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

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A R T I C L E   I N F O

A B S T R A C T

Nitrogen dioxide (NO_2), 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_2 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_2 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_2 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.

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

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_2) 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_2 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_2 (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:

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

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:

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

where β_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:

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

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:

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