



# Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema

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**This study found that exposure to total oxidants at birth increased the risk of developing asthma by 17% and eczema by 7%. Adverse impacts of exposure to air pollutants, particularly ozone and nitrogen dioxide, may have their origins in early life.** <http://bit.ly/33PCIYN>

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## ABSTRACT

**Rationale:** There is growing evidence that air pollution may contribute to the development of childhood asthma and other allergic diseases. In this follow-up of the Toronto Child Health Evaluation Questionnaire (T-CHEQ) study, we examined associations between early life exposures to air pollution and incidence of asthma, allergic rhinitis and eczema from birth through adolescence.

**Methods:** 1286 T-CHEQ participants were followed from birth until outcome (March 31, 2016) or loss to follow-up, with a mean of 17 years of follow-up. Concentrations of nitrogen dioxide (NO<sub>2</sub>), ozone (O<sub>3</sub>) and particulate matter with a 50% cut-off aerodynamic diameter of 2.5 µm (PM<sub>2.5</sub>) from January 1, 1999 to December 31, 2012 were assigned to participants based on their postal codes at birth using ground observations, chemical/meteorological models, remote sensing and land-use regression models. Study outcomes included incidence of physician-diagnosed asthma, allergic rhinitis and eczema. Cox proportional hazard regression models were used to estimate hazard ratios per interquartile range of exposures and outcomes, adjusting for potential confounders.

**Results:** Hazard ratios of 1.17 (95% CI 1.05–1.31) for asthma and 1.07 (95% CI 0.99–1.15) for eczema were observed for total oxidants (O<sub>3</sub> and NO<sub>2</sub>) at birth. No significant increase in risk was found for PM<sub>2.5</sub>.

**Conclusions:** Exposures to oxidant air pollutants (O<sub>3</sub> and NO<sub>2</sub>) but not PM<sub>2.5</sub> were associated with an increased risk of incident asthma and eczema in children. This suggests that improving air quality may contribute to the prevention of asthma and other allergic disease in childhood and adolescence.

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## Introduction

Earlier studies have shown that immunological development and maturation starts during pregnancy and continues during early childhood [1]. Health risks from exposures at birth may serve as a surrogate indicator of exposures throughout pregnancy. Exposures during the first 3 years of life represent a critical period of immune development that may modify immune responses and cells, and thus influence the risk of allergies and other immune diseases later in life. Recent systematic reviews by KHREIS *et al.* [2] and BOWATTE *et al.* [3] suggested that childhood exposure to traffic-related air pollution (TRAP) contributes to the development of asthma. Assessing exposures both at birth and during early life is therefore important.

While a number of studies have examined the longitudinal association between childhood air pollution exposure and incidence of asthma or other allergic diseases [3–8], few have investigated this association into late adolescence. Furthermore, fewer have examined independent or concurrent associations with other environmental exposures such as greenness [9]. Thus, a gap in evidence exists on longitudinal studies of how air pollution may affect the development and persistence of new and prevalent cases of asthma and other allergic conditions (*e.g.* allergic rhinitis and eczema) in the adolescent population.

The Toronto Child Health Evaluation Questionnaire (T-CHEQ) study in Canada established a population-based cohort of 5619 grade 1 and 2 (aged 5–9 years) Toronto school children in 2006 using modified International Study of Asthma and Allergies in Childhood (ISAAC) methodology [10]. Parent-reported lifetime asthma prevalence in this population of Toronto children was high (16.1%) [10]. This study reported that nitrogen dioxide (NO<sub>2</sub>), a surrogate measure of TRAP exposure, was associated with the development and persistence of asthma in early childhood [11, 12]. In the 2006 T-CHEQ survey, participants were asked to provide permission/consent to use their unique Health Card Number (HCN) for data linkage in future research. The consented T-CHEQ participants who were born in Ontario were linked to the Ontario population-based health administrative databases. It has been suggested ozone (O<sub>3</sub>) and NO<sub>2</sub> can trigger an oxidative stress process in the lungs which can lead to cell death, inflammation, injury and loss of function [13]. Therefore, in addition to measuring the associations between individual air pollutant and disease risks, our current study also estimated the impact of these pollutants together as total oxidants. With this linked birth cohort, we aimed 1) to determine the incidence of asthma and other common allergic conditions (allergic rhinitis, eczema) in children through prospective follow-up from birth to adolescence, and 2) to examine the associations between air pollution and incidence of asthma and other allergic diseases.

## Methods

### *Study population and data linkage*

The original T-CHEQ study included 5619 grade 1 and 2 school children aged 5–9 years who were recruited in 2006 from 283 randomly sampled public schools in Toronto (ON, Canada) to participate in the survey. About half of the T-CHEQ participants (n=2735 (48.7%)) gave consent to use their unique HCN for future data linkage, and 1286 of them were born in Ontario, were successfully linked to the Ontario Registered Persons Database housed at the Institute for Clinical Evaluative Sciences (ICES) and had complete data on all covariates. These children made up the T-CHEQ birth cohort for this study. More details can be found in the supplementary material.

### *Measures*

#### *Outcome measures*

Children and youths were classified as having incident asthma by International Classification of Disease (ICD) codes (ICD-9: 493 and ICD-10: J45, J46) if they had: one or more asthma hospital admissions or two or more asthma Ontario Health Insurance Plan (OHIP) claims for physician services in 2 consecutive years (where the first claim is considered the diagnosis date). This case definition has been validated with 84% sensitivity and 76% specificity [14]. Allergic rhinitis (ICD-9: 477 and ICD-10: J301–J304) and eczema (ICD-9: 691.8 and ICD-10: L20) were identified by any physician health services claim for these conditions by their respective ICD codes. With the unique HCN, the T-CHEQ participants who met the inclusion criteria were traced back to their birth records to recreate the birth cohort for this study. All children in this study were followed prospectively from birth to their index date of outcomes of interest, death, end of study or loss to follow-up. The health administrative databases used in this study included the National Ambulatory Care Reporting System (emergency department visits), the Canadian Institute for Health Information Discharge Abstract Database (hospital admissions) and the OHIP Claims Database (physician outpatient claims), to capture health services use.

#### *Air pollution exposures*

The Ontario Registered Persons Database (RPDB) was used to compile the history of residential address of the birth cohort from birth to the end of the study. Given the peak incidence of asthma and other allergic

disease in early childhood [15], we focused on air pollution exposures at baseline (birth) and early life (0–3 years of age). The exposures in the first 3 years of life were calculated based on all reported addresses during the first 3 years of life.

#### Pollutants

Particulate matter with a 50% cut-off aerodynamic diameter of 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) exposures were derived from total column aerosol depth retrievals from the Moderate Resolution Imaging Spectroradiometer (MODIS) that were related to near-surface  $\text{PM}_{2.5}$  using the GEOS-Chem chemical transport model and adjusted with local ground-based observations through geographically weighted regression [16].  $\text{NO}_2$  exposures were estimated from a temporally adjusted national land-use regression model that combined National Air Pollution Surveillance (NAPS) fixed-site monitoring data, satellite  $\text{NO}_2$  estimates, road length within 10 km, industrial land-use areas within various buffers and summer rainfall [17]. Ozone exposures were estimated for the months of May to October (8 h daily maximum) using a temporally adjusted model combining modelled  $\text{O}_3$  from the Canadian Hemispheric Regional Ozone and  $\text{NO}_x$  system (CHRONOS) operational regional air quality forecast model [18] with ground-based observations from monitors in Canada and the USA [19]. In addition to individual pollutants, we also employed total oxidants as a composite measure, with pollutant weights equivalent to their respective redox potentials (total oxidants =  $((1.07 \times \text{NO}_2) + (2.075 \times \text{O}_3)) / 3.145$ ) [20]. Exposure surface concentrations of air pollution were then assigned to participants using the centroids of their postal codes at birth and cumulated from birth onwards. The  $\text{PM}_{2.5}$  estimates showed good agreement ( $R^2=0.82$ ) with monitors over North America; the  $\text{NO}_2$  land-use regression model explained 74% of the variability in fixed-site monitoring concentrations and 43% of within-city  $\text{NO}_2$  concentrations from an independent dataset measured using Ogawa passive samplers in seven Canadian cities [17].

#### Greenness

The Normalised Difference Vegetation Index (NDVI) Landsat Time Series was used to measure greenness [16–19]. Annual NDVI metrics were linked to all six-digit DMTI Spatial single postal code locations and surrounding areas within 100 m [9]. NDVI values typically range from  $-1$  to  $+1$ , where  $-1$  represents water, 0 corresponds to bare surfaces (e.g. rock, sand, rooftops and roads) and  $+1$  represents healthy green vegetation [21]. The greenness data surfaces for Ontario from 1996 to 2015 were obtained from the Canadian Urban Environmental Health Research Consortium (CANUE) (<https://canue.ca>). More details can be found in the supplementary material.

#### Covariates

There were three domains of covariates collected by the 2006 T-CHEQ survey: child, parental/demographic and home environmental factors. Child factors include age, sex, low birthweight ( $<2500$  g), prematurity ( $<37$  weeks gestation), breastfeeding and enrolment in childcare. Parental/demographic factors include parental asthma and atopy, parental education level, and income adequacy. Home environmental factors include crowding (number of people living in household) and home exposures during first year of life (damp spots, use of gas to cook or heat, exposure to environmental tobacco smoke, pets, cockroaches and mould in the home). More details can be found in the supplementary material.

#### Statistical analysis

The number and proportion of children who developed asthma, allergic rhinitis or eczema were stratified by child, parental/demographic and home environmental factors to compare children who developed these outcomes of interest with those who did not. Chi-squared tests were used to assess differences in proportions by group where a p-value of  $<0.05$  indicates a statistically significant difference. The relationship between outcomes of interest and exposure was examined using the Cox proportional hazards regression model. All hazard ratios were presented with 95% confidence intervals and were calculated per pollutant/NDVI interquartile range (IQR). The Cox proportional hazards regression models were repeated for exposures: at birth, averaged over the first 3 years of life and by three health outcomes (asthma, allergic rhinitis and eczema). All three domains of covariates (child, parental/demographic and home environmental factors) were included in the multivariable Cox proportional hazards regression models to adjust for potential confounding. Plots of the Martingale-based residuals were examined to check for evidence of violation of the proportional hazards assumption [22]. Covariates that did not meet the proportional hazards assumption were removed from the regression model. None of the covariates kept in the final Cox models violated the proportional hazards assumption.

We used Moran's  $I$  to measure the overall spatial autocorrelation and to test for clustering of exposures and cases. Our Moran's  $I$ -values on air pollutants and cases were all  $<0.2$  (close to 0) indicating no autocorrelation.

We also modelled NO<sub>2</sub> and O<sub>3</sub> together as total oxidants, and examined the hazards of PM<sub>2.5</sub> and outcomes stratifying by tertile of total oxidants [23], an approach suggested by WEICHTHAL *et al.* [23], which showed that PM<sub>2.5</sub> was associated with mortality in the highest tertile of the hazard ratios of oxidants but not in lower tertiles. All analyses were carried out using SAS Enterprise guide 6.1 (SAS Institute, Cary, NC, USA).

**Ethics approval**

Ethics approval for this study was obtained from the Hospital for Sick Children and Health Canada Research Ethics Boards (Toronto and Ottawa, ON, Canada, respectively). Individual informed study consent was received from each study participant’s parent or guardian at the time of participation in the T-CHEQ survey, and permission was given for the HCN to be used for data linkage.

**Results**

1286 children were linked to birth records and health administrative databases using their unique HCN. They were born between 1996 and 2001, and were followed to March 31, 2016, for an average of 17 years.

**Descriptive statistics**

Figure 1 shows that among the 1286 children, 28.5% had asthma (n=366), 39.7% had allergic rhinitis (n=511) and 74.5% had eczema (n=958), while nearly 14% (n=177) had all three conditions. Only 2.3% had asthma alone (n=30) and 12.4% had asthma and either allergic rhinitis or eczema (n=159). Table 1 compares child, parent/demographic and home environmental factors among children who had asthma, allergic rhinitis and eczema with those who did not. A higher proportion of children with asthma compared with children who did not have asthma were born with low birthweight (9.0% versus 5.8%; p=0.035), were male (62.0% versus 49.2%; p<0.001), were not breastfed (11.5% versus 6.4%; p=0.002) and had a parental history of asthma (28.7% versus 19.5%; p<0.001). Conversely, a lower proportion of children with asthma had pets in their home in the first year of life (31.1 versus 38.0%; p=0.02). Similar patterns were observed comparing children with allergic rhinitis with those without and children with eczema with those without (table 1).

**Mean levels of exposures**

Table 2 shows the mean distributions of exposures to pollutants and greenness at birth and averaged over the first 3 years of life. The levels did not differ significantly between those with versus without asthma, allergic rhinitis or eczema. Furthermore, the mean levels of pollutants at birth did not differ significantly from those averaged over the first 3 years of life. Table 3 shows correlations among exposures. O<sub>3</sub> and NO<sub>2</sub> at birth were strongly negatively correlated, while O<sub>3</sub> and PM<sub>2.5</sub> at birth were moderately positively correlated, and NO<sub>2</sub> and PM<sub>2.5</sub> at birth were weakly negatively correlated. With the exception of O<sub>3</sub> and NO<sub>2</sub>, correlations were weaker based on exposures over the first 3 years.

<b>Asthma</b>	
Asthma only	30 (2.3)
Asthma+allergic rhinitis	28 (2.2)
Asthma+eczema	131 (10.2)
Asthma+allergic rhinitis+eczema	177 (13.8)
Total asthma	366 (28.5)
<b>Allergic rhinitis</b>	
Allergic rhinitis only	66 (5.1)
Allergic rhinitis+asthma	28 (2.2)
Allergic rhinitis+eczema	240 (18.7)
Allergic rhinitis+asthma+eczema	177 (13.8)
Total allergic rhinitis	511 (39.7)
<b>Eczema</b>	
Eczema only	410 (31.9)
Eczema+asthma	131 (10.2)
Eczema+allergic rhinitis	240 (18.7)
Eczema+asthma+allergic rhinitis	177 (13.8)
Total eczema	958 (74.5)

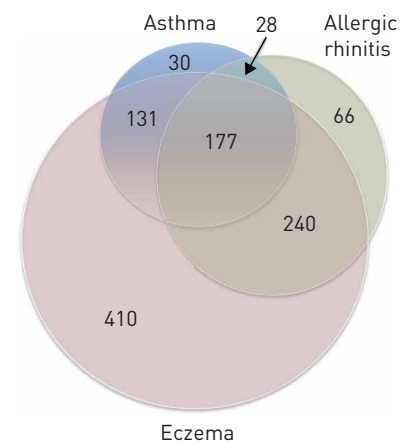


FIGURE 1 Distribution of asthma, allergic rhinitis and eczema in the study cohort. Data are presented as n (%) or n. Groups are not mutually exclusive. Percentages are calculated of the total.

TABLE 1 Distribution of covariates by prevalence of asthma, allergic rhinitis and eczema in the study cohort

	Asthma			Allergic rhinitis			Eczema		
	With	Without	p-value	With	Without	p-value	With	Without	p-value
<b>Subjects</b>	366	920		511	775		958	328	
<b>Child factors</b>									
Sex									
Female	139 (38.0)	467 (50.8)	<0.001	216 (42.3)	390 (50.3)	0.005	438 (45.7)	168 (51.2)	0.085
Male	227 (62.0)	453 (49.2)		295 (57.7)	385 (49.7)		520 (54.3)	160 (48.8)	
Child age at survey years									
Mean±SD	6.70±0.67	6.67±0.63	0.383	6.67±0.63	6.68±0.65	0.825	6.69±0.65	6.66±0.62	0.462
Median (IQR)	7.00 (6.00–7.00)	7.00 (6.00–7.00)	0.498	7.00 (6.00–7.00)	7.00 (6.00–7.00)	0.915	7.00 (6.00–7.00)	7.00 (6.00–7.00)	0.578
Child age at asthma, allergic rhinitis or eczema years									
Mean±SD	3.33±3.60	NA		6.31±4.41	NA		2.89±4.12	NA	
Median (IQR)	2.00 (1.00–5.00)			5.00 (3.00–10.00)			1.00 (0.00–4.00)		
Low birthweight (<2500 g)	33 (9.0)	53 (5.8)	0.006	33 (6.5)	53 (6.8)	0.789	68 (7.1)	18 (5.5)	0.314
Born within 3 weeks of the calculated date	37 (10.1)	60 (6.5)	0.028	38 (7.4)	59 (7.6)	0.907	77 (8.0)	20 (6.1)	0.251
Child breastfed	324 (88.5)	861 (93.6)	0.002	460 (90.0)	725 (93.5)	0.021	880 (91.9)	305 (93.0)	0.512
Child ever attend a childcare facility/nursery school	232 (63.4)	629 (68.4)	0.087	322 (63.0)	539 (69.5)	0.015	640 (66.8)	221 (67.4)	0.849
Time to asthma, allergic rhinitis, eczema or end of follow-up years									
Mean±SD	3.80±3.61	17.00±1.84	<0.001	6.79±4.43	16.95±2.00	<0.001	3.32±4.17	16.85±2.24	<0.001
Median (IQR)	2.42 (1.06–5.52)	17.22 (16.70–17.76)	<0.001	5.98 (3.29–10.28)	17.20 (16.68–17.75)	<0.001	1.42 (0.44–4.75)	17.22 (16.66–17.75)	<0.001
<b>Parental/demographic factors</b>									
Income adequacy									
Lowest	37 (10.1)	65 (7.1)	<0.001	51 (10.0)	51 (6.6)	<0.001	88 (9.2)	14 (4.3)	0.006
Lower middle	53 (14.5)	98 (10.7)		86 (16.8)	65 (8.4)		117 (12.2)	34 (10.4)	
Upper middle	93 (25.4)	163 (17.7)		94 (18.4)	162 (20.9)		197 (20.6)	59 (18.0)	
Highest	183 (50.0)	594 (64.6)		280 (54.8)	497 (64.1)		556 (58.0)	221 (67.4)	
People in the household n									
≤3	50 (13.7)	126 (13.7)	0.997	79 (15.5)	97 (12.5)	0.076	138 (14.4)	38 (11.6)	0.433
4	186 (50.8)	467 (50.8)		256 (50.1)	397 (51.2)		489 (51.0)	164 (50.0)	
≥5	130 (35.5)	327 (35.5)		176 (34.4)	281 (36.3)		331 (34.6)	126 (38.4)	
Parent's highest level of education									
Some college or below	100 (27.3)	205 (22.3)	0.02	147 (28.8)	158 (20.4)	<0.001	246 (25.7)	59 (18.0)	0.001
College diploma	87 (23.8)	178 (19.3)		116 (22.7)	149 (19.2)		205 (21.4)	60 (18.3)	
University degree	130 (35.5)	341 (37.1)		172 (33.7)	299 (38.6)		349 (36.4)	122 (37.2)	
Master/doctorate	49 (13.4)	196 (21.3)		76 (14.9)	169 (21.8)		158 (16.5)	87 (26.5)	
Either of the parents ever had asthma	105 (28.7)	179 (19.5)	<0.001	132 (25.8)	152 (19.6)	0.009	215 (22.4)	69 (21.0)	0.596
Parental history of atopy	217 (59.3)	496 (53.9)	0.08	291 (56.9)	422 (54.5)	0.378	537 (56.1)	176 (53.7)	0.451
<b>Home environmental factors</b>									
Mould in home in first year of life	34 (9.3)	65 (7.1)	0.177	42 (8.2)	57 (7.4)	0.569	78 (8.1)	21 (6.4)	0.308
Cockroaches in home in first year of life	32 (8.7)	59 (6.4)	0.141	42 (8.2)	49 (6.3)	0.194	76 (7.9)	15 (4.6)	0.041
Gas cook/heat in first year of life	261 (71.3)	704 (76.5)	0.051	357 (69.9)	608 (78.5)	<0.001	707 (73.8)	258 (78.7)	0.079
ETS exposure in first year of life	32 (8.7)	62 (6.7)	0.213	36 (7.0)	58 (7.5)	0.767	74 (7.7)	20 (6.1)	0.329
Pets in home in first year of life	114 (31.1)	350 (38.0)	0.02	159 (31.1)	305 (39.4)	0.003	337 (35.2)	127 (38.7)	0.249

Data are presented as n (%), unless otherwise stated. IQR: interquartile range; ETS: environmental tobacco smoke.

TABLE 2 Mean distributions of exposures to air pollution and greenness at birth and averaged over the first 3 years of life

	Asthma	Non-asthma	Allergic rhinitis	Non-allergic rhinitis	Eczema	Non-eczema
<b>Subjects</b>	366 (28.5)	920 (71.5)	511 (39.7)	775 (60.3)	958 (74.5)	328 (25.5)
<b>NO<sub>2</sub> ppb</b>						
At birth						
Mean±SD	27.00±4.95	26.31±4.45	26.55±4.44	26.48±4.71	26.68±4.64	25.99±4.46
Median (IQR)	27.03 (24.77–29.24)	26.50 (24.54–28.56)	26.73 (24.56–28.81)	26.59 (24.61–28.68)	26.73 (24.71–28.94)	26.37 (24.03–28.21)
Averaged over first 3 years						
Mean±SD	26.45±4.57	26.01±4.32	26.07±4.22	26.18±4.51	26.28±4.40	25.70±4.35
Median (IQR)	26.53 (24.38–28.52)	26.24 (24.17–28.08)	26.27 (24.06–28.22)	26.29 (24.38–28.24)	26.37 (24.38–28.42)	26.01 (23.76–27.70)
<b>O<sub>3</sub> ppb</b>						
At birth						
Mean±SD	43.63±1.72	43.61±1.52	43.67±1.60	43.58±1.57	43.60±1.58	43.65±1.59
Median (IQR)	43.26 (42.41–44.26)	43.39 (42.53–44.24)	43.36 (42.52–44.32)	43.34 (42.49–44.20)	43.32 (42.51–44.23)	43.40 (42.52–44.29)
Averaged over first 3 years						
Mean±SD	43.75±1.61	43.71±1.49	43.78±1.54	43.68±1.51	43.71±1.52	43.75±1.52
Median (IQR)	43.37 (42.60–44.38)	43.48 (42.69–44.35)	43.52 (42.69–44.42)	43.44 (42.62–44.30)	43.44 (42.66–44.34)	43.47 (42.65–44.38)
<b>PM<sub>2.5</sub> mg·m<sup>-3</sup></b>						
At birth						
Mean±SD	10.04±2.29	10.21±2.14	10.08±2.29	10.22±2.11	10.16±2.19	10.18±2.18
Median (IQR)	10.63 (8.60–11.80)	10.80 (8.70–11.80)	10.70 (8.60–11.80)	10.80 (8.70–11.90)	10.70 (8.70–11.80)	10.80 (8.70–11.80)
Averaged over first 3 years						
Mean±SD	10.82±1.44	10.90±1.28	10.83±1.36	10.91±1.31	10.88±1.35	10.87±1.25
Median (IQR)	11.00 (10.13–11.80)	11.10 (10.33–11.73)	10.97 (10.13–11.70)	11.15 (10.33–11.80)	11.13 (10.23–11.80)	11.00 (10.33–11.71)
<b>NDVI (postal code)</b>						
At birth						
Mean±SD	0.32±0.11	0.33±0.11	0.32±0.10	0.34±0.12	0.33±0.11	0.34±0.11
Median (IQR)	0.32 (0.25–0.40)	0.33 (0.26–0.41)	0.32 (0.25–0.39)	0.34 (0.27–0.41)	0.32 (0.26–0.40)	0.34 (0.26–0.41)
Averaged over first 3 years						
Mean±SD	0.34±0.10	0.35±0.11	0.34±0.10	0.36±0.11	0.34±0.10	0.36±0.11
Median (IQR)	0.35 (0.27–0.41)	0.35 (0.29–0.43)	0.34 (0.27–0.41)	0.36 (0.29–0.43)	0.35 (0.28–0.42)	0.36 (0.28–0.43)

NO<sub>2</sub>: nitrogen dioxide; IQR: interquartile range; O<sub>3</sub>: ozone; PM<sub>2.5</sub>: particulate matter with a 50% cut-off aerodynamic diameter of 2.5 µm; NDVI: Normalised Difference Vegetation Index.

**Hazard ratios from Cox regression models**

The results of single- and multi-pollutant adjusted Cox proportional hazards regression models are shown in table 4 and figure 2. All regression models were fully adjusted for child, parental/demographic and home environmental factors (detailed in the Methods section). Exposure to O<sub>3</sub> at birth was not associated with asthma, allergic rhinitis or eczema in single-pollutant models, but a 1.2-fold higher risk of asthma (HR 1.22, 95% CI 1.04–1.43) and allergic rhinitis (HR 1.15, 95% CI 1.00–1.31) per IQR was observed adjusting for NO<sub>2</sub>, PM<sub>2.5</sub> and NDVI in the multi-pollutant model. Exposure to NO<sub>2</sub> at birth was more strongly associated with asthma and eczema in a multi-pollutant model also including O<sub>3</sub>, PM<sub>2.5</sub> and NDVI (HR 1.17, 95% CI 1.05–1.31 and HR 1.07, 95% CI 0.99–1.15, respectively). In multi-pollutant models, exposures to NO<sub>2</sub> and O<sub>3</sub> in the first 3 years of life showed a similar trend of increasing the risk of asthma, allergic rhinitis and eczema. Total oxidants (the weighted sum of NO<sub>2</sub> and O<sub>3</sub>) were associated with asthma and eczema in both single- (HR 1.14, 95% CI 1.02–1.28 and HR 1.07, 95% CI 1.00–1.15, respectively) and multi-pollutant models with PM<sub>2.5</sub>, NDVI and other covariates (HR 1.17, 95% CI 1.05–1.31 and HR 1.07, 95% CI 0.99–1.15, respectively). We repeated the multi-pollutant regression model to examine the association stratified by age groups (onset of asthma ≤4 and >4 years old). Results from the age-stratified analysis (table 5) showed that there was no difference in the hazard ratios by age at onset. The hazard ratios of PM<sub>2.5</sub> and outcomes when stratified by tertile of total oxidants showed similar results to that of the multi-pollutant model of total oxidants and PM<sub>2.5</sub> (supplementary material). Our results did not demonstrate a gradient effect of oxidants on PM<sub>2.5</sub> and outcomes.



TABLE 3 Correlations among exposure variables for the 1286 participants with complete covariate data

	Mean±SD	Pearson correlation coefficient r			
		NO <sub>2</sub>	O <sub>3</sub>	PM <sub>2.5</sub>	NDVI
<b>NO<sub>2</sub> ppb</b>					
At birth	26.51±4.60		-0.6139 (p<0.0001)	-0.1600 (p<0.0001)	-0.2313 (p<0.0001)
Averaged over first 3 years	26.14±4.40		-0.6220 (p<0.0001)	-0.0516 (p=0.0648)	-0.2055 (p<0.0001)
<b>O<sub>3</sub> ppb</b>					
At birth	43.61±1.58			0.4442 (p<0.0001)	0.0060 (p=0.8296)
Averaged over first 3 years	43.72±1.52			0.1890 (p<0.0001)	-0.0313 (p=0.2630)
<b>PM<sub>2.5</sub> mg·m<sup>-3</sup></b>					
At birth	10.16±2.19				-0.0810 (p=0.0037)
Averaged over first 3 years	10.88±1.33				0.0114 (p=0.6835)
<b>NDVI</b>					
At birth	0.33±0.11				
Averaged over first 3 years	0.35±0.11				

NO<sub>2</sub>: nitrogen dioxide; O<sub>3</sub>: ozone; PM<sub>2.5</sub>: particulate matter with a 50% cut-off aerodynamic diameter of 2.5 µm; NDVI: Normalised Difference Vegetation Index.

**Discussion**

This study represents the longest longitudinal study of the health of school-aged children in Canada with >17 years of follow-up. The lifetime incidence of asthma in the T-CHEQ cohort (28.5%) was somewhat higher than our previous estimate using the same methods of case ascertainment of 22% by age 20 years based on Ontario-wide data from 1996 to 2007 [15], which could be attributable to differences between the T-CHEQ cohort and the Ontario population. We found a 17% increase in risk of developing asthma and 8% increase in risk of allergic rhinitis for each IQR increase in exposure to total oxidants (O<sub>3</sub> and NO<sub>2</sub>) at birth. Associations with O<sub>3</sub> and NO<sub>2</sub> in single- versus multi-pollutant models were less stable than

TABLE 4 Adjusted hazard ratios (95% CIs) for asthma, allergic rhinitis, eczema and exposures at birth and over the first 3 years of life from single-pollutant, multi-pollutant and oxidants models

	Asthma		Allergic rhinitis		Eczema	
	At birth	First 3 years	At birth	First 3 years	At birth	First 3 years
<b>Single-pollutant model</b>						
NO <sub>2</sub>	1.09 (0.99–1.20)	1.06 (0.96–1.16)	0.97 (0.90–1.05)	0.94 (0.87–1.02)	1.05 (0.99–1.12)	1.05 (0.99–1.11)
O <sub>3</sub>	1.01 (0.90–1.14)	1.02 (0.90–1.14)	1.07 (0.98–1.18)	1.08 (0.99–1.19)	0.99 (0.92–1.06)	0.99 (0.92–1.06)
Oxidants <sup>#</sup>	1.14 (1.02–1.28)	1.10 (0.98–1.23)	1.02 (0.93–1.12)	0.98 (0.89–1.08)	1.07 (1.00–1.15)	1.06 (0.99–1.14)
PM <sub>2.5</sub>	0.88 (0.76–1.02)	0.94 (0.83–1.06)	0.92 (0.82–1.05)	0.94 (0.85–1.04)	0.98 (0.89–1.07)	1.01 (0.93–1.09)
NDVI	1.02 (0.88–1.18)	1.02 (0.88–1.19)	0.92 (0.82–1.04)	0.95 (0.84–1.07)	0.96 (0.88–1.04)	0.95 (0.87–1.03)
<b>Multi-pollutant model (NO<sub>2</sub>+O<sub>3</sub>+PM<sub>2.5</sub>+NDVI)</b>						
NO <sub>2</sub>	1.17 (1.05–1.31)	1.12 (1.00–1.26)	1.02 (0.92–1.12)	0.97 (0.88–1.08)	1.07 (0.99–1.15)	1.05 (0.98–1.14)
O <sub>3</sub>	1.22 (1.04–1.43)	1.13 (0.97–1.31)	1.15 (1.00–1.31)	1.07 (0.95–1.22)	1.05 (0.95–1.16)	1.03 (0.93–1.13)
PM <sub>2.5</sub>	0.82 (0.69–0.97)	0.92 (0.81–1.04)	0.85 (0.74–0.98)	0.92 (0.83–1.03)	0.97 (0.87–1.07)	1.00 (0.93–1.08)
NDVI	1.05 (0.91–1.22)	1.06 (0.91–1.23)	0.91 (0.81–1.03)	0.94 (0.83–1.07)	0.97 (0.89–1.06)	0.96 (0.88–1.05)
<b>Oxidants model (oxidants<sup>#</sup>+PM<sub>2.5</sub>+NDVI)</b>						
Oxidants <sup>#</sup>	1.17 (1.05–1.31)	1.12 (1.00–1.25)	1.01 (0.92–1.12)	0.98 (0.88–1.08)	1.07 (0.99–1.15)	1.05 (0.98–1.13)
PM <sub>2.5</sub>	0.85 (0.73–0.99)	0.92 (0.81–1.05)	0.91 (0.80–1.04)	0.94 (0.85–1.05)	0.96 (0.88–1.06)	0.99 (0.92–1.08)
NDVI	1.06 (0.91–1.23)	1.06 (0.91–1.23)	0.92 (0.81–1.04)	0.94 (0.82–1.07)	0.97 (0.89–1.06)	0.96 (0.88–1.05)

NO<sub>2</sub>: nitrogen dioxide; O<sub>3</sub>: ozone; PM<sub>2.5</sub>: particulate matter with a 50% cut-off aerodynamic diameter of 2.5 µm; NDVI: Normalised Difference Vegetation Index. Hazard ratios are calculated per interquartile range increase in exposure; all Cox models presented in the table met the proportional hazard assumption according to the Schoenfeld residuals. Cox models for asthma and allergic rhinitis are adjusted for all covariates: age, sex, parental education level, income adequacy, number of people in household, low birthweight, breastfeeding, enrolment in childcare, whether child was born within 3 weeks of due date, home exposures during first year of life (damp spots, use of gas to cook or heat, exposure to environmental tobacco smoke, pets, cockroaches and mould) and parental history of asthma and atopy. Covariates excluded in the Cox models for eczema due to violation of the proportionality assumption: income adequacy, low birthweight, child was born within 3 weeks of due date, breastfeeding, use of gas to cook or heat, parental history of asthma and atopy. <sup>#</sup>: oxidants=[(1.07×NO<sub>2</sub>)+(2.075×O<sub>3</sub>)]/3.145.

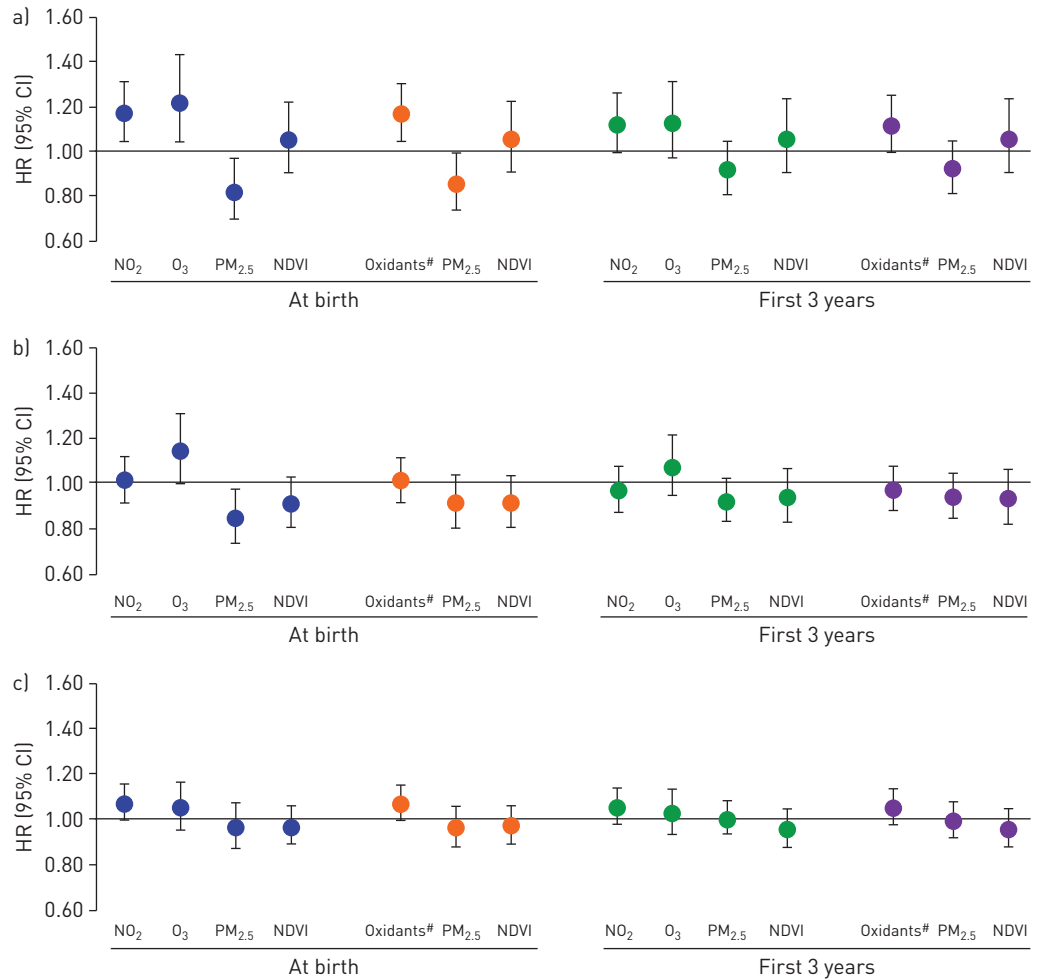


FIGURE 2 Forest plot of hazard ratios (95% CI) for a) asthma, b) allergic rhinitis and c) eczema by air pollutants and Normalised Difference Vegetation Index (NDVI) from multivariable multi-pollutant Cox regression models. #: oxidants= $[(1.07 \times \text{NO}_2) + (2.075 \times \text{O}_3)] / 3.145$ .

for total oxidants, probably because of their strong negative correlation. These findings are important because they examined the effects of early life exposures to air pollution and their subsequent influence on health throughout childhood to adolescence.

Our study provides reliable exposure measurements as we compiled complete address histories from birth and assigned exposures according to residential address throughout those periods. Our results showed that the association of exposure and outcomes throughout early childhood is rather consistent. The point estimates of the hazard ratios at birth and those at the first 3 years differed by <10% and the direction of the point estimates was consistent over time. The wider 95% confidence intervals of hazard ratios at the first 3 years could be partially attributable to a larger variance of exposures from year to year.

Exposures to ambient air pollutants including O<sub>3</sub>, PM<sub>2.5</sub> and NO<sub>2</sub> have been associated with worsening lung function and asthma symptoms in children [24–27]. Respiratory viruses and air pollutants such as O<sub>3</sub> target the airway epithelium specifically as a means of entry to the underlying airways; when combined with an impaired ability to mount an antioxidant response, this results in an already susceptible airway epithelium that is more easily damaged [28]. WENDT *et al.* [29] used data from Texas in the USA between 2005 and 2007, a large population at high risk for asthma and living in an area with historically high O<sub>3</sub> levels, to study the risk of incident asthma and O<sub>3</sub>. Similar to our study, WENDT *et al.* [29] found a significant association of exposure to O<sub>3</sub> and incident asthma in children.

Our birth cohort study did not find a positive association of early life exposure to PM<sub>2.5</sub> and risks of developing childhood respiratory or allergic conditions. This lack of association might reflect weak or partially unresolved spatial gradients across the study area. YANG *et al.* [30] used the Netherlands Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort data to measure the



TABLE 5 Adjusted hazard ratios for asthma and exposures at birth from multi-pollutant models stratified by age groups (onset of asthma ≤4 and >4 years old).

	Asthma onset	
	≤4 years	>4 years
<b>Subjects</b>	258	108
<b>Multi-pollutant model (NO<sub>2</sub>+O<sub>3</sub>+PM<sub>2.5</sub>+NDVI)</b>		
NO <sub>2</sub>	1.19 (1.04–1.36)	1.19 (0.96–1.46)
O <sub>3</sub>	1.23 (1.02–1.49)	1.24 (0.91–1.68)
PM <sub>2.5</sub>	0.82 (0.67–1.01)	0.80 (0.59–1.09)
NDVI	1.05 (0.88–1.25)	1.10 (0.83–1.44)

Data are presented as n or HR (95% CI). NO<sub>2</sub>: nitrogen dioxide; O<sub>3</sub>: ozone; PM<sub>2.5</sub>: particulate matter with a 50% cut-off aerodynamic diameter of 2.5 µm; NDVI: Normalised Difference Vegetation Index. Hazard ratios are calculated per interquartile range increase in exposure; all Cox models presented in the table met the proportional hazard assumption according to the Schoenfeld residuals. Cox models for asthma are adjusted for all covariates: age, sex, parental education level, income adequacy, number of people in household, low birthweight, breastfeeding, enrolment in childcare, whether child was born within 3 weeks of due date, home exposures during first year of life (damp spots, use of gas to cook or heat, exposure to environmental tobacco smoke, pets, cockroaches and mould) and parental history of asthma and atopy.

associations of long-term exposure to oxidative potential with respiratory health in 3701 children until they turned 12–14 years of age. Our risk estimates of exposure to NO<sub>2</sub> and asthma and rhinitis are consistent with those YANG *et al.* [30] reported in the PIAMA birth cohort. They also did not find a significant association between respiratory health and PM<sub>2.5</sub> mass.

GEHRING *et al.* [31] used a combined cohort of 14126 participants from four prospective birth cohort studies from Germany, Sweden and the Netherlands to measure the longitudinal associations between exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence. This multiple birth cohort study found that the risk of incident asthma up to age 14–16 years increased with increasing exposure to NO<sub>2</sub> and PM<sub>2.5</sub> at the birth address, and suggested that exposure to air pollution early in life might contribute to the development of asthma throughout childhood and adolescence. GEHRING *et al.*'s [31] estimates of risk of asthma and NO<sub>2</sub> are consistent with our findings.

BOWATTE *et al.* [3] conducted a systematic review and meta-analysis that included 19 studies, 11 of which were birth cohort studies, from the late 1990s to 2014. While there was a wide variability in the odd ratios across studies, the point estimates of NO<sub>2</sub> at age 1, 2, 3, 4 and 6 years were consistent with ours in the single-pollutant model. The results of this study highlighted that early childhood exposure to TRAP from birth to 5 years of age was associated with new onset of asthma throughout childhood and there was evidence to suggest that TRAP exposure may have an ongoing effect with a lag time of ~3 years [3].

KHREIS *et al.* [2] published a systematic review in 2017 and included 21 studies in their quantitative analyses. Our overall estimate of risk of NO<sub>2</sub> and asthma was consistent with their finding that increase in exposure to NO<sub>2</sub> in early childhood increases the risk of asthma. However, while KHREIS *et al.* [2] suggested an overall increase in risk of exposure to PM<sub>2.5</sub> and asthma, we did not find an independent increase in risk of early life exposure to PM<sub>2.5</sub> and asthma in our multi-pollutant model. KHREIS *et al.* [2] concluded that based on their meta-analysis, they supported the hypothesis that childhood exposure to TRAP contributes to the development of asthma.

Recent studies suggested that residential greenness may play a role in the aetiology of allergic respiratory diseases. However, the literature has been inconsistent, with some reporting protective effects [9, 32] and others suggesting that trees along roadsides can trap air pollution, decrease the air quality in the immediate vicinity [33] and therefore may pose a negative impact on health [32, 34]. The recent systematic reviews and meta-analysis conducted by LAMBERT *et al.* [35, 36] assessed the role of residential greenness on allergic respiratory diseases in children and adolescents. The results of the meta-analysis showed no significant overall association between residential greenness and asthma or allergic rhinitis. Similarly, our study did not find significant associations with exposure to residential greenness and allergic respiratory diseases.

It is well established that short-term exposure to air pollution can decrease lung function, exacerbate asthma, increase the risk of respiratory infections, and contribute to hospitalisation and mortality [37], and it has been reported that long-term exposure can lead to disease progression, such as from asthma to

chronic obstructive pulmonary disease [38, 39]. Meta-analyses of 18–41 primary studies have consistently reported significant positive pooled estimates of the association between NO<sub>2</sub> and asthma prevalence and/or incidence, while associations with particulate matter were less consistent [2, 3, 5, 40]. A recent systematic review of ozone and asthma incidence reported that findings were inconsistent among 11 primary studies [41]. Our T-CHEQ Birth Cohort Study has a 17-year follow-up, which allowed us to study exposures to air pollution from birth and in early life, and to quantify their long-term subsequent risks of development of common childhood respiratory and allergic conditions such as asthma, allergic rhinitis and eczema. Some studies have suggested that ozone depletes antioxidant activity and increases indications of inflammation in the respiratory tract fluid lining and affects lung growth [42, 43]. Short-term exposure to ozone can decrease lung function and increase the risk of respiratory infections in children. Children are at a higher risk because their lungs and other respiratory organs are smaller, and their immune, metabolism and detoxification systems are not well developed [44, 45]. Our observed elevated risks for asthma and allergic rhinitis associated with exposure to ozone, and eczema to nitrogen dioxide, imply that the adverse impacts of exposure to air pollutants, particularly to ozone and nitrogen dioxide, may have their origins in early life.

This study has several strengths, including the use of a birth cohort design with 17 years of follow-up with complete data on the residential history (home address) of every child. Data were linked to population health administrative databases to ascertain physician-diagnosed (instead of self or parental report) incidence of asthma, allergic rhinitis and eczema. The study is also strengthened by adjustment for a multitude of potential confounding risk factors including child, parental/demographic and home environmental factors. Additionally, although survey questions in which respondents are asked to recall events/behaviours in the past may be subject to potential recall bias, recall bias did not seem to be substantial in this study. For example, none of the home environment variables in the first year of life were significantly different in prevalence between children with or without asthma or eczema. Despite these strengths, a few limitations should be noted. Firstly, exposures in this study were assigned based on concentrations of air pollution estimated for place of residence. Therefore, misclassification (over- or under-estimation) of exposures is possible. Despite the small sample size, the study has sufficient statistical power to detect the effects of NO<sub>2</sub> and O<sub>3</sub> on asthma, O<sub>3</sub> on allergic rhinitis, and NO<sub>2</sub> on eczema in the multi-pollutant and multi-covariate adjusted model. However, it is a limitation that we may not have sufficient statistical power to measure smaller effects of pollutants on some of the outcomes. Additionally, we did not have data on the incidence of conditions by month to permit analysis by seasons or data to differentiate asthma types such as atopic and non-atopic asthma. Lastly, while we have adjusted for many potential confounding risk factors, residual confounding may still exist in relation to unmeasured confounders. Future research should explore spatiotemporal correlation between pollutants and how they may be influenced by meteorological factors such as wind speed and relative humidity.

In conclusion, this birth cohort study adds evidence of associations between early life exposure to air pollutants and risks of major respiratory and allergic conditions in young children. Improving air quality and providing advice on reducing air pollution exposure especially to O<sub>3</sub> and NO<sub>2</sub> may contribute to the prevention of asthma and other allergic disease in childhood and adolescence.

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**Author contributions:** T. To and D. Stieb initiated and designed the study, interpreted findings and drafted the manuscript. J. Zhu conducted all statistical analysis. N. Gray and I. Fong conducted a search of the literature, summarised relevant study findings and reviewed the manuscript. S. Dell and M. Jerrett interpreted findings, reviewed and commented on drafts. L. Pinault carried out the annual adjustments to air pollution surfaces and mapped them to postal codes. A. Robichaud, R. Menard and J.R. Brook created the ozone surface, A. van Donkelaar and R.V. Martin created the particulate matter surface, and P. Hystad created the nitrogen dioxide surface. All authors have seen and approved the final version.

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