors, temporally adjusted LUR	Mean 15.2 ppb (monitor)	Monitors: −140.6 g (95% CI −250.0, 3.8) Model: −193.8 g (95% CI −486.4, 98.8)	
Liu et al., 2003	Vancouver	1986–1998	229,085	Term SGA, preterm birth	Fixed site monitors	Mean 19.4 ppb	SGA: OR 1.10 (95% CI 1.02, 1.21) based on 1st month gestation Preterm birth: OR 1.08 (0.99, 1.17 based on last month)	SGA association remained significant in joint model with other gases
Liu et al., 2007	Montreal, Calgary Edmonton	1986–2000	386,202	Term SGA	Fixed site monitors	Mean 24.0 ppb	OR by trimester of 1.14–1.16	Associations of NO_2, PM2.5 with SGA not significant in model with CO
Madsen et al., 2010	Oslo	1999–2002	25,229	Term: LBW SGA Birth weight	Fixed monitoring sites, dispersion model	Mean 18.9 ppb (monitor)	No consistent associations	
Malmqvist et al., 2011	Southern Sweden	1999–2005	81,110	SGA, LBW, birth weight, preterm birth	Dispersion model	Mean 16.4 μg/m^3 NOx	SGA: OR 1.09 (95% 1.01, 1.18) for highest quartile (SGA) Preterm birth negatively associated with NOx, traffic density	Only in mothers who did not move during pregnancy
Pedersen et al., 2013 (includes ABCD, EDEN, INMA, PIAMA cohorts)	12 European cohorts	1994–2011	74,178	Term LBW Term birth weight	Temporally adjusted LUR	Mean 13.9 ppb	OR 1.39 (95% CI 1.00, 1.94) −1 g (–6, 4) g	
Pereira et al., 2012	Perth, Australia	2000–2006	23,452	Fetal growth restriction	Temporally adjusted LUR	Mean 23.04 ppb	OR 1.37 (95% CI 1.0, 1.74) (2nd trimester)	
Wilhelm et al., 2011	Los Angeles	2004–2006	112,915	Preterm birth	Temporally adjusted and unadjusted LUR	Mean 25.2 ppb	LUR: OR 1.21 (95% CI 1.10, 1.38) Temporally adjusted LUR: OR 0.90 (95% CI 0.80, 1)	

[a] Infancia y Medio Ambiente Sabadell.
[b] Infancia y Medio Ambiente.
[c] Amsterdam Born Children and their Development.
[d] Prevention and Incidence of Asthma and Mite Allergy.
[e] Étude des Déterminants pré et postnatals du développement et de la santé de l'ENfant.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.04.025.

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