The Timing of Modifiable Environmental Exposures during Childhood Affects the Age of Asthma Development

By

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Institute of Health Policy, Management and Evaluation

University of Toronto

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Abstract

Background: Childhood asthma is a multifactorial condition influenced by hereditary and modifiable environmental traits.

Objective: I investigated longitudinal associations between childhood asthma development and three modifiable environmental exposures: maternal second-hand smoke exposure in pregnancy, neighborhood walkability, which captures community features that promote walking, and material deprivation, a comprehensive measure of socioeconomic status.

Methods: In a population-based cohort of 5619 seven-year-old Toronto children, parents reported age of physician-diagnosed asthma development and maternal active and passive smoking in pregnancy. Administrative data housed at the Institute for Clinical Evaluative Sciences described the 1997-2003 Toronto birth cohorts (326 383 children). Home neighborhood
walkability and deprivation quintiles were reported in validated indices and incident asthma was defined by time of entry into the validated Ontario Asthma Surveillance Information System (OASIS) database. The associations between incident asthma and the exposures were measured using Cox proportional and discrete-time hazard survival analysis. The associations between asthma visits and walkability or deprivation in each year of life were measured using Generalized Estimating Equations and generalized linear mixed models.

**Results:** In the population-based cohort, 15.5% of children developed asthma. Children of non-smoking mothers with home second-hand smoke exposure during pregnancy were more likely to develop asthma (HR 1.34; 95% CI, 1.01-1.76). In the administrative data cohort, OASIS asthma criteria were met for 21% of children. Low birth neighborhood walkability (HR 1.11; 95% CI, 1.08-1.14) and high birth neighborhood deprivation (HR 1.11; 95% CI, 1.09-1.13) were associated with increased risk of incident asthma. These trends persisted for currently-symptomatic incident asthma, lifetime exposure to low walkability or high deprivation and healthcare visits for asthma in each year of life.

**Conclusions:** Home second-hand smoke exposure for non-smoking mothers during pregnancy is associated with incident childhood asthma. Children living in neighborhoods with low walkability or high deprivation are also at increased risk of asthma.
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Chapter 1

Introduction and Literature Review

Childhood asthma is a multifactorial condition affecting up to 25% (1-3) of children in Canada. Longitudinal studies using cohort and administrative data have shown associations between childhood asthma development and environmental, lifestyle, dietary and family characteristics, including exposure to maternal smoking in pregnancy (4), second-hand smoke exposure in the first 3 months of life (5-7), obesity (8-13), chronic low income (14), chronic family (15) and community (16) stress, and atopy or family history of atopy (4).

This thesis focuses on three modifiable environmental exposures that may contribute to the development of childhood asthma and ongoing asthma symptoms. Second-hand smoke exposure is well accepted as a trigger for asthma symptoms and maternal smoking in pregnancy is a known risk factor for asthma development. My first thesis project builds on these studies and evaluates the risk of childhood asthma development associated with home second-hand smoke exposure during pregnancy in non-smoking mothers. The associations of childhood asthma development with activity levels have been variable. My second thesis project evaluates a validated community measure of activity, neighborhood walkability, which refers to features of a neighborhood that promote walking. Finally, income is often used as a surrogate for socioeconomic status, but does not account for other factors relating to socioeconomic well-being. My third thesis project compares childhood asthma development and neighborhood deprivation, which encompasses adults without high school graduation, lone parent families,
government transfers, unemployment and homes needing major repairs, in addition to low income.

1.1 Project 1: Maternal Second-Hand Smoke Exposure in Pregnancy and Childhood Asthma

Exposure to second-hand smoke remains widespread among Canadian children (9-12%) (17, 18). Cross-sectional associations between the development of childhood asthma or wheezing and second-hand smoke (odds ratios 1.2-3.4) (19-33) have been consistently demonstrated. Individual studies that have evaluated childhood exposure to second-hand smoke at different ages have suggested that the timing of exposure may affect the magnitude of association with asthma development (19, 23).

Within individual studies that have compared prenatal or early-life smoke exposure and exposure in later life, the prenatal and early childhood exposures have often shown the stronger associations with childhood asthma development. For example, Martel et al showed an odds ratio (OR) of 1.22 (95% confidence interval [CI], 1.00-1.49) for prenatal exposure and OR 1.17 (95% CI, 0.96-1.43) for lifetime exposure (19). Jaakkola et al found an OR of 2.46 (95% CI, 1.19-5.08) for prenatal exposure, an OR of 1.38 (95% CI, 0.93-2.06) for exposure in early life, and an OR of 1.05 (95% CI, 0.70-1.58) for exposure at ages 8-12 years (23).

Strong associations were also seen between second-hand smoke exposure and early wheezing. Midodzi et al showed an association between parental smoking and preschool wheezing in
children ages 0 to 5 years (OR 1.53; 95% CI, 1.14–2.06) (20). Martinez et al showed stronger associations between maternal smoking and transient wheezing less than age 3 years (OR 2.2; 95% CI, 1.3-3.7) and persistent wheezing occurring both before age 3 years and after age 6 years (OR 2.3; 95% CI, 1.2-4.4) than for late onset wheezing occurring only after age 6 years (OR 1.6; 95% CI, 0.9-2.9) (30). Infante-Rivard et al showed an association between maternal heavy smoking (>20 cigarettes per day) and incident childhood asthma cases diagnosed at ages 3-4 years with persistent asthma symptoms 6-7 years after diagnosis (OR 3.84; 95% CI, 1.68, 8.76), but not among incident asthma cases who did not continue to have asthma symptoms after diagnosis (OR 1.07; 95% CI, 0.35, 3.26), suggesting a contribution of maternal smoking to persistent asthma (34).

Dose responses were shown for several studies that evaluated the effects of smoking; Jaakkola et al showed an OR of 1.20 (95% CI, 1.04-1.38) for maternal smoking of less than 10 cigarettes per day during pregnancy and 1.31 (95% CI, 1.09-1.58) for smoking more than 10 cigarettes per day (25). Similarly, Lewis et al found an OR of 1.12 (95% CI, 0.94-1.33) for maternal smoking of 1-4 cigarettes per day during pregnancy, 1.36 (95% CI, 1.22-1.52) for smoking 5-14 cigarettes per day and 1.44 (95% CI, 1.27-1.63) for smoking at least 15 cigarettes per day (31).

After adjustment for early childhood history, parental and household factors, and other demographic variables, a study from the National Longitudinal Survey of Children and Youth (NLSCY) demonstrated longitudinal associations between maternal smoking of more than 5 cigarettes per day during pregnancy and asthma development (hazard ratio [HR] 1.29; 95% CI, 1.07-1.57) (4). Two longitudinal studies found associations between parental smoking in the first
three months of life and asthma development (5-7). In one of these studies, the association was present only until age two years (HR 1.34; 95% CI, 1.24-1.45) and disappeared after age two years (HR 1.00; 95% CI, 0.84-1.17) (5). Other longitudinal studies that evaluated current exposure in children at or above age six years did not show an association between second-hand smoke exposure in childhood and asthma development (14, 15, 35-37).

These findings suggest that the importance of second-hand smoke exposure for childhood asthma development may change over time and may be greatest during pregnancy. The dose response supports a causative effect of second-hand smoke exposure on childhood asthma development.

The timing of exposure to second-hand smoke remains an important association for childhood asthma development and further study of this exposure is needed. Associations have not been demonstrated between childhood asthma development and home second-hand smoke exposure during pregnancy among non-smoking mothers. In the first thesis project, I hypothesized that children whose mothers are exposed to second-hand smoke during pregnancy will be more likely to develop childhood asthma and have earlier asthma development, even if the mother does not smoke actively.
1.2 Project 2: Neighborhood Walkability and Childhood Asthma

The Walkability Index (38) was developed to evaluate associations between diabetes and neighborhood features in the Greater Toronto Area. Based on the diabetes literature, neighborhoods with lower walkability have higher rates of diabetes (39). Neighborhoods with higher rates of diabetes have lower average household income and higher concentrations of visible minority residents and immigrants, lower levels of walking and cycling, poorer access to stores selling fresh fruit and vegetables and fewer parks and recreation centers. However, the diabetes literature does not suggest that socioeconomic status (SES) is on the causal pathway between walkability and measures of health, because walkability appears to be protective even in some neighborhoods with other high risk factors, such as low SES.

Other factors that may be related to neighborhood walkability and responsible for the associations seen between chronic medical conditions and walkability include obesity and lower levels of activity or exercise. To our knowledge, the relationship between childhood asthma and walkability has not been evaluated and associations between childhood asthma with obesity and activity levels have shown variable results.

Many studies have demonstrated associations between being obese or overweight and childhood asthma development (8-13, 40-42), including a study of 3-year-old urban children in Boston showing increased odds of asthma among obese children (OR 2.3; 95% CI, 1.5-3.3) (40).
Other studies have not suggested an association between obesity and childhood asthma (43-45). For example, a study of 536 6- to 19-year-old children, the Child Health and Environment Cohort in Hesse, Germany, did not show an association between airway hyper-reactivity and body mass index (BMI) above the 85th percentile (44). Some studies have shown interaction between gender and obesity (9). In a cohort of 1037 9- to 26-year-old participants, being overweight was associated with asthma in females (OR 1.10; 95% CI, 1.02-1.18) but not in males (OR 1.06; 95% CI, 0.98-1.15) (46).

The timing of being overweight or obese may influence the association with childhood asthma development (12), although results have not been consistent regarding how the age of obesity onset influences the risk of asthma. In a birth cohort of 3756 children in the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, children with a BMI >85th percentile at age 6-7 years had increased odds of dyspnea (OR 1.68; 95% CI, 1.18-2.39) and measured bronchial hyper-reactivity (OR 1.66; 95% CI, 1.10-2.52) at age 8 years. However, children who developed a normal BMI by age 6-7 years were not at increased risk, even if their BMI had been previously high. However, a pooled analysis of 12 050 children in 8 European birth cohorts (13), including PIAMA, found that rapid BMI increase until age 2 years was associated with increased risk of asthma development (HR 1.27; 95% CI, 1.06-1.51), even if the BMI trajectory normalized between ages 2 and 6 years.

Randomized controlled trials of adults and children suggest a physiologic mechanism by which exercise could be inversely associated with asthma. Among 68 adults from ages 20 to 50 years with moderate- to severe-persistent asthma, decreased signs of bronchial inflammation including
sputum eosinophil counts (p=0.004), exhaled nitric oxide (p=0.009), symptom-free days (p<0.001) and exacerbation rates (p<0.01) were seen in the group receiving aerobic training, but not in the group receiving only eduction and breathing exercises (47). Among 71 children ages 6-18 years with moderate-persistent allergic asthma, methacholine challenge PC\textsubscript{20} showed improvement in the treatment group after 3 months of twice-weekly 60-minute swim training sessions (p=0.008) compared with a control group who showed no improvement (p=0.185) (48).

Despite physiologic associations between exercise and asthma, epidemiological studies of the associations between activity level and asthma have shown variable results. In a sample of 463 children participating in the New York City Head Start Program, activity level measured by a watch accelerometer was not cross-sectionally associated with current physician-diagnosed asthma (OR 0.91; 95% CI, 0.46-1.80) (49). Among teenagers in Manitoba, Canada (50), daily screen time of 1 hour or more at ages 8-9 years was associated with asthma diagnosed by a pediatric allergist at ages 12-14 years (OR 2.11; 95% CI, 1.14–3.89) and the association was stronger for obese adolescents (OR 3.95; 95% CI, 1.70-9.12). However, reported inactive lifestyle was not associated with asthma development in the same cohort (OR 1.03; 95% CI, 0.78-1.37).

These results suggest a need for clarification of the associations among obesity, activity and childhood asthma development. My goal for the second thesis project was to determine the associations between childhood asthma and the walkability index, a community-based measure of active lifestyle, evaluating obesity as a potential confounder of this association.
1.3 Project 3: Neighborhood Deprivation and Childhood Asthma

Socio-demographic factors have also been associated with childhood asthma development and asthma control or risk of exacerbation. Surrogates for SES have been associated with childhood asthma development and control in some populations. In a study of 2614 Swedish children, the OR for asthma was 3.03 (95% CI, 1.52-5.88) among children with the lowest tertile of parental income compared with the highest tertile (51). In a prospective study of 1000 participants born in Dunedin, New Zealand, no association was seen between asthma development and SES (52). Income adequacy is based on an algorithm comparing the household income to the number of household members. In a retrospective cohort of Ontario children with asthma, children with medium or high income adequacy had 28% fewer asthma exacerbations compared to those with low income adequacy (53). In an Australian birth cohort study that followed longitudinal family income trends for 1796 14-year-old participants, teenagers with chronic low family income had a higher risk of asthma development (OR 2.21; 95% CI, 1.17-4.17), but those with increasing (OR 0.83; 95% CI, 0.39-1.74) or decreasing (OR 1.25; 95% CI, 0.84-1.85) family income did not (14). This study also controlled for asthma risk factors and chronic family stress.

Community indices other than SES have shown variable associations with asthma development in children. In a study of 2071 children ages 0–9 years from the Project on Human Development in Chicago Neighborhoods, adjusted analyses showed an association between increased asthma risk and medium (OR 1.60; 95% CI, 1.17–2.19) and high (OR 1.56; 95% CI, 1.12–2.18) levels of community violence, relative to low community levels of violence (54). In the Chicago Initiative to Raise Asthma Health Equity, a cross sectional study of children attending public and Catholic Chicago schools from 2003-2005 surveyed 45 177 students from 105 schools stratified by high
or low attendance by black students and middle or low income (55). Parents or guardians reported demographic factors, physician- or nurse-diagnosed asthma, age of asthma development and asthma control. Community factors were assessed by the Community Vitality Index score, which includes evenly-weighted scores for Social Capital, Economic Potential and Community Amenities. Neighborhoods with greater community diversity, civic engagement, economic vigour, commercial vitality, buying power and workforce vitality (p<0.0001), and cultural entertainment and restaurants and community amenities (p<0.05) had lower asthma prevalence. However, neighborhoods with more interaction potential (p<0.0001), stability (p<0.05) and community institutions such as libraries and universities (p<0.05) had higher asthma prevalence.

Material deprivation, a validated community measure that includes income and related SES factors, is a dimension in the Ontario Marginalization Index (ONMarg) (56), which was developed to aid understanding of inequalities in measures of health and social well-being among various populations or regions in Ontario. Deprivation included no high school graduation, lone parent families, government transfers, unemployment, low income and homes needing major repairs; deprivation has a score from -2 (low deprivation) to +6 (high deprivation) and is also reported in quintiles with the first quintile (Q1) being the least deprived and the fifth quintile (Q5) the most deprived.

Higher rates of emergency department visits for asthma and chronic obstructive pulmonary disorder have been observed in dissemination areas with high material deprivation when compared to overall visit rates in the Peel region of Ontario (57). Similar trends have been reported with diabetes, arthritis, rheumatism, and circulatory system disease. Deprivation has not
been routinely applied to childhood asthma in Ontario and may represent a helpful tool for evaluating the effects of inequality and social well-being on the likelihood of developing childhood asthma. In the third thesis project, I hypothesized that high neighborhood deprivation would be associated with development of childhood asthma after adjusting for other neighborhood and individual contributors to asthma development.
1.4 Specific Aims

The specific aims of these projects were to:

1. Evaluate the associations between childhood asthma development from birth to age 7 years and maternal active smoking and home second-hand smoke exposure during pregnancy in the Toronto Child Health Evaluation Questionnaire (TCHEQ) cohort, a population-based cohort of children living in Toronto, Canada.

2. Determine the association between home neighborhood walkability and childhood asthma in a longitudinal, prospective birth cohort of Toronto children using administrative data housed at the Institute for Clinical Evaluative Sciences (ICES).

3. Determine the association between neighborhood deprivation and childhood asthma in a longitudinal, prospective birth cohort of Toronto children using ICES data.

The TCHEQ study phases 1 and 2 were conducted from 2006-2008 and raw study data was available at the start of the thesis project. I contributed to data collection during a later phase of the TCHEQ study (the Lung Health Study) and I have conducted other studies using Lung Health Study data. As described in projects 2 and 3, administrative data housed at ICES is collected through billing data as part of the Ontario healthcare system. The de-identified ICES dataset used for projects 2 and 3 was generated by an ICES analyst with access to the full datasets containing identifiers, such as date of birth. I conducted all of the dataset derivation and analyses for the three thesis projects.
Chapter 2

Maternal Second-Hand Smoke Exposure in Pregnancy is Associated with Childhood Asthma Development

2.1 Introduction

Childhood asthma affects up to 20% (1, 2) of children in Canada and exposure to second-hand smoke remains widespread among Canadian children (9-12%) (17, 18). Cross-sectional associations between the development of childhood asthma or wheezing and smoke exposure in pregnancy or childhood (odds ratios ranging from 1.2-3.5) (19-28, 58-60) have been consistently demonstrated. Results of studies that have evaluated childhood exposure to second-hand smoke at different ages have suggested that the timing of exposure may affect the magnitude of association with asthma development (19, 23, 26, 28, 59, 60). The results of one longitudinal analysis have also suggested an association between maternal smoking in pregnancy and asthma development in the first 5 years of life (4). However, the longitudinal association between childhood asthma development and maternal home second-hand smoke exposure in pregnancy, independent of active maternal smoking, has not been previously reported. We evaluated the associations between childhood asthma development from birth to age 7 years and maternal active smoking and home second-hand smoke exposure during pregnancy in a population-based cohort of children living in Toronto, Canada.
2.2 Methods

2.2.1 Study Design and Population

A population-based cohort of 5619 grades 1 and 2 school children were recruited from a random sample of 283 public schools in the Greater Toronto Area (1) during the 2006 Toronto Child Health Evaluation Questionnaire Study. In phase 1, cross-sectional exposure data and lifetime outcome data from birth until age 6 or 7 years were collected by validated parent- or guardian-completed questionnaires for all 5619 children. In phase 2, parents or guardians of a randomly-selected nested case-control subset of 1497 children, half of whom had reported a history of asthma or wheezing in phase 1, participated in a detailed telephone survey that included information on lifetime home exposures from pregnancy until age 6 or 7 years. The study was approved by the Hospital for Sick Children Research Ethics Board.

2.2.2 Exposures

For all 5619 participants, parents or guardians reported maternal smoking during pregnancy, in the child’s first year of life, and at age 6 or 7 years; they also reported any smokers currently living in the child’s home at age 6 or 7 years. For the nested case-control sample of 1497 children, retrospective longitudinal data were collected regarding the presence of any smokers living in every home inhabited by the child from pregnancy until age 6 or 7 years. The month and year of moving into each home were also recorded.
2.2.3 Outcomes

Among the full cohort of 5619 children, age of asthma diagnosis by a physician was reported retrospectively for children who developed asthma between birth and age 6 or 7 years. The presence of current wheezing within the past 12 months was also reported.

2.2.4 Definitions of Covariates and Derived Variables

Questionnaire data were collected regarding the child’s current age, height, weight, sex, the duration of breastfeeding (at least six months versus less than six months, dichotomized based on the current breastfeeding recommendations) (61), preterm birth (born more than 3 weeks early), birth weight (<2500 g versus >2500 g), the presence of older or younger siblings, daycare attendance, maternal and paternal histories of asthma, hayfever, and eczema, the highest education level of parent or guardian, and income bracket and number of people per household for determination of income adequacy (1).

For children participating in phase 2, home second-hand smoke exposure in each year of life was derived by subtracting the child’s month and year of birth from the month and year of moving into each home inhabited by the child from pregnancy until age 6 or 7 years and separating the ages of exposure into each year of life. If a child was exposed at any time during a year, he or she was considered exposed in that year. For children who did not participate in phase 2, non-maternal home smoking in pregnancy was imputed as being present for children whose mothers did not smoke but were exposed to home second-hand smoke at age 6 or 7 years.
2.2.5 Missing Data

Data coded as ‘unknown’ were recoded as missing. Data regarding age of asthma development were missing for 200 children (3.6%) and data regarding maternal smoking or maternal home second-hand smoke exposure during pregnancy were missing for 411 children (7.3%). The majority of covariates had missing data for less than 5% of participants. Data on preterm birth were missing for 459 children (8.2%) and income adequacy derived from household income and number of people living in the household could not be calculated for 378 children (6.7%). Breastfeeding duration was not reported for 961 children (17.1%); status of breastfeeding duration for at least six months was imputed first as 0 and then as 1 for all children with unknown breastfeeding duration. Reported current age was missing for 838 children (14.9%). Subtracting the child’s date of birth from the date of interview allowed determination of age for another 36 children and the remainder of current ages were imputed as the median current age (7 years, interquartile range 1.0). Body mass index was imputed as the median (16.0 kg/m\(^2\), interquartile range 3.5 kg/m\(^2\)) for the 45.0% of children with missing data. After imputation, complete data were present for 4703 children in the final model.

2.2.6 Bias

We attempted to minimize selection bias by using a population-based sampling strategy for the original cohort. For the nested case-control study, multiple attempts were made to contact families and telephone interviews were offered in the family’s first language using a commercial translation service. We attempted to minimize information bias by collecting questionnaire data using a validated instrument. To minimize recall bias, parents were advised that the study was about breathing, nose, and skin problems in children, but they were not aware of the primary
exposure and outcome. For the retrospective, nested case-control data, we also tried to minimize recall bias of second-hand smoke exposure by grouping the exposures by home to aid recall.

### 2.2.7 Statistical Analysis

The effect of maternal smoking and home second-hand smoke exposure on age of physician-diagnosed childhood asthma development was determined by using time-to-event analysis to generate asthma-free survival curves for children with and without second-hand smoke exposure in each year of life from pregnancy to age 6 or 7 years. Cox proportional hazard models were used to estimate adjusted hazard ratios of childhood asthma development for home second-hand smoke exposure in pregnancy and the first year of life. Discrete-time hazard models (62) were performed to confirm the results of the Cox proportional hazard models, and to allow simultaneous evaluation of home second-hand smoke exposure from pregnancy until age 6 or 7 years and asthma development from birth until age 6 or 7 years. As described in the supplementary methods (Section 2.6.3), data on home smoke exposure from ages 1 to 5 years were imputed for children who did not participate in phase 2.

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Adjusted models were generated by including the child’s current age and body mass index, sex, and histories of preterm birth, breastfeeding for at least 6 months, older or younger siblings, ever being in childcare, highest parental education, income adequacy, and maternal asthma as covariates in the full models and removing single variables by backwards elimination (p>0.05). For covariates with a priori likelihood of interaction with second-hand smoke exposure, the analysis was repeated, including interaction terms. For covariates with possible interaction based on this model, the
analysis was repeated using indicator variables for each of the four categories of home second-hand smoke exposure (0, 1) and the covariate (0, 1). Validity of the proportional hazards assumption was confirmed for the primary exposure and all covariates that remained in the final models (sex, preterm birth, breastfeeding for at least 6 months and maternal asthma). Goodness of fit for the final models was verified using deviance residuals to evaluate for influential outliers.
2.3 Results

2.3.1 Participants

Details regarding school (80%) and child (25%) participation in the study have been previously reported (1). In phase 2, the response rate was 90.9%.

2.3.2 Descriptive Data

The prevalence of maternal smoking in pregnancy was 5.0% and 6.2% of mothers were non-smokers but exposed to home second-hand smoke during pregnancy; 15.5% of children developed physician-diagnosed asthma by age 6 or 7 years, 49.7% were boys, 8.4% had a history of preterm birth, 65.2% had been breastfed for at least 6 months and 9.8% had a history of maternal asthma (Table 2.1).

2.3.3 Cross-sectional Analysis

In bivariate analyses, maternal smoking or home second-hand smoke exposure in pregnancy and the first year of life carried increased risk of physician-diagnosed asthma development (relative risk [RR] 1.45; 95% CI, 1.21-1.74 and 1.23; 95% CI, 1.04-1.47, respectively). Other factors related to physician-diagnosed asthma development included male sex (RR 1.59; 95% CI, 1.40-1.80), preterm birth (RR 1.55; 95% CI, 1.29-1.86), and a history of maternal asthma (RR 2.64; 95% CI, 2.31-3.01). Being breastfed for at least the first 6 months of life showed a protective association against asthma development (RR 0.79; 95% CI, 0.69-0.91) (Table 2.1).
Table 2.1 Physician-diagnosed incident asthma and home second-hand smoke exposure during pregnancy and the first year of life

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>Unadjusted relative risk (95% confidence interval)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Home smoking in pregnancy</td>
<td>Home smoking in first year</td>
<td>Physician-diagnosed asthma</td>
</tr>
<tr>
<td>Male sex</td>
<td>2772 (49.7)</td>
<td>0.88 (0.75-1.02)</td>
<td>0.82 (0.72-0.94)</td>
<td>1.59 (1.40-1.80)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>546 (10.2)</td>
<td>1.03 (0.79-1.33)</td>
<td>0.97 (0.76-1.22)</td>
<td>1.06 (0.86-1.29)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>435 (8.4)</td>
<td>1.19 (0.91-1.56)</td>
<td>1.19 (0.94-1.51)</td>
<td>1.55 (1.29-1.86)</td>
</tr>
<tr>
<td>Breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>4709 (86.0)</td>
<td>0.46 (0.38-0.54)</td>
<td>0.48 (0.41-0.55)</td>
<td>0.90 (0.76-1.07)</td>
</tr>
<tr>
<td>For at least 6 months</td>
<td>3035 (65.2)</td>
<td>0.61 (0.51-0.73)</td>
<td>0.61 (0.52-0.71)</td>
<td>0.79 (0.69-0.91)</td>
</tr>
<tr>
<td>Older siblings</td>
<td>2748 (49.8)</td>
<td>1.12 (0.96-1.30)</td>
<td>1.05 (0.92-1.21)</td>
<td>0.97 (0.86-1.10)</td>
</tr>
<tr>
<td>Younger siblings</td>
<td>2480 (44.9)</td>
<td>0.86 (0.73-1.00)</td>
<td>0.84 (0.73-0.96)</td>
<td>0.98 (0.87-1.12)</td>
</tr>
<tr>
<td>Ever in Childcare</td>
<td>3183 (57.4)</td>
<td>0.84 (0.72-0.98)</td>
<td>0.91 (0.79-1.05)</td>
<td>1.04 (0.92-1.18)</td>
</tr>
<tr>
<td>Low Income Adequacy</td>
<td>2095 (40.0)</td>
<td>1.41 (1.21-1.66)</td>
<td>1.29 (1.12-1.49)</td>
<td>1.00 (0.87-1.13)</td>
</tr>
<tr>
<td>Highest Education High School/College vs. University</td>
<td>2915 (54.4)</td>
<td>3.31 (2.73-4.01)</td>
<td>3.31 (2.73-4.01)</td>
<td>1.20 (1.06-1.36)</td>
</tr>
<tr>
<td>Parental conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Asthma</td>
<td>552 (9.8)</td>
<td>1.54 (1.25-1.90)</td>
<td>1.44 (1.19-1.75)</td>
<td>2.64 (2.31-3.01)</td>
</tr>
<tr>
<td>Maternal Hayfever</td>
<td>719 (12.8)</td>
<td>0.93 (0.74-1.17)</td>
<td>0.88 (0.71-1.08)</td>
<td>1.57 (1.35-1.82)</td>
</tr>
<tr>
<td>Maternal Eczema</td>
<td>645 (11.5)</td>
<td>1.07 (0.85-1.35)</td>
<td>1.13 (0.92-1.38)</td>
<td>1.50 (1.28-1.76)</td>
</tr>
<tr>
<td>Paternal Asthma</td>
<td>414 (7.4)</td>
<td>1.11 (0.85-1.46)</td>
<td>0.95 (0.73-1.24)</td>
<td>2.60 (2.25-3.00)</td>
</tr>
<tr>
<td>Paternal Hayfever</td>
<td>694 (12.4)</td>
<td>0.82 (0.64-1.05)</td>
<td>0.95 (0.77-1.16)</td>
<td>1.36 (1.15-1.60)</td>
</tr>
<tr>
<td>Paternal Eczema</td>
<td>428 (7.6)</td>
<td>1.01 (0.76-1.33)</td>
<td>0.98 (0.76-1.27)</td>
<td>1.56 (1.30-1.87)</td>
</tr>
<tr>
<td>Physician-diagnosed in child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>846 (15.5)</td>
<td>1.45 (1.21-1.74)</td>
<td>1.23 (1.04-1.47)</td>
<td>--</td>
</tr>
<tr>
<td>Hayfever</td>
<td>531 (9.7)</td>
<td>1.04 (0.80-1.34)</td>
<td>1.16 (0.93-1.44)</td>
<td>1.67 (1.42-1.97)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1177 (21.4)</td>
<td>0.99 (0.82-1.20)</td>
<td>1.01 (0.85-1.19)</td>
<td>2.41 (2.14-2.73)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>322 (5.9)</td>
<td>0.86 (0.60-1.22)</td>
<td>0.99 (0.73-1.33)</td>
<td>3.38 (2.94-3.88)</td>
</tr>
<tr>
<td>Home Smoking (Pregnancy)</td>
<td>585 (11.2)</td>
<td>--</td>
<td>--</td>
<td>1.45 (1.21-1.74)</td>
</tr>
<tr>
<td>Maternal</td>
<td>256 (5.0)</td>
<td>--</td>
<td>--</td>
<td>1.53 (1.15-2.03)</td>
</tr>
<tr>
<td>Non-maternal only</td>
<td>329 (6.2)</td>
<td>--</td>
<td>--</td>
<td>1.42 (1.09-1.85)</td>
</tr>
<tr>
<td>Home Smoking (1st year)</td>
<td>708 (13.5)</td>
<td>--</td>
<td>--</td>
<td>1.23 (1.04-1.47)</td>
</tr>
<tr>
<td>Maternal</td>
<td>401 (7.8)</td>
<td>--</td>
<td>--</td>
<td>1.17 (0.92-1.50)</td>
</tr>
<tr>
<td>Non-maternal only</td>
<td>307 (5.7)</td>
<td>--</td>
<td>--</td>
<td>1.31 (0.99-1.73)</td>
</tr>
</tbody>
</table>

*Total sample size = 5619. Frequencies are adjusted for missing values.
†Significant associations (p<0.05 level)
‡Significant associations (p<0.01 level)
§Significant associations (p<0.001 level)
¶Significant associations (p<0.0001 level)
2.3.4 Survival Analysis

After adjustment for sex, preterm birth, maternal asthma, and breastfeeding duration, maternal active smoking or home second-hand smoke exposure during pregnancy was associated with a 30% increased adjusted hazard of childhood asthma development (HR 1.30; 95% CI, 1.06-1.60) (Table 2.2). The association between physician-diagnosed childhood asthma and maternal home second-hand smoke exposure in pregnancy persisted in children without active maternal smoking in pregnancy (N = 4384, HR 1.34; 95% CI, 1.01-1.76) (Table 2.2). The association was also present for the 539 children (10.0%) with physician-diagnosed asthma and current wheezing in the past 12 months (HR 1.36; 95% CI, 1.03-1.79).

Table 2.2 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal active and passive smoking (entire cohort, N=4703)</td>
</tr>
<tr>
<td></td>
<td>Maternal active smoking (entire cohort, N=4625)</td>
</tr>
<tr>
<td></td>
<td>Excluding children with maternal active smoking in pregnancy (N =4384)</td>
</tr>
<tr>
<td>Home smoke (pregnancy)</td>
<td>1.30 (1.06-1.60)†</td>
</tr>
<tr>
<td></td>
<td>1.27 (0.95-1.69)</td>
</tr>
<tr>
<td></td>
<td>1.34 (1.01-1.76)†</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.69 (1.45-1.96)§</td>
</tr>
<tr>
<td></td>
<td>1.68 (1.44-1.95)§</td>
</tr>
<tr>
<td></td>
<td>1.78 (1.51-2.08)§</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.64 (1.32-2.05)§</td>
</tr>
<tr>
<td></td>
<td>1.61 (1.28-2.02)§</td>
</tr>
<tr>
<td></td>
<td>1.55 (1.22-1.97)†</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.77 (2.33-3.30)§</td>
</tr>
<tr>
<td></td>
<td>2.76 (2.31-3.29)§</td>
</tr>
<tr>
<td></td>
<td>2.82 (2.34-3.40)§</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.84 (0.72-0.98)†</td>
</tr>
<tr>
<td></td>
<td>0.83 (0.71-0.97)†</td>
</tr>
<tr>
<td></td>
<td>0.85 (0.73-1.00)†</td>
</tr>
</tbody>
</table>

*Results of Cox proportional hazard models.
†Significant associations (p<0.05 level)
‡Significant associations (p<0.001 level)
§Significant associations (p<0.0001 level)

Maternal home second-hand smoke exposure in pregnancy showed evidence of possible interaction with income adequacy (p=0.015), history of maternal asthma (p=0.012), breastfeeding (p=0.09) and sex (p=0.08). Among children with maternal home second-hand smoke exposure in pregnancy, only children from families with higher income adequacy had an
increased risk of incident childhood asthma (HR 1.52; 95% CI, 1.17-1.99) (Table 2.3). Children with maternal asthma were at risk for incident asthma, regardless of whether they were unexposed (HR 3.03; 95% CI, 2.50-3.66) or exposed (HR 2.76; 95% CI, 1.88-4.06) to maternal second-hand smoke in pregnancy (Table 2.4); the risk of incident asthma associated with maternal home second-hand smoke exposure in pregnancy was lower for children without maternal asthma (HR 1.49, 95% CI, 1.17-1.89).
### Table 2.3 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy, accounting for interaction between home second-hand smoke exposure in pregnancy and income adequacy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home smoke (pregnancy) and high income adequacy</td>
<td>1.52 (1.17, 1.99)‡</td>
</tr>
<tr>
<td>Home smoke (pregnancy) and low income adequacy</td>
<td>0.99 (0.70, 1.41)</td>
</tr>
<tr>
<td>No home smoke (pregnancy) and low income adequacy</td>
<td>1.10 (0.92, 1.31)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.68 (1.43, 1.96)§</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.63 (1.29, 2.05)§</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.80 (2.33, 3.35)§</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.85 (0.73, 1.00)†</td>
</tr>
</tbody>
</table>

*Results of a Cox proportional hazard model. Children without maternal home second-hand smoke exposure in pregnancy and of high income adequacy are the reference group.

‡Significant associations (p<0.01 level)

§Significant associations (p<0.0001 level)

### Table 2.4 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy, accounting for interaction between home second-hand smoke exposure in pregnancy and history of maternal asthma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home smoke (pregnancy) and no maternal asthma</td>
<td>1.49 (1.17, 1.89)‡</td>
</tr>
<tr>
<td>Home smoke (pregnancy) and maternal asthma</td>
<td>2.76 (1.88, 4.06)§</td>
</tr>
<tr>
<td>No home smoke (pregnancy) and maternal asthma</td>
<td>3.03 (2.50, 3.66)§</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.69 (1.45, 1.96)§</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.64 (1.31, 2.05)§</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.83 (0.72, 0.96)†</td>
</tr>
</tbody>
</table>

*Results of a Cox proportional hazard model. Children without maternal home second-hand smoke exposure in pregnancy or maternal asthma are the reference group.

†Significant associations (p<0.05 level)

‡Significant associations (p<0.01 level)

§Significant associations (p<0.0001 level)
When considering interaction with income adequacy and maternal asthma in a single model, maternal home second-hand smoke exposure was associated with incident asthma only among children of high income adequacy (HR 1.81; 95% CI, 1.34-2.44) for children without maternal asthma; children with maternal asthma had an increased risk of asthma regardless of their income adequacy status (Table 2.5). The risk of incident asthma associated with maternal home second-hand smoke exposure in pregnancy was also greater among children breastfed for less than 6 months (HR 1.45; 95% CI, 1.13-1.87) (Table 2.6) and boys (HR 1.96; 95% CI, 1.45-2.64) (Table 2.7).

**Table 2.5 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy, accounting for interaction between home second-hand smoke exposure in pregnancy, income adequacy and history of maternal asthma**

<table>
<thead>
<tr>
<th>Condition of Smoke Exposure</th>
<th>Maternal History</th>
<th>Adjusted Hazard Ratio of Incident Asthma (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No home smoke (pregnancy), no maternal asthma, low income adequacy</td>
<td></td>
<td>0.98 (0.81, 1.20)</td>
</tr>
<tr>
<td>No home smoke (pregnancy), maternal asthma, high income adequacy</td>
<td></td>
<td>2.59 (2.04, 3.29)†</td>
</tr>
<tr>
<td>No home smoke (pregnancy), maternal asthma, low income adequacy</td>
<td></td>
<td>4.65 (3.37, 6.42)†</td>
</tr>
<tr>
<td>Home smoke (pregnancy), no maternal asthma, high income adequacy</td>
<td></td>
<td>1.81 (1.34, 2.44)‡</td>
</tr>
<tr>
<td>Home smoke (pregnancy), no maternal asthma, low income adequacy</td>
<td></td>
<td>1.02 (0.66, 1.56)</td>
</tr>
<tr>
<td>Home smoke (pregnancy), maternal asthma, high income adequacy</td>
<td></td>
<td>2.49 (1.42, 4.34)‡</td>
</tr>
<tr>
<td>Home smoke (pregnancy), maternal asthma, low income adequacy</td>
<td></td>
<td>2.48 (1.36, 4.55)‡</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>1.67 (1.43, 1.95)†</td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td>1.64 (1.30, 2.06)†</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td></td>
<td>0.85 (0.73, 0.99)†</td>
</tr>
</tbody>
</table>

*Results of a Cox proportional hazard model. Children without maternal home second-hand smoke exposure in pregnancy, without maternal asthma and of high income adequacy are the reference group.
†Significant associations (p<0.05 level)
‡Significant associations (p<0.01 level)
§Significant associations (p<0.001 level)
/uni01C1Significant associations (p<0.0001 level)
Table 2.6 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy, accounting for interaction between home second-hand smoke exposure in pregnancy and history of being breastfed for at least 6 months

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home smoke (pregnancy) and breastfed for at least 6 months</td>
<td>0.92 (0.63, 1.34)</td>
</tr>
<tr>
<td>Home smoke (pregnancy) and breastfed for less than 6 months</td>
<td>1.45 (1.13, 1.87)†</td>
</tr>
<tr>
<td>No home smoke (pregnancy) and breastfed for at least 6 months</td>
<td>0.88 (0.75, 1.03)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.68 (1.45, 1.96)‡</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.64 (1.31, 2.04)‡</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.74 (2.30, 3.27)‡</td>
</tr>
</tbody>
</table>

*Results of a Cox proportional hazard model. Children without maternal home second-hand smoke exposure in pregnancy and breastfed for less than 6 months are the reference group.
†Significant associations (p<0.01 level)
‡Significant associations (p<0.0001 level)

Table 2.7 Association between age of physician-diagnosed incident asthma and maternal home second-hand smoke exposure during pregnancy, accounting for interaction between home second-hand smoke exposure in pregnancy and sex

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home smoke (pregnancy) and male</td>
<td>1.96 (1.45, 2.64)§</td>
</tr>
<tr>
<td>Home smoke (pregnancy) and female</td>
<td>1.62 (1.20, 2.18)‡</td>
</tr>
<tr>
<td>No home smoke (pregnancy) and male</td>
<td>1.80 (1.52, 2.12)§</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.64 (1.32, 2.05)§</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.77 (2.33, 3.30)§</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.84 (0.72, 0.97)†</td>
</tr>
</tbody>
</table>

*Results of a Cox proportional hazard model. Female children without maternal home second-hand smoke exposure in pregnancy are the reference group.
†Significant associations (p<0.05 level)
‡Significant associations (p<0.01 level)
§Significant associations (p<0.0001 level)

The association between maternal smoking or home second-hand smoke exposure in pregnancy and childhood asthma development persisted after adjustment for child second-hand smoke exposure in the first year of life (Table 2.8). All discrete-time hazard models showed increased odds of childhood asthma development associated with maternal smoking or home second-hand smoke exposure in pregnancy, after adjusting for child second-hand smoke exposure from birth until age 7 years (Table 2.9). Child second-hand smoke exposure in the first year and from birth to age 7 years were not associated with asthma development in multivariable Cox proportional
and discrete-time hazard models, with or without adjustment for maternal smoking and home second-hand smoke exposure in pregnancy (Tables 2.8, 2.9 and 2.10). There was co-linearity between the variables for second-hand smoke exposure in pregnancy, the first year of life, and childhood until age 7 years, so direct conclusions cannot be drawn regarding the relative associations of these exposures from a single model. The increased risks of childhood asthma development associated with male sex, history of preterm birth and maternal asthma, and the decreased risk associated with being breastfed for at least 6 months remained consistent among all multivariable Cox proportional and discrete-time hazard models. Accounting for cluster sampling by school did not change the associations.
### Table 2.8: Association between age of physician-diagnosed incident asthma and child’s home second-hand smoke exposure during the first year of life

<table>
<thead>
<tr>
<th></th>
<th>Home smoke exposure in pregnancy and 1st year (N = 4679)</th>
<th>Home smoke exposure in 1st year of life (N = 4714)</th>
<th>Home smoke exposure in 1st year (no pregnancy exposure) (N = 4028)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home smoke (pregnancy)</td>
<td>1.78 (1.16-2.75)‡</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Home smoke (1st year)</td>
<td>0.69 (0.45-1.05)</td>
<td>1.14 (0.93-1.39)</td>
<td>0.90 (0.55-1.46)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.68 (1.44-1.95)‡</td>
<td>1.69 (1.46-1.97)†</td>
<td>1.79 (1.51-2.12)†</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.65 (1.32-2.06)º</td>
<td>1.62 (1.30-2.03)‡</td>
<td>1.63 (1.27-2.10)§</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.79 (2.34-3.32)‡</td>
<td>2.79 (2.35-3.33)‡</td>
<td>3.09 (2.55-3.74)†</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.84 (0.72-0.98)º</td>
<td>0.82 (0.71-0.96)‡</td>
<td>--</td>
</tr>
<tr>
<td>Parental university education</td>
<td>--</td>
<td>1.21 (1.03-1.43)‡</td>
<td></td>
</tr>
</tbody>
</table>

*Results of Cox proportional hazard models. The association between home smoke exposure in pregnancy and asthma development persists after adjustment for second-hand smoke exposure in the first year of life. Relative effects of second-hand smoke exposure in pregnancy and the first year cannot be determined due to co-linearity.

†Significant associations (p<0.05 level)
‡Significant associations (p<0.01 level)
§Significant associations (p<0.0001 level)

### Table 2.9: Association between age of physician-diagnosed incident asthma and home second-hand smoke exposure during pregnancy and childhood (N=5590)

<table>
<thead>
<tr>
<th></th>
<th>Imputation for children with same exposure in the 1st and current years (N = 3436)</th>
<th>Further imputation for children with different exposure in the 1st and current years (N = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imputed no exposure from ages 1 to 5 years</td>
<td>Imputed full exposure from ages 1 to 5 years</td>
</tr>
<tr>
<td>Home smoke (pregnancy)</td>
<td>1.58 (1.10-2.27)‡</td>
<td>1.39 (1.04-1.87)‡</td>
</tr>
<tr>
<td>Home 2nd-hand smoke (birth-7 years)</td>
<td>0.85 (0.58-1.26)</td>
<td>0.94 (0.67-1.31)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.70 (1.45-2.00)‡</td>
<td>1.69 (1.44-1.97)‡</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.59 (1.24-2.02)§</td>
<td>1.56 (1.22-1.97)§</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.88 (2.38-3.48)†</td>
<td>2.99 (2.49-3.60)†</td>
</tr>
<tr>
<td>Breastfed for at least 6 months</td>
<td>0.84 (0.72-0.99)‡</td>
<td>0.82 (0.70-0.96)‡</td>
</tr>
</tbody>
</table>

*Results of discrete-time hazard models. All discrete-time hazard models use the full sample because all children had data for home second-hand smoke exposure in pregnancy and the first and current years. The association between home smoke exposure in pregnancy and asthma development persists after adjustment for second-hand smoke exposure from birth to age 7 years. Relative effects of second-hand smoke exposure in pregnancy and from birth to age 7 years cannot be determined due to co-linearity.

†Children exposed in the first and current years were assumed to be exposed in all years and those unexposed in the first and current years were assumed to be unexposed in all years.
‡Significant associations (p<0.05 level)
§Significant associations (p<0.0001 level)
Table 2.10 Association between age of physician-diagnosed incident asthma and home second-hand smoke exposure during childhood (N=5590)*

<table>
<thead>
<tr>
<th></th>
<th>Imputation for children with same exposure in the 1st and current years (N = 3436)†</th>
<th>Further imputation for children with different exposure in the 1st and current years (N = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imputed no exposure from ages 1 to 5 years</td>
<td>Imputed full exposure from ages 1 to 5 years</td>
</tr>
<tr>
<td>Home 2nd-hand smoke</td>
<td>1.21 (0.95, 1.55)</td>
<td>1.18 (0.92, 1.51)</td>
</tr>
<tr>
<td>(birth-7 years)</td>
<td></td>
<td>1.14 (0.94, 1.39)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.71 (1.45, 2.00)</td>
<td>1.69 (1.45, 1.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.69 (1.45, 1.97)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.57 (1.23, 2.01)</td>
<td>1.50 (1.19, 1.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.50 (1.19, 1.90)</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>2.87 (2.37, 3.47)</td>
<td>3.08 (2.57, 3.69)</td>
</tr>
<tr>
<td>Breastfed for at least</td>
<td>0.83 (0.71, 0.97)</td>
<td>0.80 (0.69, 0.93)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td>0.80 (0.69, 0.93)</td>
</tr>
</tbody>
</table>

*Results of discrete-time hazard models. All discrete-time hazard models use the full sample because all children had data for home second-hand smoke exposure in pregnancy and the first and current years.
†Children exposed in the first and current years were assumed to be exposed in all years and those unexposed in the first and current years were assumed to be unexposed in all years.
‡Significant associations (p<0.05 level)
§Significant associations (p<0.01 level)
/uni01C1/uni01C1Significant associations (p<0.001 level)
|uni01C1/uni01C1Significant associations (p<0.0001 level)
2.4 Discussion

2.4.1 Key Results

To our knowledge, this is the first population-based study to quantify a longitudinal association between maternal home second-hand smoke exposure in pregnancy and childhood asthma development. Children whose mothers smoked actively or were exposed to home second-hand smoke during pregnancy were more likely to develop physician-diagnosed asthma and also developed asthma sooner than children whose mothers were not exposed (HR 1.30; 95% CI, 1.06-1.60). Children of non-smoking mothers with home second-hand smoke exposure in pregnancy also had an increased risk of childhood asthma development (HR 1.34; 95% CI, 1.01-1.76).

2.4.2 Strengths and Limitations

This study was conducted in a population-based sample of children (1) and the detailed longitudinal exposure and outcome data were collected by using a validated instrument. The absence of maternal home second-hand smoke exposure data among children who did not participate in phase 2 is a limitation of this study. Among children who participated in phase 2, only 7% had any changes in home second-hand smoke exposure between pregnancy and age 6 or 7 years. Given the small number of children in the full phase 1 cohort for whom the current exposure might not reflect the exposure in pregnancy, we felt that the imputation was justified.

For mothers who did not smoke, imputing data regarding maternal second-hand smoke exposure in pregnancy based on child second-hand smoke exposure at age 6 or 7 years showed that 6.2% of mothers were non-smokers with exposure to second-hand smoke in pregnancy. Among
children who participated in phase 2, 12.6% of mothers reported to be nonsmokers and have home second-hand smoke exposure in pregnancy. Maternal active smoking in pregnancy was also more common among children who participated in phase 2 (5.6% vs. 5.0% among the full cohort). Therefore, there may have been an underestimation of maternal home second-hand smoke exposure in pregnancy among children who did not participate in phase 2. This exposure misclassification would likely have been nondifferential and would be expected to bias our results towards the null; hence, we may have underestimated the true association. Although phase 2 did not have sufficient statistical power to answer this question, the association between maternal home second-hand smoke exposure during pregnancy and incident childhood asthma was similar among the phase 2 participants (N=1327, HR 1.24; 95% CI, 0.89-1.73) compared with the full cohort.

We did not have information about the number of smokers present in the household or about pack-years of exposure. In the reported adjusted models, missing breastfeeding duration was imputed as less than 6 months, reasoning that mothers who breastfed for at least 6 months would be more likely to remember and report the duration. A sensitivity analysis showed similar results when missing breastfeeding duration was imputed as at least 6 months and when breastfeeding duration was not imputed. As with any observational study, the possibility of residual confounding by variables not included in the final model remains an inherent limitation.

Selection bias in the Toronto Child Health Evaluation Questionnaire Study data has been evaluated by comparison with data from the Census and the National Longitudinal Survey of Children and Youth; the populations were found to be similar with respect to demographic characteristics and the primary study outcomes (1). The risk of recall bias due to retrospective
data collection was minimized by the method of data collection, which focused on the home addresses and on recall of exposures within each home. Under-reporting of second-hand smoke exposure due to the stigma of smoking is possible, but the proportion of children with reported exposure to second-hand smoke in this 2006 cohort was similar to national data collected in the 2006 Canadian Tobacco Use Monitoring Survey (9%) (17). Although laboratory measures of current smoking were not obtained, reporting of second-hand smoke among 6- to 11-year-old children in the 2007-2009 Canadian Health Measures Survey has been shown to accurately reflect exposure measured by cotinine levels, with mean cotinine of 69.6 ng/mL (95% CI, 58.4-78.9) among children with reported second-hand smoke exposure and 7.7 ng/mL (95% CI, 5.6-10.3) among children reported to have no exposure (63). Similar associations with prevalent asthma in toddlers have also been shown for reported smoking versus measured cotinine levels (60).

2.4.3 Interpretation

Our findings are consistent with previous cross-sectional analyses that showed associations between maternal smoking in pregnancy and childhood asthma development (19, 23, 26, 28, 59, 60). Our findings also corroborate a longitudinal study using 1996-1999 National Longitudinal Survey of Children and Youth data, which demonstrated an association between maternal smoking of more than 5 cigarettes per day during pregnancy and asthma development up to age 5 years (HR 1.29; 95% CI, 1.07-1.57) (4). The proportion of mothers who reported smoking during pregnancy (18.8%) (4) was higher than reported in the current study, consistent with higher overall exposure to second-hand smoke among Canadian children in the 2000 Canadian Tobacco Use Monitoring Survey compared with 2006 (17).
Two longitudinal studies found associations between parental smoking in the first 3 months of life and asthma development (5-7), but in one of these studies, the association was present only until age 2 years (HR 1.34; 95% CI, 1.24-1.45) and disappeared after age 2 years (HR 1.00; 95% CI, 0.84-1.17) (5); neither study evaluated exposure during pregnancy, and these early life exposures may also have reflected continued exposure from pregnancy. These results differed slightly from our study, which did not distinguish home second-hand smoke exposure in the first 3 months of life from exposure at any time during the first year of life. Our results were consistent with other longitudinal studies that evaluated current exposure in children at or above age 6 years and did not show an association between second-hand smoke exposure later in childhood and asthma development (35, 64).

This study extends the results of published longitudinal studies by determining that maternal home second-hand smoke exposure during pregnancy is associated with childhood asthma development, even if the mother is not an active smoker during pregnancy. The risks of active maternal smoking during pregnancy have been described (4), but longitudinal associations between asthma development and maternal home second-hand smoke exposure from household smokers in the absence of active maternal smoking during pregnancy have not been previously demonstrated.

We found evidence of statistical interaction between maternal home second-hand smoke exposure in pregnancy and several of the confounding variables. Among children without a history of maternal asthma, only children from families with higher income adequacy had an increased risk of incident childhood asthma associated with maternal home second-hand smoke exposure (HR 1.81; 95% CI, 1.34-2.44). One possible explanation for this finding is that other
harmful exposures not measured in this study, such as chronic family (14) and maternal (15) stress, community crime (36), proximity to major roads (37) and poor outdoor (65) or indoor (66, 67) air quality may be more common exposures among mothers of lower income adequacy and may mask the additional effect of second-hand smoke exposure in their children. Associations have been shown between chronic lower socioeconomic status and asthma development in other studies (14), but the associations between income adequacy and incident asthma remain under investigation; additional studies will be needed to confirm the presence or absence of a true biological interaction.

Our findings also suggest a slightly lower risk of incident asthma for children with a history of maternal asthma if they were also exposed to maternal home second-hand smoke during pregnancy (HR 2.76; 95% CI, 1.88-4.06) compared to those who were not exposed (HR 3.03; 95% CI, 2.50-3.66). This finding may be due to the small number (n=87, 1.5%) of children with home second-hand smoke exposure and a history of maternal asthma. Once again, additional studies will be needed to confirm or refute a true biological interaction. Maternal asthma is a well established risk factor for childhood asthma development (4) and remained associated with incident childhood asthma in all the models.

The stronger association between maternal home second-hand smoke exposure in pregnancy and incident asthma among children without breastfeeding for at least 6 months and in male children may represent interaction or additive effects of risk factors. Recent studies of breastfeeding and childhood asthma development have shown variable associations (4, 20, 68-77). The stronger association between maternal home second-hand smoke exposure in pregnancy and incident asthma among children without breastfeeding for at least 6 months (HR 1.45; 95% CI, 1.13-1.87)
may also reflect children being held and fed by smokers living in the home, rather than by the non-smoking mother. Male children have generally been shown to have an increased risk of asthma compared with female children (4, 19, 20); smaller airways in male children may increase susceptibility to the effects of smoking as well as increasing the inherent risk of asthma.

2.4.4 Generalizability

The demographic (1), outcome (1), and exposure (17) variables in this cohort were similar to national data, which suggests that these results should be generalizable to other urban centres in Canada. Some communities in Canada have much higher rates of maternal smoking and exposure to home second-hand smoke than the national average (78). Our results may not be generalizable to children who live in these communities.
2.5 Conclusions

Children whose mothers have home second-hand smoke exposure during pregnancy are more likely to develop physician-diagnosed asthma and to develop asthma sooner, even if the mother does not smoke actively during pregnancy. This study highlights the continued importance of reducing children's exposure to home second-hand smoke and suggests that childhood asthma prevention programs should include strategies for smoking cessation targeted towards smokers living in the homes of smoking and non-smoking pregnant women, as well as women who smoke actively in pregnancy. Maternal smoking during pregnancy has decreased over time (1, 4), which suggests that messages regarding the dangers of maternal smoking during pregnancy have had a positive effect. We suggest that messages recommending smoking cessation for pregnant women should also advise smoking cessation for household contacts of all smoking and non-smoking pregnant women.
2.6 Supplemental Methods for Project 1

2.6.1 Sample Size

Sample size calculations were conducted in Epi Info™ (Center for Disease Control, Atlanta, GA) with \( \alpha \) of 0.05. With data available for 5619 children and assuming a 15.5% prevalence of physician-diagnosed asthma (1) and 11.1% exposure to smoking in pregnancy, the study had a power of 80% to detect a hazard ratio of 1.3 for childhood asthma development associated with smoke exposure in pregnancy (4).

2.6.2 Derivation of Longitudinal Exposure Data in Phase 2

For the 1497 children participating in phase 2, the dates of moving into each home inhabited by the child from birth to age seven years were used to calculate the ages at which the child lived in each home. The year a child moved into each home was converted into 4-digit character format using the \texttt{put} statement. The month was converted from a 1- or 2-digit number (e.g. 1 or 01) to a 3-digit character format (e.g. ‘Jan’), with missing months relabeled as missing. If the move-in year and month variables were present for a given home, the day of moving was set as the first day of the month (‘01’). The move-in year, month and day variables were concatenated into a single move-in date variable of the format ‘27 Mar 1986’ and the spaces removed using the \texttt{compress} statement. The concatenated character dates were changed to the date9 format using the \texttt{informat} statement and the child’s date of birth was also changed to the date9 format. The ages of living in each home were derived by subtracting the child’s date of birth from the date of moving into each home from pregnancy until age seven years and separating the ages of exposure into each year of life. Negative age values occurring as a result of estimating the move-in day as the first day of the month were converted to 0.
Data were available for up to 6 homes. Homes inhabited by the child during the first year of life were identified if the child’s move-in age was greater than or equal to 0 and less than 12 months for homes 2-6 and less than 12 months for home 1. Homes inhabited by the child during the second year of life were identified if the child’s move-in age was less than 24 months. Similarly, the homes inhabited in the third to tenth years of life were determined by using ages 36, 48, 60, 72, 84, 96 and 120 months as the cut points.

Once the child’s years of life in each of home were established, the home exposure to second-hand smoke in each home was matched to the year of life. Many children lived in more than one home during a given year of life. If a child was exposed to home second-hand smoke at any time during a year of life, he or she was considered exposed in that year. Most children lived in a home for several years of life. If a child was exposed to home second-hand smoke while living in a home, he or she was considered exposed in each year of life during which he or she lived in that home.

Children whose exposure to home second-hand smoke did not change regardless of their home were coded as either exposed or unexposed in all years of life. For children whose home exposure changed with their different homes (4 of 7 children with data reported for 6 homes, 13 of 20 children with data reported for 5 homes, 16 of 52 children with data reported for 4 homes, 29 of 186 children with data reported for 3 homes and 49 of 593 children with data reported for 2 homes), the data were examined and second-hand smoke exposure reported for each year of life.
The mothers of 1267 of the 1497 children lived in the same home during their pregnancy as during the child’s first year of life. Their maternal second-hand smoke exposure during pregnancy was coded the same as the child’s exposure in the first year of life. For the remaining children, those with maternal exposure while living in any home during pregnancy were considered to have maternal second-hand smoke exposure in pregnancy.

2.6.3 Exposure Imputation for Children Who Did Not Participate in Phase 2

Home second-hand smoke exposure data were imputed for children who did not participate in phase 2 and therefore did not have reported exposure data from ages 1 to 5 years. Children reported in phase 1 as being exposed in both the first and current years were assumed to be exposed throughout their childhood and children without exposure in both the first and current years were assumed to be unexposed throughout their childhood, allowing inclusion of 3436 participants who did not participate in phase 2. In two separate sensitivity analyses, children with different home second-hand smoke exposure status in their first and current years were all assumed to be unexposed and then all assumed to be exposed from ages 1 to 5 years, allowing inclusion of 657 additional children.

For children who did not participate in phase 2, non-maternal home smoking in pregnancy was imputed as being present for children whose mothers did not smoke but were exposed to home second-hand smoke at age 6 or 7 years.
2.7 Supplemental Results for Project 1

2.7.1 Model Verification

For the crude models of second-hand smoke exposure in pregnancy (Figure 2.1) and the first year of life (Figure 2.2), proportional hazards assumptions were justified, as shown by parallel functions for unexposed (0) and exposed (1) children.
Figure 2.2 Evaluation of proportional hazards assumption for maternal second-hand smoke exposure during the first year of life

Log of Negative Log of Estimated Survivor Functions

Exposure in the first year of life

0 Unexposed
1 Exposed
All final models were evaluated for multi-collinearity. The models for maternal active smoking or home second-hand smoke exposure during pregnancy (Table 2.11) and for maternal home second-hand smoke exposure in pregnancy, excluding active maternal smokers (Table 2.12) show small condition indices (less than 10). None of the proportions of variation between pairs of individual variables approach 0.5, reducing the likelihood that multi-collinearity is present in the models.

### Table 2.11 Collinearity diagnostics and evaluation for multi-collinearity in the final model of maternal active smoking and home second-hand smoke exposure in pregnancy

<table>
<thead>
<tr>
<th>Number</th>
<th>Eigenvalue</th>
<th>Condition Index</th>
<th>Intercept</th>
<th>Maternal active smoking or home second-hand smoke exposure in pregnancy</th>
<th>Sex</th>
<th>Prematurity</th>
<th>Breastfed for at least 6 months</th>
<th>Maternal asthma</th>
</tr>
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<tr>
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<td>2.71292</td>
<td>1.00000</td>
<td>0.03077</td>
<td>0.02297</td>
<td>0.04374</td>
<td>0.01932</td>
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</table>

### Table 2.12 Collinearity diagnostics and evaluation for multi-collinearity in the final model of maternal home second-hand smoke exposure in pregnancy, excluding smoking mothers

<table>
<thead>
<tr>
<th>Number</th>
<th>Eigenvalue</th>
<th>Condition Index</th>
<th>Intercept</th>
<th>Maternal home second-hand smoke exposure in pregnancy, excluding active maternal smokers</th>
<th>Sex</th>
<th>Prematurity</th>
<th>Breastfed for at least 6 months</th>
<th>Maternal asthma</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.00000</td>
<td>0.03237</td>
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<td>0.01559</td>
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</table>
Figure 2.3 Schoenfeld residuals plots of variables in the Cox proportional hazards model of second-hand smoke in pregnancy

- Schoenfeld Residual for Second-Hand smoke Exposure in Pregnancy
- Schoenfeld Residual for Sex
- Schoenfeld Residual for Preterm Birth
- Schoenfeld Residual for Breastfeeding Duration
- Schoenfeld Residual for Maternal Asthma
Schoenfeld plots show residuals between -1 and +1 for the Cox proportional hazards model of second-hand smoke in pregnancy (Figure 2.3). The absence of linearity for some variables suggests that the model fit is not optimized and that stratification may be needed.

**Figure 2.4 Deviance residuals plots of variables in the Cox proportional hazards model of second-hand smoke in pregnancy**

The deviance residuals for the unstratified Cox proportional hazards model comparing maternal second-hand smoke exposure in pregnancy and childhood asthma development (Figure 2.4) are not symmetrically distributed around 0, suggesting that the unstratified model fit is not optimal.
2.8 Chapter 2 Summary

Maternal home second-hand smoke exposure in pregnancy is associated with childhood asthma development, even if the mother does not smoke actively, but lives in the same home as a smoker. Given the possibility of interaction with factors such as maternal asthma, income adequacy and breastfeeding, the models have reasonable fit. Maternal second-hand smoke exposure is modifiable at both the individual and societal levels and prevention strategies including individual counselling of parents and prospective parents, labeling of tobacco products with the harmful effects of smoking in pregnancy and restriction of locations in which smoking is permissible, should continue.

Another potential contributor to childhood asthma development, a sedentary lifestyle, is increasingly determined to be modifiable at the societal level, as well as the individual level. In Chapter 3, I discuss my evaluation of the association between childhood asthma development and neighborhood walkability, or characteristics conducive to walking.
Chapter 3

Neighborhood Walkability is Associated with Childhood Asthma Development

3.1 Introduction

Asthma development in early life has been associated with childhood obesity (8-13), but has been less consistently associated with childhood activity levels (49, 50, 79). Activity predictors have included reports of both episodic physical activity and an active lifestyle with less sedentary time. Our goal was to determine the associations between childhood asthma and a community-based measure of active lifestyle.

Neighborhood walkability is a distinct concept referring to features of a neighborhood that promote walking, and may include components such as street connectivity, residential density, residential- and commercial-area land-use mix, and public transportation. Variable associations have been demonstrated among walkability, obesity and activity levels (80-83), and all three variables are discrete measures. Among adults, neighborhood walkability has been shown to be protective against another chronic disease, diabetes, after controlling for socioeconomic status (39). To our knowledge, associations between neighborhood walkability and childhood asthma have not been previously published. In this longitudinal, prospective birth cohort study, we evaluated the association between home neighborhood walkability and childhood asthma.
3.2 Methods

3.2.1 Data Sources

We used prospectively-collected Ontario health administrative data housed at the Institute for Clinical Evaluative Sciences, including data from Ontario Health Insurance Plan (OHIP) records of clinic visits, National Ambulatory Care Reporting System (NACRS) records of Emergency Department visits and Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD) records of hospitalizations. Children who were born between 1997 and 2003, inclusive, and who had lived in the Greater Toronto Area (GTA) at any time during their lives were identified through the Registered Persons Database (RPDB) and followed from birth to the end of the study (March 31, 2012). Children born in 1997 had up to 15 years of data and children born in 2003 had up to 8 years of data. This study was approved by Research Ethics Boards at the Hospital for Sick Children and the University of Toronto.

The Walkability Index includes four dimensions: population density, dwelling density, access to all retail and services, and street connectivity or intersection density (38). The index was developed by factor analysis, beginning with neighborhood characteristics such as land-use heterogeneity, number of parks and schools and walking time to the nearest bus, subway or streetcar stop, in addition to the four dimensions retained. The index was validated among adults by comparison with actual levels of walking and physical activity in the 2006 Canada Census, the Transportation Tomorrow Survey and the Canadian Community Health Survey (38). The walkability index was reported in quintiles (1-low walkability and 5-high walkability) for each neighborhood in the GTA, and was dichotomized into the two lowest quintiles versus the two highest quintiles.
Entry into the Ontario Asthma Surveillance Information System (OASIS) database with a diagnosis of asthma requires two outpatient visits for asthma within two consecutive years or ever being hospitalized for asthma (84), and has been validated with good sensitivity and specificity against a clinical diagnosis of childhood asthma made by a physician (85) and by parental reporting of physician-diagnosed asthma in children (86). Asthma encounters were defined by the OHIP code or the primary diagnostic ICD-9/ICD-10 code in NACRS and CIHI-DAD (Table 3.1). For children in the OASIS database, asthma visits recorded in the OHIP, NACRS, and CIHI databases were available for each year of life during which the child lived in Ontario. Three main outcomes were defined in this study: incident asthma, currently-symptomatic incident asthma, and asthma by year of life. Incident asthma was defined as the timing of entry into the OASIS database. Currently-symptomatic incident asthma was defined as the timing of entry into the OASIS database for children with any healthcare visit for asthma between April 1, 2011 and March 31, 2012, which would have occurred between ages 8-15 years for children in this cohort. Asthma by year of life was defined as at least one healthcare visit for asthma in a given year of the child’s life.

The covariates included sex and census tract-level neighborhood income quintile (dichotomized into the lowest two quintiles versus the highest two quintiles) obtained from the RPDB, and any diagnostic coding for history of preterm birth (before 37 weeks gestation), obesity (weight greater than the 95th percentile for sex and age), or other atopic conditions (at least one of allergic rhinitis, eczema and food allergy) from the OHIP, NACRS and CIHI databases (Table 3.1).
Table 3.1 OHIP, ICD-9 and ICD-10 diagnostic codes

<table>
<thead>
<tr>
<th>Condition</th>
<th>OHIP</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>493</td>
<td>493</td>
<td>J45</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>765</td>
<td>765.00 to 765.19</td>
<td>P070, P071, P072, P073</td>
</tr>
<tr>
<td>Obesity</td>
<td>278</td>
<td>278.00</td>
<td>E660, E668, E669</td>
</tr>
<tr>
<td>Other atopic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>477</td>
<td>477.00, 477.08, 477.09</td>
<td>J301, J302, J303, J304</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>691</td>
<td>691.80</td>
<td>L208, L209</td>
</tr>
<tr>
<td>Food allergy</td>
<td>995</td>
<td>995.00</td>
<td>T7800, T7801, T7802, T7803, T7804, T7805, T7806, T7807, T7808, T7809</td>
</tr>
</tbody>
</table>

3.2.2 Management of Missing Data

Data regarding history of asthma, preterm birth, obesity and other atopic conditions were determined from Ontario administrative records and were complete for children who had lived in Ontario for all of their lives. Children who met the diagnostic criteria for asthma while living in Ontario had a defined age of incident asthma, but 597 children (0.2%) with asthma had an uncertain age of incident asthma, suggesting that they had lived outside Ontario at some time and met the diagnostic criteria for asthma during the first year they lived in or returned to Ontario. These children could have developed asthma at an earlier age than their Ontario records suggested and were excluded from the analyses of incident and currently-symptomatic incident asthma. Children not born in an Ontario hospital (27.8%) may have been missing data regarding preterm birth and children who did not live in Ontario throughout the study period may have been missing data regarding asthma, obesity or other atopic conditions if they had been coded as having these diagnoses only while living outside Ontario.
Most missing data for walkability quintile and income quintile reflected movement into and out of the Greater Toronto study area; 38.2% of children did not live in the GTA throughout the study. Birth neighborhood walkability data were missing for 9.8% of children. Walkability data were missing for 10.7-35.4% of children in any given year, with more missing data in later years, mirroring changes in the Greater Toronto population over that time (Loreto 2009, OMF 2011). Neighborhood income was not available in 1997-1998. Birth neighborhood income data were missing for 2.4-4.6% of children born in 1999-2003 and less than 10% of income data were missing in any given year. Children were included in analyses during years for which they had available walkability and income data. Sensitivity analyses were performed to evaluate the effects of all missing data.

3.2.3 Statistical analyses

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). We conducted asthma-free survival analysis comparing the time to incident asthma for the lowest two quintiles of neighborhood walkability versus the highest two quintiles. The association between low home neighborhood walkability at birth and age of incident childhood asthma was determined in unadjusted and multivariable Cox proportional hazards models. The association between low home neighborhood walkability in each year of the child’s life and age of incident asthma was evaluated using discrete-time hazard models (62). The Cox proportional and discrete-time hazard analyses were repeated for children with currently-symptomatic asthma requiring healthcare visits from April 1, 2011 to March 31, 2012.
The associations between at least one asthma visit and low walkability in each year of the child’s life were evaluated by Generalized Estimating Equations (GEE) (87) with an exchangeable correlation structure, which model the mean association in a population-average approach, and generalized linear mixed models (GLMM) with random intercepts and slopes, which model the within-subject covariance in a subject-specific approach. Both methods account for the non-independent clusters or repeated measures of healthcare visits for asthma by year of life for each child. Each covariate had previously-established association with incident asthma (4, 12, 13, 88) and was compared with walkability and asthma in unadjusted models. In the adjusted models, all covariates were included as potential confounders and removed one-at-a-time by backwards elimination if their association was non-significant (p ≥ 0.05). Effect modification with neighborhood walkability was evaluated for all confounders with a priori likelihood of interaction. Interaction terms were included in the model, and for variables showing evidence of statistical interaction, the models were re-run using indicator variables for each of the four categories of walkability (0, 1) and each covariate (0, 1). The least squares means were plotted for each of the four walkability-covariate categories in the GLMM.

The proportional hazards assumption and multi-collinearity were evaluated and proportional hazards model fit was determined using Schoenfeld residuals. The fit of fixed- and random-intercept and -slope GLMM were compared, and the simplest model with a good fit was chosen.
3.3 Results

Among the 326 383 children in the 1997-2003 birth cohorts, 69 628 (21.3%) met the OASIS criteria for incident asthma and 14 050 (4.3%) had currently-symptomatic incident asthma with healthcare visits for asthma from April 1, 2011 to March 31, 2012. The median age of asthma diagnosis was 2.5 years (interquartile range 4.0) for all children with asthma and 3.5 years (interquartile range 5.3) among children with currently-symptomatic incident asthma.

In unadjusted analyses, low birth neighborhood walkability was associated with any incident asthma (HR 1.12; 95% CI, 1.10-1.14) and currently-symptomatic incident asthma (HR 1.15; 95% CI, 1.11-1.20) (Table 3.2). Incident asthma was also associated with low birth neighborhood income, male sex, preterm birth, obesity and atopic conditions other than asthma (Table 3.2).

Table 3.2 Characteristics of the study cohort (N = 326 383)

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>N (%a)</th>
<th>Unadjusted hazardb of incident asthma (95% CIc)</th>
<th>Unadjusted hazardb of currently-symptomatic incident asthma (95% CIc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth walkability</td>
<td>115 600 (39.25)</td>
<td>1.12 (1.10-1.14)</td>
<td>1.15 (1.11-1.20)</td>
</tr>
<tr>
<td>Low birth income</td>
<td>59 551 (30.46)</td>
<td>1.08 (1.06-1.11)</td>
<td>1.11 (1.06-1.16)</td>
</tr>
<tr>
<td>Male sex</td>
<td>167 560 (51.3)</td>
<td>1.43 (1.41-1.46)</td>
<td>1.58 (1.52-1.63)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>22 639 (6.9)</td>
<td>1.71 (1.67-1.75)</td>
<td>1.69 (1.61-1.79)</td>
</tr>
<tr>
<td>Any healthcare visit for obesity</td>
<td>18 071 (5.5)</td>
<td>1.67 (1.62-1.71)</td>
<td>1.66 (1.57-1.76)</td>
</tr>
<tr>
<td>Any visit for an atopic condition other than asthma</td>
<td>222 667 (68.2)</td>
<td>3.08 (3.01-3.14)</td>
<td>3.87 (3.67-4.08)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Percentages are adjusted for missing data.</td>
</tr>
<tr>
<td>b Results of unadjusted Cox proportional hazards models.</td>
</tr>
<tr>
<td>c Confidence interval</td>
</tr>
</tbody>
</table>
After adjusting for birth neighborhood income, sex, preterm birth, obesity and other atopic conditions, children with low home neighborhood walkability at birth were at increased risk of incident asthma (HR 1.11; 95% CI, 1.08-1.14) and currently-symptomatic incident asthma (HR 1.10; 95% CI, 1.04-1.16) (Table 3.3). Younger children born between 2001 and 2003 had a lower risk of incident asthma (HR 0.92; 95% CI, 0.90-0.95), consistent with having had fewer years of life in which to develop asthma, but higher risk of currently-symptomatic incident asthma (HR 1.25; 95% CI, 1.18-1.33), consistent with having had fewer years to outgrow non-persistent asthma. When neighborhood walkability and income quintile were considered by year, children with low home neighborhood walkability had increased odds of incident asthma (OR 1.12; 95% CI, 1.09-1.15) and currently-symptomatic incident asthma (OR 1.11; 95% CI, 1.05-1.17) (Table 3.3). Associations of incident asthma with neighborhood income, sex, preterm birth, obesity and other atopic conditions were consistent among Cox proportional and discrete-time hazard models, demonstrating robust relationships.
Table 3.3 Association between incident asthma and neighborhood walkability among children in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incident asthma</td>
<td>Currently-symptomatic</td>
</tr>
<tr>
<td>Low walkability</td>
<td>1.11 (1.08-1.14)</td>
<td>1.10 (1.04-1.16)</td>
</tr>
<tr>
<td>Low income</td>
<td>1.06 (1.03-1.09)</td>
<td>1.04 (0.98-1.10)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.45 (1.41-1.48)</td>
<td>1.59 (1.50-1.68)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.57 (1.51-1.64)</td>
<td>1.50 (1.38-1.64)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.48 (1.41-1.56)</td>
<td>1.48 (1.34-1.64)</td>
</tr>
<tr>
<td>Other atopic conditions</td>
<td>2.99 (2.88-3.10)</td>
<td>3.60 (3.30-3.92)</td>
</tr>
</tbody>
</table>

\(^a\)Confidence Interval
Results of multivariable Cox proportional\(^b\) and discrete-time\(^c\) hazards models

After adjusting for neighborhood income in each year of life, sex, preterm birth, obesity, other atopic conditions and year of life, and taking repeated measures into account, children with low neighborhood walkability in a given year of life had increased odds of healthcare visits for asthma in that year (OR 1.11; 95% CI, 1.09-1.13) (Table 3.4). There was no interaction between neighborhood walkability and the covariates.

Table 3.4 Association between asthma visits in each year of life and neighborhood walkability among children living in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Adjusted odds ratio of healthcare visits for asthma (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generalized Estimating Equations(^b)</td>
</tr>
<tr>
<td>Low walkability</td>
<td>1.11 (1.09-1.13)</td>
</tr>
<tr>
<td>Low income</td>
<td>1.07 (1.05-1.09)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.35 (1.32-1.38)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.52 (1.47-1.58)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.52 (1.47-1.58)</td>
</tr>
<tr>
<td>Other atopic conditions</td>
<td>2.97 (2.89-3.06)</td>
</tr>
</tbody>
</table>

\(^a\)Confidence interval
Results of population average\(^b\) and subject-specific\(^c\) models, also adjusted for year of life.
The associations between walkability and asthma did not change when different cut points were used for walkability and income. Similar associations were also seen after including children whose date of incident asthma was uncertain (Table 3.5), and after restricting the analyses to children who were born between 1999 and 2003, children who were born in Ontario, and children who had lived in the GTA continuously since birth (Table 3.6).

Table 3.5 Sensitivity analyses: association between prevalent asthma\(^a\) and neighborhood walkability among children living in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Adjusted hazard ratio of prevalent asthma(^b) (95% CI(^c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low walkability</td>
<td>1.11 (1.06-1.17)</td>
</tr>
<tr>
<td>Low income</td>
<td>1.06 (1.01-1.12)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.60 (1.52-1.69)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.56 (1.44-1.70)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.54 (1.40-1.69)</td>
</tr>
<tr>
<td>Other atopic conditions</td>
<td>3.41 (3.17-3.67)</td>
</tr>
</tbody>
</table>

\(^a\)Including children whose timing of asthma diagnosis (entry into OASIS) is uncertain
\(^b\)Results of multivariable Cox proportional hazards models
\(^c\)Confidence interval

Table 3.6 Sensitivity analyses: Association between incident asthma and neighborhood walkability among children living in the Greater Toronto Area\(^a\)

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>1999-2003 birth cohorts(^e)</th>
<th>Born in Ontario(^d)</th>
<th>Lived in the Greater Toronto Area since birth(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low walkability</td>
<td>1.11 (1.08-1.14)</td>
<td>1.12 (1.09-1.16)</td>
<td>1.11 (1.08-1.14)</td>
</tr>
<tr>
<td>Low income</td>
<td>1.06 (1.03-1.09)</td>
<td>1.12 (1.09-1.15)</td>
<td>1.06 (1.03-1.09)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.45 (1.41-1.48)</td>
<td>1.46 (1.42-1.51)</td>
<td>1.45 (1.41-1.49)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.57 (1.51-1.64)</td>
<td>1.33 (1.27-1.39)</td>
<td>1.59 (1.52-1.66)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.48 (1.41-1.56)</td>
<td>1.37 (1.30-1.45)</td>
<td>1.47 (1.40-1.55)</td>
</tr>
<tr>
<td>Other atopic conditions</td>
<td>2.99 (2.88-3.10)</td>
<td>2.08 (1.99-2.17)</td>
<td>2.97 (2.86-3.09)</td>
</tr>
</tbody>
</table>

\(^a\)Results of multivariable Cox proportional hazards models
\(^b\)Confidence interval
\(^c\)Excluding children born in 1997-1998
\(^d\)Excluding children born outside Ontario
\(^e\)Excluding children who had lived outside Ontario for at least one whole year of life
There was no evidence of multi-collinearity between variables in the final Cox proportional hazards model and the Schoenfeld residuals suggested good model fit. The GEE standard errors were small, indicating reasonable fit for the population-average models. The fixed- and random-intercept GLMM yielded almost identical results and the random slope model showed a negligible and non-significant slope for walkability, suggesting that the fixed-intercept model fit the data appropriately. The results of the population-average and subject-specific models were very similar, demonstrating robust analyses.
3.4. Discussion

To our knowledge, neighborhood walkability has not been previously reported as a predictor of childhood asthma. Our results show that lower home neighborhood walkability is associated with greater incident asthma in Toronto children, after adjustment for obesity, neighborhood income and other factors associated with incident childhood asthma. This association persists for children with currently-symptomatic incident asthma at ages 8-15 years. Neighborhood walkability in a given year of life is also associated with current visits for asthma in that year.

Better fitness and conditioning is a possible mechanism of association between lower neighborhood walkability and asthma, and randomized control trials have shown decreased asthma symptoms, airway inflammation and bronchial hyper-reactivity with exercise among children (48) and adults (47) with asthma. Observational studies have not shown protective associations between incident childhood asthma and activity measured by accelerometer (49) and reported activity frequency (50).

Screen time, a surrogate for sedentary activity, has shown associations with both obesity and incident asthma. In Dunedin, New Zealand (79), number of hours of weekday television watching from ages 5-15 years was correlated with higher body-mass index at age 5 years and remained correlated at age 26 years, after adjusting for viewing at age 21 years. In Manitoba, Canada (50), daily screen time of 1 hour or more at ages 8-9 years was associated with physician-diagnosed asthma at ages 12-14 years (OR 2.11; 95% CI, 1.14–3.89) and the association was stronger for obese adolescents (OR 3.95; 95% CI, 1.70-9.12). Toronto children with asthma living within walking distance of their school were more likely to be driven by
school bus than children without asthma (OR 1.71; 95% CI, 1.06-2.76) (89), and reverse causation may have been the mechanism of this association, with a lifestyle involving less walking to school contributing to asthma development.

The association of asthma with sedentary activity and the absence of a protective association seen with activity levels in these studies may reflect differences between the effects of episodic moderate-to-vigorous physical activity versus an overall more active lifestyle with less sedentary time. Differences between these measures of activity have been seen for cardio-metabolic risk factors in other studies (90) and may also apply to childhood asthma. The walkability index used in this study is designed to be representative of an overall active lifestyle (38) and may be more predictive of lower sedentary activity than reports of moderate-to-vigorous exercise.

Obesity could have been an intervening variable on the causal pathway between walkability and asthma; however, if all of the relationship between walkability and asthma was explained by children living in less walkable neighborhoods being more obese, we would expect the association between neighborhood walkability and incident childhood asthma to decrease or disappear after adjusting for obesity. In our results, obesity remained a significant predictor for asthma in all models, but did not eliminate or substantially attenuate the association between asthma and walkability.

Studies have generally shown associations between being obese or overweight and childhood asthma development (8-13), although some have shown different associations between genders
This association may also depend on the asthma phenotype and age of onset (91) and there is evidence of common genetic mechanisms for asthma and obesity (92).

Recent longitudinal studies have suggested variable associations between the timing of obesity or overweight and childhood asthma. In the Prevention and Incidence of Asthma and Mite Allergy birth cohort (12), 8-year-old children had increased odds of dyspnea and bronchial hyper-reactivity only if their body mass index was above the 85th percentile at age 6-7 years, regardless of their body mass index at age 2 years. However, a pooled analysis of 12,050 children in 8 European birth cohorts (13) found that rapid body mass index increase until age 2 years was associated with increased risk of asthma development (HR 1.27; 95% CI, 1.06-1.51), even if the body mass index trajectory normalized between ages 2 and 6 years.

Variables such as subway stop density (81) and convenient exercise facilities (82) have been associated with lower risks of obesity among children and adolescents, but components of the validated walkability index used for this analysis, including the density of population, dwellings or intersections, have not been consistently associated with obesity (81-83).

Neighborhood income quintile (a surrogate measure for SES) was also evaluated as a potential confounder and effect modifier, and has been associated with asthma development in some populations (14, 36, 51), but not in others (52). In a prospective Australian birth cohort (14), physician-diagnosed asthma at age 14 years was associated with chronic low income (OR 2.21; 95% CI, 1.17-4.17), but not with transient low income. Among elementary school children in
southern California (36), children attending schools with >40% of children living in poverty had an increased risk of asthma development (HR 1.68; 95% CI, 1.10-2.56).

Our findings have extended the results of these published studies by documenting a novel and robust longitudinal association between low neighborhood walkability and childhood asthma that persists after adjustment for history of obesity, income and other covariates associated with asthma. These results support community-level interventions to modify home neighborhood environment in ways that are associated with positive changes in individual activity levels and decreased asthma development.

The prospectively-collected administrative data used in this study carry a low risk of reporting bias for walkability, asthma development and the covariates; bias due to reporting of conditions such as asthma, obesity and other atopic conditions is likely to be non-differential and bias the study results towards the null. Participant selection bias was minimized by adhering to the prospectively-determined study entry criteria and performing sensitivity analyses, which suggested that the study results were not biased by missing asthma, neighborhood walkability and covariate data.

This study’s strengths include up to 8-15 years of prospectively-collected administrative data, which has allowed evaluation of the temporal relationship between walkability and asthma in a large number of children. The OASIS asthma outcome has been validated against physician diagnosis of asthma in children (85) with high sensitivity and specificity (91.4% and 82.9%, respectively). The walkability index used in this study has been validated against actual activity
levels in adults (38) and is a reasonable surrogate for individual activity. Although parental activity levels have been correlated with children’s activity levels in previous studies (93, 94), the associations between parental and adolescent activity levels have been less clear (95). Published cross-sectional studies have shown variable associations between non-validated measures of walkability and actual activity levels in children (81) and adolescents (96), reaffirming the importance of using a validated walkability index for these analyses.

Limitations of this study include the neighborhood-level walkability index and income quintile data; individual-level cohort studies should be conducted to evaluate the associations between walkability, asthma and other personal exposures. This study included only data from the GTA, which may not be generalizable to all urban centers or suburban or rural communities. The healthcare administrative data for preterm birth, obesity and other atopic conditions have not been validated against clinical diagnoses, although they show reasonable face validity. Obesity and other atopic conditions were also reported as time-independent covariates and information regarding timing of diagnosis with obesity and atopic conditions was not available. Data regarding family history of asthma and personal and household exposure variables such as smoking and air pollution were not available.

3.5. Conclusions

Children living in neighborhoods with low walkability are at increased risk of incident asthma and current healthcare visits for asthma, after adjusting for other neighborhood and individual characteristics associated with asthma. Improvement of neighborhood walkability, for example, by greater placement of services such as banks and grocery stores within residential
neighborhoods and adding pedestrian paths between roads to improve street connectivity, may offer strategies for primary asthma prevention. These findings suggest that walkability should be promoted in neighborhoods under development and renovation.
3.6 Supplemental Methods for Project 2

3.6.1 Dataset Derivation for Asthma-Free Survival Analysis and Cox Proportional Hazards Models

Neighborhood walkability quintile in each child’s year of birth was generated from the year of birth and walkability quintile in each fiscal year. Three dichotomous walkability predictor variables were generated for each child’s year of birth, comparing the three lowest versus two highest quintiles, the four lowest versus the highest quintile and the two lowest versus the two highest quintiles. Similarly, neighborhood income quintile in each child’s year of birth was generated from the year of birth and income quintile in each fiscal year. Three dichotomous income predictor variables were generated, comparing the three lowest versus the two highest quintiles, the four lowest versus the highest quintile and the two lowest versus the two highest quintiles.

An approximate date of birth was generated from the child’s year of birth by estimating the birth month as ‘07’ and the birth day as ‘01’. The estimated birth month, estimated birth day and four-digit year of birth were concatenated in an estimated date of birth using the cat x formula and spaces were removed using the compress formula. The estimated date of birth was then changed to the mmddyy8. SAS format to use in calculations. The date of incident asthma was available from the OASIS dataset and was defined as the date of the second health care visit for asthma within two years of a first health care visit for asthma or the date of the first hospitalization for asthma, whichever came first.
To calculate the approximate age of asthma development in days, the estimated date of birth was subtracted from the date of incident asthma. Those with ages of asthma development less than 0 due to the estimation of date of birth were recoded with an age of asthma development of 0. The age of asthma development was divided by 365 to convert to age in years.

Survival analysis was conducted using Cox proportional hazards models. To determine the gradient of association between walkability and asthma development, the hazard of asthma development for each of the four lower quintiles of neighborhood walkability was sequentially compared with the hazard of asthma development in the highest walkability quintile. Similar analyses were conducted for neighborhood income.

Cox proportional hazards models were then generated for each of the dichotomous walkability predictors, comparing the lower to the higher walkability quintiles. The results were similar regardless of the walkability quintile cut point and the dichotomous walkability variable was defined as the two lowest versus the two highest walkability quintiles. Similar analyses were conducted for neighborhood income, with similar results for each of the three dichotomous income variables; the dichotomous income variable was defined as the two lowest versus the two highest income quintiles.

Cox proportional hazards models of asthma development were conducted comparing low versus high walkability and adjusted for income, sex, preterm birth, obesity, other atopic conditions and year of birth. In addition to the models comparing the two lowest quintiles versus the two highest quintiles of walkability described in section 3.2, proportional hazards models of asthma
development were generated using continuous walkability and categorical quintiles of walkability as predictors.

3.6.2 Dataset Derivation for the Discrete Hazard Models

The age of asthma development was changed from a continuous decimal variable to an integer using the int() function. The integer age of asthma development was then converted to the year of life of asthma development by adding one (e.g. a child who developed asthma when they were 2 years old developed asthma in their third year of life).

In a wide dataset, incident asthma variables were generated for each year of life from 1 to 15. Based on the child’s age of asthma development, the presence or absence of incident asthma in each year of the child’s life was coded from the first year up to the greatest available year of life. For children with asthma, these variables were set to equal the year of life during which asthma developed in the year of life where asthma developed and to 0 in the other years of life (e.g. a child who developed asthma during his or her fourth year of life would have ‘4’ in the fourth year of life column and ‘0’ in columns Designating earlier year of life). The years of life after asthma development were censored by coding them as missing. Children without asthma (i.e. children who had not yet developed asthma) had incident asthma set to ‘0’ in all years of life.

Dichotomous neighborhood walkability comparing the two lowest versus the two highest walkability quintiles in each year of life was assigned based on the year of birth and the walkability in each fiscal year. For example, for a child born in 1997, the walkability in their first year of life was set as their walkability in 1997 and the walkability in their second year of life
was set as their walkability in 1998, etc., until 2011. Dichotomous neighborhood income was generated for each year of life in a similar fashion.

The incident asthma, walkability and income datasets were changed from wide to long format. The longitudinal datasets for incident asthma, walkability and income were then merged by unique identifier and year of life. An indicator variable (1-15) was added for each possible year of life and set to 99 for years with missing asthma data. Years of life in which the child did not live in the GTA were recoded as missing. For the younger children, years of life that the child had not yet reached were also recoded as missing (e.g. a child with asthma born in 2003 would have been 8 at the end of the study and would have had data up to the 9th year of life and no data for later years of life).

The time-invariant covariates were merged into the model by the child’s unique identifier, and appeared in each year of life. In order to compare walkability simultaneously in each year of life and age of asthma development, discrete-time hazard models were run using logistic regression. The predictors included dichotomous walkability and income in each year of life available and the outcome was incident asthma; models were also adjusted for the time-invariant covariates.

3.6.3 Dataset Derivation for Generalized Linear Mixed Models and Generalized Estimating Equations

In the long-format asthma claims dataset, the age of each asthma healthcare visit in days was calculated by subtracting the estimated date of birth from the date of service and was converted to age in years by dividing by 365 days/year. The age of service was then converted to an integer
using the integer function. The integer age of service was then converted to the year of life for each asthma visit by adding 1 year.

With the data still in long format, indicator variables were generated for the presence or absence of a visit for asthma in each year of life. Duplicates that were identical in all variables for children with multiple visits for asthma in a given year of life were removed by the ‘nodupkey’ instruction. A year variable was created for each year of life (1-15). A yearly asthma visit variable was designated 1 for each year of life in which the child had a visit for asthma and missing if the child did not have a visit for asthma in that year of life. For children without asthma, both the year and asthma visit variables were missing for each year of life. Because the claims dataset only contained children with an OASIS diagnosis of asthma, no child without asthma had a non-missing asthma visit.

A separate dataset was generated to distinguish the number of years of life for which each child should have data. A wide dataset was generated with year = 1 for each child with data in a given year of life: year = 1 in years 1-9 for all children, year = 1 in year 10 for those born in 1997-2002, year = 1 in year 11 for those born in 1997-2001, year = 1 in year 12 for those born in 1997-2000, year = 1 in year 13 for those born in 1997-1999, year = 1 in year 14 for those born in 1997-1998, and year = 1 in year 15 for those born in 1997. The dataset was changed to long format and the empty years removed for children born after 1997, who were not old enough to have data for all 15 years.
The long-format year dataset and long-format asthma visit dataset were merged by unique identifier and year of life. For children with asthma, but no visit in a given year of life, the visit variable was recoded as 0 in that year of life. For children without asthma, the visit variable was recoded as 0 for all years of life.

Walkability and income data for each year of life had been generated for the discrete-time hazard analysis as described in section 3.6.2. The walkability and income by year of life datasets were merged with the asthma visit by year of life dataset by unique identifier and year of life. The time-independent covariates (sex, preterm birth, obesity, and other atopic conditions) were merged by unique identifier, so that they were present in all years of life for which a child’s asthma visit, walkability and income data were available.
3.7 Supplemental Results for Project 2

3.7.1 Gradient of Association between Walkability Quintile and Asthma

In the unadjusted models comparing the lower three walkability quintiles with the highest or most walkable quintile, the hazards of asthma development were closely clustered, with slightly larger hazards of asthma development seen for each successively higher quintile of walkability compared with the highest quintile in almost every year (Figure 3.1). The fourth (second highest) quintile of walkability showed more variable and less precise hazard ratios of asthma development when compared to the highest quintile. One possible reason for this variability includes a lack of walkability homogeneity within these neighborhoods, for example highways and side streets with widely varying walkability within a small area. Different levels of walkability within a neighborhood are a limitation of neighborhood-level data. Defining neighborhoods with smaller areas could reduce the walkability variation within a neighborhood, but could still include locations of varying walkability.

Similar results were seen for sequentially comparing the hazards of asthma development in the lower four neighborhood income quintiles versus the highest income quintile (Figure 3.2). The second-highest income quintile with the least precise hazard ratio of asthma development may represent neighborhoods with variable individual income, such as a combination of high-income homes and public housing.
Figure 3.1 Crude hazard ratios of incident asthma associated with the four lowest walkability quintiles compared with the highest walkability quintile

Figure 3.2 Crude hazard ratios of incident asthma associated with the four lowest income quintiles compared with the highest income quintile
3.7.2 Walkability as a Continuous Variable

Continuous walkability score (HR 1.02; 95% CI, 1.00-1.04) and categorical walkability quintile (HR 1.02; 95% CI, 1.00-1.04) were associated with an increased hazard of asthma development (Table 3.7). Although the risk of asthma development was attenuated (2% increased risk) by using the categorical and continuous walkability predictors compared with the dichotomous walkability predictor (12% increased risk), the significant association between asthma and walkability remained. The dichotomous walkability results allow greater ease of interpretation, but the persistence of an association with the continuous and categorical walkability predictor are reassuring that the association did not appear as a result of dichotomizing the predictor variable.

Table 3.7 Adjusted hazard ratio of incident asthma among children living in neighborhoods with lower walkability, as a continuous or categorical variable*

<table>
<thead>
<tr>
<th></th>
<th>Adjusted hazard ratio of incident asthma (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous walkability score †</td>
</tr>
<tr>
<td>Walkability (birth)</td>
<td>1.02 (1.00, 1.04)</td>
</tr>
<tr>
<td>Income (birth)</td>
<td>1.03 (0.98, 1.08)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.37 (1.20, 1.55)</td>
</tr>
<tr>
<td>Preterm</td>
<td>1.27 (1.05, 1.53)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.68 (1.29, 2.19)</td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>3.95 (3.34, 4.66)</td>
</tr>
<tr>
<td></td>
<td>Categorical walkability quintile</td>
</tr>
<tr>
<td>Walkability (birth)</td>
<td>1.02 (1.00, 1.04)</td>
</tr>
<tr>
<td>Income (birth)</td>
<td>1.03 (0.98, 1.08)</td>
</tr>
<tr>
<td>Male sex</td>
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</tr>
<tr>
<td>Preterm</td>
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</tr>
<tr>
<td>Obesity</td>
<td>1.68 (1.29, 2.19)</td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>3.95 (3.35, 4.66)</td>
</tr>
</tbody>
</table>

*Results of multivariable Cox proportional hazard models
†For years 2001-2003
3.7.3 Evaluation of Cox Proportional Hazards Model Fit Using Schoenfeld Residuals

Schoenfeld plots show horizontal linear residuals between -1 and +1 for all variables in the Cox proportional hazards models comparing the hazard of asthma development for the two lowest versus the two highest walkability quintiles (Figure 3.3), suggesting good model fit.

Figure 3.3 Schoenfeld Residuals for fit of Cox proportional hazards model of walkability
Figure 3.4 Directed acyclic graph describing potential confounding and interaction between neighborhood walkability, asthma and covariates

Legend:

One variable affects another →

Variables inter-related ↔

Sex

Obesity

Year of life

Neighborhood walkability

Neighbourhood income

Preterm

Atopy

Birth year

Asthma
3.7.4 Evaluation of Interaction between Walkability and Covariates in the Generalized Linear Mixed Models

Based on the Directed Acyclic Graph (Figure 3.4), interaction with walkability was evaluated for income and obesity and interaction with income was evaluated for preterm birth and atopy. Interaction was not seen for any of these variables, as shown by the lack of crossing slopes for the plots of least squares mean versus neighborhood walkability (Figures 3.5.1 and 3.5.2) or neighborhood income (Figures 3.5.3 and 3.5.4) for both values of the covariate.

**Figure 3.5.1 Evaluation for interaction between walkability and obesity**

**Figure 3.5.2 Evaluation for interaction between walkability and income**
Figure 3.5.3 Evaluation for interaction between income and atopy

Figure 3.5.4 Evaluation for interaction between income and preterm birth


3.8 Chapter 3 Summary

Childhood asthma is predicted by neighborhood walkability, even after adjustment for income and other characteristics previously determined to be associated with asthma, such as gender, preterm birth and atopic conditions other than asthma. Good model fit is demonstrated and there is no evidence of interaction between walkability or income and other predictors of childhood asthma. These results show an association between childhood asthma development and neighborhood walkability, a community measure of neighborhood features conducive to walking, and suggest that society may contribute to decreased incidence of childhood asthma by promoting walkability within neighborhoods.

Family income may not be an ideal measure of socioeconomic status, especially for children. As presented in the next chapter, further analyses have been conducted to evaluate the associations between childhood asthma and neighborhood deprivation, a comprehensive measure of socioeconomic well-being, which considers parental education, single parenthood, unemployment, government aid and poor home repair, as well as income.
Chapter 4

Neighborhood Deprivation is Associated with Childhood Asthma Development

4.1 Introduction

Parental income or income bracket is often used as a surrogate for child socioeconomic status (SES). Some cross-sectional and longitudinal studies have shown associations between parental income or SES and incident childhood asthma, but the associations have not been consistent.

Material deprivation, which takes education, single parenthood, unemployment, government aid and poor home repair into account, as well as income, has been proposed as a more comprehensive measure of childhood SES and has been measured as part of the Ontario Marginalization Index (ON-Marg) (56).

Adults with high material deprivation have increased odds of asthma (OR 1.23; 95% CI, 1.17-1.28) (56). In the Peel region of Ontario, higher rates of emergency department visits for asthma and chronic obstructive pulmonary disease have been observed in areas with high material deprivation compared to overall visit rates (57). Material deprivation has also been associated with poor glycemic control in children with type I diabetes (97). To our knowledge, this index has not been studied in association with childhood asthma and may represent a helpful tool for evaluating the effects of disparities in health and social advantages on the likelihood of
developing and continuing to need healthcare visits for childhood asthma. We evaluated the associations between material deprivation and childhood asthma among children living in the Greater Toronto Area (GTA).
4.2 Methods

4.2.1 Data Sources

As previously described (98), we obtained prospectively-collected Ontario health administrative data regarding clinic visit records from the Ontario Health Insurance Plan (OHIP), emergency department records from the National Ambulatory Care Reporting System (NACRS) and hospitalization data from the Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD), housed at the Institute for Clinical Evaluative Sciences (ICES). We used the Registered Persons Database (RPDB) to identify children who were born between 1997 and 2003 and had lived in the Greater Toronto Area (GTA) at any time during their lives; these children were followed from birth until the end of the study (March 31, 2012). Children born in 1997 had up to 15 years of data and children born in 2003 had up to 8 years of data. This study was approved by Research Ethics Boards at the Hospital for Sick Children and the University of Toronto.

ON-Marg was developed by Matheson et al (56) to create a standardized measure of marginalization in Ontario and to aid understanding of inequalities in measures of health and social well-being in various population groups and geographical areas. The index was generated using principal components factor analysis, in which any of 42 initial 2001 census measures with low factor loadings were removed on an iterative basis. The final index contained 18 census tract measures within 4 dimensions and was validated by comparison with 2006 census tract measures and with 2001 and 2006 dissemination areas within the census tracts. Each dimension represents a separate validated index and one of the dimensions, material deprivation, includes adults with no high school graduation, lone parent families, government transfers, unemployment, low
income, and homes needing major repairs. The material deprivation index ranges from a score of -2 (low deprivation) to +6 (high deprivation) and was reported in quintiles, with the lowest quintile being the least deprived and the highest quintile the most deprived. For this analysis, deprivation was dichotomized into the two highest quintiles versus the two lowest quintiles.

Children are defined as having asthma and entered into the OASIS database after they have two outpatient visits for asthma within two consecutive years or are hospitalized for asthma (84). These criteria are sensitive and specific compared to physician-diagnosed childhood asthma (85) and parental report of physician-diagnosed childhood asthma (86). As previously reported (98), asthma encounters were defined by the OHIP or the primary diagnostic ICD-9/ICD-10 code in NACRS and CIHI-DAD (Table 3.1). For children in the OASIS database, asthma visits recorded in the OHIP, NACRS, and CIHI databases were available for each year of life during which the child lived in Ontario. Three main asthma outcomes were evaluated: incident asthma, currently-symptomatic incident asthma, and asthma by year of life. Incident Asthma was defined as the timing of entry into the OASIS database. Currently-symptomatic incident asthma was defined as the timing of entry into the OASIS database for children with any healthcare visit for asthma between April 1, 2011 and March 31, 2012, which would have occurred between ages 8-15 years for children in this cohort. Asthma by year of life was defined as at least one healthcare visit for asthma in a given year of the child’s life.

Data from the RPDB were used to determine sex and data from the OHIP, NACRS and CIHI databases were used to determine history of preterm birth, and any diagnostic coding for obesity (weight or body mass index >95th percentile) and for atopic conditions other than asthma,
(allergic rhinitis, eczema and food allergy). The validated Walkability Index included four dimensions: population density, dwelling density, access to all retail and services, and street connectivity (38), and was reported as a quintile (1-low walkability and 5-high walkability) for each neighborhood in the GTA and dichotomized into the two lowest quintiles versus the two highest quintiles.

4.2.2 Management of Missing Data

Birth neighborhood deprivation data were missing for 2.7-5.7% of children and neighborhood deprivation data were missing for 3.8-5.7% of children in any given year. Age of incident asthma was missing for 597 children (0.2%) with asthma, who may have developed asthma while living outside Ontario. Children who lived outside Ontario at some point may have been missing data regarding asthma, obesity or other atopic conditions if these diagnoses were not reported while they lived in Ontario. Preterm birth may have been missing for some of the 27.8% of children who were not born in an Ontario hospital. Birth neighborhood walkability data were missing for 9.8% of children and walkability data were missing for 10.7-35.4% of children in any given year.

Sensitivity analyses were conducted to evaluate the effects of missing data by restricting the participants to children born in an Ontario hospital or living in the GTA continuously since birth. The analyses were also repeated excluding the walkability covariate.

4.2.3 Statistical Analyses

All analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC). Asthma-free survival analysis was used to compare the time to asthma development for the highest two quintiles of
home neighborhood deprivation versus the lowest two quintiles. Unadjusted and adjusted Cox proportional hazards models were used to determine the association between high deprivation at birth and age of childhood asthma development. The association between high deprivation in each year of the child’s life and age of asthma development was determined using discrete-time hazard models (62). The Cox proportional and discrete-time hazards analyses were repeated for development of currently-symptomatic childhood asthma. Generalized Estimating Equations (GEE) and generalized linear mixed models (GLMM) were used to evaluate the associations between at least one asthma visit and high deprivation in each year of the child’s life, accounting for the clustering or repeated measures of asthma healthcare visits in each year of life for each child.

Covariates associated with asthma development (4, 12, 13, 88, 98) and deprivation in unadjusted models were included as potential confounders in the full model and removed individually by backwards elimination if the association with asthma development was non-significant (p>0.05). Similarly, covariates with a priori likelihood of interaction with neighborhood deprivation were evaluated for effect modification by plotting GLMM least squares means for each of the four deprivation-covariate categories.
4.3 Results

Of the 326 383 participants in the 1997-2003 Toronto birth cohorts, 69 628 children (21.3%) met the OASIS criteria for incident asthma, with a median age of diagnosis of 2.5 years (interquartile range 4.0), and 14 050 children (4.3%) met the criteria for currently-symptomatic incident asthma at ages 8-15 years, with a median age of diagnosis of 3.5 years (interquartile range 5.3).

In unadjusted proportional hazards models, high-deprivation birth neighborhood was associated with development of any (HR 1.14; 95% CI, 1.12-1.16) and currently-symptomatic (HR 1.16; 95% CI, 1.11-1.20) asthma (Table 4.1). Male sex, preterm birth, obesity, atopic conditions other than asthma and low walkability of the birth neighborhood were also associated with childhood asthma development (Table 4.1). Obesity, atopic conditions other than asthma and neighborhood walkability were also associated with high birth neighborhood deprivation (Table 4.1).

Table 4.1 Characteristics of the study cohort (N = 326 383)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N (%)(^a)</th>
<th>HR (95% CI)(^b) of high deprivation</th>
<th>HR (95% CI)(^b) of incident asthma</th>
<th>HR (95% CI)(^b) of currently-symptomatic(^c) incident asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High birth deprivation</td>
<td>170 096 (52.1)</td>
<td>--</td>
<td>1.14 (1.12, 1.16)</td>
<td>1.16 (1.11, 1.20)</td>
</tr>
<tr>
<td>Low birth walkability</td>
<td>120 259 (36.8)</td>
<td>1.10 (1.09, 1.11)</td>
<td>1.11 (1.09, 1.13)</td>
<td>1.15 (1.11, 1.19)</td>
</tr>
<tr>
<td>Male sex</td>
<td>167 560 (51.34)</td>
<td>1.00 (0.99, 1.00)</td>
<td>1.37 (1.35, 1.39)</td>
<td>1.56 (1.51, 1.61)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>22 639 (6.94)</td>
<td>0.99 (0.97, 1.00)</td>
<td>1.56 (1.53, 1.59)</td>
<td>1.66 (1.58, 1.75)</td>
</tr>
<tr>
<td>Obesity</td>
<td>18 071 (5.54)</td>
<td>1.12 (1.11, 1.13)</td>
<td>1.55 (1.52, 1.59)</td>
<td>1.64 (1.55, 1.73)</td>
</tr>
<tr>
<td>Atopic conditions other than asthma</td>
<td>222 667 (68.22)</td>
<td>1.09 (1.08, 1.10)</td>
<td>2.79 (2.73, 2.84)</td>
<td>3.79 (3.59, 3.99)</td>
</tr>
</tbody>
</table>

\(^a\)Percentages account for missing data.
\(^\text{b}\)Unadjusted hazard ratio (95% confidence interval)
\(^\text{c}\)At ages 8-15 years
In proportional hazards models adjusted for sex, preterm birth, obesity and atopic conditions other than asthma, children with high birth neighborhood deprivation were at increased risk of incident asthma (HR 1.11; 95% CI, 1.09-1.14) and currently-symptomatic incident asthma at ages 8-15 years (HR 1.11; 95% CI, 1.05-1.16) (Table 4.2).

Table 4.2 Associations between incident asthma and neighborhood deprivation among children living in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)(^a) of incident asthma</th>
<th>HR (95% CI)(^a) of currently-symptomatic incident asthma</th>
<th>OR (95% CI)(^c) of incident asthma</th>
<th>OR (95% CI)(^c) of currently-symptomatic incident asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High deprivation</td>
<td>1.11 (1.09, 1.14)</td>
<td>1.11 (1.05, 1.16)</td>
<td>1.11 (1.09, 1.14)</td>
<td>1.10 (1.02, 1.18)</td>
</tr>
<tr>
<td>Low walkability</td>
<td>1.08 (1.06, 1.10)</td>
<td>1.10 (1.06, 1.15)</td>
<td>1.10 (1.08, 1.12)</td>
<td>1.10 (1.04, 1.17)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.44 (1.42, 1.47)</td>
<td>1.56 (1.49, 1.63)</td>
<td>1.47 (1.44, 1.50)</td>
<td>1.60 (1.50, 1.70)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.57 (1.52, 1.62)</td>
<td>1.48 (1.38, 1.59)</td>
<td>1.64 (1.58, 1.70)</td>
<td>1.53 (1.39, 1.69)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.46 (1.41, 1.51)</td>
<td>1.59 (1.48, 1.72)</td>
<td>1.47 (1.41, 1.52)</td>
<td>1.54 (1.39, 1.71)</td>
</tr>
<tr>
<td>Atopic conditions other than asthma</td>
<td>2.98 (2.90, 3.07)</td>
<td>3.85 (3.59, 4.12)</td>
<td>3.01 (2.93, 3.10)</td>
<td>4.01 (3.65, 4.42)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted hazards ratio (95% confidence interval), also adjusted for year of birth. Results of multivariable Cox proportional hazard models

\(^b\)At ages 8-15 years

\(^c\)Adjusted odds ratio (95% confidence interval), also adjusted for year of birth. Results of discrete-time hazard models

Birth year was a significant covariate of the association between high deprivation and asthma development, both as a continuous variable and when dichotomized into younger and older age groups. Children born from 2001-2003 were less likely to have developed asthma (HR 0.99; 95% CI, 0.97-1.00) than those born from 1997-2000, consistent with having had fewer years in which to develop asthma, but were more likely to have developed currently-symptomatic asthma (HR 1.50; 95% CI, 1.45-1.56), having had less time to outgrow transient asthma symptoms.
Children with higher home neighborhood deprivation in each year of life had an increased odds of incident asthma (OR 1.11; 95% CI, 1.09-1.14) and currently-symptomatic incident asthma at ages 8-15 years (OR 1.10; 95% CI, 1.02-1.18) (Table 4.2).

Children with high neighborhood deprivation in a given year of life had increased odds of having at least one healthcare visit for asthma in that year (OR 1.10; 95% CI, 1.07-1.12) (Table 4.3). The population-average and subject-specific results were similar. Effect modification was not present for any covariate.

Table 4.3 Association between asthma visits and neighborhood deprivation in each year of life among children living in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)a of asthma visits by year using Generalized Estimating Equationsb</th>
<th>OR (95% CI)a of asthma visits by year using fixed-intercept generalized linear mixed modelsc</th>
</tr>
</thead>
<tbody>
<tr>
<td>High deprivation</td>
<td>1.10 (1.07, 1.12)</td>
<td>1.09 (1.06, 1.11)</td>
</tr>
<tr>
<td>Low walkability</td>
<td>1.10 (1.08, 1.13)</td>
<td>1.11 (1.08, 1.13)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.35 (1.32, 1.38)</td>
<td>1.34 (1.31, 1.37)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.55 (1.49, 1.61)</td>
<td>1.52 (1.47, 1.57)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.52 (1.46, 1.58)</td>
<td>1.53 (1.48, 1.59)</td>
</tr>
<tr>
<td>Atopic conditions other than asthma</td>
<td>2.93 (2.85, 3.02)</td>
<td>3.00 (2.91, 3.08)</td>
</tr>
</tbody>
</table>

aAdjusted odds ratio of asthma visits (95% confidence interval), also adjusted for year of life Results of population average and subject-specific models

Similar associations between high neighborhood deprivation and asthma were seen after restricting the analyses to children who were born in an Ontario hospital or children who had lived in the GTA continuously since birth (Table 4.4), and when the walkability covariate was excluded from the Cox proportional and discrete-time hazard models (Table 4.5) and the GEE and GLMM models (Table 4.6).
Table 4.4 Sensitivity analyses: Associations between incident asthma and birth neighborhood deprivation among children living in the Greater Toronto Area

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)\textsuperscript{a} of incident asthma</th>
<th>HR (95% CI)\textsuperscript{a} of currently-symptomatic\textsuperscript{b} incident asthma</th>
<th>HR (95% CI)\textsuperscript{a} of incident asthma</th>
<th>HR (95% CI)\textsuperscript{a} of currently-symptomatic\textsuperscript{b} incident asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High deprivation</td>
<td>1.18 (1.16, 1.21)</td>
<td>1.15 (1.10, 1.22)</td>
<td>1.11 (1.08, 1.14)</td>
<td>1.19 (1.06, 1.18)</td>
</tr>
<tr>
<td>Low walkability</td>
<td>1.11 (1.09, 1.14)</td>
<td>1.10 (1.05, 1.15)</td>
<td>1.10 (1.07, 1.12)</td>
<td>1.13 (1.07, 1.19)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.46 (1.43, 1.49)</td>
<td>1.57 (1.49, 1.65)</td>
<td>1.46 (1.42, 1.49)</td>
<td>1.58 (1.50, 1.67)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1.32 (1.28, 1.36)</td>
<td>1.36 (1.26, 1.46)</td>
<td>1.59 (1.53, 1.65)</td>
<td>1.46 (1.34, 1.58)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.34 (1.29, 1.39)</td>
<td>1.48 (1.37, 1.61)</td>
<td>1.50 (1.44, 1.57)</td>
<td>1.55 (1.42, 1.70)</td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>1.99 (1.93, 2.05)</td>
<td>3.06 (2.81, 3.33)</td>
<td>2.89 (2.79, 2.99)</td>
<td>3.64 (3.36, 3.94)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted hazards ratio of incident asthma (95% confidence interval), also adjusted for year of birth. Results of multivariable Cox proportional hazards models

\textsuperscript{b}At ages 8-15 years

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Table 4.5 Association between incident asthma and neighborhood deprivation among children living in the Greater Toronto Area, excluding the walkability covariate

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)\textsuperscript{a} of incident asthma</th>
<th>HR (95% CI)\textsuperscript{a} of currently-symptomatic\textsuperscript{b} incident asthma</th>
<th>OR (95% CI)\textsuperscript{c} of incident asthma</th>
<th>OR (95% CI)\textsuperscript{c} of currently-symptomatic\textsuperscript{b} incident asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High deprivation</td>
<td>1.11 (1.09, 1.13)</td>
<td>1.11 (1.06, 1.15)</td>
<td>1.12 (1.09, 1.14)</td>
<td>1.09 (1.02, 1.17)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.43 (1.41, 1.46)</td>
<td>1.55 (1.50, 1.62)</td>
<td>1.47 (1.44, 1.50)</td>
<td>1.60 (1.50, 1.70)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1.58 (1.54, 1.62)</td>
<td>1.51 (1.42, 1.60)</td>
<td>1.64 (1.58, 1.69)</td>
<td>1.53 (1.39, 1.69)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.46 (1.42, 1.51)</td>
<td>1.56 (1.46, 1.66)</td>
<td>1.46 (1.41, 1.52)</td>
<td>1.54 (1.39, 1.71)</td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>2.96 (2.89, 3.03)</td>
<td>3.89 (3.67, 4.14)</td>
<td>3.02 (2.94, 3.11)</td>
<td>4.03 (3.66, 4.44)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted hazards ratio (95% confidence interval), also adjusted for year of birth. Results of multivariable Cox proportional hazard models

\textsuperscript{b}At ages 8-15 years

\textsuperscript{c}Adjusted odds ratio (95% confidence interval), also adjusted for year of birth. Results of discrete-time hazard models
Table 4.6 Association between asthma visits and neighborhood deprivation in each year of life among children living in the Greater Toronto Area, excluding the walkability covariate

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)$^a$ of asthma visits by year using Generalized Estimating Equations$^b$</th>
<th>OR (95% CI)$^a$ of asthma visits by year using fixed-intercept generalized linear mixed models$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>High deprivation</td>
<td>1.03 (1.02, 1.05)</td>
<td>1.03 (1.02, 1.05)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.37 (1.36, 1.39)</td>
<td>1.36 (1.34, 1.37)</td>
</tr>
<tr>
<td>Preterm</td>
<td>1.52 (1.48, 1.56)</td>
<td>1.47 (1.44, 1.51)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.47 (1.44, 1.51)</td>
<td>1.48 (1.45, 1.51)</td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>2.79 (2.74, 2.85)</td>
<td>2.82 (2.77, 2.87)</td>
</tr>
</tbody>
</table>

$^a$Adjusted odds ratio (95% confidence interval), also adjusted for year of life
Results of population average$^b$ and subject-specific$^c$ models

The Schoenfeld residuals showed good Cox proportional hazards model fit. The GEE standard errors were small, indicating reasonable fit for the population-average models. Results of the fixed- and random-intercept GLMM were similar, suggesting that the fixed-intercept model described the data appropriately. The random slope model had a negligible and non-significant slope for deprivation.
4.4 Discussion

Childhood asthma development is associated with neighborhood deprivation at birth and in each year of life; these associations persist for development of childhood asthma that remains symptomatic at ages 8-15 years. Children with deprivation in a given year of life also have increased odds of healthcare visits for asthma in that year of life. The presence of an association among children who continued to have asthma visits until ages 8-15 years and when compared with asthma visits in each year of life suggests that the deprivation-asthma association holds true for persistent asthma, as well as transient reactive airways in early childhood.

Few published studies have evaluated associations between deprivation and asthma, but parental or household income has been more commonly evaluated as a predictor of incident childhood asthma. In a study of 2614 Swedish children, those with the lowest parental income tertile had higher odds of asthma compared with the highest parental income tertile (OR 3.03; 95% CI, 1.52-5.88) (51). A longitudinal Canadian study showed an increased hazard of incident childhood asthma at age 5 years among children with low (HR 1.33; 95% CI, 0.98-1.78) and very low (HR 1.35; 95% CI, 1.01-1.82) SES index (4). Among New York City children, a gradient of incident asthma was seen with three lower family income brackets compared to the highest income bracket (99), with the highest odds of asthma in the lowest income bracket (OR 2.10; 95% CI, 1.25-3.52). Neighborhood income quintile has also been associated with incident childhood asthma in Toronto, Canada (HR 1.06; 95% CI, 1.03-1.09) (98).

However, a prospective study of 1000 participants in Dunedin, New Zealand (52) showed no association between asthma and SES. A birth cohort of children in Manitoba, Canada (15)
showed no association between family income and risk of incident asthma at age 7 years after adjusting for maternal distress, suggesting that some of the variability in associations between childhood asthma and income may be due to other covariates considered in the models.

There is also evidence that the timing of income status may influence its association with incident childhood asthma. In a prospective Australian birth cohort, family income trajectories were modeled and physician-diagnosed asthma at age 14 years was associated with chronic low income (OR 2.21; 95% CI, 1.17-4.17) (14), while 14-year-old teenagers from families with increasing and decreasing income did not have an increased odds of asthma.

The variability of associations between income and incident childhood asthma, depending on the population and on the other covariates included, suggests that a more comprehensive measure of childhood well-being and SES should be used as a predictor in these models. The material deprivation index considers adults with no high school graduation, lone parent families, government transfers, unemployment, and homes needing major repairs in addition to family income.

Mold and moisture damage is the most frequently studied characteristic related to home repair. Systematic reviews have generally shown associations between childhood asthma and home exposure to mold or moisture (100-103), although the results of individual cohort studies have been more variable (19, 104-106). In a 6-year prospective cohort study of Finnish children without asthma (104), mold odor (OR 2.44; 95% CI, 1.07-5.60) was associated with incident asthma, but moisture damage and visible mold were not. In a nested case-control study of
Canadian children (19), parent-reported visible mold exposure in pregnancy and childhood were not associated with asthma. In a nested case-control study of Taiwanese children without asthma (105), mold odor (OR 2.09; 95% CI, 1.30–3.37), parent-reported visible mold (OR 1.76; 95% CI, 1.18–2.62) and water damage (OR 2.80; 95% CI, 0.59–13.3) were associated with new-onset asthma. In a Swedish nested case-control study, inspector-observed moldy odor along the skirting board was associated with asthma (106). Home structural damage has been evaluated as a predictor of asthma control (107), but to our knowledge has not been reported as a predictor of new-onset childhood asthma.

Other components of the deprivation index, including adults without high school graduation, lone parent families, government transfers, and unemployment, have been previously included as covariates in the longitudinal evaluation of associations with incident asthma in children. Single-parent families have shown an increased hazard of childhood incident asthma by age 5 years (HR 1.43; 95% CI, 1.17-1.76) (4). Among elementary school children in southern California, Title I Funding supporting academic achievement in schools with >40% of children living in poverty has been associated with incident asthma (HR 1.68; 95% CI, 1.10-2.56) (36). Maternal receipt of social welfare has been associated with incident childhood asthma in a Canadian nested case-control study (OR 1.87; 95% CI, 1.43-2.44) (19). Low parental education (OR 2.62; 95% CI, 1.07-6.39) and unemployment (OR 2.38; 95% CI, 1.16-4.90) have been associated with maternal depressive symptoms (108), which have, in turn, been associated with incident childhood asthma (OR 1.25; 95% CI, 1.01-1.55) (15).
Our study adds to the literature by demonstrating a robust and novel association between neighborhood deprivation and childhood asthma in a large birth cohort of children. This study’s strengths include its large sample size, population-based sampling and the utilization of prospectively-collected administrative data for the exposure, outcome and covariate variables. We investigate a validated, comprehensive measure of material deprivation in children, which takes into account parental education, single parenthood, government transfers, unemployment and homes in need of major repairs, as well as parental income. We also use a validated outcome measure with good sensitivity and specificity (91.4% and 82.9%, respectively) (85). Sensitivity analyses suggest that missing data due to children living outside of Ontario or the GTA for part of their lives do not substantially alter the associations between material deprivation and childhood asthma.

One limitation of this study is the neighborhood-level material deprivation data, which may not apply to all individuals within a neighborhood. However, individual-level family income and home repair data often pose potential problems, including higher rates of missing data if participants prefer not to report their income or state of home repair. Parental or observer reports of mold and moisture damage are difficult to standardize among different studies, which may also detract from the usefulness of individual-level home repair data. This study was conducted in a large urban centre in Canada and may not be generalizable to all urban centres or to suburban or rural communities. Another limitation of our study is that we did not have information regarding family history of asthma and personal exposures outside the home. Individual-level cohort studies will be needed to evaluate the associations of these covariates with material deprivation.
4.5 Conclusions

At birth and during childhood, neighborhood material deprivation is associated with childhood asthma development, even among children who remain currently-symptomatic at ages 8-15 years, and asthma visits in each year of the child’s life. This study demonstrates the utility of a validated measure of material deprivation in studies of childhood asthma and suggests the potential for neighborhood improvements to reduce aspects of material deprivation, for example by improving high school graduation rates and housing conditions, as possible community-driven strategies to prevent childhood asthma.
4.6 Supplemental Methods for Project 3

4.6.1 Dataset Derivation for the Cox Proportional Hazards Models

The age of asthma development variable generated in section 3.6.1 to evaluate the walkability-asthma association was also used to evaluate the association between neighborhood deprivation and asthma development.

The gradient of birth neighborhood deprivation-asthma associations was established by sequentially comparing the hazards of asthma development for each of the highest four (more deprived) deprivation quintiles with the hazard of asthma development for the lowest (least deprived) deprivation quintile.

As described previously for neighborhood walkability and income in section 3.6.1, neighborhood deprivation was dichotomized as the two highest versus the two lowest quintiles. Dichotomous neighborhood deprivation in the birth year was assigned based on the year of birth and the deprivation in each fiscal year.

4.6.2 Dataset Derivation for the Discrete Hazard Models

The derived variable for asthma development by year of life described in section 3.6.1 was also used to determine the associations between deprivation and asthma in the discrete hazard models. Using the method described for walkability in section 3.6.2, dichotomous neighborhood deprivation in each year of life was assigned based on the year of birth and the deprivation in each year and merged with the asthma-walkability dataset and the covariates.
4.6.3 Dataset Derivation for Generalized Linear Mixed Models and Generalized Estimating Equations

The dataset describing the presence or absence of a healthcare visit for asthma in each year of life (section 3.6.3) was also used to examine the association between deprivation and asthma in each year of life. Deprivation by year of life was generated for the discrete-time hazard model (section 4.6.2) and was derived as described in detail for walkability in section 3.6.2. Asthma, deprivation and walkability by year of life were merged by unique identifier and year of life; the time-independent covariates were merged by unique identifier, so that they were present in all years of life for which asthma visit, deprivation and walkability data were available.
4.7 Supplemental Results for Project 3

4.7.1 Gradient of Association between Deprivation Quintile and Asthma

In the models sequentially comparing higher deprivation quintiles with the lowest (least deprived) quintile, lower hazard ratios of asthma development were seen for each successively lower or less deprived quintile among the highest three deprivation quintiles (Figure 4.1). This pattern suggests a logical gradient with less deprivation associated with a lower hazard of asthma development; the narrow confidence intervals suggest good homogeneity of the deprivation predictor within these high-deprivation neighborhoods. However, the second lowest quintile of deprivation showed more variable hazard ratios of asthma development when compared with the least deprived quintile, possibly due to variability in any one of the measures comprising the deprivation index, including income, education, single parenthood, unemployment, government aid and poor home repair. A neighborhood with a majority of less deprived individuals may have an apartment block of mostly unemployed people receiving government aid and the reverse may be true as well, with a high-deprivation neighborhood containing a street of lower deprivation. This variability remains a limitation of neighborhood-level data, although defining neighborhoods by smaller areas could reduce the variation within a neighborhood.
Figure 4.1 Crude hazard ratios of incident asthma associated with the four highest deprivation quintiles compared with the lowest (least deprived) quintile
4.7.2 Evaluation of Cox Proportional Hazards Model Fit using Schoenfeld Residuals

Schoenfeld plots showed horizontal linear residuals between -1 and +1 for all variables in the Cox proportional hazards model comparing the hazard of asthma development for the two highest versus the two lowest (least deprived) deprivation quintiles (Figure 4.2), suggesting good model fit.

Figure 4.2 Schoenfeld residuals for fit of Cox proportional hazards model of deprivation
Figure 4.3 Directed acyclic graph describing potential confounding and interaction between neighborhood deprivation, asthma and covariates

Legend:

One variable affects another

Variables inter-related

Legend:

One variable affects another

Variables inter-related

- Sex
- Obesity
- Year of life
- Preterm
- Atopy
- Birth year
- Neighborhood deprivation
- Neighbourhood walkability
- Asthma
4.7.3 Evaluation of Interaction between Deprivation and Covariates in the Generalized Linear Mixed Models

Based on the Directed Acyclic Graph (Figure 4.3), interaction with neighborhood deprivation was evaluated for neighborhood walkability, preterm birth, obesity and atopy. Interaction was not seen for any of these variables, as shown by the lack of crossing slopes for the plots of least squares mean versus neighborhood deprivation (Figures 4.4.1, 4.4.2, 4.4.3, 4.4.4).

Figure 4.4.1 Evaluation for interaction between deprivation and walkability

Figure 4.4.2 Evaluation for interaction between deprivation and preterm birth
Figure 4.4.3 Evaluation for interaction between deprivation and obesity

![Graph showing the interaction between deprivation and obesity](image)

Least Squares Mean vs Deprivation

- **Obesity = 1**
- **Obesity = 0**

Figure 4.4.4 Evaluation for interaction between deprivation and atopy

![Graph showing the interaction between deprivation and atopy](image)

Least Squares Mean vs Deprivation

- **Atopy = 1**
- **Atopy = 0**
4.8 Chapter 4 Summary

Childhood asthma is predicted by deprivation, even after adjustment for characteristics previously determined to be associated with asthma, such as gender, preterm birth and atopic conditions other than asthma. Good model fit is demonstrated and there is no evidence of interaction between deprivation and other predictors of childhood asthma.

The risk of asthma development is greater for children living in neighborhoods with high deprivation in this study (11% increased risk) than for children living in neighborhoods with low income in the previous study (6% increased risk), after identical adjustment for neighborhood walkability and other confounders in both analyses. Therefore, these results also suggest that the additional consideration of education, single parenthood, unemployment, government aid and poor home repair, which distinguish neighborhood deprivation from neighborhood income, is relevant to the study of childhood asthma.
5.1 Thesis Summary

These studies show associations between lifetime exposure to modifiable environmental predictors and the development of childhood asthma. Each study suggests a change in policy that will hopefully lead to changes in individual behavior.

Maternal second-hand smoke exposure from living in the same home as a smoker during pregnancy is associated with childhood asthma development, even if the mother does not smoke actively. This association between maternal home second-hand smoke exposure for non-smoking mothers and childhood asthma development suggests that asthma prevention programs should include smoking cessation strategies targeted towards smokers living in the homes of smoking and non-smoking pregnant women.

Existing campaigns encouraging smoking cessation in pregnant women have effectively reduced the rates of smoking in pregnancy. The importance of initiatives directed at the smoking partners of smoking pregnant women to reduce their return-to-smoking rates has also been recognized (109, 110). There is a need for similar strategies targeting smoking partners of non-smoking pregnant women to reduce their home exposure to second-hand smoke. Individual-level prevention strategies include counselling of parents and prospective parents and referrals to smoking cessation programs when the smoker is willing to attempt quitting. Societal-level interventions include labeling of tobacco products with the harmful effects of second-hand smoke in pregnancy and continued restriction of smoking in public places.
Genetic and epigenetic interactions have been demonstrated with exposure to maternal smoking during pregnancy and second-hand smoke exposure during childhood. These interactions will also need to be evaluated for maternal second-hand smoking in pregnancy.

Another contributor to childhood asthma development, a sedentary lifestyle, may now be modifiable at the societal, as well as the individual level. The concept of reducing children’s sedentary lifestyle rather than focusing on brief bouts of intense exercise may become increasingly important in the management of childhood asthma and obesity. The neighborhood walkability index, a community measure of neighborhood features conducive to walking, allows the study of this predictor at the community level.

Childhood asthma development is associated with neighborhood walkability, even after adjustment for neighborhood income and other characteristics known to be associated with childhood asthma, such as gender, preterm birth and other atopic conditions. This association suggests a potential means of primary asthma prevention and that society may contribute to decreased incidence of childhood asthma by promoting walkability within neighborhoods. Neighborhood walkability improvement, such as adding pedestrian paths to increase street connectivity and encouraging placement of services within walkable distances, are strategies that communities could use to encourage walkability and decrease the sedentary lifestyle of community members.

The paradigm is also shifting from considering obesity and activity as possible predictors of childhood asthma to evaluating epidemiological and epigenetic associations of asthma and
obesity as chronic disorders of common genetic origin, with activity or walkability as a lifestyle covariate. Future studies will need to consider genetic and epigenetic markers for risk of asthma and obesity, and their effects on the association between childhood asthma and walkability.

Childhood asthma is also associated with neighborhood deprivation, a comprehensive measure of socioeconomic well-being, which considers parental education, single parenthood, unemployment, government aid and poor home repair, as well as family income.

Childhood asthma development is more strongly associated with high-deprivation neighborhood than with low neighborhood income, after identical adjustment for neighborhood walkability and other covariates. These results support the concern that family income may not be an ideal measure of SES, especially for children, and also suggest that the additional consideration of education, single parenthood, unemployment, government aid and poor home repair, which distinguish neighborhood deprivation from neighborhood income, is relevant to the study of childhood asthma.

Neighborhood deprivation offers a comprehensive measure of SES and can be used to identify neighborhoods at high risk. The increased risk of childhood asthma development seen among children living in high-deprivation neighborhoods provides additional impetus for community improvement among these neighborhoods, for example by increasing high school graduation rates, reducing unemployment, improving the repair of public housing and providing incentive for private homes to remain in good repair.
Further studies of the walkability and deprivation predictors of childhood asthma would benefit from determination of individual measures of home walkability and deprivation, but these measures will require time-consuming prospective data collection. The validated neighborhood measures of walkability and deprivation will remain a useful tool for assessing the impact of neighborhood characteristics on childhood asthma and other chronic health conditions.

Overall, these results suggest strategies for primary prevention of childhood asthma. Further studies evaluating the associations between these three modifiable exposures and the genetic or epigenetic characteristics of individual children will be needed to further elucidate the biological mechanisms by which these exposures contribute to childhood asthma.
References


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