



# Presence of other allergic disease modifies the effect of early childhood traffic-related air pollution exposure on asthma prevalence



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## ABSTRACT

Nitrogen dioxide (NO<sub>2</sub>), a surrogate measure of traffic-related air pollution (TRAP), has been associated with incident childhood asthma. Timing of exposure and atopic status may be important effect modifiers. We collected cross-sectional data on asthma outcomes from Toronto school children aged 5–9 years in 2006. Lifetime home, school and daycare addresses were obtained to derive birth and cumulative NO<sub>2</sub> exposures for a nested case-control subset of 1497 children. Presence of other allergic disease (a proxy for atopy) was defined as self-report of one or more of doctor-diagnosed rhinitis, eczema, or food allergy. Generalized estimating equations were used to adjust for potential confounders, and examine hypothesized effect modifiers while accounting for clustering by school. In children with other allergic disease, birth, cumulative and 2006 NO<sub>2</sub> were associated with lifetime asthma (OR 1.46, 95% CI 1.08–1.98; 1.37, 95% CI 1.00–1.86; and 1.60, 95% CI 1.09–2.36 respectively per interquartile range increase) and wheeze (OR 1.44, 95% CI 1.10–1.89; 1.31, 95% CI 1.02–1.67; and 1.60, 95% CI 1.16–2.21). No or weaker effects were seen in those without allergic disease, and effect modification was amplified when a more restrictive algorithm was used to define other allergic disease (at least 2 of doctor diagnosed allergic rhinitis, eczema or food allergy). The effects of modest NO<sub>2</sub> levels on childhood asthma were modified by the presence of other allergic disease, suggesting a probable role for allergic sensitization in the pathogenesis of TRAP initiated asthma.

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## 1. Introduction

Risk factors for the development of asthma can be divided into host factors and environmental factors. Allelic distributions of genes predisposing to atopy, bronchial hyperresponsiveness or both are likely

important host factors (Djik et al., 2013). Well described potential environmental factors include allergens (house dust mites, furred animals, cockroach, mouse, molds, pollens), infections (mainly viruses), occupational and chemical sensitizers, environmental tobacco smoke (ETS), indoor and outdoor air pollutants, psychosocial factors and diet (Eder et al., 2006). Studies of asthma pathogenesis and allergic immune response both using rodent models and in humans have elucidated mechanisms whereby allergen and pollutant (mainly ETS and diesel exhaust) co-exposures may lead to the development of asthma (Diaz-Sanchez et al., 2003; Maes et al., 2010; Nel et al., 1998).

The association between traffic-related air pollution (TRAP) and asthma symptoms has been recognized for some time (WHO, 2005). Recently, epidemiological evidence has emerged from European (Brauer et al., 2007; Gehring et al., 2010; Morgenstern et al., 2008; Nordling et al., 2008) and North American (Clark et al., 2010; Jerrett et al., 2008; McConnell et al., 2010; Ryan et al., 2009) cohort studies that

**Abbreviations:** ETS, environmental tobacco smoke; GEE, generalized estimating equations; IDW, inverse distance weighting; LUR, land use regression; T-CHEQ, Toronto Child Health Evaluation Questionnaire; TRAP, traffic-related air pollution.

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TRAP exposure may play a role in the development of incident asthma in children. Reviews of the evidence have suggested that there is a possible causal association (Anderson et al., 2013; Health Effects Institute, 2010). Results regarding effect modification by atopy have been mixed. The role of inherent genetic susceptibility in the effects of air pollutants, particularly the role of the null variant of glutathione S-transferase Mu 1 in the oxidative stress pathway, has already been studied (Yang et al., 2008).

For other putative exposures, it has become apparent that timing of exposure may be important, with exposures around the time of birth possibly driving much of childhood asthma and allergy (Selgrade et al., 2006). Birth cohort studies measuring TRAP exposures at the time of birth have generally shown the strongest associations with incident asthma while studies that have measured effects of later childhood TRAP exposure have shown mixed results (Braback and Forsberg, 2009). A lack of longitudinal exposure measures over the child's lifetime has been a weakness of previous studies that hampers the ability to detect the importance of timing of exposure (Ryan and Holguin, 2010).

The objectives of this research were to address these gaps in the evidence by (1) determining the associations between TRAP at different periods of exposure (birth, school age and lifetime cumulative exposure) and asthma in Toronto school children and (2) exploring the role of atopy in these associations.

## 2. Material and methods

### 2.1. Study subjects

The Toronto Child Health Evaluation Questionnaire (T-CHEQ) Phase 1 study established a population-based cohort of 5619 grades one and two (aged 5 to 9 years) Toronto school children in 2006 using modified *International Study of Asthma and Allergies in Childhood* methodology. Details of the study design, population representativeness and asthma prevalence were previously reported (Dell et al., 2010). Briefly, parents completed a self-administered questionnaire reporting information about the health of their child, household and individual level demographics, and current (2006) residential and school address data.

Parent-reported asthma outcomes (lifetime and current) were previously validated in this population (Yang et al., 2011). "Lifetime" asthma was defined as ever having been diagnosed with asthma by a doctor. "Current" asthma was defined as lifetime (ever) doctor-diagnosed asthma with wheeze or use of asthma medication in the last 12 months. We also examined current (last 12 months) and lifetime wheeze (ever having wheezed). Presence of other allergic disease (a proxy for atopy) was defined as self-report of one or more of doctor-diagnosed rhinitis, eczema, or food allergy.

A subsequent nested case–control study (Phase 2) in 2006 randomly sampled 1497 children (90.9% of those selected agreed to participate) who had lived in Toronto since birth (Fig. 1). Cases (704) reported lifetime asthma or wheeze, while controls (793) were free of asthma and asthma symptoms. A telephone interview was conducted in the case–control sample to ascertain lifetime residential, daycare and school addresses of the child. Ethical approval for this research was obtained from the Hospital for Sick Children's and Health Canada's research ethics boards.

### 2.2. Traffic-related air pollution (TRAP) exposures

TRAP exposures were estimated with land use regression (LUR) (Jerrett et al., 2007, 2009) and inverse distance weighting (IDW) (Jerrett et al., 2005, 2009) models by mapping lifetime addresses to derive current, birth and cumulative nitrogen dioxide (NO<sub>2</sub>) exposure estimates. Distance-from-roadway metrics were also used to establish current and birth exposures (Jerrett et al., 2005). "Current" refers to the study recruitment year (2006). Validated LUR surfaces for NO<sub>2</sub> were based on two-week sampling campaigns over two seasons during

fall of 2002 and spring of 2004 using Ogawa passive diffusion samplers at 150 locations across Toronto (Jerrett et al., 2009). Surfaces for 2002 and 2004 were averaged. IDW interpolation employed published Ontario Ministry of the Environment and National Air Pollution Surveillance network annual statistics for NO<sub>2</sub> (1997 and 2002 data) (Jerrett et al., 2007, 2009). Addresses at birth were the same as prenatal addresses in nearly all subjects.

To conduct the time-weighted exposure profile analysis (cumulative exposure score) it was assumed that any changes in average pollution concentration over the study period were linear over time. As such, the pollution concentrations for individual subjects can be interpolated between measurement years using a 1st order linear equation of the form:

$$y_{is}(t) = C_{0s} + \frac{C_{ns} - C_{0s}}{T_n - T_0} t \quad (1)$$

where  $y_{is}(t)$  is the generalized equation describing the continuous concentration as a function of time,  $t$ , between some time interval  $T_0$  to  $T_n$  for individual  $i$  at location  $s$ . The concentration at location  $s$  varies from  $C_{0s}$  to  $C_{ns}$  over the time period  $T_0$  to  $T_n$ . For ease of interpretation the equation will be written as:

$$y_{is}(t) = C_{0s} + \beta_s t \quad (2)$$

where  $\beta_s$  can be thought of as the individual-location-specific pollution gradient over the time  $T_0$  to  $T_n$ .

With a generalized exposure concentration equation (Eq. 2) an accumulated exposure can then be calculated over a given time period, at a given location. By integrating Eq. 2 between two time periods,  $t_a$  to some time  $t_b$ :

$$\int_{t_a}^{t_b} y_{is}(t) dt = \int_{t_a}^{t_b} (C_{0s} + \beta_s t) dt = C_{0s}(t_b - t_a) + \frac{\beta_s}{2} (t_b^2 - t_a^2). \quad (3)$$

This will produce estimates of accumulated exposure over the time period  $t_a$  to  $t_b$ . For this project, a base unit of 1-month has been used, so the units of accumulated exposure take the form [concentration · months]. This value can be divided by the total time that the subject is involved in the study,  $T_t$ , to derive a time-weighted average with a standard pollution concentration unit.

The subjects' activity locations in this study were characterized by place of residence and school/daycare location. It was therefore necessary to approximate the proportion of time that a subject spent at each location. This allowed for estimated exposure profiles that accounted for time spent at home, daycare and school.

To assess the contributions of pollution from each of the different sources (multiple residences and school/daycare), location weights had to be calculated to represent the proportions of time spent at home or school. Estimates of exposure take into account that daycare continues throughout the entire year, while the typical school year starts in September and finishes at the end of June. Prior to a child's entry to daycare or school, 100% of the exposure will be associated with the residence. When the subject is in daycare or school, a percentage of a subject's total exposure is based on the number of hours per month spent at the school or a daycare facility.

Combining this into the weighted exposure assignments means that, for example, if a child lives in two different residential locations over the study period and goes to only one school, there will be four parts to the total weighted exposure. The first will be only in the first residence with no time at school. Second will be exposure experienced at the second residence prior to beginning school. Third will be exposure experienced at the second residence after being enrolled in school. Last, is the exposure experienced while in school. This can be summarized by:

$$E_{\text{total}(i)} = E_{R1} + E_{R2} + E_{R2Sc} + E_{ScR2} \quad (4)$$

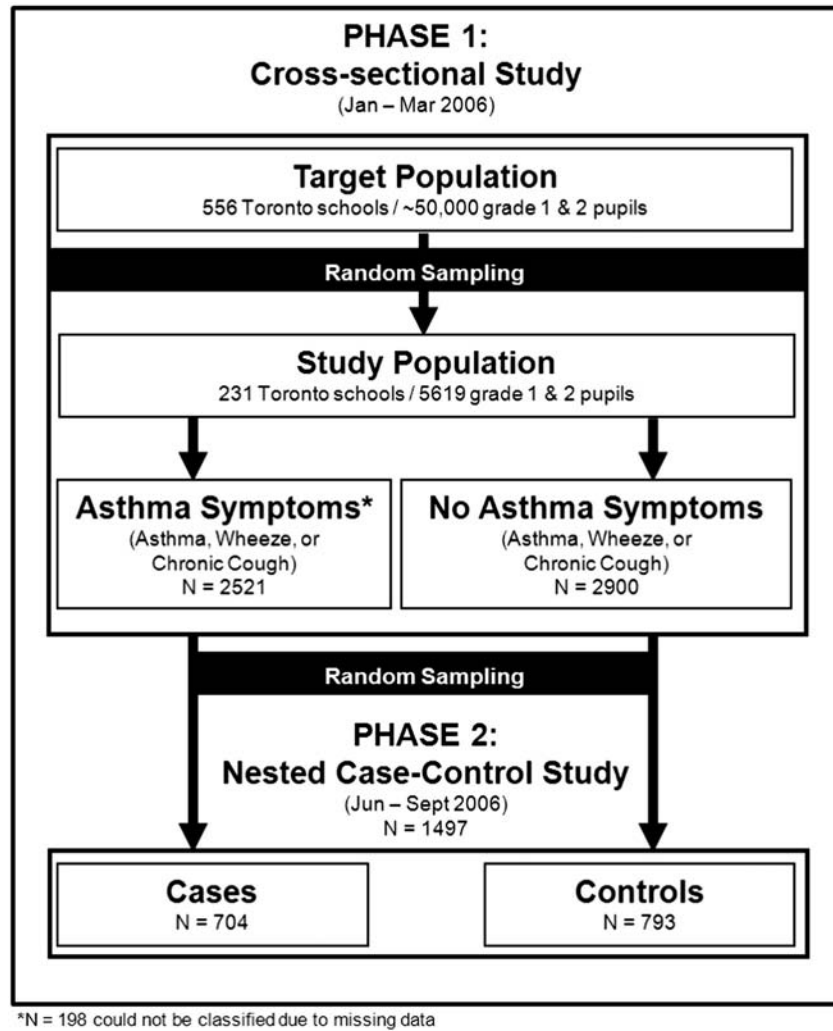


Fig. 1. Study design and sampling scheme.

where  $E_{\text{total}(i)}$  is the total accumulated exposure over the study period;  $E_{R1}$  is the accumulated exposure acquired at the first place of residence;  $E_{R2}$  is the accumulated exposure acquired at the second place of residence prior to enrolling in school;  $E_{R2Sc}$  is the accumulated exposure acquired at the second place of residence after having enrolled in school; and  $E_{ScR2}$  is the accumulated exposure acquired at school while living at the second place of residence. This can be generalized as:

$$E_{\text{total}(i)} = \sum_{s=1}^q \sum_{i=1}^m W_s P_{is} \quad (5)$$

where for individuals  $i$ , at location  $s$ , the total accumulated exposure  $E_{\text{total}(i)}$  is equal to the sum of the product of the weighting factor  $W_s$  (for example, for residence prior to the start of school  $W_s = 1.0$ ; for school  $W_s = 0.16$ ; for residence when attending school  $W_s = 0.84$ ) at location  $s$  for a given individual while experiencing an accumulated exposure  $P_{is}$  over the time spent at  $s$ .

### 2.3. Statistical analyses

Generalized estimating equations (GEE) were used to estimate the effect of  $\text{NO}_2$  on asthma and wheeze prevalence for each exposure/outcome

pair (12 models), adjusting for potential clustering by school, and selected potential confounders. Potential confounders considered included age, sex, parental asthma, prematurity (<37 weeks gestation), breast feeding, low birth weight (<2500 g), crowding (number of people living in home), lifetime daycare attendance, income adequacy, respondent's education level, and home exposures (both current and in the first year of life) to environmental tobacco smoke (ETS), gas stoves, pets, cockroaches, damp spots and mold. Bivariate analyses were conducted for all potential confounding variables against each of the outcome measures. If a variable exhibited a statistically significant ( $p < 0.05$ ) association with an outcome, an additional regression was conducted including the variable in question and the primary exposure variable (TRAP) against the associated outcome. Variables that changed the magnitude of the association between TRAP and the outcome by at least 10% when added to the model were considered confounders (Greenland, 2008). A correlation matrix was then created to ensure that no highly correlated confounders were entered into the same model. Pairs of confounders exhibiting correlations stronger than 0.3 were reviewed and of these, the variable which caused the greater magnitude change in the TRAP effect size was selected for inclusion in the multivariate model. Next we inserted interaction terms into the models using a priori hypothesized effect modifier variables (presence of other allergic disease, ETS exposure, parental asthma history and sex). The final adjusted model included only those confounders and interaction terms that maintained their statistical significance when

added to the multivariate model. Where significant ( $p < 0.05$ ) interactions were found, a stratified analysis was conducted. Analyses were based on Phase 2 participants for whom lifetime address histories were available ( $n = 1497$ ). However, as a sensitivity analysis, we also examined associations with 2006 exposures in the Phase 1 participants ( $n = 5619$ ).

Additional analyses conducted to explore the robustness of our findings included: (1) sensitivity analysis of the algorithm used to determine the presence of other allergic disease (requiring one vs. two or more of doctor-diagnosed rhinitis, eczema, or food allergy); (2) including subjects from Phase 1 who lived at the same address since birth in the analysis of birth TRAP exposure; and (3) evaluation of reverse causality (subjects with asthma moving to areas of lower TRAP exposure) as a possible source of bias. It is possible that families who have children with asthma may move to areas of decreased air pollution by school age because of perceived health benefit from cleaner air, which would bias the results of our current analyses toward the null. To determine whether our results were susceptible to this bias, we examined residential mobility in the sample, and tested the hypothesis that children with lifetime asthma or wheeze were more likely to move to areas of lower air pollution, compared to children without lifetime asthma or wheeze. The primary exposure variable was moving to an area of lower TRAP exposure. This dichotomous variable was derived by determining the difference in TRAP exposure between the child's birth home and 2006 home. A decrease in  $\text{NO}_2$  from birth to 2006 address of greater than one interquartile range was defined as moving to an area of lower TRAP exposure. Reverse causality was considered to be present if there was a statistically significant association between asthma and

moving to an area of lower pollution. Final adjusted models were created using the same procedure used in the main analysis.

Odds ratios (OR) were scaled to represent the change in the outcome relative to an interquartile change in each exposure metric. All statistical analyses were conducted using SAS statistical software version 9.1.

### 3. Results

#### 3.1. General characteristics and distribution of asthma outcomes

5619 Toronto school children from 231 schools participated in Phase 1 of the T-CHEQ study from January to March 2006 (Fig. 1). Response rates, general characteristics and comparison of this sample to census data have been reported elsewhere (Dell et al., 2010). The distribution of sex, household income, dwelling type and household size, environmental tobacco smoke exposure, and asthma and wheeze prevalence were similar to census data and population-based national surveys (Dell et al., 2010). A random sample of 1497 children (response rate 90.9%) participated in the nested case–control Phase 2 telephone survey to obtain lifetime home, childcare and school address history (Tables 1a and 1b, Fig. 1).

#### 3.2. Exposure to TRAP

Nitrogen dioxide exposure levels were modest (Table 2, Fig. 2) and generally below WHO recommended maximum levels (WHO, 2006). There was less variability of exposure for IDW compared to LUR and for the cumulative LUR model compared to the birth and current LUR

**Table 1a**  
Characteristics of children participating in Phases 1 and 2.

| Variable                                                              | Phase 1 (N = 5619) | Phase 2 (N = 1497) <sup>a</sup> |
|-----------------------------------------------------------------------|--------------------|---------------------------------|
|                                                                       | N (%) <sup>b</sup> | N (%) <sup>b</sup>              |
| Male sex                                                              | 2772 (49.7)        | 774 (51.7)                      |
| Age (mean)                                                            | 6.75               | 6.69                            |
| Lifetime asthma                                                       | 847 (15.5)         | 309 (20.8)                      |
| Current (2006) asthma                                                 | 619 (11.3)         | 231 (15.5)                      |
| Lifetime wheeze                                                       | 1627 (29.2)        | 656 (43.9)                      |
| Current (2006) wheeze                                                 | 790 (14.2)         | 320 (21.4)                      |
| Lifetime eczema                                                       | 1177 (21.4)        | 410 (27.6)                      |
| Lifetime rhinitis                                                     | 531 (9.7)          | 99 (6.7)                        |
| Food allergy                                                          | 259 (4.7)          | 83 (5.6)                        |
| Peanut allergy                                                        | 155 (2.8)          | 72 (4.9)                        |
| Family history asthma                                                 | 903 (16.1)         | 348 (23.2)                      |
| Prematurity (born > 3 weeks early)                                    | 435 (8.4)          | 112 (7.8)                       |
| Low birth weight (<2500 g)                                            | 546 (10.2)         | 105 (7.2)                       |
| Daycare                                                               | 3183 (57.4)        | 981 (66.0)                      |
| Breast feeding                                                        | 4806 (86.2)        | 1355 (90.6)                     |
| Hospitalization in the first year of life                             | 828 (14.9)         | 229 (15.4)                      |
| Hospitalization for a respiratory condition in the first year of life | 270 (4.9)          | 88 (5.9)                        |
| Home occupancy (# in home)                                            |                    |                                 |
| 2                                                                     | 166 (3.0)          | 38 (2.6)                        |
| 3                                                                     | 983 (17.7)         | 196 (13.2)                      |
| 4                                                                     | 2435 (43.9)        | 712 (47.8)                      |
| 5+                                                                    | 1958 (35.3)        | 542 (36.4)                      |
| Income adequacy <sup>c</sup>                                          |                    |                                 |
| Lowest income                                                         | 935 (17.8)         | 110 (7.6)                       |
| Lower middle income                                                   | 1160 (22.1)        | 222 (15.4)                      |
| Upper middle income                                                   | 1201 (22.9)        | 296 (20.6)                      |
| Highest income                                                        | 1945 (37.1)        | 811 (56.4)                      |
| Parental education (some or completed)                                |                    |                                 |
| Elementary–secondary only                                             | 1074 (19.8)        | 211 (14.3)                      |
| College education only                                                | 1841 (34.0)        | 510 (34.5)                      |
| University                                                            | 2506 (46.2)        | 758 (51.3)                      |

<sup>a</sup> Nested case–control study of 1497 randomly selected school children who reported living in Toronto since birth in Phase 1. Cases reported asthma or asthma symptoms (wheeze or night-time cough not associated with a cold or chest infection) while controls were free of asthma and asthma symptoms.

<sup>b</sup> Adjusted for missing values.

<sup>c</sup> Income adequacy: a derived variable defined by Statistics Canada as (income, persons in household) Lowest income: <\$15,000, 1–2 or <\$20,000, 3–4 or <\$30,000, 5+; Lower middle income: \$15,000 to \$29,999, 1–2, or \$20,000 to \$39,999, 3–4, or \$30,000 to \$59,999, 5+; Upper-middle income: \$30,000 to \$59,999, 1–2, or \$40,000 to \$79,999, 3–4, or \$60,000 to \$79,000, 5+; Highest income \$60,000+, 1–2, or \$80,000+, 3+.

**Table 1b**  
2006 and lifetime household exposures of children participating in Phases 1 and 2.

| Variable                     | Phase 1 (N = 5619)<br>N (%) <sup>b</sup> | Phase 2 (N = 1497) <sup>a</sup><br>N (%) <sup>b</sup> |
|------------------------------|------------------------------------------|-------------------------------------------------------|
| 2006                         |                                          |                                                       |
| ETS <sup>c</sup> (lifetime)  | 769 (14.8)                               | 199 (14.0)                                            |
| ETS (2006)                   | 630 (11.2)                               | 156 (10.4)                                            |
| Gas stove                    | 1083 (19.7)                              | 425 (28.9)                                            |
| Pets                         |                                          |                                                       |
| No pets inside home          | 3624 (70.5)                              | 804 (58.9)                                            |
| Dog inside home              | 601 (11.7)                               | 242 (17.7)                                            |
| Cat inside home              | 599 (11.7)                               | 209 (15.3)                                            |
| Other furry pets inside home | 181 (3.5)                                | 74 (5.4)                                              |
| Bird inside home             | 132 (2.6)                                | 37 (2.7)                                              |
| Cockroaches                  | 547 (10.1)                               | 77 (5.2)                                              |
| Damp spots                   | 385 (7.2)                                | 118 (8.2)                                             |
| Mold                         | 339 (6.3)                                | 116 (7.9)                                             |
| First year of life           |                                          |                                                       |
| ETS (first year of life)     | 401 (7.8)                                | 118 (8.3)                                             |
| ETS (pregnancy)              | 256 (5.0)                                | 78 (5.6)                                              |
| Gas stove                    | 1590 (31.2)                              | 300 (21.2)                                            |
| Pets                         |                                          |                                                       |
| No pets inside home          | 3448 (74.3)                              | 797 (64.4)                                            |
| Dog inside home              | 557 (12.0)                               | 205 (16.6)                                            |
| Cat inside home              | 529 (11.4)                               | 200 (16.2)                                            |
| Other furry pets inside home | 31 (0.7)                                 | 15 (1.2)                                              |
| Bird inside home             | 76 (1.6)                                 | 20 (1.6)                                              |
| Cockroaches                  | 618 (12.4)                               | 103 (7.4)                                             |
| Damp spots                   | 446 (9.1)                                | 134 (9.8)                                             |
| Mold                         | 360 (7.3)                                | 122 (8.9)                                             |

<sup>a</sup> Nested case–control study of 1497 randomly selected school children who reported living in Toronto since birth in Phase 1. Cases reported asthma or asthma symptoms (wheeze or night-time cough not associated with a cold or chest infection) while controls were free of asthma and asthma symptoms.

<sup>b</sup> Adjusted for missing values.

<sup>c</sup> Environmental tobacco smoke.

models. Very few participants lived within 100 m of a highway (1.0% at birth and currently) (Table 2).

### 3.3. Associations between covariates and asthma outcomes

Among personal characteristics, male sex, food allergy, eczema, history of hospitalization and respiratory hospitalization in the first year, preterm birth, history of parental asthma and income adequacy were most consistently associated with asthma outcomes (Table 3). Walking to school was negatively associated with asthma outcomes. Among home exposures, presence of dampness and mold as well as roaches

in the first year of life exhibited positive associations, while use of gas as a heating fuel and number of household occupants exhibited negative associations with asthma outcomes. ETS exhibited significant associations only with lifetime wheeze.

### 3.4. Associations between TRAP and asthma outcomes

Children exposed to higher levels of TRAP (IDW) at birth had higher odds of having lifetime wheeze (Table 4). No associations were seen between current or cumulative TRAP exposure, or distance to roadway metrics, and any asthma outcome. When analyses of 2006 exposures and asthma and wheeze were repeated for all cross-sectional subjects, associations with TRAP were similar, but confidence intervals were narrower, and associations with distance to roadway metrics were smaller and remained non-significant. Analyses employing LUR based exposures generally revealed similar associations (Table A2 of online supplement) and those employing a fixed set of covariates generally produced slightly larger TRAP effect estimates than our empirical covariate selection approach (Table A3 of online supplement).

### 3.5. Stratified analyses

Statistically significant interactions were found in the association between TRAP exposures and asthma outcomes by presence of other allergic disease (i.e. parental report of doctor diagnosed rhinitis, eczema or food allergy), and exposure to ETS, but not by sex or family history of asthma. Stratification by presence of other allergic disease revealed that risk estimates deviated from the null only in those with other allergic disease. The strongest associations were observed for TRAP (IDW) in 2006 and at birth, which were associated with both 2006 (current) and lifetime asthma, as well as 2006 (current) and lifetime wheeze in children with other allergic disease (Table 5). A sensitivity analysis using a more restrictive algorithm to define other allergic disease (at least 2 of doctor diagnosed allergic rhinitis, eczema or food allergy) increased the effect size but was associated with greater variability due to the smaller sample sizes. Analyses employing LUR based exposures generally revealed weaker associations (Table A4 of online supplement). The association between TRAP exposure based on IDW and current and lifetime wheeze was observed only in children without lifetime ETS exposure (OR 1.14, 95% CI 1.01–1.29, current TRAP, current wheeze; OR 1.20, 95% CI 1.01–1.44, birth TRAP, current wheeze; OR 1.16, 95% CI 1.06–1.27, current TRAP, lifetime wheeze; 1.20 95% CI 1.02–1.40, birth TRAP, lifetime wheeze).

**Table 2**  
Distribution of estimated TRAP exposures.

| NO <sub>2</sub> exposure                    | Mean (ppb) | Min (ppb) | Max (ppb)  | Standard deviation (ppb) | Inter-quartile range (ppb) |
|---------------------------------------------|------------|-----------|------------|--------------------------|----------------------------|
| 2006                                        |            |           |            |                          |                            |
| IDW <sup>a</sup> (n = 1470)                 | 22.2       | 20.1      | 26.1       | 0.9                      | 1.2                        |
| LUR <sup>b</sup> (n = 1452)                 | 27.4       | 17.9      | 46.8       | 4.1                      | 5.3                        |
| Cumulative                                  |            |           |            |                          |                            |
| IDW <sup>a</sup> (n = 1493)                 | 23.4       | 18.5      | 29.0       | 1.1                      | 1.3                        |
| LUR <sup>b</sup> (n = 1479)                 | 18.3       | 10.1      | 27.9       | 2.7                      | 3.3                        |
| Birth                                       |            |           |            |                          |                            |
| IDW <sup>a</sup> (n = 1441)                 | 22.3       | 20.2      | 26.1       | 0.9                      | 1.1                        |
| LUR <sup>b</sup> (n = 1432)                 | 28.3       | 17.9      | 47.7       | 4.4                      | 5.7                        |
|                                             |            |           | N (%)      |                          | 95% Confidence limit       |
| Distance to roadway                         |            |           |            |                          |                            |
| <100 m of highway (birth) (n = 1484)        |            |           | 15 (1.0)   |                          | (0.5, 1.5)                 |
| <100 m of highway (2006) (n = 1454)         |            |           | 15 (1.0)   |                          | (0.5, 1.6)                 |
| <50 m of a major roadway (birth) (n = 1484) |            |           | 200 (13.5) |                          | (11.7, 15.2)               |
| <50 m of a major roadway (2006) (n = 1454)  |            |           | 218 (15.0) |                          | (13.2, 16.8)               |

<sup>a</sup> Inverse distance weighting.

<sup>b</sup> Land use regression.

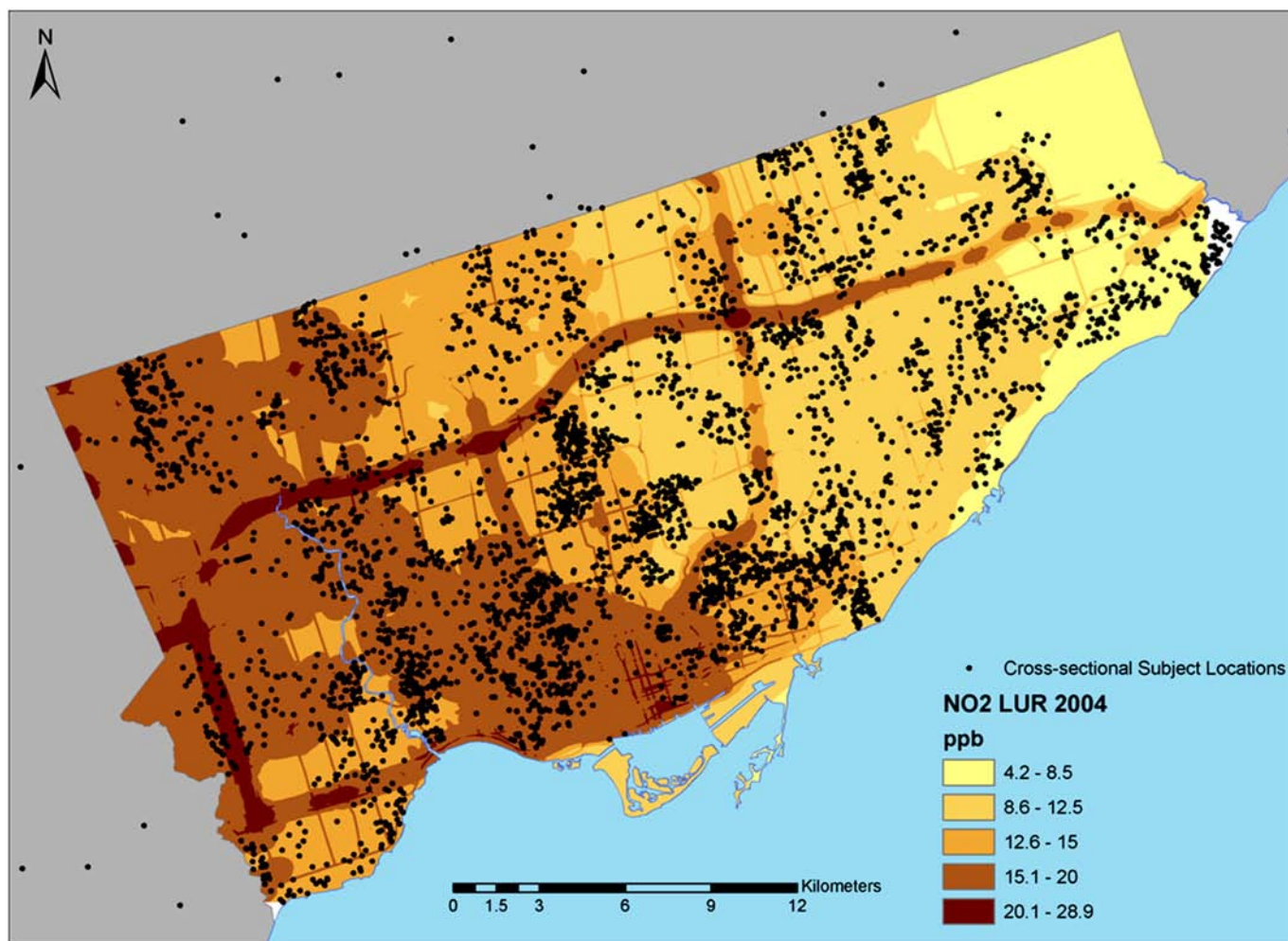


Fig. 2. Map displaying distribution of Phase 1 participants and 2004 NO<sub>2</sub> land use regression (LUR) surface.

### 3.6. Additional sensitivity analyses

Including subjects from Phase 1 who lived at the same address since birth increased the effective sample size from 1441 to 2616 for IDW and from 1432 to 2595 for LUR. The sensitivity analysis revealed risk estimates for the associations with asthma outcomes similar in direction and magnitude to those seen using the Phase 2 case control sample (Table A5 of the online supplement).

Children with asthma moved homes more frequently (61.8%) as compared to those without asthma (54.1%) ( $p = 0.002$ ) (Table A6 of the online supplement). However, there was no statistically significant difference in the proportion of children moving to an area of lower TRAP, comparing children with vs. without asthma (Table A7 of the online supplement). After adjusting for age, the association between asthma and moving to an area of lower TRAP was not statistically significant (OR 1.32, 95% CI 0.68–2.55 for IDW, OR 0.99, 95% CI 0.55–1.77 for LUR). Results were similar when the analysis was restricted to children with both asthma and wheeze.

## 4. Discussion

Our results show that even modest TRAP exposures experienced in the North American urban environment have detectable effects on the prevalence of asthma outcomes in school age children who have other allergic disease. Our study adds to the accumulating body of literature that links TRAP to the development of childhood asthma and is novel

because we have developed a longitudinal exposure profile for each child. This allowed us to extend previous observations by exploring the relative effect of exposures at different times. The public health implication of our research is that infants, and potentially pregnant women, should be protected from potentially harmful TRAP exposures, particularly in combination with sensitizing levels of allergen exposure.

The potential importance of the method of characterizing TRAP exposure has been recently reviewed (Brauer, 2010). Exposure characterization is important because if the correct measure is not chosen, an association between the risk factor and disease may not be evident. For example, we observed an association between current TRAP exposure and asthma outcomes in school age children with other allergic disease, while others have not consistently observed effects of exposures in later childhood (Braback and Forsberg, 2009). The generally decreased TRAP effect seen in school age cohorts compared to birth cohorts in previous studies would suggest that exposures during the perinatal period are important (Braback and Forsberg, 2009).

We also found that IDW based exposure estimates resulted in larger associations than more highly spatially resolved LUR-based estimates. Although more spatially heterogeneous, the estimates from the LUR model were based on just four weeks of sampling data collected in the fall of 2002 and the spring of 2004. Previous analyses have shown the spatial pattern to be fairly stable over time (correlation between common sites in 2002 and 2004 sampling campaigns was 0.82), indicating that the short-term monitoring campaigns capture the long-term spatial patterns well (Jerrett et al., 2009; Su et al., 2009). Yet it is possible that

**Table 3**

Bivariate models of the association between covariates and asthma outcomes (Phase 2 only; n = 1497).

|                                                                         | 2006 asthma              | Lifetime asthma          | 2006 wheeze              | Lifetime wheeze          |
|-------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                                                         | OR (95% CI) <sup>a</sup> |                          |                          |                          |
| Personal characteristics                                                |                          |                          |                          |                          |
| Sex (referent = male)                                                   | <b>0.47 (0.34, 0.64)</b> | <b>0.49 (0.37, 0.64)</b> | <b>0.63 (0.48, 0.82)</b> | <b>0.61 (0.50, 0.75)</b> |
| Age (per year)                                                          | 1.25 (0.98, 1.58)        | 1.17 (0.95, 1.44)        | 1.09 (0.90, 1.32)        | 1.09 (0.91, 1.29)        |
| Food allergy (any)                                                      | <b>11.0 (5.81, 20.9)</b> | <b>8.32 (4.40, 15.7)</b> | <b>3.57 (2.17, 5.90)</b> | <b>4.69 (2.63, 8.38)</b> |
| Eczema                                                                  | <b>3.94 (2.86, 5.43)</b> | <b>3.42 (2.55, 4.60)</b> | <b>2.11 (1.62, 2.75)</b> | <b>2.28 (1.78, 2.91)</b> |
| Parental asthma (Y/N)                                                   | <b>4.37 (3.22, 5.93)</b> | <b>4.05 (3.07, 5.34)</b> | <b>2.57 (1.96, 3.36)</b> | <b>2.90 (2.28, 3.69)</b> |
| Body mass index (per unit)                                              | 1.05 (1.00, 1.10)        | 1.04 (0.99, 1.09)        | 1.03 (0.98, 1.08)        | <b>1.06 (1.02, 1.10)</b> |
| Preterm birth                                                           | <b>1.92 (1.12, 3.29)</b> | <b>2.21 (1.36, 3.59)</b> | 1.43 (0.90, 2.27)        | <b>1.57 (1.06, 2.34)</b> |
| Birth weight (<2500 g vs 2500 g +)                                      | 0.71 (0.40, 1.24)        | 0.72 (0.42, 1.22)        | 0.70 (0.44, 1.12)        | 0.70 (0.45, 1.09)        |
| Attended daycare                                                        | 0.99 (0.74, 1.32)        | 1.08 (0.84, 1.40)        | 0.86 (0.68, 1.10)        | 1.10 (0.89, 1.37)        |
| Breast fed                                                              | 0.75 (0.46, 1.23)        | 0.81 (0.51, 1.28)        | 0.74 (0.51, 1.07)        | 0.95 (0.66, 1.37)        |
| Hospitalization — any (In the first year of life)                       | <b>2.47 (1.66, 3.67)</b> | <b>2.58 (1.80, 3.70)</b> | <b>1.45 (1.06, 2.00)</b> | <b>1.66 (1.27, 2.18)</b> |
| Hospitalization — for respiratory condition (In the first year of life) | <b>8.74 (4.70, 16.3)</b> | <b>8.91 (4.92, 16.1)</b> | <b>2.61 (1.70, 4.00)</b> | <b>5.10 (3.05, 8.51)</b> |
| Income adequacy (referent = lowest)                                     |                          |                          |                          |                          |
| Low-middle                                                              | 0.87 (0.45, 1.66)        | 0.76 (0.43, 1.33)        | 1.30 (0.73, 2.31)        | 1.14 (0.72, 1.79)        |
| High-middle                                                             | 0.80 (0.45, 1.43)        | 0.77 (0.46, 1.31)        | 1.24 (0.72, 2.13)        | 1.24 (0.78, 1.96)        |
| Highest                                                                 | <b>0.54 (0.31, 0.95)</b> | <b>0.52 (0.32, 0.85)</b> | 0.78 (0.47, 1.31)        | 0.88 (0.59, 1.33)        |
| Walking to school (referent = car, bus, school bus, or other)           | <b>0.69 (0.53, 0.90)</b> | <b>0.78 (0.62, 0.99)</b> | <b>0.74 (0.58, 0.93)</b> | <b>0.74 (0.62, 0.88)</b> |
| Home exposures                                                          |                          |                          |                          |                          |
| Number living in household (per person)                                 | 0.85 (0.71, 1.02)        | <b>0.85 (0.73, 0.99)</b> | <b>0.88 (0.80, 0.98)</b> | <b>0.88 (0.80, 0.97)</b> |
| Environmental tobacco smoke exposure (2006)                             | 1.28 (0.75, 2.18)        | 1.35 (0.85, 2.12)        | 1.08 (0.71, 1.64)        | <b>1.42 (1.01, 1.99)</b> |
| Environmental tobacco smoke exposure (first year of life)               | 0.90 (0.49, 1.66)        | 0.92 (0.55, 1.53)        | 1.22 (0.81, 1.84)        | <b>1.48 (1.06, 2.07)</b> |
| Damp spots in the home (2006)                                           | <b>1.65 (1.03, 2.65)</b> | <b>1.54 (1.01, 2.36)</b> | 1.39 (0.90, 2.15)        | <b>1.69 (1.18, 2.41)</b> |
| Damp spots in the home (first year of life)                             | <b>2.74 (1.66, 4.53)</b> | <b>2.53 (1.61, 3.99)</b> | <b>2.01 (1.36, 2.97)</b> | <b>2.25 (1.56, 3.24)</b> |
| Gas as cooking fuel (2006)                                              | 0.79 (0.58, 1.08)        | 0.78 (0.58, 1.05)        | 0.83 (0.63, 1.09)        | 0.95 (0.78, 1.17)        |
| Gas as cooking fuel (first year of life)                                | 0.94 (0.66, 1.32)        | 0.95 (0.68, 1.33)        | 0.96 (0.70, 1.32)        | 1.21 (0.95, 1.55)        |
| Gas as heating fuel (2006)                                              | <b>0.69 (0.49, 0.99)</b> | <b>0.63 (0.45, 0.87)</b> | 0.82 (0.61, 1.10)        | <b>0.73 (0.57, 0.94)</b> |
| Gas as heating fuel (first year of life)                                | 0.83 (0.57, 1.20)        | 0.83 (0.59, 1.15)        | 0.86 (0.64, 1.15)        | 0.92 (0.71, 1.18)        |
| Pets inside the home (2006) (referent = none)                           |                          |                          |                          |                          |
| Dog                                                                     | 0.70 (0.44, 1.13)        | 0.79 (0.52, 1.19)        | 0.71 (0.48, 1.05)        | 0.99 (0.73, 1.34)        |
| Cat                                                                     | <b>0.53 (0.34, 0.83)</b> | 0.81 (0.55, 1.18)        | 0.74 (0.49, 1.11)        | 0.87 (0.63, 1.20)        |
| Other furry pets                                                        | 0.62 (0.31, 1.25)        | 0.50 (0.25, 1.01)        | 0.62 (0.33, 1.16)        | 0.72 (0.46, 1.11)        |
| Bird                                                                    | 0.76 (0.24, 2.46)        | 0.93 (0.34, 2.57)        | 1.74 (0.84, 3.59)        | 1.83 (0.88, 3.78)        |
| Pets inside the home (first year of life) (referent = none)             |                          |                          |                          |                          |
| Dog                                                                     | 0.84 (0.53, 1.34)        | 0.87 (0.57, 1.34)        | 1.02 (0.71, 1.47)        | 1.03 (0.75, 1.42)        |
| Cat                                                                     | 0.73 (0.45, 1.18)        | 0.89 (0.59, 1.36)        | 0.75 (0.51, 1.10)        | 1.01 (0.73, 1.40)        |
| Other furry pets                                                        | 0.80 (0.16, 3.95)        | 1.26 (0.36, 4.43)        | 1.25 (0.39, 3.98)        | 1.13 (0.39, 3.31)        |
| Bird                                                                    | 0.32 (0.04, 2.56)        | 1.01 (0.31, 3.30)        | 0.60 (0.17, 2.11)        | 1.29 (0.55, 3.05)        |
| Pets outside the home (2006) (referent = none)                          |                          |                          |                          |                          |
| Dog                                                                     | <b>0.59 (0.40, 0.88)</b> | <b>0.67 (0.47, 0.94)</b> | 0.81 (0.58, 1.14)        | 1.00 (0.78, 1.28)        |
| Cat                                                                     | 0.97 (0.52, 1.82)        | 1.16 (0.68, 2.00)        | 0.84 (0.49, 1.45)        | 1.17 (0.76, 1.81)        |
| Pets outside the home (first year of life) (referent = none)            |                          |                          |                          |                          |
| Dog                                                                     | <b>0.54 (0.31, 0.91)</b> | 0.67 (0.44, 1.01)        | 0.72 (0.47, 1.08)        | 0.88 (0.64, 1.20)        |
| Cat                                                                     | 1.09 (0.51, 2.33)        | 1.52 (0.83, 2.78)        | 0.95 (0.51, 1.75)        | 1.55 (0.97, 2.48)        |
| Mold in the home (2006)                                                 | <b>1.95 (1.25, 3.05)</b> | <b>1.73 (1.14, 2.62)</b> | 1.45 (0.98, 2.15)        | <b>1.72 (1.20, 2.47)</b> |
| Mold in the home (first year of life)                                   | <b>2.60 (1.64, 4.10)</b> | <b>2.20 (1.43, 3.40)</b> | <b>1.92 (1.35, 2.74)</b> | <b>1.88 (1.30, 2.71)</b> |
| Roaches in the home (2006)                                              | 1.78 (0.91, 3.49)        | 1.72 (0.94, 3.16)        | 1.41 (0.85, 2.33)        | 1.33 (0.83, 2.11)        |
| Roaches in the home (first year of life)                                | <b>1.89 (1.04, 3.44)</b> | <b>2.06 (1.25, 3.41)</b> | 1.21 (0.73, 1.99)        | 1.34 (0.86, 2.10)        |

Bold text in body of table indicates statistically significant association (p &lt; 0.05).

<sup>a</sup> Odds ratio (95% confidence interval).**Table 4**Adjusted<sup>a</sup> odds ratios of the association between TRAP exposures and asthma outcomes.

| Exposure metric                                 | Outcomes                 |                   |                   |                          |
|-------------------------------------------------|--------------------------|-------------------|-------------------|--------------------------|
|                                                 | 2006 asthma              | Lifetime asthma   | 2006 wheeze       | Lifetime wheeze          |
|                                                 | OR (95% CI) <sup>b</sup> |                   |                   |                          |
| 2006 IDW <sup>c</sup> (n = 1470)                | 0.96 (0.77, 1.19)        | 0.89 (0.72, 1.10) | 1.03 (0.86, 1.22) | 1.11 (0.97, 1.27)        |
| Cumulative IDW <sup>c</sup> (n = 1493)          | 1.05 (0.85, 1.28)        | 0.98 (0.81, 1.20) | 1.06 (0.92, 1.22) | 1.08 (0.95, 1.22)        |
| Birth IDW <sup>c</sup> (n = 1441)               | 1.16 (0.93, 1.45)        | 1.15 (0.96, 1.38) | 1.15 (0.98, 1.34) | <b>1.18 (1.02, 1.35)</b> |
| 2006 lived <100 m from highway (n = 1454)       | 2.91 (0.98, 8.68)        | 2.02 (0.68, 5.99) | 2.52 (0.89, 7.13) | 0.94 (0.33, 2.70)        |
| 2006 lived <50 m from major roadway (n = 1454)  | 1.09 (0.65, 1.84)        | 1.03 (0.63, 1.69) | 1.41 (0.95, 2.09) | 0.99 (0.71, 1.40)        |
| Birth lived <100 m from highway (n = 1484)      | 1.91 (0.46, 7.94)        | 1.28 (0.33, 4.96) | 1.35 (0.38, 4.82) | 0.75 (0.23, 2.44)        |
| Birth lived <50 m from major roadway (n = 1484) | 0.98 (0.60, 1.60)        | 0.93 (0.61, 1.43) | 1.10 (0.76, 1.59) | 0.80 (0.55, 1.15)        |

Bold text in body of table indicates statistically significant association (p &lt; 0.05).

<sup>a</sup> Covariates selected from: Age, food allergy, peanut allergy, birth weight, body mass index, breast fed, damp spots in the home (2006), damp spots in the home (first year of life), being the eldest child, exposure to gas as cooking fuel (2006), exposure to gas as cooking fuel (first year of life), exposure to gas as heating fuel (2006), exposure to gas as heating fuel (first year of life), height, hospitalization for a respiratory condition (first year of life), mold in the home (2006), mold in the home (first year of life), household size, preterm birth, roaches in the home (2006), roaches in the home (first year of life), sex, ETS exposure (first year of life), ETS exposure (during pregnancy), ETS exposure (2006), mode of transportation to school, weight (see Table A1 of online supplement for covariates included in each final model).<sup>b</sup> Odds ratio (95% confidence interval) per increase of 1 inter-quartile range.<sup>c</sup> Inverse distance weighting.

**Table 5**Adjusted<sup>a</sup> odds ratios of the association between TRAP exposure<sup>b</sup> and asthma outcomes stratified by presence of other allergic disease.

| Exposure metric                                                                             | Outcomes                 |                   |                          |                   |                          |                          |                          |                          |
|---------------------------------------------------------------------------------------------|--------------------------|-------------------|--------------------------|-------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                                                                             | 2006 asthma              |                   | Lifetime asthma          |                   | 2006 wheeze              |                          | Lifetime wheeze          |                          |
|                                                                                             | Other allergic disease   |                   | Other allergic disease   |                   | Other allergic disease   |                          | Other allergic disease   |                          |
|                                                                                             | Present                  | Absent            | Present                  | Absent            | Present                  | Absent                   | Present                  | Absent                   |
| OR (95% CI) <sup>c</sup>                                                                    |                          |                   |                          |                   |                          |                          |                          |                          |
| <i>Allergic disease = one or more of doctor-diagnosed rhinitis, eczema, or food allergy</i> |                          |                   |                          |                   |                          |                          |                          |                          |
| 2006 TRAP (n = 1470)                                                                        | <b>1.58 (1.09, 2.30)</b> | 0.78 (0.51, 1.17) | <b>1.60 (1.09, 2.36)</b> | 0.80 (0.56, 1.13) | <b>1.48 (1.15, 1.89)</b> | 0.90 (0.65, 1.24)        | <b>1.60 (1.16, 2.21)</b> | 0.92 (0.76, 1.10)        |
| Cumulative TRAP (n = 1493)                                                                  | <b>1.42 (1.04, 1.94)</b> | 0.85 (0.62, 1.19) | <b>1.37 (1.00, 1.86)</b> | 0.87 (0.66, 1.15) | 1.13 (0.91, 1.41)        | 1.04 (0.81, 1.35)        | <b>1.31 (1.02, 1.67)</b> | 1.03 (0.86, 1.23)        |
| Birth TRAP (n = 1441)                                                                       | <b>1.53 (1.11, 2.09)</b> | 0.82 (0.53, 1.27) | <b>1.46 (1.08, 1.98)</b> | 0.98 (0.71, 1.35) | <b>1.41 (1.09, 1.83)</b> | 0.91 (0.67, 1.24)        | <b>1.44 (1.10, 1.89)</b> | 1.01 (0.85, 1.21)        |
| <i>Allergic disease = two or more of doctor-diagnosed rhinitis, eczema, or food allergy</i> |                          |                   |                          |                   |                          |                          |                          |                          |
| 2006 TRAP (n = 1470)                                                                        | 4.10 (0.99, 16.9)        | 1.05 (0.82, 1.33) | 4.01 (0.96, 16.8)        | 1.01 (0.81, 1.26) | 0.86 (0.46, 1.62)        | 1.19 (0.97, 1.46)        | 3.37 (0.94, 12.1)        | 1.06 (0.92, 1.22)        |
| Cumulative TRAP (n = 1493)                                                                  | 2.12 (0.77, 5.86)        | 1.09 (0.84, 1.39) | 2.03 (0.77, 5.36)        | 1.03 (0.83, 1.29) | 0.63 (0.36, 1.09)        | <b>1.21 (1.01, 1.44)</b> | 1.80 (0.81, 4.00)        | 1.11 (0.96, 1.27)        |
| Birth TRAP (n = 1441)                                                                       | <b>3.64 (1.14, 11.6)</b> | 1.14 (0.90, 1.44) | <b>3.60 (1.09, 11.9)</b> | 1.15 (0.94, 1.40) | 0.81 (0.40, 1.64)        | <b>1.23 (1.02, 1.49)</b> | <b>2.92 (1.09, 7.79)</b> | <b>1.14 (1.00, 1.29)</b> |

Bold text in body of table indicates statistically significant association (p &lt; 0.05).

<sup>a</sup> Adjusted for age, sex, preterm birth parental asthma, environmental tobacco smoke exposure in the first year of life, gas cooking in the first year of life.<sup>b</sup> based on inverse distance weighting.<sup>c</sup> Odds ratio (95% confidence interval) per increase of 1 inter-quartile range.

the long-term averaging of the IDW weighting model captures aspects of the spatial pattern of exposure that were not present during the four weeks of monitoring for the LUR regression models. This may in part explain the larger effects observed with the IDW. In addition, the smoother spatial patterns depicted by the IDW may capture some of the larger exposure patterns due to activities near, but not directly at the home address. As shown by Almanza et al. (2012), the activity space of children may extend beyond the proximate areas around their home, and activities at nearby parks and other green spaces may be of higher intensity, which would increase their inhalation rate. In this case, the more spatially smooth NO<sub>2</sub> surface may capture the exposure of the children in locations outside the home more accurately than the LUR surface. NO<sub>2</sub> concentrations based on IDW may also represent a different pollutant mix than those estimated from LUR. Similar findings of larger IDW-based effect estimates than the LUR-based estimates were reported recently in other Canadian studies (Clark et al., 2010; Neupane et al., 2010).

Results have been mixed in previous human studies regarding atopy as an effect modifier of the association between TRAP and asthma. In one study similar to ours but at higher average ambient concentrations of NO<sub>2</sub>, traffic density before 3 years of age was associated with asthma only in those with at least one positive skin prick test (Zmirou et al., 2004). In other studies, associations of asthma with TRAP were larger in non-atopic children (Gehring et al., 2010; Nordling et al., 2008) or children without hay fever (Sahsuvoroglu et al., 2009). The effect modification seen in our study suggests that mechanisms of TRAP effect may be similar to those demonstrated in rodent models (Maes et al., 2010). TRAP effects may be explained by one or both of two mechanisms in the pathogenesis of asthma: (1) TRAP may act as an adjuvant for allergic sensitization early in childhood, so that when children are subsequently allergen challenged, airway inflammation and bronchial hyperresponsiveness develop, or (2) TRAP may potentiate the airway inflammatory effects of allergen challenge in previously sensitized children, leading to airway hyperresponsiveness and airway remodeling. The effect seen with early TRAP exposure around the time of birth suggests that both mechanisms may be acting together synergistically. Generally, food allergies and eczema predate the development of asthma in children (Spergel, 2010; Worth and Sheikh, 2010). Hence, it is reasonable to hypothesize that allergic sensitization occurs first and is then followed by development of airways disease. Not surprisingly, when we made the definition of other allergic disease more restrictive (2 allergic conditions versus 1), the magnitude of TRAP effect increased (OR from 1.53 (1.11–2.09) to 3.64 (1.14–11.6)), which may be either due to increased specificity of

the definition, increased severity of allergic disease or a spurious finding due to increased variability with a smaller sample size.

Our study has two major strengths compared to many previous studies examining the association between TRAP and asthma outcomes: (1) the recruitment of a very large, socially and ethnically diverse, and representative population sample that supports generalization of our results to the population (Dell et al., 2010) and (2) the collection of longitudinal exposure data to evaluate the differential impact of exposures at different periods in a child's life. There are also several limitations to our study that should be considered. While the study incorporated a retrospective longitudinal assessment of exposure, outcomes were determined and analyses were conducted cross-sectionally, making it vulnerable to recall bias concerning asthma outcomes. However, we found that children with asthma were no more likely than children without asthma to move to areas of low TRAP, and hence it is unlikely that reverse causality (i.e. children with asthma moving to lower areas of TRAP due to onset of their respiratory symptoms) could bias effects toward the null. Another limitation is that NO<sub>2</sub> probably acts as a surrogate measure for a mixture of traffic pollutants, admitting the possibility of misclassification of TRAP exposure. However, this is the most feasible way of measuring exposure in a large cohort sample, and any non-differential misclassification would tend to bias our results toward the null (Vogel and Gefeller, 2002). Our LUR-based longitudinal exposure estimates also assumed that spatial patterns of TRAP exposure were the same up to 9 years prior to the year upon which LUR surfaces were based. In other centers, these estimates have been found to be stable over time (Cesaroni et al., 2012; Eeftens et al., 2011). Information on past addresses and on potential confounding factors, including exposure to indoor air contaminants, was based on self-report, which could also introduce reporting biases. Retrospective assessment of residence history has been used previously to estimate exposure to air pollution and other factors, and has been found to be reproducible (Grembowski et al., 1993; Kunzli et al., 1996; Reider and Hubble, 2000). We have also established the validity of several self-reported indoor exposures compared to objective measures in a subsample of our subjects' homes (Loo et al., 2010). Our definitions of asthma and allergic disease were also based on self-report, which may result in misclassification, but questionnaire-based reporting of asthma is widely accepted as the standard for epidemiological studies of childhood asthma risk (Jenkins et al., 1996; Remes et al., 2002), and we have previously established the validity of self-reported asthma in our study population (Yang et al., 2011). We also conducted sensitivity analyses with two alternative definitions of allergic disease and the associations remained positive, suggesting that our findings are robust. Self report of

allergic rhinitis (Braun-Fahrlander et al., 1997) and eczema (Williams et al., 1996) have also been previously validated relative to skin-test positivity and clinical diagnosis respectively.

The selection criterion for the Phase 2 study (having lived in Toronto since birth) means that effects of timing of exposure could be examined only for children born and moving within Toronto. Despite small variation in exposure levels, we nevertheless were still able to detect their effects. Our very low level of ETS exposure (9%) may have made it easier to identify TRAP effects. Finally, we have conducted multiple hypothesis tests which could result in false positive associations, but we have focused on findings that were consistent across outcomes, and driven by a priori hypotheses. Evaluating differential timing during childhood was an a priori hypothesis and alternative exposure metrics are important to evaluate when the true exposure agent is unknown. We employed an empirical approach to model building based on the influence of covariates on the dependent variable and on the association between TRAP and the dependent variable. Results employing a fixed set of covariates generally produced larger TRAP effect estimates, potentially reflecting residual confounding. We have presented results from the more complex approach as a more conservative reflection of the association.

## 5. Conclusions

In a population-based sample of Toronto school children who were exposed to modest levels of traffic-related air pollution, the presence of other allergic disease was a susceptibility factor for increased effect size. Our data could be used in future cohort studies to evaluate potential ongoing effects of TRAP in adolescents and adults. In addition, existing prospective birth cohort studies should collect longitudinal data on TRAP exposures and development of atopy to evaluate critical time periods of susceptibility for TRAP effects and to determine the causal role of atopy in this association.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2014.01.002>.

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