Spatiotemporal Variations in Ambient Ultrafine Particles and the Incidence of Childhood Asthma

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At a Glance Commentary:

Scientific Knowledge on the Subject: Ambient fine particulate matter ($PM_{2.5}$) exposure *in utero* has been associated with the development of childhood asthma. However, little is known regarding the impact of ambient ultrafine particles (<0.1 μm) (UFPs) on childhood asthma development

What this Study Adds to the Field: Our findings suggest that UFPs exposure during the second trimester of pregnancy was associated with an increased risk of developing asthma in children before age 6 independent of other air pollutants including NO_2 and $PM_{2.5}$. These findings highlight the need for further research on the effects of UFPs during the perinatal period on respiratory health in children.

Online Data Supplement: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournls.org

ABSTRACT

Rationale: Little is known regarding the impact of ambient ultrafine particles (<0.1 μm) (UFPs) on childhood asthma development. **Objective**: To examine the association between prenatal and early postnatal life exposure to UFPs and development of childhood asthma. **Methods**: A total of 160,641 singleton live births occurring in the City of Toronto, Canada between April 1st 2006 and March 31st 2012 were identified from a birth registry. Associations between exposure to ambient air pollutants and childhood asthma incidence (up to age 6) were estimated using random-effects Cox proportional hazards models, adjusting for personal- and neighborhood-level covariates. We investigated both single- and multi-pollutant models accounting for co-exposures to $PM_{2.5}$ and NO_2. **Measurements and Main Results**: We identified 27,062 children with incident asthma diagnosis during the follow-up. In adjusted models, second trimester exposure to UFPs (Hazard Ratio (HR) per interquartile (IQR) increase = 1.09, 95% CI: 1.06 - 1.12) was associated with asthma incidence. In models additionally adjusted for $PM_{2.5}$ and NO_2, UFPs exposure during the second trimester of pregnancy remained positively associated with childhood asthma incidence (HR per IQR increase = 1.05, 95% CI: 1.01 – 1.09). **Conclusion:** This is the first study to evaluate the association between perinatal exposure to UFPs and the incidence of childhood asthma. Exposure to UFPs during a critical period of lung development was linked to the onset of asthma in children, independent of $PM_{2.5}$ and NO_2.

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Key words: ultrafine particle, fine particulate matter, asthma, perinatal exposure, sensitive windows

Introduction

The prevalence of asthma in children has been increasing worldwide over the last decades (1-3). Evidence links ambient air pollution exposures during pregnancy and early life with lung function deficits in children (4-7) as well as childhood asthma incidence (8-18). While most studies have focused on traffic-related air pollutants such as nitrogen oxides (NO_x) and particulate matter (PM), there is still considerable uncertainty as to whether these pollutants are primarily responsible for the observed adverse effects. In fact, increased attention is being directed towards ultrafine particles (≤ 0.1 micrometers in diameter; UFPs), which are produced in large numbers by diesel vehicles and other combustion processes (19), but little is known regarding the impact of UFPs on childhood asthma incidence.

A small number of studies have reported positive associations between short term exposure to UFPs and respiratory health in children (20-26). However, to date, no epidemiological study has investigated the effect of longer-term exposure to UFPs during the perinatal period on the incidence of childhood asthma. Recently, a study among 8 to 11-year-old school children in Brisbane, Australia found that annual average exposure to UFPs was associated with systemic inflammation, and airway inflammation specifically among atopic individuals (27). This is consistent with the fact that UFPs can penetrate deep into peripheral airways and alveoli and, subsequently affect children's health (19). In fact, exposure to UFPs during pregnancy may impact important phases of lung development which can translate into later risk of developing asthma (10, 28-30). Therefore, additional evidence is required in order to better characterize the impact of UFPs on respiratory health in children, which can have important implications for the establishment of ambient air quality standards.

We conducted a population-based cohort study in Toronto, Canada to evaluate the association between UFP exposures during pregnancy and early postnatal life and childhood asthma incidence. We also evaluated if ambient UFPs are independently associated with childhood asthma incidence after adjusting for nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameters $\leq$2.5 μm ($PM_{2.5}$).

Methods

Study Population and Design

Data on singleton live births between April 1st 2006 and March 31st 2012 from a cohort of women who have birth in Toronto, Canada was used. We obtained mother-infant pair data from the Better Outcomes Registry & Network (BORN) Ontario, a province wide birth registry that captures perinatal health information (31). It was previously shown that 96% of all births delivered in Ontario were captured in BORN (31). In addition, ascertainment of births improved from approximately 89% of births in Ontario in the 2006–2007 fiscal year to 100% of births in the 2010–2011 and 2011–2012 fiscal years. We used the Postal Code Conversion File Plus (PCCF+) to obtain the geographic coordinates of maternal place(s) of residence based on residential postal code(s) reported in health administrative data. Linkages of health administrative data was conducted at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada using encrypted unique identifiers. We excluded from the study population pregnancies with residential postal codes outside Toronto, missing postal code value, those without a valid health card number, those with missing date of birth and those with missing sex

information. We obtained information from the BORN database on first trimester ultrasound dating and the mother's last menstrual period in order to establish gestational age.

Ascertainment of Asthma Incidence

Incident cases of childhood asthma (International Classification of Diseases [ICD]-10: J45) were identified based on a previously published case algorithm using the Ontario ASTHMA cohort database (32). We identified incidence cases between birth and < 6 years of age (10, 12) for the time period of April 1st 2006 to March 31st 2015. Pregnant mothers who had a history of asthma were identified using the Ontario ASTHMA database (33).

Exposure Assessment for Ambient Air Pollutants

Ambient air pollutant concentrations were assigned based on the geographical location(s) of each participant's residential postal codes. In Toronto, 6-character postal codes are generally represented by one side of a city block or a large apartment complex. For each pollutant, we assigned exposure during each week of pregnancy and each month of childhood from birth until the end of follow-up (i.e. date of asthma diagnosis, end of follow-up or death). Residential location changes during pregnancy and during childhood were captured using health administrative data and ambient air pollution exposure was assigned by weighting the time spent at each location.

We assigned residential exposure to ambient UFPs derived from a land use regression (LUR) model developed using mobile monitoring data collected for two weeks in the summer (September 2010) and one week in the winter (March 2011) including data from 405 road segments distributed across the city of Toronto (34). In brief, the monitoring was conducted using 3 separate vehicles equipped with rooftop monitoring devices (TSI model 3007; TSI Inc.,

Shoreview, Minnesota) measuring real-time ambient UFPs at 1-second resolution. The terms in the LUR model include the logarithm of distances to highways, major roads, the central business district, Toronto Pearson International Airport, and bus routes. The LUR model also includes variables for the numbers of on-street trees, parks and open spaces, the length of bus routes within a 100-m buffer, as well as linear and quadratic terms for ambient temperature which were found to be important determinants of temporal variations in ambient UFPs (34-37). The final model explained 67% of the variation in mean UFPs. Therefore, this model allowed us to estimate both spatial and temporal variations in outdoor UFP concentrations. Specifically, we assigned exposures during each week of pregnancy and for each month of childhood by incorporating daily average ambient temperature surfaces in our UFPs LUR model at the 6-digit postal code resolution for the city of Toronto. The surfaces were provided by the Canadian Urban Environmental Health Research Consortium (CANUE) and were developed by the Canadian Forest Service of Natural Resources Canada (38, 39).

Weekly $PM_{2.5}$ concentrations during pregnancy and monthly $PM_{2.5}$ concentrations during childhood were derived from satellite surfaces available at a 1 × 1 km resolution. Satellite surfaces were obtained based on van Donkelaar et al. (2015) that used 1 × 1 km optimal estimation (OE) aerosol optical depth (AOD) which was related to $PM_{2.5}$ with a chemical transport model and accounted for regional bias by applying a geographically weighted regression (GWR) using ground monitors for $PM_{2.5}$ (40, 41). Exposure to ambient NO_2 was based on a LUR model derived from a monitoring campaign of ground-level concentrations of NO_2 conducted in the City of Toronto (42).

We applied a temporal adjustment to the satellite-derived $PM_{2.5}$ estimates and LUR NO_2 model in order to more precisely identify exposures on a weekly basis during pregnancy and

monthly basis during childhood (18). A ratio was calculated based on weekly mean $PM_{2.5}$ and NO_2 concentrations at each ground monitor location in the City of Toronto to the long term satellite-derived and LUR model estimated concentrations for each of these monitor locations. The ambient concentrations of $PM_{2.5}$ and NO_2 at each fixed-site monitor locations were obtained from Environment Canada. Scaling surfaces were then created for each week of the study period by applying inverse distance weighting (IDW) spatial interpolation methods for each postal code located within 25km of a ground monitor. The weekly $PM_{2.5}$ and NO_2 surface concentrations were obtained by applying the scaling surfaces to the long-term estimates (43). Weekly surfaces were then used to estimate exposures during pregnancy averaged up and assigned on a monthly basis for each month after birth in order to obtain childhood exposures.

Covariates

We used information available from health administrative databases to extract the following individual-level covariates, based on prior literature (10, 12, 18): birth weight, infant sex, gestational age (in weeks), maternal age at delivery (< 20, 20-34, ≥ 35 or missing), maternal cigarette smoking anytime during pregnancy (yes, no or missing), parity (0, 1, ≥ 2), maternal breastfeeding intentions on discharge (yes, no or missing), maternal history of asthma (33) and season of birth ((winter (January to March), spring (April to June), summer (July to September) and fall (October to December)). Since we did not have individual-level socioeconomic status (SES) information, we captured SES variables from the 2006 Canadian census dissemination area (DA) data (i.e. median family income in the DA, proportion of visible minority in the DA, and percentage of female aged 25-64 years who completed postsecondary education in the DA).

Finally, we obtained estimates of exposure to green space at the residential location during pregnancy using the Normalized Difference Vegetation Index (NDVI). The NDVI is derived from satellite data and characterizes the coverage and density of green vegetation (44). Since the greenness measures were available as annual averages for each postal code, we calculated the weighted average of exposure during pregnancy using consecutive years. The NDVI has been used in prior epidemiological studies focusing in the pregnancy period (18, 45).

Statistical analysis

The associations between exposure to ambient air pollution and incidence of childhood asthma were evaluated with random-effects Cox proportional hazards models. We assigned random-effects by neighborhoods (n=140) and we assumed that any two neighborhoods were independent (46, 47). We also used random effects in order to account for clustering within families (i.e. accounting for births to the same mother) (48). Follow-up time was measured as each children's age in months from birth until any of the following: diagnosis of childhood asthma, death, becoming ineligible for provincial health insurance, movement out of Toronto, or end of follow-up. We created risk sets based on failure times (i.e. age in months) of cohort participants. Distributed lag non-linear models (DLNMs) were used to evaluate associations between ambient air pollution and childhood asthma incidence. The use of DLNMs allowed the simultaneous estimation of *exposure-response associations* and nonlinear effects across the *lag-response associations* (i.e. weekly exposures during pregnancy and monthly exposures during childhood) (49). Recent studies have used DLNMs in the context of air pollution and birth outcomes in order to identify sensitive windows of exposure and simultaneously account for potential confounding

by other time periods of exposure (50, 51). For each pollutant, DLNMs were defined through two "cross-basis" matrices, one for exposures during gestational weeks 1 to 40 and one for childhood exposures from the first month after birth until the end of follow-up. For childhood exposures, we created cross-basis matrices of exposure for each person-time observation (i.e. time varying exposure from birth until each month of follow-up during childhood). *Lag-response associations* were modeled using natural cubic splines with 4 degrees of freedom for exposure during pregnancy and using a constant-risk model during childhood. The number of degrees of freedom and models were chosen based on the Akaike information criterion (AIC) (52). The exposure-response functions were assumed to be linear, but exposure-response curves, allowing non-linearity, were evaluated for statistically significant findings in sensitivity analyses. Separate analyses were conducted for the cumulative effect estimates during the 3 trimesters of pregnancy (i.e. weeks 1-13, weeks 14-26, and weeks 27-40), the overall pregnancy (i.e. from time of conception until delivery) and for overall childhood (i.e. from birth until date of asthma diagnosis, end of follow-up or death). All models investigating the cumulative effect over each trimester and the overall pregnancy were adjusted for childhood exposures. Similarly, models investigating the cumulative effect of childhood exposures were adjusted for pregnancy exposures. After investigating the cross product of each variable with the natural logarithm of the time variable, we did not find any violations of the proportional hazards assumption ($p>0.05$). We presented findings using the hazard ratio (HR) and 95% confidence interval (CI) which corresponded to increases across the interquartile ranges (IQR) of UFPs, NO_2 and $PM_{2.5}$.

Potential confounders were evaluated in the multivariable models using covariates previously mentioned using a backward deletion approach (53). We first adjusted for all potential confounders and then removed the covariate with the largest p-value one by one in a stepwise

manner as long as the total proportional change in the hazard ratio compared with the fully adjusted model was less than 10%. Covariates that were not found to be confounders, but increased the precision of the hazard ratio were kept in the final model. We also made use of a directed acyclic graph (DAG), built using DAGitty version 2.3, to ensure proper adjustment for potential confounders. Using the DAG presented in supplementary Figure E2 and the DAG theory, we identified the minimal sufficient adjustment set of variables for estimating the direct effect of ambient air pollution exposure on development of childhood asthma. In all models, missing values for covariates were categorized as "missing" or "unknown" so that all observations were retained in the models. For example, maternal cigarette smoking status during pregnancy was categorized as "yes", "no" or "missing", for those with missing or unknown values for this variable. We also assessed potential effect modification by stratifying by maternal history of asthma status, whether pregnant women smoked during pregnancy, birth weight, gestational age and infant sex. The significance of effect modification was evaluated by specifying cross product interaction terms between each pollutant (i.e. UFPs, $PM_{2.5}$ and NO_2) and each potential effect modifier. We used Wald's method to assess the statistical significance of interaction terms (i.e. p-value for interaction less than 0.05).

Several sensitivity analyses were conducted. We stratified analyses by the child's age at diagnosis (<1 year vs. 1–5 years of age), restricted our analyses according to mothers who did not change residence during the course of their pregnancy, restricted our analyses to those with maternal information on pre-pregnancy body mass index, restricted to term births weighting over 2500 grams, and examined two- and three-pollutant models. All analyses were conducted with R (version 3.1.4), using the "coxme" and "dlnm" packages. Ethics approval for this study was

granted by the Research Ethics Boards of Health Canada and the Ottawa Health Science Network

Results

In total, 160,641 singleton live births occurred between April 1st 2006 and March 31st 2012 (Table 1). Before age 6, 27,062 children were diagnosed with asthma. Asthmatic children had a significantly smaller birth weight (3276.4 ± 588.3 vs. 3321.8 ± 530.4 grams), a shorter gestational length (38.6 +/- 2.1 vs. 38.9 +/- 1.9 weeks), were more often born to mothers with a history of asthma (7.6% vs. 4.4%) and mothers who smoked during pregnancy (4.7% vs. 4.3%) (p-values <0.001). The average age at which children were diagnosed with asthma was 2.1 years. We found that 7,960 mothers had a previous diagnosis of asthma and 26,692 mothers had multiple pregnancies.

The mean concentration of exposure to UFPs during the whole pregnancy period was 28,910 count/cm^3 (Table 2). Average exposures and IQRs for UFPs were similar across the different trimesters. Exposure to UFPs during the whole pregnancy period were not correlated with $PM_{2.5}$ (Pearson correlation coefficient, r=0.04) or NO_2 (r=0.01) (Supplementary Table E1). No correlations were observed between UFPs and the other two pollutants during each trimester of pregnancy and during childhood years ($r < 0.05$) (results not shown). In fact, weak or no correlations have also been found in previous studies evaluating health effects of UFPs in Montreal and Toronto in Canada (47, 54). We found moderate correlations between $PM_{2.5}$ and NO_2 during the full pregnancy period (r = 0.41) (Supplementary Table E1). The IQRs for UFPs,

$PM_{2.5}$ and NO_2 over the whole pregnancy period were 10,820 count/cm^3, 3.8 μg/m^3 and 9.7 ppb, respectively (Table 3).

The associations between each pollutant (i.e. UFPs, $PM_{2.5}$ and NO_2) and childhood asthma incidence are presented in Table 3. All models were mutually adjusted for the distributed lag weekly exposures of the selected pollutant during the pregnancy period, distributed lag monthly childhood exposures to the selected pollutant, maternal age at birth, infant sex, parity, breastfeeding status, maternal smoking status during pregnancy, maternal atopy, gestational age, birth weight, residential green space exposure during pregnancy, three neighbourhood-level socioeconomic status (SES) variables, a frailty term for neighbourhood in the city of Toronto, and random effects for clustering within families. UFP concentrations during the second trimester were positively associated with childhood asthma incidence [HR = 1.09; 95% CI: 1.06, 1.12 for a 10,770 count/cm^3 (IQR) increase], while associations for other time periods were close to the null and not statistically significant. We also found a linear association between UFPs during the second trimester and childhood asthma incidence when conducting an exposure-response analysis (Figure 1). Hazard ratios for exposures to $PM_{2.5}$ [HR = 1.08; 95% CI: 1.05, 1.11 for a 3.8 μg/m^3 (IQR) increase] and NO_2 [HR = 1.12; 95% CI: 1.09, 1.15 for a 9.7 ppb (IQR) increase] during the second trimester were also statistically significant. Exposure-response curves for associations between $PM_{2.5}$ and NO_2 and childhood asthma incidence are reported in supplementary Figure E1. In the multi-pollutant models adjusted for $PM_{2.5}$ and NO_2, exposure to UFPs during the second trimester remained positively associated with childhood asthma incidence (HR: 1.05; 95%CI: 1.01-1.09) (Table 4). The independent effect of $PM_{2.5}$ and NO_2 remained statistically significant after adjustment for the other pollutants (Supplemental Tables

E2 & E3). In the stratified analyses, we did not observe statistically significant effect modification by the selected characteristics (Supplementary Table E4).

In the sensitivity analyses, the stratification of hazard ratios by the child's age at diagnosis of asthma (<1 year vs. 1–5 years of age) did not reveal any significant differences (results not shown). However, the hazard ratios limited to children <1 year were not statistically significant. In addition, restricting our analyses to mothers who did not move residences during pregnancy did not materially alter the results (results not shown). Additional adjustment for maternal pre-pregnancy body mass index (BMI) in a subset of our cohort (i.e. about 20% of our cohort had BMI information) did not change the hazard ratios (results not shown). Finally, hazard ratios were materially unchanged when we restricted our analyses to term births over 2500 grams (Supplemental Table E5).

Discussion

A small number of studies have reported respiratory health effects in children following short-term exposure to UFPs (20-26). In this study, we evaluated associations between gestational and early life exposures to UFPs and childhood asthma incidence. Our findings suggest that exposure to UFPs during the second trimester increases risk of asthma incidence in children up to age 6. These findings remained positive after adjustment for $PM_{2.5}$ and NO_2 in multi-pollutant models.

Several epidemiological studies have reported positive associations between exposure to air pollution and incidence of childhood asthma (4-18). Among those studies, some reported associations between exposure to air pollution, in particular $PM_{2.5}$ and to a lesser extent NO_2,

during the prenatal period and asthma onset in children (10, 14, 15). Despite the documented effects of particulate air pollution on childhood asthma incidence and concerns that UFPs might be more toxic than the larger particulate matter, the effects of UFPs on asthma onset in children are not well studied. Previous research has primarily focused on the short-term effects of UFPs on respiratory health in children with studies reporting associations between UFPs and wheezing symptoms (21, 22), current asthma (26), spirometry and exhaled nitric oxide measurements (23) and health care utilization-related visits for respiratory outcomes (25). A recent cross-sectional study conducted among 655 children aged 8 to 11 years in the Brisbane Metropolitan Area, Australia, found that annual average exposure to UFP was associated with systemic inflammation, as measured by serum C-reactive protein (CRP). In addition, UFP exposure was associated with airway inflammation in atopic children (27).

The vulnerable weeks of exposure to air pollution identified in this study correspond to important phases (i.e. late pseudoglandular and canicular phases) of lung development during the fetal period (55). In fact, a number of important functions and tissues are developing during those phases including the development of airways, airway epithelium differentiation and immune modulators secretion (28). The immune and respiratory systems of the developing fetus may be affected by increases in inflammation and increased sensitivity of the airways following exposure to ambient air pollution (56), enhancing susceptibility to asthma (10, 28-30). Indeed, our findings suggesting an association between UFP exposures during the second trimester of pregnancy and childhood asthma incidence are generally in agreement with prior studies on other air pollutants including $PM_{2.5}$ and NO_2. Specifically, we previously reported that exposures to $PM_{2.5}$ and NO_2 during the second trimester of pregnancy were associated with childhood asthma incidence (18). In a study conducted in Boston, Massachusetts, authors found that exposure to

$PM_{2.5}$ during pregnancy was associated with asthma incidence in children by age 6 years only during weeks corresponding to the second trimester of pregnancy (10, 15). In addition, results based on 2,598 children enrolled in a study in China found that second trimester exposure to NO_2 was associated with asthma incidence (OR = 1.72, 95% CI: 1.02, 2.97) (14). Morales et al. also showed that exposure to NO_2 during the second trimester was associated with a reduction in lung functions measured at 4.5 years of age (4). Therefore, our findings related to second trimester exposure to UFPs and childhood asthma incidence are generally consistent with prior literature and corresponds to an important time-period for the developing respiratory system.

Several limitations of this analysis should be noted. First, our UFPs and NO_2 exposures estimates for the time period were assigned using LUR models based on data collected from short-term monitoring campaigns using a temporal scaling adjustment in order to capture different periods of exposure. We were therefore unable to obtain spatial-temporal ground estimates measured across the City of Toronto due to technological challenges and high costs. However, we applied previously published methods in order to capture as accurately as possible temporal changes in UFPs and NO_2 (34, 43). Secondly, we need to acknowledge that there may be potential residual confounding. For instance, no individual-level information was available for income, education, ethnicity and maternal stress levels. While we were able to conduct a sensitivity analysis using pre-pregnancy body mass index information in a subset of our population, we did not have information on maternal gestational weight gain, an important risk factor for childhood asthma development (57). However, controlling for some neighbourhood-level SES factors may have partially accounted for these missing variables. In addition, we did not have information on asthma phenotypes, asthma severity in children and medications to treat or control asthma during the pregnancy period.

To our knowledge, this is the first study to examine the effects of prenatal and early postnatal exposure to UFPs on childhood asthma incidence. Some of the strengths of this study include the air pollution exposure estimates that captured both spatial and temporal variation, the large sample size and the residential mobility information during pregnancy. We also identified incident cases using province-wide registries and validated algorithms with high sensitivity and specificity. The risk of selection bias was likely reduced due to the population-based approach we used.

In this large population-based study, we found that exposure to UFPs during the second trimester of pregnancy was associated with an increased risk of developing asthma in children before age 6 independent of other air pollutants including NO_2 and $PM_{2.5}$. These findings reinforce the importance of conduction further research on the effects of UFPs during the perinatal period on respiratory health in children.

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Figure legend

Figure 1. Exposure-response curve using natural cubic splines with 3 degrees of freedom for the association between exposure to UFPs during the second trimester of pregnancy and childhood asthma incidence in Ontario, Canada (2006 – 2012). Middle line reflects point estimates and upper and lower lines reflect 95% confidence intervals. The reference concentration by which the hazard ratios are computed is 29000 cm^3 (approximately median value). Model mutually adjusted for the distributed lag weekly exposures of the selected pollutant during the pregnancy period, distributed lag monthly exposures after birth to the selected pollutant, 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, a frailty term for neighbourhood in the city of Toronto and random effects for clustering within families..

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

Characteristics	Total cohort	Asthmatic children	Non-asthmatic children
n	160,641	27,062	133,579
Maternal age	30.0 (5.5)	30.1 (5.53)	30.0 (5.5)
Gestational length (weeks)	38.8 (1.8)	38.6 (2.1)	38.9 (1.8)
Birth weight (grams)	3314.1 (540.9)	3276.4 (588.3)	3321.8 (530.4)
Infant sex			
Male	82,709 (51.5)	16,434 (60.7)	66,275 (49.6)
Female	77,932 (48.5)	10,628 (39.3)	67,304 (50.4)
Parity			
0	92,252 (57.4)	14,811 (54.7)	77,441 (58.0)
1	48,679 (30.3)	8,602 (31.8)	40,077 (30.0)
≥ 2	19,710 (12.3)	3,649 (13.5)	16,061 (12.0)
Intention to breastfeed			
Yes	133,006 (82.8)	21,946 (81.1)	111,060 (83.1)
No	7,991 (5.0)	1,429 (5.3)	6,562 (4.9)
Missing	19,644 (12.2)	3,687 (13.6)	15,957 (11.9)
Maternal smoking status during pregnancy			
Yes	6,961 (4.3)	1,270 (4.7)	5,691 (4.3)
No	137,365 (85.5)	22,740 (84.0)	114,625 (85.8)
Missing	16,315 (10.2)	3,052 (11.3)	13,263 (9.9)
Maternal asthma			
Yes	7,960 (5.0)	2,065 (7.6)	5,895 (4.4)
No	152,681 (95.0)	24,997 (92.4)	127,684 (95.6)
Median family income			
Quintile 1	31,879 (19.8)	5,726 (21.2)	26,153 (19.6)
Quintile 2	31,897 (19.9)	5,575 (20.6)	26,322 (19.7)
Quintile 3	31,927 (19.9)	5,332 (19.7)	26,595 (19.9)
Quintile 4	31,926 (19.9)	4,609 (17.0)	27,317 (20.5)
Quintile 5	984 (0.6)	117 (0.4)	867 (0.6)
Missing	31,879 (19.8)	5,726 (21.2)	26,153 (19.6)
Percent of females completed postsecondary education (age 25+)			
Quintile 1	22,856 (19.5)	5,085 (21.8)	27,941 (19.9)
Quintile 2	22,798 (19.5)	5,048 (21.6)	27,846 (19.8)
Quintile 3	23,458 (20.1)	4,645 (19.9)	28,103 (20.0)
Quintile 4	23,161 (19.8)	4,492 (19.2)	27,653 (19.7%)
Quintile 5	23,914 (20.4)	3,970 (17.0)	27,884 (19.9%)
Missing	776 (0.7)	102 (0.4)	878 (0.6%)
Percent visible minority			
Quintile 1	27,103 (20.3)	4,780 (17.7)	31,883 (19.8)
Quintile 2	26,944 (20.2)	4,996 (18.5)	31,940 (19.9)
Quintile 3	26,430 (19.8)	5,454 (20.2)	31,884 (19.8)
Quintile 4	26,385 (19.8)	5,561 (20.5)	31,946 (19.9)
Quintile 5	25,788 (19.3)	6,139 (22.7)	31,927 (19.9)
Missing	929 (0.7)	132 (0.5)	1,061 (0.7)

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

Table 2. Descriptive statistics of UFPs and Pearson correlation coefficients across time periods.

				UFP (count/cm^3)				
	Mean	SD	IQR	1st trimester	2nd trimester	3rd trimester	Pregnancy average	Childhood cumulative exposure
UFP (count/cm^3)								
1st trimester	28,905	9,145	10,862	1.00				
2nd trimester	28,953	9,151	10,770	0.66	1.00			
3rd trimester	28,870	9,154	10,853	0.62	0.63	1.00		
Pregnancy average	28,910	9,150	10,820	0.59	0.62	0.69	1.00	
Childhood cumulative exposure	27,504	9,145	10,551	0.55	0.54	0.64	0.61	1.00

Table 3. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between UFPs (per IQR), $PM_{2.5}$ (per IQR) and NO_2 (per IQR) over specific periods and childhood asthma risk.

Exposure period	UFPs		$PM_{2.5}$		NO_2	
	IQR (count/cm^3)	Adjusted model[a] HR (95% CI)	IQR (in µg/m3)	Adjusted model[a] HR (95% CI)	IQR (in ppb)	Adjusted model[a] HR (95% CI)
1st trimester	10,862	1.01 (0.97 – 1.05)	3.8	1.00 (0.97 – 1.03)	9.8	1.02 (0.98 – 1.06)
2nd trimester	10,770	1.09 (1.06 – 1.12)	3.8	1.08 (1.05 – 1.11)	9.7	1.12 (1.09 – 1.15)
3rd trimester	10,853	1.04 (1.00 – 1.08)	3.7	1.03 (0.99 – 1.06)	9.6	1.01 (0.98 – 1.05)
Entire pregnancy	10,820	1.03 (0.99 – 1.07)	3.8	1.03 (1.00 – 1.06)	9.7	1.02 (0.98 – 1.06)
Childhood exposure	10,551	1.03 (1.00 – 1.06)	3.4	1.02 (0.99 – 1.05)	8.7	1.01 (0.97 – 1.05)

[a] Model mutually adjusted for the distributed lag weekly exposures of the selected pollutant during the pregnancy period, distributed lag monthly exposures after birth to the selected pollutant, 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,a frailty term for neighbourhood in the city of Toronto and random effects for clustering within families.
IQR, interquartile range

Table 4. Hazard ratios[a] (HR) and 95% confidence intervals (95% CI) for the associations between UFPs (per IQR) over specific periods and childhood asthma risk with additional adjustment for $PM_{2.5}$ and NO_2.

Exposure period	IQR (count/cm^3)	UFPs + $PM_{2.5}$	UFPs + NO_2	UFPs + $PM_{2.5}$ + NO_2
		HR (95% CI)[b]	HR (95% CI)[b]	HR (95% CI)[b]
1st trimester	10,862	0.99 (0.96 – 1.02)	1.00 (0.97 – 1.03)	1.01 (0.97 – 1.05)
2nd trimester	10,770	1.07 (1.04 – 1.10)	1.02 (0.98 – 1.06)	1.05 (1.01 – 1.09)
3rd trimester	10,853	1.02 (0.99 – 1.06)	1.00 (0.96 – 1.04)	1.01 (0.97 – 1.05)
Entire pregnancy	10,820	1.01 (0.99 – 1.04)	1.00 (0.97 – 1.03)	1.01 (0.98 – 1.04)
Childhood cumulative exposure	10,551	1.01 (0.97 – 1.04)	0.99 (0.96 – 1.02)	1.00 (0.97 – 1.04)

[a] Model mutually adjusted for the distributed lag weekly exposures of the selected pollutant during the pregnancy period, distributed lag monthly exposures after birth to the selected pollutant, 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, a frailty term for neighbourhood in the city of Toronto and random effects for clustering within families.

[b] Includes adjustment for the other pollutant(s) in the same exposure period.

IQR, interquartile range

Figure 1. Exposure-response curve using natural cubic splines with 3 degrees of freedom for the association between exposure to UFPs during the second trimester of pregnancy and childhood asthma incidence in Ontario, Canada (2006 – 2012).