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Original article

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Effect modification of perinatal exposure to air pollution and childhood asthma incidence

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"Take home message": Maternal asthma enhances the effect of air pollution during pregnancy on the risk of developing asthma in children

Perinatal exposure to ambient air pollution has been associated with childhood asthma incidence, however, less is known regarding the potential effect modifiers in this association. We examined whether maternal and infant characteristics modified the association between perinatal exposure to air pollution and development of childhood asthma.

761,172 births occurring between 2006 and 2012 were identified in the province of Ontario, Canada. Associations between exposure to ambient air pollutants and childhood asthma incidence (up to age 6) were estimated using Cox regression models.

110,981 children with asthma were identified. In models adjusted for postnatal exposures, second trimester exposures to particulate matter with a diameter ≤ 2.5µm ($PM_{2.5}$) (Hazard Ratio (HR) per interquartile (IQR) increase = 1.07, 95% CI: 1.06 - 1.09) and nitrogen dioxide (NO_2) (HR per IQR increase = 1.06, 95% CI: 1.03 - 1.08) were associated with childhood asthma development. Enhanced impacts were found among children born to mothers with asthma, those who smoked during pregnancy, boys, those born preterm, of low birth weight and among those born to mothers living in urban areas during pregnancy.

Prenatal exposure to air pollution may have a differential impact on the risk of asthma development according to maternal and infant characteristics.

Word count: 199

Introduction

Asthma is one of the leading prevalent paediatric chronic diseases in the world [1]. Evidence shows that both genetic and environmental factors are responsible for the development of asthma [2]. A number of epidemiological studies have reported associations between ambient air pollution and childhood asthma incidence [3,4] as well as lung function deficits [5-8], with recent studies suggesting that this relationship may begin *in utero* [5,9-16]. However, most studies have been restricted to urban populations living in the vicinity of air pollution monitoring stations and, therefore, further evidence is required when comparing urban and rural populations in childhood asthma risk. As well, further evidence is needed in order to disentangle the importance of different prenatal and postnatal periods of exposure for childhood asthma incidence.

One of the strongest risk factors for childhood asthma development is the presence of a maternal history of asthma [17-19]. Asthma is the most common chronic disease to affect pregnant women [20], but no studies to date have evaluated whether the effect of prenatal exposure to outdoor air pollution on childhood asthma incidence is enhanced among children of mothers with a history of asthma or whether their joint effects increase risk of childhood asthma. Sex differences in the relationship between exposure to outdoor air pollution and risk of childhood asthma development have also been observed, but inconsistent findings have been reported [9,11,12]. For instance, it is hypothesized that male infants could be more

susceptible to the harmful effects of air pollution due to their specific pulmonary phenotype compared to female infants [7]. One previous study also showed that infants born preterm and of low birth weight are at increased risk of developing asthma when exposed to increased levels of outdoor air pollution [11], but this requires further investigations. Other potential modifying factors for which further evidence is needed include maternal smoking during pregnancy and maternal atopy [21].

In this study, we made use of a large population-based sample encompassing both urban and rural areas to evaluate the associations between exposures during pregnancy and early postnatal life to nitrogen dioxide (NO_2) as a marker of traffic related air pollution and particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$) as a marker of the complex mixture of outdoor air pollution, with childhood asthma incidence. We further examined whether these associations were modified by maternal history of asthma, maternal atopy, maternal smoking during pregnancy, infant sex, gestational age, birth weight and maternal place of residence (urban/rural areas).

Methods

Study population & design

We identified a retrospective cohort of pregnant women who gave birth to live born singleton infants in the Province of Ontario, Canada. Mother-infant pair data was obtained from a province wide birth registry for the time period between April 1st 2006 and March 31st 2012 [22]. Each mother's residential location(s) during pregnancy was obtained based on residential postal code(s) reported from health administrative databases. Gestational age was determined by first trimester ultrasound dating and the mother's last menstrual period (see online supplement for more details on study population).

Childhood asthma ascertainment

We identified incident childhood asthma cases (International Classification of Diseases [ICD]-10: J45) for the time period of April 1st 2006 to March 31st 2013 using the Ontario Asthma Surveillance Information System (OASIS) which is a population-based system that identifies and tracks individuals living with asthma in Ontario, Canada [23]. A previously validated case definition of asthma was used to identify individuals with asthma (see online supplement for more details). We examined incident childhood asthma diagnosed between birth and < 6 years of age, consistent with prior literature [9,11]. The data linkage process across databases and linkage with exposure estimates is described in the online supplement (Figure S1). For instance, a total of 222,864 participants could be assigned exposure estimates to both $PM_{2.5}$ and NO_2

(exposure assessment described below). These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Exposure assessment

Air pollution exposure estimates were assigned to the geographical coordinates representing the centroid of each subject's residential 6-digit postal codes, as previously described [24,25]. In brief, we assigned exposure to $PM_{2.5}$ during each trimester of pregnancy, during the first year of life and for the cumulative exposure after birth, respectively, based on monthly satellite surfaces at a 1 × 1 km resolution [26,27]. Estimates were obtained for trimester-specific periods of exposure and were averaged to obtain estimates for the entire pregnancy.

A national land use regression (LUR) model was used to assign prenatal and post-natal exposure estimates to ambient NO_2 to residential postal codes [25,28,29]. We applied a temporal adjustment to the LUR NO_2 model which allowed us to more precisely obtain estimates of exposure to NO_2 during each trimester of pregnancy, during the first year of life and for the cumulative exposure after birth. We captured residential mobility during pregnancy by calculating the time spent at each postal code and assigned pollutant exposure accordingly. Additional details can be found in the online supplement regarding exposure assessment methods to ambient air pollutants.

Covariates

The following variables were available from health administrative databases and were investigated as potential confounders and/or effect modifiers [9,11]: maternal age at delivery (< 20, 20-34, ≥ 35 or missing), infant sex, parity (0, 1, ≥ 2), maternal intention to breastfeed on discharge (yes, no or missing), maternal cigarette smoking anytime during pregnancy (yes, no or missing), maternal history of asthma [30], maternal atopy status (see supplemental material regarding maternal asthma and atopy case definitions) [9], gestational age (in weeks), birth weight , , , and an indicator for urban/rural place of residence (see supplemental material regarding details on urban/rural indicator). Exposure to residential greenness during pregnancy was obtained using the satellite-derived Normalized Difference Vegetation Index (NDVI) and exposure was assigned at the postal code level [31] (see supplemental material regarding exposure assessment of NDVI). We also abstracted three contextual socioeconomic status (SES) variables (i.e. median family income, proportion of visible minority, and percentage of female aged 25-64 years who completed postsecondary education).

Statistical analysis

We employed random-effects Cox proportional hazards models to evaluate the associations between exposure to air pollution during pregnancy and incidence of childhood asthma, in which random effects were represented by two levels of spatial clusters: census division (equivalent in size to a county) and census tract within census divisions [24,32]. Follow-up time (i.e. child age in days) was measured from birth until incidence of childhood asthma, death,

ineligibility for provincial health insurance, or end of follow-up. We conducted analyses for whole pregnancy, trimester-specific exposures, first year of life and childhood exposures. Models were conducted with and without mutual adjustment for average pregnancy exposure, first year of life exposure and cumulative exposure after birth. For instance, in the mutually adjusted models, effect estimates for the average pregnancy exposure were additionally adjusted for the first year of life exposure and the cumulative exposure after birth. Hazard ratios for trimester-specific exposures in mutually adjusted models accounted for average pregnancy exposure, first year of life exposure and cumulative exposure after birth. We also adjusted for pregnancy average exposure in postnatal exposure models. Proportional hazards assumptions were verified by adding the cross product of each variable with the natural logarithm of the time variable, but we did not find any significant violations of this assumption ($p>0.05$). Results are expressed as the hazard ratio (HR) and 95% confidence interval (CI) corresponding to an increase across the interquartile range (IQR) of NO_2 and $PM_{2.5}$. Concentration response curves were evaluated using recently published methods [33].

We conducted stratified analyses to assess potential effect modification by selected individual (i.e. maternal history of asthma, maternal atopy status, maternal smoking during pregnancy, birth weight, gestational age, infant sex) and contextual (i.e. urban/rural status) characteristics. We evaluated the significance of effect modification on the multiplicative scale by including a cross product interaction term between each exposure of interest (i.e. $PM_{2.5}$ and NO_2) and each characteristic. Wald's method was used to assess the presence of interaction on the multiplicative scale. Effect modification was considered statistically significant if the interaction

term p-value was less than 0.05. We also investigated the interaction between air pollution and maternal asthma as well as maternal atopy on the additive scale using the relative excess risk due to interaction (RERI) given that joint effects are also of interest. We categorised $PM_{2.5}$ and NO_2 in quartiles for this analysis. We used mothers without asthma (or mothers without an atopic disease) in the first exposure quartiles of either $PM_{2.5}$ or NO_2 as the reference category for the following groups (annotations in parentheses): presence of maternal asthma (or maternal atopy) and fourth quartile exposure of either $PM_{2.5}$ or NO_2 (HR_{10}); absence of maternal asthma (or maternal atopy) and first quartile exposure of either $PM_{2.5}$ or NO_2 (HR_{01}); presence of maternal asthma (or maternal atopy) and fourth quartile exposure of either $PM_{2.5}$ or NO_2 (HR_{11}). We calculated the RERI as $HR_{11} - HR_{10} - HR_{01} + 1$. A RERI of 0 indicates no interaction and a statistically significant RERI > 0 indicates the presence of supra-additivity or synergistic interaction [34]. The RERI and its 95% CI were calculated according to the delta method [35].

We conducted a number of sensitivity analyses including: stratifying analyses by the child's age at diagnosis restricting our analysis according to subjects that did not move during pregnancy and conducting two-pollutant models. Statistical analyses were carried out in R (version 3.0.1), using the "coxme" package. Ethics approval for this study was granted by the Research Ethics Boards of Health Canada, the Children's Hospital of Eastern Ontario and the Ottawa Health Science Network

Results

Descriptive statistics

A total of 761,172 singleton live births occurring between April 1st 2006 and March 31st 2012 were identified in the province of Ontario, Canada (Table 1). Among these, 110,981 children developed asthma before age 6 with a mean age at asthma diagnosis of 2.1 years. Children with asthma had a smaller birth weight (3327.9 ± 596.3 vs. 3397.1 ± 540.5), a slightly shorter gestational age (38.6 +/- 2.1 vs. 38.9 +/- 1.7) and were more frequently born to mothers with a history of asthma (8.4% vs. 5.6%). There was also a male predominance among asthmatic children (60.5% vs. 49.8%). Furthermore, a total of 45,443 mothers were found to have a history of asthma.

The IQR for $PM_{2.5}$ was 3.7 $\mu g/m^3$ and the IQR for NO_2 was 8.6 ppb over the whole pregnancy period (Table 2). $PM_{2.5}$ was moderately correlated with NO_2 during the entire pregnancy period (r = 0.49) (Supplementary Table S1). Moderate correlations were observed between trimester-specific periods and exposures after birth to $PM_{2.5}$ (r = 0.54–0.74). Moderate Pearson correlations were also found between specific periods of exposure to NO_2 (r = 0.51–0.78). Average long term air pollution exposure (i.e. combining pregnancy exposure and exposures after birth) in mothers with asthma was slightly lower (7.2 $\mu g/m^3$ for $PM_{2.5}$ and 12.5 ppb for NO_2) compared to mothers without asthma (7.4 $\mu g/m^3$ for $PM_{2.5}$ and 13.3 ppb for NO2) (results not shown in tables). We observed negative correlations between long term $PM_{2.5}$ (r = -0.44) and NO_2 (r = -0.43) exposures with residential greenness exposure during pregnancy.

Air pollution and childhood asthma associations

The associations between exposure to $PM_{2.5}$ and NO_2 on childhood asthma incidence over specific time periods of pregnancy are presented in Table 2. We found that additional adjustment for the pregnancy average exposure and the exposures after birth decreased effect estimates in most associations. In fact, we found statistically significant hazard ratios for exposures to NO_2 (HR = 1.06, 95% CI: 1.03 - 1.08) and $PM_{2.5}$ (HR = 1.07, 95% CI: 1.06 - 1.09) only for the second trimester when additionally adjusting for exposures to the selected pollutant during the whole pregnancy and exposures after birth. Supplementary analyses using concentration-response functions using natural cubic splines with three degrees of freedom [36] for NO_2 and $PM_{2.5}$ during the second trimester with adjustment for all the same covariates reported in Table 2 (i.e. mutually adjusted model) confirmed linearity of associations with incident asthma throughout the distribution of air pollutant concentrations (Supplemental Figure S2). Exposure to residential greenness during pregnancy appeared to be independently associated with reduced risk of childhood asthma (HR = 0.83, 95% CI: 0.82 – 0.83) after adjustment for air pollution measures (result not shown).

Air pollution and childhood asthma effect modification

Stratified analyses, adjusted for a number of covariates including the mutual adjustment for pregnancy average and exposures after birth, are presented in Tables 3 and 4. Analyses stratified according to gestational age showed that children born preterm were at highest risk

(HR = 1.11, 95% CI: 1.08 – 1.14) of developing childhood asthma per 9.7 ppb increase in exposure to NO_2 during the second trimester when compared to the risk for those born at term (HR = 1.06, 95% CI: 1.03 – 1.08) (p value = 0.04) (Table 3). Stratification by maternal place of residence showed that children born to mothers who were living in urban areas during their pregnancy had a heightened impact of exposure to NO_2 during the first trimester on childhood asthma development (p value for effect modification = 0.04). We also found statistically significant effect modification by infant sex, with boys having higher risks of developing asthma, for exposures to $PM_{2.5}$ in trimesters 1 and 2 (p values for effect modification $\leq$ 0.04) (Table 4). Stratified regressions also revealed that low birth weight infants, those born preterm and those born from mothers who smoked during pregnancy were at an increased risk for asthma when exposed to increased levels of PM2.5 compared to their counterparts (p values for effect modification $\leq$ 0.04). Given that maternal smoking during pregnancy is negatively associated with gestational age and birth weight, we also restricted our analysis of effect modification by gestational age and birth weight to those that did not smoke during pregnancy. Results for effect modification by gestational age and birth weight remained statistically significant (p values for effect modification $\leq$ 0.04; results not shown).

The risk of childhood asthma diagnosed before 6 years of age was significantly increased when evaluating effect modification on the additive scale for the combined effect of maternal asthma and exposure to NO_2 (Table 5). The highest effect was observed among children whose exposure to NO_2 during the second trimester was in the highest category of exposure (i.e. 4^{th} quartile) and whose mothers had asthma (HR = 1.87, 95% CI: 1.69 – 2.07). RERI estimates for

joint effects of high NO_2 exposure and maternal asthma on childhood asthma incidence exceeded 0 for second trimester exposure and RERI was statistically significant, which suggests supra-additivity (i.e. synergistic effects) for interaction on the additive scale. No evidence of effect modification on the additive scale was found for the other associations investigated (Tables 5 and 6) and for effect modification by maternal atopy on the additive scale (results not shown).

Sensitivity analyses

We conducted a number of sensitivity analyses. When stratifying the analysis by the child's age at diagnosis (<1 year vs. 1–5 years of age), we found no differences in effect estimates (data not shown). We also found less than 3% differences in risk estimates when comparing those that did not move during pregnancy or during childhood years compared to all subjects (results not shown). In two-pollutant models, we found that effect estimates for both pollutants decreased slightly when adjusting for the other pollutant (Supplemental Table S2). We also found that effect estimates for single pollutant models restricted to those where both exposure estimates could be assigned were similar to the overall models (Supplemental Table S2). The same pattern was observed when investigating two-pollutant models when evaluating effect modification (i.e. less than 3% difference in risk estimates; results not shown). Results of the evaluation of the joint effects between NO_2 during the second trimester and maternal asthma were robust to adjustment for cumulative exposures after birth (results not shown). We also investigated associations restricted to term births weighting over 2500 grams (i.e. without

adjustment for birth weight and gestational age since these factors may be on the causal pathway between prenatal exposure to air pollution and childhood asthma), but risk estimates were materially unchanged (results not shown). We also investigated whether parity was an effect modifier in the relationship between air pollution variables and asthma development, but findings did not reveal presence of effect modification (p value for effect modification ≥ 0.11; results not shown).

Discussion

In this population-based study in the largest province of Canada, we examined associations between prenatal and early postnatal life exposure to air pollution and early childhood asthma incidence. We found that second trimester exposures to NO_2 and $PM_{2.5}$ were associated with increased risks of developing asthma in children up to age 6. We also found suggestive evidence that children of mothers who had asthma and who were in the upper quartile of exposure to NO_2 during the second trimester were about two times more at risk to develop asthma before 6 years of age. Increased effects of exposure to air pollution on childhood asthma incidence were also found for those born preterm, of low birth weight, boys, those born to mothers who smoked during pregnancy and among those born to mothers living in urban areas during pregnancy.

Many studies have investigated the association between childhood exposure to air pollution and asthma onset in children [3,4], but few studies have investigated the effect of exposure to

air pollution during specific periods of pregnancy on the risk of development of childhood asthma [9,13,14]. In a study conducted in China among 2,598 children, exposure to increased levels of NO_2 during the second trimester was associated with the development of asthma (OR = 1.72, 95% CI: 1.02, 2.97) [13]. A study conducted in Boston, Massachusetts evaluated the effect of weekly exposures to $PM_{2.5}$ during pregnancy on the development of asthma among 736 full-term children [9,14]. They found that $PM_{2.5}$ exposure during the second trimester was associated with asthma development by age 6 years, but only among boys. As well, Morales et al. showed that second-trimester NO_2 exposure was associated with decreased lung function at 4.5 years of age [5]. Therefore, findings of our study for an effect of exposure to NO_2 and $PM_{2.5}$ during the second trimester of pregnancy on childhood asthma incidence are somewhat consistent with prior literature. Exposure to air pollution in utero may potentially have harmful effects on critical periods of development of the immune and respiratory systems [37]. In particular, lung development in the second trimester of pregnancy may be affected through an increase in inflammation and airway hyper-responsiveness, which may enhance susceptibility to asthma [9,38-40].

We also found that exposure to air pollution during the first year of life with additional adjustment for pregnancy exposure was not associated with childhood asthma development. Although few studies have attempted to disentangle these relationships, Morales et al. found that early postnatal life exposure to outdoor air pollutants was not associated with lung function deficits at preschool age [5]. However, a recent study showed that exposure to traffic-related air pollution in infancy is negatively associated with FEV1 at 16 years of age [8]. This

could imply that effects of exposure during the first year of life may not be long enough for having an impact on childhood asthma development. Therefore, further studies are required to disentangle the impact of prenatal and postnatal exposure to air pollution on development of respiratory outcomes in later childhood and adolescence.

We found evidence that impacts on childhood asthma diagnosed before 6 years of age increased in a synergistic manner when evaluating the joint effect of maternal asthma and high levels of exposure to NO_2 during the second trimester of pregnancy. To our knowledge, no previous study has investigated this important issue. Prior literature has shown that inhalation of gaseous pollutants can induce proinflammatory processes in the lungs of pregnant women [41]. Inflammation is also a characteristic feature of the pathophysiology of asthma [17]. It is therefore biologically plausible that inflammation from exposure to air pollution during pregnancy combined with inflammation due to maternal presence of asthma induces a synergistic effect on childhood asthma development. This could occur through an alteration of immune responses [42]. Our findings could also reflect the fact that traffic pollution may potentiate airway inflammation in already sensitized children through an epigenetic pathway (i.e. those with a genetic susceptibility to develop asthma) [43]. These findings require further investigation.

Our results confirm the previously reported finding that children weighting less than 2,500 grams at birth were at higher risk of developing asthma during childhood following exposure to

air pollution during the gestational period [11]. As well, we found stronger impacts from exposure to air pollution on development of childhood asthma among children born preterm as compared to those born full-term, and those born to mothers living in urban areas during pregnancy compared to rural areas. This finding is relevant as it shows greater susceptibility among those living in urban areas [44]. This may relate to the "hygiene hypothesis" where living in urban areas characterized by wealthy lifestyles and wealthy housing characteristics may increase risk of developing asthma. In addition, protective effect of microbial exposures from rural environments has been previously reported [45]. We also found higher effects for those born to mothers who smoked during pregnancy. Our findings for higher effects of prenatal exposure to $PM_{2.5}$ on childhood asthma incidence among boys is consistent with one previous study [9,14].

Some limitations of our study need to be acknowledged. First, we could assign NO_2 exposures only to participants that were within 25km from a ground monitor in order to apply the temporal scaling described in the online supplement. This decreased the sample sizes for analysis when investigating NO_2 exposures, but likely reduced the likelihood of misclassification bias in exposure [46]. Secondly, while we included a number of important confounding factors, we cannot rule out potential residual confounding. For example, we did not have individual-level information on ethnicity, income, education or maternal stress levels. However, adjustment for area-level SES factors may have partially accounted for confounding for some of these missing variables. We also did not have information on maternal obesity in pregnancy or maternal gestational weight gain, both of which are important risk factors for childhood asthma

development [47]. However, a sensitivity analysis among a subset of our cohort (i.e. about 20% of our cohort) with information on maternal pre-pregnancy body mass index indicated that adjustment for this factor did not materially change the main effect estimates (results not shown). Another limitation is related to the fact that we identified cases of asthma based on health administrative databases which may lead to some level of misclassification bias. For example, we did not have information on asthma phenotypes and asthma severity. We also did not have information on medications used to treat or control asthma during pregnancy. However, a recent Canadian study that used a similar physician-diagnosed asthma case ascertainment as our study showed that traffic-related air pollution was associated with asthma status that was maintained over a 10-year follow-up. Therefore, this provides support that we likely captured "true" asthma cases. In addition, children less than 5 years of age with symptoms of wheeze due to viral infections may be misdiagnosed as having asthma [23,48]. However, we used a validated case definition in identifying asthma among both children and adults [30]. Finally, we could have underestimated asthma diagnosis in mothers since the data we used to identify maternal asthma went as far back as to 1991 and therefore we would not identify those diagnosed with asthma during childhood. Also, if these mothers had asthma during their early childhood and were well controlled afterwards without any documented health care use attributed to asthma, we would have missed them. Thus, we assume most of the mothers with asthma that we captured through the health administrative database would be "prevalent" cases and/or may be those with relatively not so well-controlled (or severe) asthma that would continue with encounters in the health care system during their adulthood [30].

Notable strengths of this study include the large sample size, availability of spatiotemporal air pollution exposure estimates available across a large geographical area and the attempt to capture residential mobility during pregnancy. The population-based approach also likely reduced risks of selection bias.

In this large population-based study, we found that exposure to ambient air pollution in pregnancy may increase the risk of asthma in young children. We also observed enhanced effects of air pollution on the onset of childhood asthma diagnosed before 6 years of age among those born to mothers with a history of asthma, those born to mothers who smoked during pregnancy, in boys and according to gestational age, birth weight and maternal place of residence. These findings highlight the need for further research to confirm relationships identified here and also the importance of developing public health and prenatal care strategies aimed at raising awareness and minimizing exposure to ambient air pollution during pregnancy.

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Table 1. Demographic and socioeconomic characteristics of study participants[a].

Characteristics	Total cohort	Asthmatic children	Non-asthmatic children
n	761,172	110,981	650,191
Maternal age	30.0 (5.5)	30.1 (5.5)	30.0 (5.5)
Gestational age (weeks)	38.9 (1.8)	38.6 (2.1)	38.9 (1.7)
Birth weight (grams)	3387.0 (549.6)	3327.9 (596.3)	3397.9 (540.6)
Infant sex			
Male	390,665 (51.3)	67,171 (60.5)	323,484 (49.8)
Female	370,507(48.7)	43,810 (39.5)	326,697 (50.2)
Parity			
0	385,336 (50.6)	55,777 (50.3)	329,559 (50.7)
1	259,543 (34.1)	39,004 (35.1)	220,539 (33.9)
≥ 2	116,293 (15.3)	16,200 (14.6)	100,093 (15.4)
Intention to breastfeed			
Yes	606,236 (79.6)	87,503 (78.8)	518,733 (79.8)
No	64,787 (8.5)	9,607 (8.7)	55,180 (8.5)
Missing	90,149 (11.8)	13,871 (12.5)	76,278 (11.7)
Maternal smoking status during pregnancy			
Yes	79,718 (10.5)	11,398 (10.3)	68,320 (10.5)
No	597,907 (78.6)	86,761 (78.2)	511,146 (78.6)
Missing	83,547 (11.0)	12,822 (11.6)	70,725 (10.9)
Maternal asthma			
Yes	45,443 (6.0)	9,299 (8.4)	36,144 (5.6)
No	715,729 (94.0)	101,682 (91.6)	614,047 (94.4)
Median family income			
Quintile 1	149,838 (19.7)	23,566 (21.2)	126,272 (19.4)
Quintile 2	149,405 (19.6)	21,798 (19.6)	127,607 (19.6)
Quintile 3	150,339 (19.8)	20,974 (18.9)	129,365 (19.9)
Quintile 4	149,788 (19.7)	21,826 (19.7)	127,962 (19.7)
Quintile 5	149,872 (19.7)	21,115 (19.0)	128,757 (19.8)
Missing	11,930 (1.6)	1,702 (1.5)	10,228 (1.6)
Percent of females completed postsecondary education (age 25+)			
Quintile 1	124,580 (19.7)	16,649 (18.0)	107,931 (20.0)
Quintile 2	125,085 (19.8)	18,278 (19.7)	106,807 (19.8)
Quintile 3	124,050 (19.6)	18,663 (20.1)	105,387 (19.5)
Quintile 4	124,767 (19.7)	18,932 (20.4)	105,835 (19.6)
Quintile 5	124,508 (19.7)	18,848 (20.3)	105,660 (19.6)
Missing	8,966 (1.4)	1,310 (1.4)	7,656 (1.4)
Percent visible minority			
Quintile 1	149,652 (19.7)	16,203 (14.6)	133,449 (20.5)
Quintile 2	149,888 (19.7)	18,687 (16.8)	131,201 (20.2)
Quintile 3	149,768 (19.7)	21,185 (19.1)	128,583 (19.8)
Quintile 4	149,744 (19.7)	24,620 (22.2)	125,124 (19.2)
Quintile 5	149,777 (19.7)	28,527 (25.7)	121,250 (18.6)
Missing	12,343 (1.6)	1,759 (1.6)	10,584 (1.6)

[a] n (%) for categorical covariates; mean (standard deviation) for continuous covariates.

Table 2. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between NO_2 (per IQR) and $PM_{2.5}$ (per IQR) over specific periods and childhood asthma risk.

Exposure period	NO_2				$PM_{2.5}$			
	Obs. cases	IQR (in ppb)	Adjusted model[a] HR (95% CI)	Mutually adjusted model[b] HR (95% CI)	Obs. cases	IQR (in µg/m3)	Adjusted model[a] HR (95% CI)	Mutually adjusted model[b] HR (95% CI)
1st trimester	28,292	9.6	1.12 (1.10 – 1.15)	1.02 (1.00 – 1.05)	84,429	4.1	1.01 (1.00 – 1.03)	1.01 (1.00 – 1.03)
2nd trimester	27,874	9.7	1.19 (1.17 – 1.21)	1.06 (1.03 – 1.08)	84,398	3.9	1.09 (1.08 – 1.10)	1.07 (1.06 – 1.09)
3rd trimester	27,260	9.5	0.99 (0.97 – 1.01)	0.98 (0.96 – 1.00)	84,056	3.8	1.02 (1.00 – 1.04)	1.01 (0.99 – 1.03)
Entire pregnancy	27,213	8.6	1.09 (1.07 – 1.12)	1.02 (0.99 – 1.05)	83,470	3.7	1.02 (0.99 – 1.04)	1.01 (0.99 – 1.04)
First year of life	27,213	8.9	1.08 (1.06 – 1.09)	1.03 (1.00 – 1.06)	83,470	3.6	0.99 (0.98 – 1.00)	0.99 (0.98 – 1.00)
Childhood cumulative exposure	26,519	8.6	1.00 (0.98 – 1.02)	1.00 (0.97 – 1.03)	82,520	3.3	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)

[a] Model adjusted for maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, maternal atopy, gestational age, birth weight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority and dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education.

[b] Includes all variables in the "adjusted model" plus the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant IQR, interquartile range

Table 3. Adjusted[a] hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between NO_2 per interquartile range over specific periods and childhood asthma risk, stratified by selected characteristics.

Variables	1st trimester	2nd trimester	3rd trimester	Entire pregnancy	First year of life	Childhood cumulative exposure
	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[b]
Maternal asthma						
Yes	1.04 (0.98 – 1.10)	1.09 (1.03 – 1.15)	1.00 (0.95 – 1.05)	1.03 (0.96 – 1.10)	1.04 (1.00 – 1.08)	1.00 (0.96 – 1.04)
No	1.02 (0.99 – 1.04)	1.06 (1.03 – 1.08)	0.98 (0.96 – 1.00)	1.02 (0.99 – 1.05)	1.03 (0.99 – 1.06)	1.00 (0.97 – 1.03)
P value for effect modification	0.65	0.38	0.42	0.49	0.64	0.75
Maternal atopy						
Yes	1.07 (1.00 – 1.14)	1.12 (1.05 – 1.19)	1.01 (0.96 – 1.07)	1.06 (0.99 – 1.13)	1.08 (1.00 – 1.15)	1.01 (0.96 – 1.05)
No	1.02 (1.00 – 1.05)	1.06 (1.03 – 1.08)	0.98 (0.96 – 1.00)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.00 (0.97 – 1.03)
P value for effect modification	0.21	0.16	0.78	0.34	0.32	0.92
Maternal smoking during pregnancy						
Yes	1.08 (1.03 – 1.13)	1.11 (1.05 – 1.16)	1.05 (1.00 – 1.10)	1.07 (1.01 – 1.13)	1.05 (1.00 – 1.10)	1.00 (0.93 – 1.07)
No	1.02 (1.00 – 1.05)	1.06 (1.03 – 1.08)	1.00 (0.98 – 1.02)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.00 (0.97 – 1.03)
P value for effect modification	0.11	0.19	0.07	0.17	0.44	0.96
Infant sex						
Boys	1.03 (1.00 – 1.06)	1.06 (1.04 – 1.08)	1.00 (0.98 – 1.03)	1.02 (0.99 – 1.04)	1.03 (1.00 – 1.06)	1.00 (0.97 – 1.04)
Girls	1.02 (1.00 – 1.05)	1.06 (1.03 – 1.08)	1.00 (0.97 – 1.03)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.00 (0.97 – 1.03)
P value for effect modification	0.55	0.88	0.74	0.92	0.57	0.84
Maternal place of residence						
Urban	1.04 (1.01 – 1.07)	1.06 (1.03 – 1.08)	1.00 (0.98 – 1.03)	1.02 (0.99 – 1.05)	1.04 (1.02 – 1.06)	1.00 (0.97 – 1.03)
Rural	0.75 (0.55 – 1.01)	0.98 (0.71 – 1.34)	1.00 (0.67 – 1.45)	0.99 (0.58 – 1.55)	1.00 (0.60 – 1.59)	0.99 (0.61 – 1.65)
P value for effect modification	0.04	0.51	0.97	0.88	0.75	0.88
Gestational age						
< 37 weeks	1.02 (1.00 – 1.05)	1.11 (1.08 – 1.14)	1.02 (0.98 – 1.06)	1.05 (1.00 – 1.09)	1.04 (0.99 – 1.09)	1.00 (0.95 – 1.05)
≥ 37 weeks	1.03 (1.00 – 1.06)	1.06 (1.03 – 1.08)	0.98 (0.96 – 1.01)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.00 (0.98 – 1.02)
P value for effect modification	0.44	0.04	0.33	0.43	0.86	0.98
Birth weight						
< 2500 g.	1.01 (0.99 – 1.04)	1.05 (0.99 – 1.11)	1.03 (0.96 – 1.10)	1.04 (0.97 – 1.11)	1.06 (0.99 – 1.13)	1.00 (0.92 – 1.08)
≥ 2500 g.	1.02 (1.00 – 1.05)	1.06 (1.02 – 1.08)	1.00 (0.98 – 1.02)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.00 (0.97 – 1.03)
P value for effect modification	0.77	0.72	0.33	0.63	0.34	0.98

[a] Models adjusted for maternal age at delivery, infant sex (except for stratified analyses by infant sex), parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy (except for stratified analyses by maternal smoking), maternal atopy (except for stratified analyses by maternal asthma and by maternal atopy), gestational age (except for stratified analyses by gestational age), birth weight (except for stratified analyses by birth weight), residential greenness exposure during pregnancy, dissemination area median family income, dissemination area

proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant,

Table 4. Adjusted[a] hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between $PM_{2.5}$ per interquartile range over specific periods and childhood asthma risk, stratified by selected characteristics.

Variables	1st trimester	2nd trimester	3rd trimester	Entire pregnancy	First year of life	Childhood cumulative exposure
	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[b]
Maternal asthma						
Yes	0.99 (0.94 – 1.02)	1.08 (1.05 – 1.11)	1.02 (0.99 – 1.05)	1.02 (0.98 – 1.07)	1.00 (0.95 – 1.06)	1.00 (0.93 – 1.08)
No	1.01 (1.00 – 1.03)	1.07 (1.06 – 1.09)	1.01 (0.99 – 1.03)	1.01 (0.98 – 1.04)	0.99 (0.98 – 1.00)	1.00 (0.99 – 1.01)
P value for effect modification	0.26	0.92	0.67	0.81	0.88	0.94
Maternal atopy						
Yes	1.03 (0.99 – 1.07)	1.09 (1.05 – 1.13)	1.02 (0.98 – 1.07)	1.03 (0.97 – 1.08)	1.02 (0.98 – 1.05)	1.00 (0.94 – 1.07)
No	1.01 (0.99 – 1.03)	1.07 (1.06 – 1.09)	1.01 (0.99 – 1.03)	1.01 (0.99 – 1.04)	0.98 (0.97 – 1.01)	1.00 (0.98 – 1.01)
P value for effect modification	0.35	0.34	0.61	0.55	0.48	0.72
Maternal smoking during pregnancy						
Yes	1.07 (1.03 – 1.12)	1.12 (1.09 – 1.14)	1.05 (1.02 – 1.08)	1.07 (1.04 – 1.11)	1.00 (0.98 – 1.03)	0.99 (0.96 – 1.01)
No	1.01 (1.00 – 1.03)	1.07 (1.06 – 1.09)	1.01 (0.99 – 1.03)	1.01 (0.98 – 1.04)	0.99 (0.98 – 1.00)	0.99 (0.98 – 1.00)
P value for effect modification	0.04	0.04	0.08	0.04	0.91	0.91
Infant sex						
Boys	1.04 (1.02 – 1.06)	1.09 (1.07 – 1.11)	1.01 (0.99 – 1.03)	1.03 (1.01 – 1.06)	1.00 (0.98 – 1.00)	1.00 (0.99 – 1.01)
Girls	1.00 (0.97 – 1.02)	1.05 (1.01 – 1.09)	1.00 (0.98 – 1.03)	1.01 (0.99 – 1.04)	1.00 (0.98 – 1.01)	1.00 (1.00 – 1.01)
P value for effect modification	0.04	0.04	0.35	0.12	0.78	0.96
Maternal place of residence						
Urban	1.01 (1.00 – 1.03)	1.08 (1.06 – 1.10)	1.01 (1.00 – 1.04)	1.01 (0.99 – 1.04)	1.00 (0.98 – 1.02)	1.00 (0.99 – 1.01)
Rural	1.02 (0.98 – 1.07)	1.06 (1.00 – 1.11)	1.00 (0.95 – 1.06)	1.01 (0.98 – 1.04)	1.00 (0.95 – 1.07)	1.00 (0.95 – 1.06)
P value for effect modification	0.42	0.36	0.60	0.86	0.67	0.76
Gestational age						
< 37 weeks	1.06 (1.03 – 1.10)	1.13 (1.09 – 1.17)	1.03 (0.99 – 1.07)	1.04 (1.00 – 1.09)	1.00 (0.95 – 1.05)	1.00 (0.95 – 1.06)
≥ 37 weeks	1.01 (1.00 – 1.03)	1.07 (1.06 – 1.09)	1.01 (0.99 – 1.03)	1.01 (0.99 – 1.04)	0.99 (0.98 – 1.00)	1.00 (1.00 – 1.01)
P value for effect modification	0.04	0.03	0.28	0.47	0.68	0.85
Birth weight						
< 2500 g.	1.05 (1.02 – 1.08)	1.12 (1.08 – 1.16)	1.08 (1.03 – 1.13)	1.08 (1.04 – 1.12)	1.00 (0.95 – 1.06)	1.01 (0.95 – 1.07)
≥ 2500 g.	1.00 (0.98 – 1.02)	1.07 (1.06 – 1.09)	1.01 (0.99 – 1.03)	1.01 (0.99 – 1.04)	0.99 (0.98 – 1.00)	1.00 (1.00 – 1.01)
P value for effect modification	0.04	0.03	0.04	0.04	0.82	0.73

[a] Models adjusted for maternal age at delivery, infant sex (except for stratified analyses by infant sex), parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy (except for stratified analyses by maternal smoking), maternal atopy (except for stratified analyses by maternal asthma and by maternal atopy), gestational age (except for stratified analyses by gestational age), birth weight (except for stratified analyses by birth weight), residential greenness exposure during pregnancy, dissemination area median family income, dissemination area

proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant,

Table 5. Adjusted[a] hazard ratios (HR) and 95% confidence intervals (95% CI) for the joint effects of maternal asthma and quartiles of NO_2 exposure over specific periods of pregnancy on childhood asthma risk.

Maternal asthma	NO2 quartiles	n	Obs. cases	HR (95% CI)
1st trimester				
No	Q1	56939	7142	Ref.
No	Q2	55953	7542	1.00 (0.96 – 1.05)
No	Q3	54914	8499	1.05 (0.99 – 1.11)
No	Q4	55204	9613	1.10 (1.02 – 1.18)
Yes	Q1	3951	767	1.59 (1.48 – 1.71)
Yes	Q2	3206	642	1.53 (1.41 – 1.66)
Yes	Q3	3012	720	1.68 (1.53 – 1.84)
Yes	Q4	2821	765	1.77 (1.67 – 1.97)
RERI[b] (95% CI) = 0.08 (-0.02 – 0.18)				
2nd trimester				
No	Q1	56836	7156	Ref.
No	Q2	55541	7593	1.02 (0.98 – 1.06)
No	Q3	54512	8290	1.09 (1.04 – 1.15)
No	Q4	54660	9504	1.16 (1.08 – 1.26)
Yes	Q1	3930	744	1.53 (1.42 – 1.65)
Yes	Q2	3214	665	1.59 (1.48 – 1.73)
Yes	Q3	2988	703	1.75 (1.60 – 1.91)
Yes	Q4	2811	755	1.87 (1.69 – 2.07)
RERI[b] (95% CI) = 0.18 (0.08 – 0.28)				
3rd trimester				
No	Q1	56139	7147	Ref.
No	Q2	55097	7669	1.00 (0.96 – 1.04)
No	Q3	54221	8207	1.02 (0.96 – 1.07)
No	Q4	54247	9171	1.06 (0.98 – 1.15)
Yes	Q1	3851	745	1.54 (1.43 – 1.66)
Yes	Q2	3240	671	1.56 (1.44 – 1.70)
Yes	Q3	2953	696	1.61 (1.47 – 1.77)
Yes	Q4	2794	748	1.66 (1.49 – 1.81)
RERI[b] (95% CI) = 0.07 (-0.03 – 0.16)				
Entire pregnancy				
No	Q1	54748	6928	Ref.
No	Q2	52430	6908	0.95 (0.91 – 1.00)
No	Q3	52598	7964	1.03 (0.97 – 1.09)
No	Q4	52374	9307	1.10 (1.02 – 1.19)
Yes	Q1	3811	738	1.55 (1.44 – 1.68)
Yes	Q2	3075	587	1.40 (1.28 – 1.53)
Yes	Q3	2794	689	1.66 (1.51 – 1.82)
Yes	Q4	2645	730	1.72 (1.54 – 1.91)
RERI[b] (95% CI) = 0.06 (-0.04 – 0.15)				
First year of life				
No	Q1	53730	6724	Ref.
No	Q2	51233	6689	1.00 (0.97 – 1.03)
No	Q3	51107	7625	1.06 (1.01 – 1.12)
No	Q4	50074	9102	1.12 (1.04 – 1.21)

Yes	Q1	3731	727	1.55 (1.43 – 1.67)
Yes	Q2	2977	562	1.60 (1.48 – 1.72)
Yes	Q3	2523	668	1.68 (1.53 – 1.83)
Yes	Q4	2427	717	1.75 (1.59 – 1.92)
RERI[b] (95% CI) = 0.08 (-0.01 – 0.18)				

[a] Models adjusted for maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, gestational age, birth weight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant,

[b] RERI indicates the relative excess risk of childhood asthma due to interaction between maternal asthma and NO_2

Table 6. Adjusted[a] hazard ratios (HR) and 95% confidence intervals (95% CI) for the joint effects of maternal asthma and quartiles of $PM_{2.5}$ exposure over specific periods of pregnancy on childhood asthma risk.

Maternal asthma	$PM_{2.5}$ quartiles	n	Obs. cases	HR (95% CI)
1st trimester				
No	Q1	145559	17807	Ref.
No	Q2	143670	19323	1.00 (0.97 – 1.02)
No	Q3	139399	20506	1.03 (1.00 – 1.07)
No	Q4	139781	21964	1.06 (1.00 – 1.12)
Yes	Q1	10162	1854	1.56 (1.49 – 1.64)
Yes	Q2	9218	1738	1.46 (1.39 – 1.54)
Yes	Q3	8531	1881	1.63 (1.54 – 1.73)
Yes	Q4	8140	1811	1.56 (1.45 – 1.67)
RERI[b] (95% CI) = -0.06 (-0.16 – 0.03)				
2nd trimester				
No	Q1	146044	17705	Ref.
No	Q2	144005	19595	1.02 (0.99 – 1.05)
No	Q3	140194	20412	1.03 (0.99 – 1.07)
No	Q4	138903	21928	1.07 (1.02 – 1.13)
Yes	Q1	10259	1779	1.49 (1.42 – 1.57)
Yes	Q2	9187	1820	1.55 (1.47 – 1.63)
Yes	Q3	8489	1849	1.62 (1.53 – 1.72)
Yes	Q4	8161	1837	1.60 (1.50 – 1.72)
RERI[b] (95% CI) = -0.04 (-0.06 – 0.13)				
3rd trimester				
No	Q1	146293	17831	Ref.
No	Q2	145118	19782	1.00 (0.97 – 1.03)
No	Q3	139473	19962	0.98 (0.95 – 1.02)
No	Q4	138104	21901	1.03 (0.98 – 1.09)
Yes	Q1	10268	1820	1.52 (1.45 – 1.60)
Yes	Q2	9262	1821	1.51 (1.43 – 1.59)
Yes	Q3	8356	1790	1.54 (1.47 – 1.64)
Yes	Q4	8218	1840	1.52 (1.42 – 1.63)
RERI[b] (95% CI) = -0.03 (-0.12 – 0.06)				
Entire pregnancy				

No	Q1	142313	16929	Ref.
No	Q2	142474	19688	1,03 (1.00 – 1.06)
No	Q3	141971	19741	0,95 (0.91 – 1.00)
No	Q4	135596	22224	1,07 (1.00 – 1.13)
Yes	Q1	10041	1768	1,55 (1.47 – 1.62)
Yes	Q2	9096	1788	1,54 (1.46 – 1.62)
Yes	Q3	8653	1808	1,50 (1.41 – 1.59)
Yes	Q4	7850	1831	1,58 (1.47 – 1.70)
RERI[b] (95% CI) = -0.04 (-0.14 – 0.05)				
First year of life				
No	Q1	141974	16918	Ref.
No	Q2	142101	19682	0.99 (0.96 – 1.02)
No	Q3	141788	19738	1.00 (0.95 – 1.05)
No	Q4	134323	22221	1.02 (0.98 – 1.07)
Yes	Q1	9874	1766	1.55 (1.46 – 1.61)
Yes	Q2	8921	1784	1.53 (1.41 – 1.60)
Yes	Q3	8365	1807	1.57 (1.45 – 1.64)
Yes	Q4	7538	1830	1.59 (1.46 – 1.69)
RERI[b] (95% CI) = 0.01 (-0.08 – 0.10)				

[a] Models adjusted for maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, gestational age, birth weight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant,

[b] RERI indicates the relative excess risk of childhood asthma due to interaction between maternal asthma and $PM_{2.5}$

Online Supplement

Effect modification of perinatal exposure to air pollution and childhood asthma incidence

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Study design population & design

Information on maternal residential location(s) based on residential postal code(s) was geo-coded using the Postal Code Conversion File Plus (PCCF+) to obtain Statistics Canada's standard geographic identifiers and dissemination area (DA) information. The encrypted unique identifier (also referred to the IKN) was used to link health administrative data at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada (see Figure S1). In urban areas, the 6-digit postal code generally represents one side of a city block or a large apartment complex while it usually represents a larger area in rural areas. We also used an indicator for urban/rural place of residence. In Canada, a six-character alphanumeric string forms part of a postal address. The second digit specifies if the postal code is in an urban or rural area. A zero indicates a rural region. Therefore, postal codes were considered rural if the second character was zero.There were 268,489 postal codes in urban areas and 1,122 postal codes in rural areas. This translated into 687,338 mother-infant pairs in urban areas and 73,834 mother-infant pairs in rural areas. Pregnancies with postal codes of residence outside Ontario (i.e. less than 1% of all pregnancies) were excluded from the analysis. We also excluded subjects without a valid health card number for data linkage, missing date of birth, sex, 6-digit postal code value and/or exposure estimates. Those who were excluded from the study due to these reasons exhibited similar sociodemographic factors to those measured in this study (data not shown).

Childhood asthma ascertainment

A previously validated case definition of asthma was used to identify individuals with asthma and included those who have had at least two primary care visit claims for asthma in two consecutive years and/or at least one hospitalization for asthma [1]. This definition has been shown to have 89% sensitivity and 72% specificity in children (aged 0-17 years). This case definition has been previously used [2-4]. All datasets were housed at the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca), where individual-level data were anonymized and linkage between datasets was achieved using encrypted health card numbers as unique identifiers.

Maternal asthma maternal atopy ascertainment

We used a previously validated case definition to identify pregnant women with physician-diagnosed asthma [5]. The case definition consists of one asthma hospitalization or two outpatient physician visits within a two year period. This yielded 84% sensitivity and 76% specificity in adults participating in a validity study when they were compared to a clinical reference standard. The date of the earliest asthma hospitalization or outpatient visit was used to determine the asthma diagnosis date. This case definition has been used in previous studies in Canada [6-8]. We identified maternal atopy based on two outpatient physician visits (i.e. any of the following diagnoses: maternal asthma identified as ICD-10 code J45, maternal atopic dermatitis identified as ICD-10 code L20, and maternal allergic rhinoconjunctivitis identified as ICD-10 codes J30 and H10) within a two year period.

Exposure assessment to ambient air pollutants

We assigned air pollution exposure estimates to the geographical coordinates representing the centroid of each subject's residential 6-digit postal codes. Exposure to $PM_{2.5}$ during pregnancy,

during the first year of life and during childhood were assigned based on satellite-derived estimates of monthly surfaces at a 1 × 1 km resolution available across North America from 2006 to 2012. Childhood exposure was assigned on a cumulative basis (i.e. from birth until diagnosis of asthma, end of follow-up or death). Satellite estimates were developed following van Donkelaar et al. (2015) using a 1 km optimal estimation (OE) aerosol optical depth (AOD) satellite retrieval that was related to $PM_{2.5}$ with a chemical transport model, which was further adjusted with ground-based $PM_{2.5}$ monitors using a geographically weighted regression (GWR) to account for regional bias across North America [9,10]. Data were also assigned based on trimester-specific periods of exposure and were averaged to obtain estimates for the entire pregnancy.

Prenatal exposure to ambient NO_2 was estimated by using a national Land Use Regression (LUR) model developed with data from National Air Pollution Surveillance (NAPS; http://www.ec.gc.ca/rnspa-naps/) monitoring data, 2005–2011 satellite NO_2 estimates, road lengths within 10 km, area of industrial land use within 2 km, and mean summer rainfall [11,12]. To capture fine-scale variations in vehicle emissions, kernel density functions describing densities of roadways were incorporated into the LUR model predictions. This model explained 73% of the variation in annual 2006 NO_2 NAPS measurements with a root mean square error of 2.9 parts per billion (ppb). The resulting LUR NO_2 surface was available for each year of the study period. Because the national NO_2 surface only provided annual values, we applied a temporal adjustment to the LUR NO_2 model. This allowed us to map NO_2 values more precisely to gestational periods in order to examine effects by trimester, as well as evaluating effects for childhood exposures. This was done by first generating a scaling factor by calculating a ratio of monthly mean NO_2 concentration for each monitor in the province of Ontario to annual values for year 2006 LUR model estimate at each monitor location. Estimates of monthly average ambient concentrations of NO_2 were obtained from the NAPS network maintained by Environment Canada which collects NO_2 levels through 46 automated fixed-site monitoring stations in the province of Ontario. We then created a scaling surface for each day of the study period by spatially interpolating the scaling factors. We applied an inverse distance weighting (IDW) spatial interpolation to 6-character postal code locations that were within 25km of a NAPS station to create the scaling surface. These daily scaling surfaces were then applied to the yearly LUR estimates to create the daily NO_2 surfaces [13]. These were then used to estimate exposure to NO_2 over pregnancy, by trimesters, during the first year of life and for the cumulative childhood exposure.

Exposure assessment to residential greenness

Exposure to residential greenness was estimated using the satellite-derived Normalized Difference Vegetation Index (NDVI). The NDVI describes the density and coverage of green vegetation on the ground, and has been shown to be effective in estimating local patterns of greenness for epidemiologic analysis [14]. The NDVI ranges from -1 to 1, with greater positive values indicating more greenness [15]. These data are available across Canada – excluding northern regions and territories – calculated as 16-day averages. We included observations only from the months of June, July, and August (when vegetation in Canada would be in full bloom)

and calculated annual maximum values for the years 2006 to 2012. We assigned annual greenness estimates within 250 metres around the annual residential postal code centroids of each subject for each year from 2006 to 2012. Since the greenness measures were available annually, 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. We used these estimates of exposure to greenness based on prior expert assessments of residential greenness exposure [14] and prior studies investigating exposure during pregnancy [16,17].

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Table S1. Descriptive statistics of air pollution measures and Pearson correlation coefficients across time periods.

				NO_2 (ppb)						$PM_{2.5}$ ($\mu g/m^3$)					
Air pollutant	Mean	SD	IQR	1st trimester	2nd trimester	3rd trimester	Pregnancy average	Child's 1st year	Childhood cumulative exposure	1st trimester	2nd trimester	3rd trimester	Pregnancy average	Child's 1st year	Childhood cumulative exposure
NO_2 (ppb)															
1st trimester	13.2	7.8	9.6	1.00											
2nd trimester	13.2	7.8	9.7	0.72	1.00										
3rd trimester	13.1	7.8	9.5	0.51	0.69	1.00									
Pregnancy average	13.2	7.8	8.6	0.69	0.78	0.74	1.00								
Child's 1st year	13.1	7.8	8.9	0.51	0.56	0.55	0.62	1.00							
Childhood cumulative exposure	13.0	7.8	8.9	0.48	0.51	0.56	0.59	0.63	1.00						
$PM_{2.5}$ ($\mu g/m^3$)															
1st trimester	7.3	3.0	4.1	0.31	0.35	0.43	0.43	0.40	0.32	1.00					
2nd trimester	7.3	3.0	3.9	0.33	0.33	0.35	0.39	0.39	0.35	0.64	1.00				
3rd trimester	7.3	3.0	3.8	0.40	0.36	0.33	0.42	0.40	0.39	0.62	0.63	1.00			
Pregnancy average	7.3	3.0	3.7	0.43	0.43	0.46	0.49	0.49	0.47	0.66	0.65	0.69	1.00		
Child's 1st year	7.3	3.0	3.7	0.39	0.41	0.40	0.43	0.42	0.44	0.59	0.62	0.71	0.72	1.00	
Childhood cumulative exposure	7.3	3.0	3.8	0.32	0.35	0.33	0.38	0.39	0.41	0.61	0.54	0.64	0.61	0.74	1.00

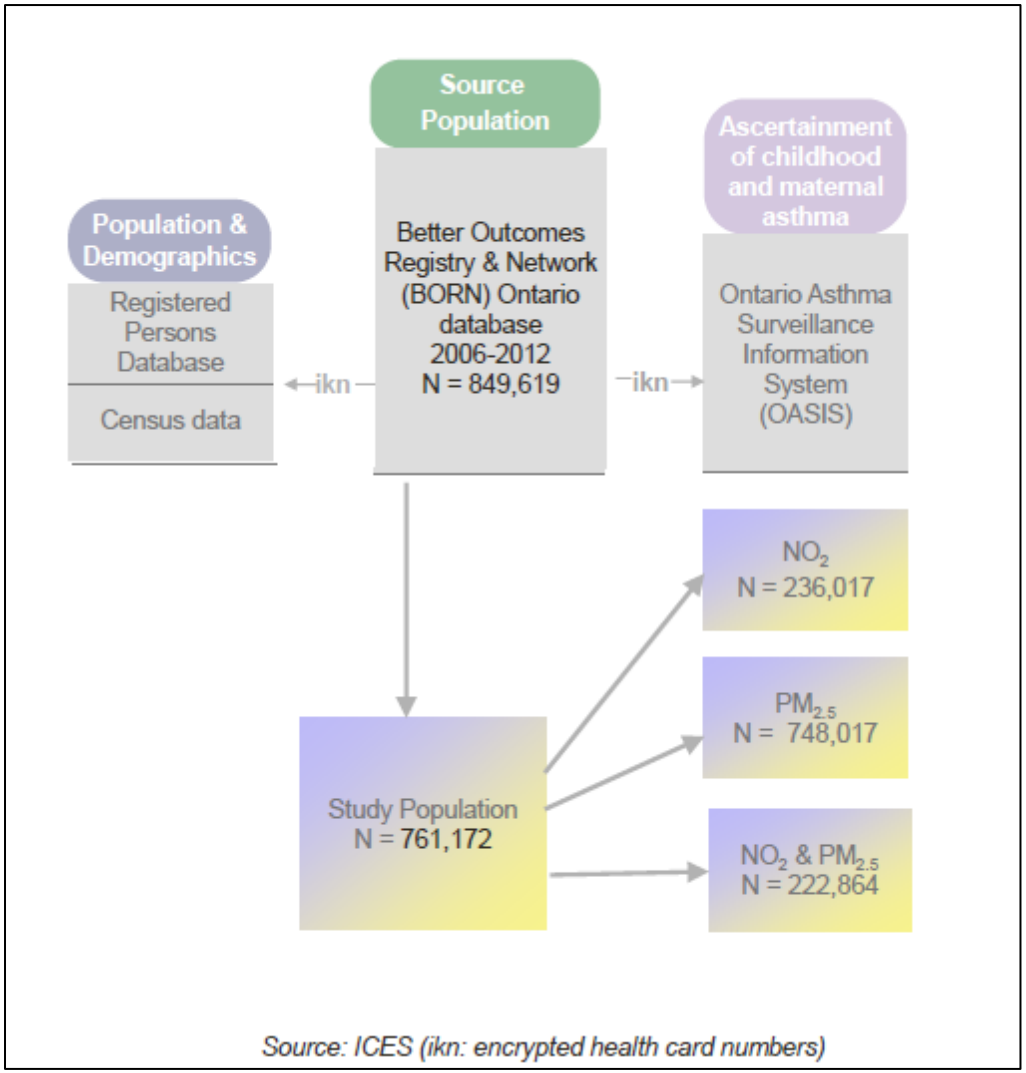
SD, standard deviation. IQR, interquartile range

Table S2. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between NO_2 (per IQR) and $PM_{2.5}$ (per IQR) in one- and two-pollutant models over specific periods and childhood asthma risk.

Exposure period	Obs. cases	NO_2		$PM_{2.5}$	
		One pollutant model[a] HR (95% CI)	Two pollutant model[b] HR (95% CI)	One pollutant model[a] HR (95% CI)	Two pollutant model[b] HR (95% CI)
1st trimester	28,201	1.02 (1.00 – 1.05)	1.01 (0.99 – 1.04)	1.00 (0.99 – 1.02)	1.00 (0.98 – 1.02)
2nd trimester	27,621	1.06 (1.03 – 1.08)	1.05 (1.02 – 1.07)	1.07 (1.05 – 1.10)	1.05 (1.03 – 1.07)
3rd trimester	27,104	0.98 (0.96 – 1.00)	0.99 (0.96 – 1.01)	1.01 (0.99 – 1.03)	1.01 (0.98 – 1.03)
Entire pregnancy	26,997	1.02 (0.99 – 1.05)	1.01 (0.99 – 1.03)	1.01 (0.98 – 1.04)	1.00 (0.98 – 1.03)
First year of life	26,997	1.03 (1.00 – 1.06)	1.01 (0.98 – 1.04)	0.99 (0.98 – 1.01)	1.00 (0.98 – 1.01)
Childhood cumulative exposure	26,105	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.00 (0.99 – 1.01)	1.00 (0.98 – 1.01)

[a] Model adjusted for maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, maternal atopy, gestational age, birth weight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant.
[b] Includes all variables in the "one pollutant model" plus the other pollutant in the same exposure period.

Figure S1. Summary of administrative data linkages.



849,619 mother-infant pairs were linked to population & demographic databases and OASIS database using the unique ikn number. From 849,619 mother-infant pairs, 88,447 pairs were excluded due to postal codes of residence outside Ontario (i.e. less than 1% of all pregnancies), missing date of birth, sex, 6-digit postal code value and/or exposure estimates. A total of 222,864 participants could be assigned exposure estimates to both $PM_{2.5}$ and NO_2.

Figure S2. Concentration-response curves (blue solid line) and 95% confidence intervals (grey shaded area) for the associations between NO_2 (a) and $PM_{2.5}$ (b) over the entire pregnancy and childhood asthma risk.