An Analysis of the Environmental Risk Factors of Childhood Asthma and Asthma-like Symptoms: Results from the National Longitudinal Survey of Children and Youth

by

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Abstract

It is known that a multitude of environmental factors are implicated in the incidence of asthma and asthma symptoms among children; however, previous research has provided inconsistent and/or insufficient evidence as to whether residing in a farming environment during childhood can lead to a reduced asthma risk in future life as predicted by the hygiene hypothesis. Similarly, observational and laboratory studies have shown that the risk of asthma attacks in asthmatic children is related to ambient air pollution exposure in childhood, but the evidence remains ambiguous as to whether air pollution can lead to *de novo* childhood asthma. In this thesis, individual-level data from the National Longitudinal Study of Children and Youth (NLSCY) were used to examine the relationships between farm residence during childhood and ambient air pollution levels, respectively, with the risk of asthma and asthmatic symptoms. Children resident in farming environments were found to have a significantly lower risk of asthma incidence compared to those residing in non-rural areas in the 14-year follow-up study. Further, higher levels of nitrogen dioxide exposure (NO_2) were found to be positively related with an increased 12-month prevalence of asthma attacks in childhood. These findings add to the evidence that farm residence and, to a lesser extent, ambient air pollution exposure is related to childhood asthma and its symptoms. Further research into the biological and genetic mechanisms, which may explain these findings, is needed to better understand the complex relationship between the environment and asthma risk in childhood.

Preface

This thesis is an original work by Marc Parsons. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board (Project: "An analysis of the neighbourhood-level risk factors of childhood asthma and wheeze using a multi-level random effects proportional hazards model"; No: Pro00052777, 02/01/2015).

Versions of Chapters 3 and 4 are being prepared for publication in peer-reviewed journals. M. Parsons was responsible for study design, data analyses, manuscript writing, and manuscript revision for the studies included in this thesis. A. Senthilselvan provided guidance to the study design, data analyses, manuscript writing, preparation for submission, and manuscript revision. J. Beach contributed to manuscript revision.

Dedication

The work presented here is dedicated to my entire family and, in particular, to the memory of my late nonna, Rosa Biasutto.

I would like to acknowledge the overwhelming support of my loving parents, Lyle and Lidia, without whom I would not have been granted the opportunity to attend higher education.

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List of Abbreviations

ANOVA	Analysis of variance
BC	British Columbia
BMI	Body mass index
CI	Confidence interval
ECD	Early Childhood Development
ECRHS	European Community Respiratory Health Survey
EU	European Union
FEV_1	Forced expiratory volume in 1 second
FSA	Forward Sortation Area
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HR	Hazard ratio
IgE	Immunoglobulin E
IgG	Immunoglobulin G
ISAAC	International Study of Asthma and Allergies in Children
LFS	Labour Force Survey
NAPS	National Air Pollution Surveillance program
NHIS	National Health Interview Survey
NLSCY	National Longitudinal Survey of Children and Youth
NO_2	Nitrogen dioxide
NO_X	Nitrogen oxides
O_3	Ozone

OR	Odds ratio
p	p-value
PARSIFAL	Prevention of Allergy Risk factors for Sensitisation In children related to Farming and Anthroposophic Lifestyle study
PH	Proportional hazards
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter
$PM_{1.0}$	Ultra-fine particulate matter
PMK	Person most knowledgeable
ppb	Parts per billion
ppm	Parts per million
R^2	Coefficient of determination
RDC	Research Data Centre
SES	Socio-economic status
Th	T-helper
Th1	T-helper type 1
Th2	T-helper type 2
UK	United Kingdom of Great Britain and Northern Island
US	United States of America
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Background of the problem

Asthma is one of the most common non-infectious diseases in childhood (1). This disease, characterised by acute spells or attacks of wheezing, coughing, and shortness of breath, is more prevalent among children than adults (1-3). Asthma attacks are triggered by a variety of stimuli including exercise or intense physical activity, poor air quality, cold or damp air, or other environmental stimuli (2). These attacks are spontaneous in nature and are often reversible through proper treatment (2).

Mortality associated with asthma is lower than that associated with other non-communicable diseases, leading researchers to suggest that it has been overlooked in the past in favour of more fatal conditions (3). In fact, the prevalence of asthma has been increasing for the past several decades, particularly in higher-income countries (2). While this trend has shown some signs of slowing in the past decade, there is evidence for a recent increase in asthma incidence in lower-income counties (4). Allergy and atopy have been shown to be related to asthma, although more recently researchers have found that only about 50-60% of asthma cases are related to these factors (3, 5). Asthma is generally recognised now as being caused by a host of environmental and genetic factors (2, 3); however, genetic factors alone cannot account for historical spatio-temporal variations in asthma prevalence (6). As such, environmental factors have been increasingly regarded as the underlying causes of the asthma epidemic (7).

1.2 Study objectives

The primary objectives of this study were: (i) to characterise the effect of living in a farming environment during childhood on the incidence of asthma; and (ii) to characterise the effect of ambient air pollution levels on the prevalence of childhood asthma and wheeze. The secondary objectives of this study were: (i) to identify possible confounders in the effects of the main exposures studied and the respiratory outcomes studied; (ii) to characterise the effects of other commonly recognised predictors of childhood asthma and wheeze; and (iii) to estimate the prevalence and incidence of asthma and wheeze in Canadian children during the time period of the study.

1.3 Thesis submitted for partial fulfillment of MSc

This thesis begins with a literature review of childhood asthma and asthma-like symptoms as well as their associations with farm living and air pollution (Chapter 2). This is followed by two studies (Chapters 3 and 4) which address each of the study objectives outlined in Section 1.2. The final chapter (Chapter 5) provides a summary of the entirety of the thesis and concluding remarks.

The beginning of Chapter 2 consists of a literature review assessing both the burden and epidemiology of asthma and asthma-like symptoms in children. This is followed by a review of the clinical practices surrounding these conditions such as their clinical and epidemiological definitions, best diagnostic practices, underlying biological mechanisms, and treatment strategies. A comprehensive review of the risk factors for asthma is included afterwards focusing on living in a farming environment and ambient air pollution exposures. This chapter concludes with a statement of the rationale behind the studies presented in Chapters 3 and 4.

The findings of the first study are presented in Chapter 3. The association between residing in a farming environment during childhood and future asthma diagnosis was assessed using a cohort of children recruited from the National Longitudinal Survey of Children and Youth longitudinal cohort. These children were followed up for up to 14 years using biennial interviews.

In Chapter 4, the findings of the second study are presented. This study examined the association between exposure to three air pollutants (nitrogen dioxide, fine particulate matter, and ground-level ozone) and the prevalence of asthma and asthma-like symptoms. This study employed data obtained from the NLSCY Cycle 7 cross-sectional cohort along with air pollution estimates obtained from both satellite- and ground level-monitoring.

The final chapter, Chapter 5, includes a discussion of the previous chapters and a final conclusion. This chapter summarises the thesis research, strengths and limitations of the studies, and the importance of the findings of this thesis.

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Chapter 2

Literature Review

2.1 Methods

This chapter consists of a review of the literature on asthma and asthmatic symptoms. The first part of this chapter includes sections on the burden, epidemiology, definitions, biological mechanisms, symptoms, diagnosis, and management of asthma. Papers were identified through searches of EBSCOhost and MEDLINE academic literature databases. Searches were limited to peer-reviewed papers written in English or French. The abstracts of studies identified from these searches were examined and studies deemed relevant were included in this literature review. Epidemiologic and burden estimates were identified from research articles and government databases. Information on the management and diagnosis of asthma was in part identified through the Global Initiative for Asthma (GINA) and other professional reports (1).

A narrative review of the risk factors for asthma and wheeze was also conducted. Potential risk factors were identified by searches of EBSCOhost and MEDLINE academic literature databases with search criteria defined as above. A focus was placed on identifying articles related to the exposures outlined in the primary objective of this thesis: poor air quality and living in a farming environment. Several review papers examining the association of living in a farming environment with asthma (2-5) and the association of air pollution with asthma and wheeze (6-16) were identified. Primary studies were also identified through the literature search. The reference lists and lists of citing articles of these review papers and the other studies identified were used to identify further relevant studies to be included in this narrative review.

2.2 Burden of asthma

A significant health, social, and economic burden from asthma can be felt in many parts of the world (17). While more common in children, asthma and its related symptoms can be present in people of any age: from newborn infants to adults and the elderly (17-19). Asthma places a significant physical burden on its sufferers, often preventing them from performing typical tasks such as exercising or being in close contact with certain environmental triggers (20). This condition has also been shown to negatively affect social and mental well-being (21). Diagnosis of asthma can lead to avoidance of activities that were important for personal health and wellness before disease onset such as regular exercise, participation in sports, and time spent outdoors (20). Studies have shown that asthma symptoms can negatively affect patient quality of life (22).

Asthma is estimated to cause approximately 180,000 deaths worldwide annually (21). These deaths are largely preventable with the proper treatment through long-term and/or acute care during the final attack (19, 21). Particularly in developing and lower-income nations, limited access to essential healthcare services is a significant barrier to reducing asthma mortality (21). In fact, lower- and middle-income countries account for more than 8 out of 10 asthma deaths worldwide (19). Over 70% of these nations are not able to provide an adequate supply of WHO-deemed essential asthma medications to their citizens (23). Access to these treatments could significantly reduce asthma mortality worldwide; however, the cost of the majority of pharmacological asthma treatments is prohibitive to their adoption in lower-income countries (18).

The economic costs of asthma have been ranked as the most significant among all chronic diseases due to the relatively high levels of hospitalisation, healthcare service uptake, and use of pharmacological treatments associated with it (24). The annual financial cost

attributable to asthma has been estimated to be in the range of $300 to $1,300 per patient per year in Western countries (21). The economic burden of asthma in Canada has been estimated at over $650 million (24). The cost of asthma medication makes up the largest direct cost associated with this condition in children (24). While the direct costs associated with asthma are large in magnitude, indirect costs also remain significant. These include losses in future earnings achieved through paid work (21, 24); asthma morbidity has been shown to significantly reduce potential individual earnings from work, thus placing a direct economic burden on asthmatics themselves (24). The indirect costs associated with asthma include lost opportunities for education. Children and adolescents experiencing asthmatic symptoms are sometimes unable to attend school; further, their parents may need to take time off work to care for them, thus forfeiting possibly important sources of income (18). Asthmatics with severe rather than mild symptoms are, unsurprisingly, the most affected economically (21). Poor control or management of current asthmatic symptoms is associated with significant increases in asthma cost (24).

2.3 Asthma epidemiology

Globally, it is estimated that approximately 300 million people are asthmatics (21); however, this measure may represent an underestimation due to under-diagnosis and may in fact be closer to 330 million (18). In the last decades of the 20th century, asthma rates generally increased in Westernised countries (4, 20). This has lead experts to suggest that this part of the world was subject to an "epidemic" of asthma during this time period which, perhaps, may continue to this day (25). It has been estimated that if there is no change in current incidence trends more than 100 million additional cases of asthma will be diagnosed by the end of the first quarter of the 21st century (17). However, recent studies have shown evidence for a slowdown or "plateau" in the rate of asthma incidence in higher-income countries in the 2000s (25-29);

although, even in countries with stagnant or declining asthma rates, different racial, socio-economic, and age groups may still be experiencing an increase in asthma incidence (25).

Between 2000 and 2003 the International Study of Asthma and Allergies in Childhood (ISAAC) Cycle 3, a large-scale international collaboration on asthma and atopic disease looking at over 700,000 children, found that about 14% of the world's children were likely to have had some sort of asthmatic symptoms in the past year (30). Of the centres studied, the majority of those reporting over 20% prevalence of asthmatic symptoms in children tended to be located in English-speaking and Latin American countries. The centres reporting prevalence lower than 5% were predominantly located in Asia, along the Eastern Mediterranean, and in Northern and Eastern Europe. While ISAAC showed that more developed countries had higher prevalence of asthmatic symptoms in children, it also suggested that less developed ones generally had higher rates of severe asthma and asthma mortality (30). Severe asthma among children with current wheeze was found to be significantly higher in Africa, the Eastern Mediterranean, and the Indian subcontinent than in English-speaking countries in ISAAC Phase 3 (30). Attempts to explain the disparity in asthma incidence between higher- and lower- income countries most notably include the hygiene hypothesis (18). Other explanations, such as urbanisation, have also been proposed (31).

In Canada more specifically, asthma has proven to be one of the most important chronic diseases among children. This condition affects more than 3 million Canadians, amounting to an estimated prevalence of 8.1% among those aged 12 and older in 2014 (32). Among children this figure becomes even higher: a Statistics Canada report found an overall asthma prevalence among Canadian children aged 12-18 of 9.0% (32). This figure is down from the 11.1% reported in 2010.

2.4 Definition of asthma

Asthma has been recognised as an important health condition as far back as ancient times (20, 33). The aetiological roots of asthma often differ between carriers of the disease; for this reason, it has been suggested that asthma is best defined in terms of its physical symptoms rather than its cause (19, 34). Asthma is considered a chronic obstructive pulmonary disorder that can lead to constriction and inflammation of the airways (19); however, there is significant heterogeneity in the symptoms presented between asthmatics. From a clinical standpoint, asthma is generally considered as consisting of one or more of the following presented in acute attacks: wheeze, shortness of breath, chest tightness, and cough (19, 20). Differential diagnosis may in fact have a larger impact on the apparent differences in asthma prevalence between population groups and geographic regions than the actual underlying factors that cause them (18).

The most recent attempt at an international collaboration to establish a unified asthma definition resulted in the following (35): "Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli."

Asthma falls into two broad categories: atopic (extrinsic) and non-atopic (intrinsic) (19). The mechanisms behind atopic asthma are generally better understood than those of non-atopic asthma (18). While carriers of both of these types of asthma present roughly the same symptoms, attacks are generally triggered by different environmental factors in each. Atopic triggers include known allergens such as pollen, mold, dander, and other allergic triggers (19). Triggers of attacks

of non-atopic asthma include cold air, poor air quality, certain viruses, airborne insecticides, and other irritating substances (19).

2.4.1 Epidemiological definitions

The large variation in presented asthmatic symptoms has resulted in a range of definitions being used in epidemiological studies, thus creating uncertainty as to the best way to define asthma (36). A 2010 study found that, in 122 published articles in the asthma literature, 60 unique definitions were employed to ascertain asthma status among subjects (37). Applying each of these to a cohort of children resulted in an extremely wide variance in prevalence estimates: from 14.9% to 65.3%.

Due to the cost of and problems associated with diagnosing asthma in large cohort studies, standardised questionnaires have become the fundamental measurement tools used to ascertain childhood asthma status in observational studies (38). Studies have shown that self-reported diagnosis of asthma is a reliable measure of actual clinical diagnosis (39-41); however, asthma recall may be biased towards those with a higher severity of symptoms. Ultimately, the use of questionnaire data in ascertaining asthma may be inevitable due to the high cost and impracticality of using physiological measurements in the context of many epidemiological studies.

In the first cycle of the NLSCY, the following is asked of the person most knowledgeable (PMK) of the subject child to ascertain their asthma status: "Does this child have asthma that has been diagnosed by a health professional?" For children older than 16 years of age and thus not in need of a PMK respondent the question was changed to: "Has a health professional diagnosed you with asthma?". Between the eight cycles of the NLSCY, these questions were not changed in

any significant way. Similar interview and questionnaire questions have been validated in previous studies. Using parent-reported asthma, a Norwegian study found extremely high sensitivity and specificity (over 95% for both) compared to clinically-diagnosed asthma (41). Other studies in Canada have found good agreement between parent-reported asthma and a gold standard diagnosis (40, 42).

2.5 Asthma symptoms

The symptoms of asthma include chest tightness, wheezing, breathlessness, coughing, and chest pain (19). These symptoms typically occur in acute episodes which are often reversible with treatment (19). Asthmatic symptoms are often categorised into different risk categories such as intermittent, mild, moderate, and severe. These categories are generally defined by the frequency of attacks, resistance to treatment, and the presence of symptoms between attacks (19). Severe asthma is of particular interest to researchers and healthcare professionals because it is the most likely to be fatal or to lead to hospitalisation; however, there are multiple definitions of severe asthma. Severe asthma diagnosed in childhood is, for most sufferers, a lifelong chronic condition (18). An Australian study found that about 75% of those diagnosed with severe asthma by age 6 still experienced asthmatic symptoms at age 50 (43).

2.5.1 Wheeze

Wheeze is generally defined as a distinctive whistling or grating noise emanating from the respiratory tract caused by narrow or blocked airways (44). Symptoms of wheeze can range from mild to severe and can be chronic or acute in nature (20, 44). In common usage, wheeze is a term employed to describe a wide range of possible noises by parents, from a loud rattling sound to a more quiet sound; however, the clinical meaning of wheeze is very specific: a soft whistling

or squeaking sound emitted from the chest exclusively during expiration rather than inspiration (20). For this reason, it is important for clinicians to ascertain whether abnormal respiratory sounds in children and infants are genuine wheeze or another condition such as large airway rattle, stridor, or stertor (20). Common clinical presentations that might be confused or misdiagnosed for wheeze are: bronchitis, pertussis, the common cough, emphysema, or vocal cord dysfunction (20, 44).

While there are many conditions that may lead to wheeze, it is fundamentally the result of blocked or restricted breathing passages in the small airways (44). The inhalation of cigarette smoke, airborne pollutants, and other fumes may also lead to short-term wheeze (44). In this way, wheezing can be considered the result of a physiological response in the airways to protect the respiratory tract from potentially harmful foreign material. Transient wheeze can be caused by mucus blockage of the airways arising from bronchitis, viral infections, allergies, or pneumonia (44). When the airways become hypersensitive to foreign materials as in asthma, wheezing becomes a persistent and chronic problem (19, 20, 44); however, while wheezing itself can cause anxiety and further respiratory issues, it is not typically considered to be a serious condition on its own (44).

Several different phenotypes of wheeze have been identified. While some of these phenotypes are associated with no decrease in future lung function, persistent wheeze has been shown to be related to an increased risk of asthma in later life (45). In younger children, a diagnosis of wheeze in general is sometimes taken as indicative of asthma; however, without knowledge of the specific phenotype this diagnosis may be premature.

From an epidemiologic standpoint, prevalence estimates of wheeze in infants and children are often dependent on parental self-report (46). A 2006 study found that 83.5% of parents of children aged 6-10 were able to correctly define clinical wheeze (46). This study included both parents with asthmatic children and those without asthmatic children. A separate study found that there was less than 50% agreement in the determination of childhood wheeze between clinicians and parents (47). It has been suggested that, due to the unclear nature of the term, the definition of wheeze should be explicitly defined in questionnaire surveys rather than left up to the discretion of the interviewee (46, 47).

2.6 Biological mechanisms of asthma

Asthma is a disease which primarily affects the bronchioles, the tubes located in the terminal parts of the lungs (19, 20). These tubes of smooth muscles can constrict or expand to allow air to flow in and out of the alveoli of the lungs, thus allowing for normal respiration (19). The bronchioles are layered with mucus produced by the body to prevent foreign material to enter too far into the lungs (19). Asthma causes the bronchioles to suddenly constrict and produce excess mucus, restricting the flow of air and causing tightness of the chest, wheeze, cough, and breathlessness. While bronchiole constriction is not necessarily unique to asthmatics, in asthma this constriction is severe enough to precipitate asthma attacks.

Pathologically, there are several processes which underlie asthma and contribute to attacks. The first is an unusually high level of airway sensitivity, causing the bronchioles to constrict and narrow upon exposure to certain airborne substances or environmental conditions (19). The second is a surplus production of mucus in the airways, further restricting the space reserved for airflow in the lungs (19, 20). Post-mortem studies of individuals who have died of

asphyxiation due to an asthma attack demonstrate abnormally high levels of thick, viscous mucus blocking the airways (20). The third pathological process which defines asthma is inflammation of the bronchial tissues (19). Clinical bronchoscopy of the lungs of non-severe asthmatics has shown that inflammation is not restricted to severe attacks (20). While attacks can cause complications such as lung collapse, they typically do not cause permanent lung damage (19).

Microscopically, asthma is associated with disruption of the epithelial lining of the airways and an increase in airway infiltration by T-helper (Th) lymphocytes of the Th2 variety, eosinophils, and mast cells (20). It has been shown that some asthmatics have higher levels of immunoglobulin E (IgE) in the blood serum than non-asthmatics (19). The presence of this substance in the blood is a diagnostic indicator for allergic sensitisation and, thus, an indicator of atopic rather than non-atopic asthma.

2.7 Asthma diagnosis

The diagnosis of asthma is complex (18, 37). It depends on identifying the presence of respiratory symptoms including wheezing, cough, and tightness in the chest and the presence of variable airflow limitation (1). If symptoms occur at night, after vigorous exercise, in cold or damp conditions, or after being exposed to common allergens or asthma triggers, the diagnosis of asthma is more probable (1, 20). An assessment of the patient's history of symptoms and known risk factors for asthma is important to the diagnosis (1, 20). Other risk factors for childhood asthma include having a family history of asthma or a family and/or personal history of atopy, allergic rhinitis, or eczema (1, 20).

The typical diagnostic test for asthma is the measurement of forced expiratory volume in one second (FEV_1) obtained through spirometry supplemented with a symptom and risk factor

history assessment (20). The higher the variation in lung function over time measured by spirometry, the higher the probability of asthma (1). Other tests can be conducted if there is a lack of certainty as to the diagnosis. These include bronchial provocation testing with methacholine, histamine, or exercise (1, 20). Provocation testing is used to assess the reversibility of asthmatic symptoms, with signs of reversibility indicating a higher likelihood of the presence of asthma. The diagnostic results are used to place a patient into different risk categories. Patients deemed at higher risk for asthma are either given further testing or are prescribed a trial of asthma medication in more severe cases (20). If patients respond to these medications, then the diagnosis of asthma can be considered complete (1, 20).

There is no gold standard diagnostic test for childhood asthma as it is not possible to perform spirometry on young children (20, 37). For this reason, wheeze is used as the principal determinant for categorising potentially asthmatic children into high or low risk categories for a future positive diagnosis (18, 20). Wheeze only during inhalation or at the start of exhalation is indicative of asthma (44).

Asthma misdiagnosis can be a significant problem (1, 19, 37). Specifically for children, there are many conditions which may be incorrectly taken as asthma. These include bronchitis, cystic fibrosis, pertussis, the presence of an inhaled foreign body, brochiectasis, congenital heart disease, and laryngomalacia (1, 20). Physicians must be careful in differentiating genuine wheeze from rattle, stridor, and stertor as parents may not understand the differences and classify all of these as wheeze (44). It is then important to assess whether or not the genuine wheeze is persistent, thus less indicative of asthma, or periodic and caused by certain triggers and thus indicative of asthma (20).

2.8 Management of asthma

Due to the lack of a definitive cure for asthma, the primary focus of physicians after successfully diagnosing asthma in a patient is to attempt to reduce or eliminate the symptoms (19, 20). It is important for physicians to view asthma as a chronic disease rather than attempting to treat each acute exacerbation individually (19). Management of asthmatic symptoms can be done both pharmacologically and through non-drug treatments using a stepwise approach (19, 20). Non-drug treatments for the management of asthma center around patient education (20). By educating asthmatics and their families, if necessary, about the nature of their disease the hope is that they will be able to successfully prevent asthma attacks and maintain normal lung function by avoiding potential triggers. Smoking cessation is a crucial component of asthma management and is recommended (20). Other non-drug approaches to asthma management include doctor-recommended exercise such as swimming (if appropriate), the installation of air filters at the asthmatic's place of residence, and practicing special breathing techniques (19).

Medicines used to treat asthma include anti-inflammatory drugs such as inhaled corticosteroids, and relievers such as β_2 agonists (18-20). These are principally self-administered by the patient through the use of inhalers or other similar devices upon the onset of an asthma attack with the goal of stopping or reducing the attack's length (19). Some drugs including corticosteroids can be taken orally or, during severe attacks, administered directly into the bloodstream by a healthcare professional (19). Pharmacological asthma treatments have generally been credited with improving asthma outcomes (18, 21, 22); however, access to treatment remains a problem in certain marginalised populations and lower-income countries (18, 21, 24). It has been shown that poor asthma control in the use of medications is related to factors such as asthma severity and socio-economic status (SES) (48).

2.9 Farming and asthma

Previous studies have suggested that living in a farming environment in early life protects against asthma from childhood into later life (4). Interestingly, this association has been shown to hold for both non-atopic and atopic asthma (4). The mechanism behind this apparent effect is often attributed to the hygiene hypothesis (4, 20, 49). This hypothesis stipulates, in short, that children residing in farming environments have higher exposure to microbial agents which activate and control immune responses, resulting in lower asthma incidence among children residing in rural farming environments than those who reside in urban ones (2).

This farming effect has been shown to be quite heterogeneous between countries (50). This is most likely due to differing farming practices between regions. This heterogeneity has prompted some researchers to investigate the potential for a dose-response relationship between farming and asthma through examining the magnitude to which children are exposed to livestock, unpasteurised milk, straw, and other farm exposures (4, 50, 51). Despite this heterogeneity, studies conducted around the globe have consistently found evidence for the farm effect. However, as of recently only a handful of longitudinal studies examining this effect have been conducted (50).

2.9.1 Hygiene hypothesis

The principal stipulation of the hygiene hypothesis is that exposure to a diverse range of microbial and infectious agents during early life can lead to a reduced risk of atopic disease. Some studies have assessed the range of microbial and infectious diversity to which children resident in farming environments are exposed (52, 53). The goal of these studies has been to ascertain whether children resident in farming environments are exposed a different magnitude

of bacterial flora than their non-farming counterparts. Diversity of exposure to microbial agents can be measured directly through samples taken from children's homes, bedding, or schools or through the use of proxy measurements such as exposure to livestock. Other studies have directly tested the relationship between exposure to microbial and infectious agents and asthma risk with the goal of testing the assertions of the hygiene hypothesis (52, 54).

A questionnaire study conducted in Egypt found significant differences in microbial exposures between urban and rural children (53). Children recruited into the study were classified as living in either urban or rural environments. Potential proxy exposures were measured by self-completed questionnaires while dust samples collected from each subject's school were tested for endotoxin. The rural group was found to have significantly higher exposure to farm animals and unpasteurised milk than the urban one. School dust samples tested for endotoxin found significantly higher levels present at the rural schools than the urban ones.

A study analysing the results of two smaller cross-sectional European studies, PARSIFAL and GABRIEL, found a significant inverse association between microbial diversity in children's mattress dust and asthma incidence (52). The PARSIFAL study recruited 6,963 children, of which 489 consented to have dust and blood samples collected for further analysis, in Bavaria, Germany. The GABRIEL study recruited 9,668 children in southern Germany, Switzerland, and Austria, of which 895 participated in further lung testing and 444 consented to environmental sampling. In both cases, farming children were found to have higher levels of microbial exposure than non-farming ones. Asthma was assessed either by a doctor's diagnosis or, in the case of the GABRIEL study, by spirometry. The researchers were able to identify broad families of species within different microbial taxa that may, at least in part, explain differences in asthma risk between non-farming and farming environments.

A cross-sectional study conducted in rural Germany, Austria, and Switzerland found an inverse relationship between endotoxin exposure in mattress dust and asthma incidence (54). Questionnaires were used to assess whether children lived on a farm or not. Mattress dust samples for 812 children aged 6-13 years from non-farming and farming families were collected and were tested for endotoxin and allergens such as house dust mite. Children who lived in farming environments were found to have significantly higher levels of endotoxin and house dust mite exposure than those who lived in non-farming environments. A strong association between atopic asthma assessed using serum specific IgE levels and an increase from the lowest to the highest quartile of endotoxin exposure was found after controlling for potential confounders (OR = 0.52; 95% CI: [0.30, 0.90]).

Illi et al. reported the results from a birth cohort study conducted in Germany in which 526 children were recruited and assessed for asthma and atopy incidence over a five year follow-up period (55). The health status of the mothers of these children during pregnancy was assessed through interviews. Endotoxin and allergen levels in the household were measured 3 months post-delivery using sampling of the subjects' mattress. Atopy was also assessed in the subjects at 1 and 5 years of age. The researchers found that the presence of endotoxin in the child's mattress was inversely related to asthma incidence (OR = 0.71; 95% CI: [0.55,0.93]) after adjusting for important confounders. In addition, the authors found that the presence of illnesses such as colds during pregnancy increased the risk of asthma in the subject children (OR = 2.31; 95% CI: [1.12, 4.78]).

2.9.2 Asthma and farming environment

Rather than using direct measurements of microbial and infectious exposures, studies assessing the hygiene hypothesis in relation to the farm effect have also used residence in a farming environment during childhood as a proxy measure of these exposures in early life. As outlined in Section 2.9.1, children who live on farms are likely to be exposed to a wider variety of microbial agents. The strongest protective exposures associated with farm living include contact with livestock and the consumption of unprocessed milk (4). By testing the association between residing in a farming environment during early life and asthma risk, researchers can implicitly test the assertions of the hygiene hypothesis without measuring microbial or infectious exposures explicitly.

A case-control study of 482 children aged 6-15 years of age in Chile assessed the association between proxy microbial and infections exposures in the first year of life and childhood asthma incidence (31). This study recruited cases with physician-diagnosed asthma and hospital-based non-asthmatic controls. The researchers also measured and controlled for other potential pre- and post-natal risk factors for asthma. Regular farm-animal contact was found to have a protective effect against asthma (OR = 0.38; 95% CI: [0.17, 0.85]). Pneumonia infection in early life was found to have a positive association with asthma (OR = 2.24; 95% CI: [1.21, 4.16]) as well as mold or dampness present in the home (OR = 1.87; 95% CI: [1.18, 2.97]). While there was initial doubt as to whether either the hygiene hypothesis or poor urban development was the root of high asthma prevalence in South America, this study concludes that the hygiene hypothesis is most likely the more influential factor.

A cross-sectional study of school-aged children in Egypt found marginal evidence for an inverse relationship between endotoxin exposure and asthma prevalence (53). Children from both a rural and an urban school (40 from each) were recruited and questionnaires were

distributed to their parents. After adjustment, the children from the urban school had higher asthma prevalence than those from the rural school, albeit at a non-significant level (OR = 5.16; 95% CI: [0.95, 28.00]). The study also found a difference in endotoxin exposure between the two groups as measured through dust samples. This study shows some evidence that residence in a predominantly farming environment can lead to reduced asthma risk, although its small sample size adds uncertainty to its conclusions.

A cross-sectional study conducted in central Europe found a significant protective effect against childhood asthma associated with living in a farming environment in early life (54). This study recruited a total of 812 children of similar German, Austrian, or Swiss ethnic origin. Standardised questionnaires and interviews including questions about asthma, exposure to livestock, residence on a farm, and exposure to farm milk were completed by the subjects. Children exposed to livestock, farm milk, or who were resident on a farm during the first year of life were considered exposed to a farming environment. Serum specific IgE levels were measured to differentiate between atopic and non-atopic asthma. Children exposed to farming environments during the first year of life had a lower prevalence of atopic asthma than the non-farming group after controlling for potential confounders (OR = 0.42; 95% CI: [0.18, 0.96]).

A cross-sectional study in Germany found a reduced prevalence of atopic disease in the children of farmers compared to those of non-farmers (56). This study enrolled 10,163 children aged 5-7 years in Bavaria and data was collected through questionnaires answered by their parents. The farming effect on asthma was found to be protective but non-significant after adjustment for potential confounders (OR = 0.65; 95% CI: [0.39, 1.09]); however, a significant effect was found comparing children of full-time farmers compared to part-time and non-farmers combined (OR = 0.38; 95% CI: [0.15, 0.97]).

A study conducted in rural Austria, Germany, and Switzerland recruited 79,888 school-aged children to complete a questionnaire on farming and asthma (55). A further 7,682 of these children responded to detailed questions ascertaining specific farm exposures that they may have encountered in the past. Children residing in a farming environment had a significantly reduced risk of developing asthma (OR = 0.68; 95% CI: [0.59, 0.78]). Using data obtained from the detailed questionnaires, the farm effect on asthma risk was found to be mainly related to straw, farm milk, and cow exposure after adjusting for potential confounders. The large sample size of this study allowed for the association between farm living and asthma to be estimated with a high degree of accuracy.

A Finnish study of 10,667 first year university students found that those who had lived on a farm during childhood had a reduced risk of physician-diagnosed asthma combined after adjusting for potential confounders (OR = 0.71; 95% CI: [0.50, 0.79]) (57). This cross-sectional study used a postal questionnaire to assess lifetime prevalence of asthma and history of living on a farm.

A case-control study conducted between 1994 and 1998 in Denmark recruited 122 asthmatic cases along with the same number of matched controls (of which 116 consented to participate) from a larger cohort of farming-school students and non-farming rural subjects (58). Asthma was diagnosed using a list of major and minor diagnostic questions: a positive response to at least 4 major questions and 2 minor ones resulted in an asthma diagnosis. Being raised on a farm in childhood was significantly associated with future asthma diagnosis (OR = 0.50; 95% CI: [0.30, 0.98]) after adjusting for major confounders.

Some studies, however, have found no association between farm living and asthma risk. A cross-sectional study also conducted in rural Switzerland found no evidence of the farm effect (OR = 1.17; 95% CI: [0.64, 2.13]); however, asthma was not the primary outcome of this study and the sample size (n = 1,620) was not particularly large (59). An international, multicentre cross-sectional study on the risk of atopic disease and exposure to farming environments found no significant association with asthma (OR = 0.82; 95% CI: [0.53, 1.27]) (60). Adult participants from the European Community Respiratory Health Survey (ECRHS) were contacted and asked questions about atopic disease (including asthma) and past residence on a farm during childhood, among other things. Subjects were recruited from 13 centres in Sweden, Belgium, The Netherlands, France, and New Zealand.

2.10 Air pollution, asthma, and asthma-like symptoms

As a respiratory condition, it has naturally been suggested that asthma may be related to ambient air quality (9, 20). Many studies assessing both long- and short-term exposure to different pollutants and respiratory outcomes have been conducted to date. The weight of the evidence suggests that the severity and frequency of exacerbations of both asthma and asthmatic symptoms are inversely related to exposure to poor air quality (9, 12, 61); however, it is much less clear whether or not ambient air pollution induces new cases of these conditions (12, 13). One factor casting doubt on the pollution-asthma relationship is that while asthma rates have steadily risen in developed countries over the past decades, air pollution levels in these same countries have decreased (12, 20). Despite this, some observers suggest that poor air quality may at least partially explain the prevalence and incidence of asthma and wheeze (9).

The biological mechanisms by which air pollution may contribute to the risk of asthma attacks, asthma induction, and wheeze include oxidative stress, airway damage, increasing inflammation and responsiveness, and increasing sensitisation to allergens (10, 12). Damage to the airways through oxidative stress results from the depletion of anti-oxidants in the respiratory system. Interactions between the airways and pollutants may lead to structural damage and/or inflammation. Further, pollutants may affect immune balance within the body. Pollutant particles may act as vessels for transport of airborne allergens, thus potentially increasing the risk of sensitisation as exposure to pollutants increases. As atopy is a well-recognised risk factor for asthma, this may increase asthma risk (62). It has also been hypothesised that pollutants may increase the permeability of the epithelial lining, thus causing a greater level of exposure to airborne allergens.

2.10.1 Air pollution exposures

Many factors can influence an individual's exposure levels to airborne pollutants. As lung development continues from birth until approximately age 6, young children and infants are more susceptible to poor air quality than adults (11, 13, 20, 63). Children also spend more time outdoors and do not have fully developed immune systems, further exacerbating the effects of air pollution (64). Geographic variability in the intensity and composition of ambient air pollution is widely acknowledged. Proximity to high traffic roadways has been shown to be an important predictor of air pollution exposure (64). For this reason, some studies have used traffic proximity as a proxy for pollutant exposure, especially for NO_2 and PM (15, 65-70). Air pollution levels differ between children resident in rural and urban areas, with the latter group potentially exposed to about two times more indoor pollution than the former (71). Indoor air pollutant levels have been shown to be high in modern homes due to a desire to reduce heating costs by

incorporating an air-tight structure in residential construction (10, 72). It has been shown that low SES children are affected by poor air quality more than their high SES counterparts (14).

Industry and transportation are the two major sources of airborne pollution, but naturally-occurring dust, cooking smoke, geologic and weather-related phenomena, and forest fires also contribute significantly (9, 64). Pollution can be formed from point sources such as factories or cars but may also arise as secondary pollutants through photochemical reactions. Air pollution is heterogeneous in nature and consists of a combination of several airborne substances. In this review, we consider three of these substances: nitrogen dioxide (NO_2), ozone (O_3), and fine particulate matter ($PM_{2.5}$). Only studies that used direct (as opposed to proxy) measurements of pollution levels were considered in this review.

Nitrogen dioxide is widely acknowledged as a significant constituent of ambient air pollution. It is sourced primarily from vehicle exhaust but also can be produced through electricity production, food preparation, and other fossil fuel-based sources (9, 73). Individual exposure to this pollutant is characterised by low level background exposure punctuated by short periods of high exposure (73). It has been shown that NO_2 exposure can cause long-term changes in lung function, inflammation, and increased airway responsiveness to airborne allergens in asthmatics (9, 73, 74).

Ground-level ozone is a highly reactive gas formed by photochemical reactions involving transportation- and industrial-emitted hydrocarbons and nitrogen oxides (9, 64). It is a significant factor in causing urban smog and haze (9). Excess exposure to ozone has been demonstrated to cause impaired lung function and increased epithelial permeability (64). Exposure to ground-

level ozone pollution has been shown to increase an individual's exposure to airborne allergens (16).

Fine particulate matter consists of all airborne particles with an aerodynamic diameter of less than 2.5μm. As the definition of particulate matter is based on the size and not the composition of the particles, it may include any number of liquid or solid chemicals (64). These particles are extremely small and, therefore, readily inhaled and deposited deep within the lungs as far as the alveoli; particles larger than 10μm generally cannot enter into the lower respiratory tract as it not likely that they will be transported any deeper than the larynx (13, 64). Significant contributors to $PM_{2.5}$ pollution are dust storms and the combustion of fossil fuels, wood, and other organic matter for industrial or transportation purposes (64). Long-term $PM_{2.5}$ exposure has been shown to be associated with decreased lung function, increased bronchial hyperresponsiveness, and high serum IgE levels (9, 13).

2.10.2 Air pollution and asthma-like symptoms

It has been hypothesised that air quality may be related to the prevalence and incidence of wheezing symptoms in children and, more specifically, asthma exacerbations among asthmatics (9, 15). Experimental and observational studies have established that poor air quality is most likely causally associated with an increased risk of asthma attacks (9). The mechanisms behind this effect are diverse. Some research has shown that pollution exposure increases airway hyperresponsiveness, thus making asthmatics more susceptible to possible triggers (9). Another mechanism in which air pollution may increase the risk of exacerbations in asthmatics is through directly causing airway inflammation or reducing lung function (9). Observational studies have shown that increases in ambient outdoor pollutant levels lead to higher rates of emergency

department visits and/or hospital admissions for asthma. As an important symptom of asthma, epidemiological studies have sometimes used wheeze as a proxy measurement of asthmatic exacerbations or attacks. In some studies on asthma, on the other hand, wheeze was a specific outcome of interest. In other studies, wheeze is ascertained in the general population rather than specifically among asthmatics. For this reason, studies on asthma symptoms (including wheeze) in asthmatics and wheeze in the broader non-adult population are both included in this section.

Evidence from experimental studies has supported the biological plausibility of the air pollution effect on asthma exacerbation. One such study found that an increase in ozone levels of 0.25 parts per million (ppm) over a three hour period caused a decrease in forced expiratory volume in one second (FEV_1) of 12.5% among mild asthmatics (75). The authors of this study suggested that their results showed that short-term exposure to ozone can increase airway hyperresponsiveness to allergens. Another study similarly found that airway hyperresponsiveness was higher in asthmatic subjects exposed to ozone followed by an allergen than those in a placebo-exposed control group (76). Both groups were exposed at rest for one hour before being tested for airway response. The authors brought attention to the small dose of ozone to which the intervention group was exposed as comparable to the level commonly found in many urban areas.

An observational study conducted in the US in 2008 found a significant association between asthma symptoms and high levels of NO_2 pollution (77). $PM_{2.5}$ and O_3 exposures were also considered in this study. The authors recruited 861 children from 7 urban centres in the US and used telephone interviews to assess each subject's history of asthma attacks at 2 month intervals over 2 years of follow up. These data were supplemented by 2 weeks of spirometry measurements every 6 months in order to assess lung function. The authors considered a three

pollutant model using NO_2, O_3, and $PM_{2.5}$ as predictors of asthma symptoms. Out of the three pollutants studied, they found that only NO_2 was associated with both the incidence of frequent wheeze and night time asthma attacks. An increase from the 10th to the 90th percentile of NO_2 exposure resulted in a 24-29% increase in asthmatic symptoms.

Some studies have considered the use of emergency asthma medications as a proxy for the incidence of asthma exacerbations. A prospective cohort study of 271 asthmatic children found that each 50 parts per billion (ppb) increase in 1-hour average ozone levels significantly translated to a 35% increase in the risk of wheeze and a 47% increase in the risk of chest tightness among those with the most severe asthma (78). This study categorized severe asthma as requiring regular use of maintenance medication. These children were also more likely to make use of their emergency medication on days of high ozone pollution. A prospective French study of 82 asthmatic children found a significant association between ozone levels and both the use of emergency medication for asthma and exacerbations of existing asthma as measured through symptom diaries (79). This study also investigated NO_2 pollution, but found no significant association between it and asthma attack incidence. Using a model that included interactions with temperature and ambient pollen levels, increased ozone levels were found to be significantly associated with asthma attacks at a lag of 0 days. The authors also found a 41% increase in the use of emergency medication associated with an increase of 10 $\mu g/m^3$ in daily mean 8-hour ozone levels. An increase in medication use due to elevated ozone levels was also observed up to 4 days after the measurements were taken, indicating a persistent time-delayed effect.

Studies of asthma-related admissions to emergency departments have found significantly increased admission counts on or shortly after days with high pollution levels. A retrospective

study conducted in a predominantly black neighbourhood in Atlanta employed ozone monitoring data and records of hospital admissions due to asthma between June 1 and August 31, 1990 (80). A total of 609 emergency visits were made during this period. The researchers found a 37% increase in risk of admissions to hospital for asthmatic symptoms on the days after exceptionally high ozone levels (0.11 ppm) than on other days. The authors concluded that black children from low-income families are affected by high levels of ozone pollution in terms of risk of asthma attacks. Another observational study conducted in Atlanta found a 23% increase in asthma hospital admissions on days with a maximum 8-hour ozone level above 0.1ppm compared to those with levels below 0.05ppm (81). A total of approximately 6,000 asthma visits were recorded during the study period (the summers of 1993, 1994, and 1995). A Toronto study found that summertime O_3 pollution was associated with 23% of all respiratory admissions, including those for asthma, during the period 1986-1988 (82). Another study conducted in the Toronto area during the last week of June in 1991-1993 enrolled between 50 and 60 asthmatic children each year from a summer "asthma camp" (83). In only recruiting children from the camp, the authors could directly estimate the level of ground ozone exposure of each of the participants. The study used peak flow meters to estimate lung function and found that it was consistently associated with O_3 measurements around the camp. In addition, a rise in the daily 1-hour maximal ozone level from 84 ppb to 160 ppb was associated with an increase in the expected number of unscheduled daily medication admissions from 20 to 28. In California, an 18-year prospective ecologic study measured the ambient levels of several pollutants and used hospital discharge data to search for an association between pollutant levels with asthma emergency visits (84). The authors of this study found that for each 10 ppb increase in the quarterly 1-hr maximum ozone

level over the 87.7 ppb median resulted in a 4.6% increase in quarterly asthma admission rates. They did not find evidence for associations between asthma admissions and NO_2.

Some studies have found significant associations between exposure to particles with an aerodynamic diameter of 2.5μm or smaller (both $PM_{2.5}$ and $PM_{1.0}$) and the incidence of asthmatic exacerbations. A panel study (85) of 133 asthmatic children aged 5-13 resident in Seattle measured ambient levels of ultrafine particulate matter ($PM_{1.0}$) to ascertain whether days of high pollution lead to increases in the frequency of days with asthma symptoms. The researchers used daily self-reports of asthma symptoms recorded in study diaries and considered a day with asthma symptoms as one with at least one recorded asthmatic episode of mild or greater severity. Each 10 $\mu g/m^3$ increase in $PM_{1.0}$ was associated with a 18% (95% CI: [5%, 33%]) increase in the odds of asthma symptoms over a 1 day lag. Similarly, another study found evidence for a 20% increase in the risk of severe asthma attacks and 10 $\mu g/m^3$ increase in $PM_{2.5}$ levels (86). An Italian study found that symptoms of asthma among 120 children recruited in the industrial Emilia-Romagna region were positively correlated with ambient $PM_{2.5}$ levels (87). The conclusions of these studies each suggest that there most likely is a positive association between $PM_{2.5}$ levels and the prevalence of asthma symptoms among asthmatic children

2.10.3 Air pollution and asthma incidence

While it is widely accepted that exposure to poor air quality can exacerbate existing asthma, the assertion that it may play a role in inducing the condition among non-asthmatics remains controversial (13, 63). The possible biological mechanisms behind this effect are not well-known (13). Most of the evidence provided by experimental studies focuses on the potential for airborne pollution exposure to lead to allergic sensitisation and then, as a result, asthma.

There has also been a lack of definitive epidemiological evidence for this effect. Past reviews and meta-analyses have shown both support for (12) and against (6) the hypothesis that poor air quality may lead to incident asthma in non-asthmatic children. Some observers, however, have suggested that the body of evidence implicating airborne pollutants in asthma induction is growing, especially for pollutants associated with vehicle traffic and diesel emissions (63).

Experimental studies have shown some evidence for a biological mechanism by which air pollution may lead to allergic sensitisation and increase the risk of future asthma (88). *In vivo* human studies have shown that exposure to diesel fumes, of which NO_2 and $PM_{2.5}$ are important constituents, can contribute to allergic sensitisation, increased inflammatory cell counts in the airways, and increased airway resistance (88).

A study in Southern California found that children resident in high ozone areas who played three or more outdoor sports had 3.3 times the odds of developing asthma than those who played none (89). This study recruited 3,535 children without a history of asthma and conducted follow-up over a 5-year period. As more active children could have been expected to be exposed to higher levels of ambient pollution than those by virtue of spending more time outdoors, this study may have established a link between ozone and asthma prevalence.

A US study of children and adolescents aged 3-17 years found that asthma prevalence was related to high levels of ozone pollution (90). In total, 34,073 subjects were recruited from the National Health Interview Survey (NHIS). Using 12-month average air pollution measurements for NO_2, O_3, and PM, the researchers found that children resident in the highest quartile of ozone pollution had 1.56 (95% CI: [1.15,2.10]) times the odds of having asthma than those resident in the lowest quartile. No associations between asthma and the other pollutants

studied were found. The authors of this study criticised the lack of national long-term exposure limits on ground-level ozone in the USA, as the current guidelines only focus on short-term exposures.

Some studies specifically measuring exposure to traffic-related air pollution such as NO_2 and PM have found that these pollutants may be related to asthma risk. A Taiwanese study found that elevated levels of nitrogen oxides (NO_X) were associated with increased asthma prevalence: each unit ppb increase was related with a 0.88% (95% CI: [0.23,1.52]) increase in the prevalence of physician-diagnosed asthma among boys and a 0.50% (95% CI: [0.03,0.97]) increase among girls (91). This study collected data on asthma using a nation-wide questionnaire, with 1,018,031 parents satisfactorily completing questionnaires on the respiratory health of their children. Air pollution measurements were calculated as mean 1994 averages using data obtained from monitoring stations. The authors concluded that air pollution is most likely related to asthma induction in childhood. An Italian birth cohort study found no evidence for such an effect, however. This study recruited 672 newborns in Rome and conducted parental interviews at birth, 6 months, 15 months, 4 years, and 7 years (92). The researchers found no significant associations between long-term traffic-related NO_2 exposures and incident asthma.

A nested case-control study of 3,482 children resident in British Columbia examined the relationship between fine particulate matter, ozone, and nitrogen dioxide pollution and the incidence of asthma (93). Administrative health data was linked to $PM_{2.5}$, NO_2, and O_3 measurements derived from monitoring data. These data were supplemented with pollution estimates using land-use regression (LUR) and inverse distance weighting (IDW) extrapolation. Each asthma case was matched to five controls by sex and age. The authors found consistent

increases in asthma risk associated with NO_2 exposure during the first year of life for both LUR and IDW. No evidence for a similar effect using ozone or $PM_{2.5}$ measurements was found.

It has been suggested that the air pollution effect on asthma differs between males and females. A Chinese study enrolling 30,139 children resident in Liaoning province used questionnaires to ascertain asthma status as previously diagnosed by a doctor (94). Exposure estimates to NO_2 and O_3 were obtained using 2006-2008 averages obtained from ground-level monitoring stations. The authors found that both NO_2 and O_3 increased asthma risk in boys but only the latter was also a factor for girls in single pollutant models. They also found evidence for an inverse relationship between atopy and gender on asthma risk: males seemed to be affected by pollutants regardless of allergic sensitisation while girls with atopy were found to be more susceptible to air pollution than non-atopic girls.

2.11 Other risk factors for childhood asthma

2.11.1 Individual risk factors for asthma

It is well known that age is a strong predictor of future asthma risk. Infants and young children are more likely to develop the condition than adolescents and adults (19). The trend of asthma risk seems to peak during the pre-school years and decline into late childhood (95). The mean age of asthma diagnosis may have decreased in the past decades; a birth cohort study in Ontario found a higher risk of being diagnosed as asthmatic in the first three years of life among children born after 1996 compared to those born between 1993-1995 (96).

Sex variations in asthma incidence have been reported in many studies (97). Male sex has been established as a risk factor for asthma incidence in young children and infants while females have been shown to have a higher risk of asthma in adolescence and beyond (19). The

mechanisms behind this age-sex interaction have not yet been established, but differences in hygiene practices between younger males and females have been proposed as a factor (98). It has also been suggested that lung size and growth (99), physician diagnostic practices (100), and hormonal changes during puberty (101) may explain the differences in asthma risk between young males and females.

Asthma has a strong atopic component and, as such, is considered to be strongly related to other atopic diseases (34). It has been suggested that approximately half of asthma cases are related to atopy (34). Atopy, generally diagnosed by a positive response to skin prick testing, is a loosely-defined term that refers to IgE sensitization and a predisposition to IgE-mediated conditions such as hay fever, atopic eczema and atopic dermatitis. Sensitisation to common allergens has been shown to increase the risk of asthma in children (20). There is also evidence that other atopic conditions such as allergic rhinitis and eczema are associated with asthma risk as well (20, 102).

Whether ethnicity is a predictor of future asthma in childhood is not completely clear. Studies conducted in the US have primarily focused on the excess asthma prevalence that exists among black children (103, 104). A cohort study enrolling 8,117 children found increased asthma incidence among the black population than the non-black one after adjusting for socio-economic factors (105). However, more recent research has suggested that socio-economic, genetic, and nutritional factors may play a strong confounding role in the hypothesised race-asthma association (106). Genetics are an important component of asthma risk; although shared ethnicity may appear to be an acceptable indicator of a shared genetic heredity, it has been shown that ethnicity is, at best, a moderate predictor of genetics (107).

Increasing rates of obesity and overweight in the Western world have been roughly paralleled by increases in asthma and other atopic diseases (20, 108). This has lead researchers to investigate the possible association between body weight and asthma incidence. Many studies have shown that both overweight and obese status confer higher asthma risk in childhood (109, 110). Other studies have shown a positive association between body mass index (BMI) growth and asthma risk (108, 111, 112). The underlying cause of this association is not yet known (20, 111). A 2013 systematic review and meta analysis found that overweight children had a 19% increase in asthma risk over non-overweight ones; this effect increased to 102% when comparing obese and non-obese children (113). Interestingly, this association was found to be stronger in boys than in girls. It has been proposed that the mechanism behind this difference lies in differential pulmonary mechanics and sleep disordered breathing between the sexes; however, this has not yet been definitively shown.

2.11.2 Pre-natal and early life risk factors for asthma

Breastfeeding has been generally shown to be a protective factor against asthma in children (114-120). Breast milk contains compounds that confer benefits to a child's passive immune system (through secretory IgG, for example) while also enhancing active immune response in infants (114, 115, 121); however, variation in the constituents of breast milk between mothers means that these effects may vary significantly between individuals (114). A 2015 systematic review found that early breastfeeding is protective against future asthma diagnosis (115). This study also showed little evidence for an increase in asthma risk in later life due to breastfeeding. A separate review conducted in 2014 found a strong protective effect of early life breastfeeding on the risk of ever asthma (OR = 0.78; 95% CI: [0.74,0.84]), the risk of recent asthmatic symptoms (OR = 0.76; 95% CI: [0.67,0.86]), and wheeze (OR = 0.81; 95% CI:

[0.76,0.87]) (117). Other studies have shown more conflicting evidence (122, 123). The methodological soundness of some primary studies on asthma and breastfeeding have been put into question, however, thus making the role of breastfeeding in asthma prevention somewhat controversial (114).

Maternal age at the time of birth has been shown to be related to numerous health outcomes in childhood (124). There is some evidence that younger mothers give birth to children who are at a higher risk for asthma and wheeze than those who were born to older ones. A case-control study in Montréal found that young maternal age increased a child's risk of asthma: the children of mothers who gave birth when aged 20 years or younger had 2.67 (95% CI: [1.08,11.22]) times the odds of developing asthma than those born to mothers older than 20 years (125). A UK study found evidence that young maternal age is independently associated with an increased risk of persistent wheeze (126). Another European study found that the children birthed to mothers aged 35-53 had a significantly lower risk of asthma over 10 years of follow-up than those birthed to mothers aged 13-19 (127). This association was also observed for wheeze. However, the number of older siblings of a child may be a potential confounder in the relationship between young maternal age and childhood asthma (127). As having older siblings has been shown to be protective against future asthma, children who are first-born and thus have both no siblings and young mothers may be at increased risk due to solely the former factor. It has also been suggested that socio-economic factors may partially or wholly explain this association (128). More limited evidence exists showing an association between older maternal age and future asthma risk. A Canadian study found that childhood asthma risk increased by 1% with each year increase in the maternal age of the mother (128). Other studies, however, have

found no association between either younger or older maternal age and childhood risk of asthma (129, 130).

Research has suggested the adverse effect on lung development associated with young gestational age and low birth weight may predispose preterm and/or underweight infants to an increased risk of asthma and wheezing symptoms in later life (131-133). As these two postnatal exposures are highly related, they are often examined concurrently. A Danish study found that, in twins, the sibling with the lower birth weight had a significantly higher risk of asthma (OR = 1.30; 95% CI: [1.10,1.54]) by age 9 than their higher birth weight counterpart (134). A large meta-analysis of 31 pre-existing cohorts including over 140,000 children and infants found that both young gestational age and higher weight gain in infancy (indicating low birth weight) were both associated with future diagnosis of asthma (131). Published findings on the effects of preterm birth and low birth weight on the development of asthma and wheeze are heterogeneous, however, and complicate attempts to infer a causal relationship (131, 132, 135, 136). It has been suggested that this heterogeneity may be due to important between-study differences in the definitions used (131).

2.11.3 Socio-economic and environmental risk factors for asthma

Certain socio-economic factors such as parental education, parental occupation, and family income have been found to be associated with the incidence of asthma and wheeze during childhood (137, 138); however, the direction of this effect is not clear. Some studies have suggested that increasing family SES indicated by higher parental education, parental occupational prestige, and family income are either related to an increased risk of childhood asthma (139) or have failed to show a clear association (140, 141). The former implication would

be in line with the notion that asthma and wheeze are positively associated with a more affluent lifestyle (20, 142). Other studies have shown a reversal effect, with lower SES levels generally increasing the risk of asthma and wheeze rather than decreasing it (143-147). Understanding these factors may play a role in the primary prevention of respiratory illness in children (148); however, confounding with other risk factors for asthma and wheeze may have led researchers to ascertain a spurious association with SES (140). Home ownership, a factor strongly related to SES, has also been identified as a possible predictor of asthmatic symptoms in children (126).

Some studies have shown that children who attend daycare regularly are at less risk for developing asthma later in childhood and adolescence than those who do not (149-153). Using the hygiene hypothesis' proposition that early life infections may lead to a decreased risk of atopic disease, the mechanism behind the apparent daycare effect has been attributed to high risk of respiratory infection among children who attend daycare regularly (149, 154, 155). Indoor air quality at childcare centres may also play a role in this effect (142). A 2014 study found that children who spent longer than 37.5 hours per week at daycare had a reduced risk of physician-diagnosed asthma by age 7 (OR = 0.6; 95% CI: [0.4-0.9]) but those whose weekly attendance did not reach that level had an increased risk (OR = 1.2; 95% CI: [1.1,1.6]) when compared to children who have never attended daycare (156). The direction of the daycare effect on asthma risk is not completely clear, however, as some studies have shown that daycare attendance does not decrease and may increase the risk of asthma and wheeze (156-159). In addition, comparing studies on the potential daycare effect is difficult due to differential ascertainment of exposure between them, limiting the scope of any potential reviews (153).

Exposure to passive smoke (also known as environmental tobacco smoke or second-hand smoke), either prenatally or postnatally, has been widely studied as a risk factor for childhood

asthma, partly due to it being an avoidable and generally removable risk (20, 160, 161). Passive exposure to the smoke emitted by cigarettes and other tobacco products has been shown to have a negative effect on nearly every organ of the human body (162). For this reason, passive smoke exposure is widely accepted as a risk factor for childhood asthma (162). An early review by Strachan and Cook found an increased risk of ever asthma among children who had at least one parent who smoked compared to those who did not (OR = 1.21; 95% CI: [1.10,1.34]) (163). This review found that maternal smoking (rather than paternal smoking) leads to the strongest increase in asthma risk; however, having a father who smoked was still found to be a significant postnatal risk factor for incident asthma, thus providing evidence for an effect that is not exclusively prenatal. More recent systematic reviews have also found evidence that exposure to passive tobacco smoke during childhood leads to an increased risk of the induction and exacerbation of both asthma (146, 160, 164-169) and wheeze (160, 166).

Many studies have reported higher prevalences of childhood asthma and wheezing symptoms in urban rather than rural areas. This has lead them to suggest that living in an urban environment may be a risk factor for childhood asthma and wheeze (31, 49, 56, 170-173). Some studies have found no evidence of a difference, however. The reason behind the differences in asthma prevalence between rural and urban areas has been attributed to the hygiene hypothesis and farm living (31, 49, 56, 174), high levels of indoor and outdoor air pollutants in urban areas (71), and other environmental or socio-economic factors (171, 175-177).

Other household factors such as poor house repair, dampness, mold, and exposure to household allergens such as dust mite, cockroaches, pet dander, and other vermin have been shown to be risk factors for the induction of asthma and wheeze in children (167, 178-186). Dampness and moisture in a dwelling can lead to changes in the microbial and fungal

populations present there (187). As an increasing body of evidence now shows that exposure to microbial agents in early life is related to an increase in the risk of atopic disease by the hygiene hypothesis, it follows that household dampness may play a role in mediating childhood asthma risk (4, 187). Childhood exposure to dampness in the home may increase the severity of respiratory disease (183). It has also been shown that dampness at a child's school may lead to an increase in the risk of adverse respiratory symptoms such as wheeze (188). Allergen exposure in early life has been shown to increase risk of atopic asthma in children through sensitisation (167, 185, 189); however the risk from early life animal dander exposure may be different between atopic and non-atopic asthma (185).

2.11.4 Parental and family risk factors for asthma

In a landmark 1989 study on hay fever and family size, Strachan investigated the inverse relationship between number of siblings and risk of hay fever (190). This has lead many researchers to investigate the effect of larger family size and, specifically, number of older siblings on incidence of asthma and other atopic disease (128, 136, 149, 152, 159, 191, 192); however, the causal mechanisms behind this effect are not known and some research suggests this may not be fully explained by the hygiene hypothesis alone (142, 192). While many studies have found that increased family size is protective against childhood asthma and/or wheeze, the strength of this association has not been established as definitively as it has been for other atopic diseases (142). Other research has focused on crowding in children's places of residence, as respiratory infections may be more easily spread among members of a crowded dwelling than a non-crowded one (142, 193-195). Measures of crowding take into account both the number of household members and the size of the dwelling as measured by the number of bedrooms, total floor space, or the presence of bed-sharing among family members. A protective effect against

asthma and/or wheeze associated with crowding or bed-sharing has been generally found (193, 196, 197).

Having a single parent has been shown to be a factor which may increase childhood asthma and wheeze risk (198). Evidence for this effect is mixed, however. The effect of single parent status on childhood physical health is probably related to other potentially more significant factors such as SES, parental smoking, and poor housing environment (198, 199). It has been shown that the negative effect of living in a single parent family on the risk of respiratory disease is stronger for infants than for older children (199). Asthma hospitalisation and re-uptake of healthcare services due to asthma have been shown to be higher among children with single parents than those from dual parent families (200, 201).

Having a family history of asthma or atopy has been consistently shown to be a predictor of asthma and wheeze in childhood (20, 161, 202). Many studies have specifically investigated these effects and found a positive association (203-205). Even when only non-atopic asthma is considered, family history of asthma or atopic disease may be an important risk factor (206). Some studies have found evidence for effect-modification of heredity on asthma and/or wheeze risk by gender of the child (203, 204), gender of the atopic and/or asthmatic parent (205), and child's atopy status (204).

2.12.5 Risk factors not considered in this study

The factors above represent widely accepted predictors for asthma in childhood. Many of them have been found to play potentially confounding roles in epidemiologic studies of asthma. For the purposes of the following chapters, these factors were treated as potential confounders. Attempts to control for their potential effects on the observed associations between the exposures

of interest and asthma incidence were done using statistical adjustment. However, many other potentially meaningful predictors of childhood asthma and wheeze have been identified by past studies. For the reasons of unavailable or incomplete data, model parsimony, and inconclusive evidence, some potentially important predictors of asthma were not included in the analyses of subsequent chapters.

There is evidence for a moderate to strong genetic component in asthma risk (3, 18, 20). As the association between genetics and asthma incidence is still largely an uncharted field and there is a high likelihood that various environmental and genetic factors may have interactive effects, there are many unanswered questions as to the exact risk factors for asthma (161, 207); in particular, the mechanisms of non-atopic asthma remain broadly unknown (18). While the following studies focus on the effects of farming environment and air pollution on asthma incidence there is a high probability that it was impossible to accurately measure and control for that many other factors associated with asthma, specifically those of a genetic nature. As more studies on the potential underlying epigenetic causes of asthma are conducted we will better understand the scale of the role that genetics plays on asthma risk in children.

2.12 Summary of the literature review

As this literature review did not employ a systematic framework, one cannot consider it exhaustive in its scope; however, the studies and reviews identified above represent a relatively large sample of the literature with respect to the primary objectives of this study. This review presented a narrative summary of the evidence for residence in a farming environment as a protective factor for childhood asthma and air pollution as a risk factor. While there was generally strong and consistent evidence found to support both the farm effect on asthma and the

positive association between air pollution on asthma exacerbations, this review found mixed evidence to support a causal link between poor air quality and incident asthma. The biological plausibility of this link was explored in this review, however, with the general consensus among studies suggesting that there does appear to be mechanisms by which asthma may be induced through exposure to high levels of ambient air pollution.

2.13 Rationale of the study

Broadly, the principal objective of the following chapters of this thesis will be to ascertain the effects of environmental exposures including living in a farming environment and long-term exposure to ambient air pollution on asthma incidence in children. This study will add to the literature that currently exists examining the farm effect on asthma incidence in children using a population-based longitudinal methodology. There have only been a small number of such studies published worldwide. To the best of the author's knowledge, no prospective study of childhood asthma and farm living has been conducted to date in Canada following subjects from childhood through to late adolescence and adulthood. This study will also provide an analysis of the effect of ambient air pollution levels on childhood asthma and asthma-like symptoms. This study will provide a unique application of merging long-term satellite- and ground-based air pollution monitoring data with individual-level data obtained from the NLSCY.

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Chapter 3

Association of living in a farming environment with asthma incidence: Results from a 14-year follow-up study of Canadian children

3.1 Introduction

Asthma is a common chronic disease among children, which is characterised by wheezing and coughing attacks as well as shortness of breath (1). These attacks may be triggered by a number of factors such as mild to vigorous exercise, poor air quality, cold air, or other environmental triggers, and can cause significant disruption of an individual's activities (2). From an economic standpoint, asthma can lead to reductions in productivity through absenteeism and costs national healthcare systems significant sums in terms of emergency department visits and hospitalization (3). The development of asthma is generally accepted to be the result of complex interactions between genetic and environmental factors, many of which are not fully understood (2).

Living in a farming environment during childhood has been shown to protect against asthma in several studies conducted in Switzerland (4, 5), Germany (4-6), Austria (4, 5, 7, 8), Canada (9-12), the United Kingdom (13), Scandinavia (14, 15), and elsewhere (16). This effect, while still not completely understood, has given rise to the 'hygiene hypothesis': briefly, that children residing in farming environments have higher exposure to microbial and infectious agents which moderates future immune responses, resulting in a lower incidence of atopic disease. The majority of these studies are cross-sectional in nature and only a few longitudinal studies on this farm effect have been conducted to date (17). Of these longitudinal studies, a Canadian study (10) found that children residing in a farming environment had significantly less

asthma incidence over a two year follow-up period than those who resided in a rural area but not on a farm, while an Austrian study (7) found a similar result in children who had parents involved in full-time farming over three years of follow-up. A German study (18) followed both farm and non-farm children from 6 to 10 years of age until late adolescence and found evidence for a strong protective effect against asthma associated with living in a farming environment during childhood. Evidence for this farm effect has been shown both in the general population, and in studies comprising only rural dwellers, reducing the likelihood that this effect can be wholly explained by differences between urban and rural environments (16, 17, 19). This study examines this farm effect using data obtained from a large population-based cohort of children followed up over time into late adolescence and adulthood.

Data from the National Longitudinal Study of Children and Youth (NLSCY) conducted by Statistics Canada were used to examine the association between living environment and asthma incidence in a large cohort of children aged 0-11 years. Children in the current study were followed over a period from 1994-95 to 2008-09, resulting in 14 years of follow-up.

3.2 Methods

The NLSCY was a biennial survey conducted by Statistics Canada to "collect information about factors influencing a child's social, emotional and behavioural development and to monitor the impact of these factors on the child's development over time" (20). In the NLSCY, 22,831 children of ages 0 to 11 years who participated at the initial survey in 1994-95 (Cycle 1) were followed up every two years until they reached 25 years of age (20). In this study, the longitudinal data from the 14-year follow-up beginning in 1994-95 (Cycle 1) until 2008-09 (Cycle 8) were used. The follow-up ended prior to Cycle 8 if children were lost to follow-up by

Statistics Canada or reached 25 years of age. Due to budget constraints, some children were dropped from the initial cohort at Cycle 2 from households with multiple children while ensuring that at least one randomly selected child per house remained in the sample, leaving 15,468 subjects in the cohort from Cycle 2 onwards. Of these subjects, 3,504 were excluded from this study as they reported asthma and/or wheeze in Cycle 1 and so could not develop incident asthma/wheeze, and 1,023 were excluded as their data on the principal exposure variable (living environment) were incomplete. This resulted in a sample size of 10,941 for this study. Statistics Canada gave consent for this study to be conducted using confidential micro-data at its Research Data Centre (RDC) in the University of Alberta.

In the NLSCY, data were collected using interviewer-administered questionnaires that were completed by the person most knowledgeable (PMK) of each subject child (20). In Cycle 1, PMKs consisted mainly of the biological mother of subject children (90.01%) while biological fathers (8.14%) and other relations such as foster parents, grandparents, or more distant relations (1.85%) were less common (Table 3.1). Upon reaching 16 years of age, children completed the questionnaire personally. The questions answered by the PMK were about the subject child, the PMK themselves, and spouse of the PMK (if applicable). Information gathered about the child included demographics, general health status, academic achievement, and other data regarding the child's well-being. Data collected about the PMK and/or spouse included socio-economic indicators and general health status. The interviewer ascertained information on the subject child’s dwelling such as its state of repair and the surrounding living environment after the conclusion of the interview.

The outcome of interest for this study was PMK- or self-reported asthma incidence diagnosed by a health professional. For subject children under 16 years of age, the PMK was

asked, "Does this child have asthma that has been diagnosed by a health professional?" while, for children 16 years of age or older, the child was asked, "Has a health professional diagnosed you with asthma?" Between each of the eight cycles some of the questions were changed slightly but the essential wording of the question on asthma remained the same throughout. The date of the first questionnaire for which an affirmative answer was given to either of these questions was considered as the time of the event. Time to asthma incidence was measured in months since the beginning of the study in Cycle 1. Subjects were considered censored if they did not report an asthma diagnosis during the 14-year follow-up period or were lost to follow-up. Overall, 47.3% of children from the original NLSCY longitudinal cohort were censored.

The independent variables considered in the study were measured at baseline in Cycle 1. The primary exposure variable in this study was the child's living environment. The trained NLSCY interviewers responded to the closed-ended question: "Based on street level frontage, how would you characterise the land-use on this block/road?" The interviewers selected from a list of eleven possible answers including "rural, farm", "primarily residential", "primarily commercial", and "rural, residential". For the purposes of this study, the responses "rural, farm" and "rural, residential" were considered as farming and rural non-farming environments, respectively. All other possible responses were categorised as non-rural environments, thus leaving the living environment variable with three categories: non-rural, rural non-farming, and farming living environments. Information on living environment was only collected for Cycle 1 and not for any future cycles.

Other independent variables (considered as potential confounders) comprised child's sex, history of allergy, parental history of asthma, health status as rated by the PMK, dwelling repair state, daycare attendance, number of older siblings, traffic volume on dwelling street, region of

residence in Canada, and number of parents residing in the household. Child's history of allergy was established through an affirmative answer by the PMK to the "Other allergies" (as opposed to “Food Allergies”) selection from a list of possible responses to the following question: "Does the child have any of the following long-term conditions that have been diagnosed by a health professional?" Child's age at baseline was categorised into three groups: 0-1, 2-4, and 5 or more years of age, inclusive. As no data on migration status were released, the child's language first learned at home was considered a proxy for migrant status with English or French used to define non-migrants and all other languages to define migrants. A crowding index was generated by taking the number of bedrooms in the subject child's dwelling divided by the total number of occupants. Socio-economic status (SES) was measured by a normalised index derived by Statistics Canada which took into account parental education, parental career prestige, and household income (21). PMK-rated child health status, any hospital stay in the past year, child prescription drug use, and number of doctor visits in the past year were considered as potential factors associated with asthma incidence and were only used in descriptive analysis to establish the baseline health status of the children in each group but not in regression modelling as potential risk factors of asthma incidence.

Statistics Canada provided a longitudinal probability weight and 1,000 replicate weights for each child included in the NLSCY. Both longitudinal probability weights and replicate weights were used in calculating proportions and asthma incidence along the independent variables and in Cox proportional hazard (PH) regression. Due to the sample size reduction by Statistics Canada between Cycles 1 and 2, the Cycle 2 weights were used for this analysis. In order to protect the privacy of NLSCY respondents and to make accurate population estimates, all proportions and statistics reported in this study were weighted using these weights.

Information on potential confounders was cross-tabulated by living environment. The distribution of these proportions was compared using a weighted chi-square goodness-of-fit test for categorical variables and weighted ANOVA for continuous variables. The cumulative probability distribution plots of remaining asthma-free over time was obtained for the three exposure groups by fitting proportional hazards (PH) regression model for the exposure variable alone without adjusting for other factors and then estimating the cumulative probability distribution plots which were functions of baseline hazard function and regression coefficients from the PH regression. The plots were truncated at 14.5 years to protect respondent privacy. Cox proportional hazards (PH) regression was used to estimate hazard ratios (HRs) for the independent variables using time to self-reported physician diagnosed asthma as the outcome.

Univariate Cox PH regression models were fitted for each of the independent variables. Wald tests were used to test the overall significance of all categorical and continuous exposure variables included in the models. Initially, univariate Cox PH regression models were fitted for each independent variable. An interim model was then fitted using results from a multivariate model including all of the independent variables that were significant at $p \leq 0.20$. Variables with p-values greater than 0.05 in the interim model were then dropped with the provision that gender and age group, as extremely important predictors of asthma, remained in the final model. Two clinically plausible interactions, parental history of asthma with living environment and age group with sex, were considered due to their established potential to modify asthma risk in children and adolescents. Plots of log[-log(survival)] vs. log(time) were generated for all variables in the final model to assess the validity of the PH assumption. All analyses were conducted in STATA 13.0 using the 'svy' set of commands to incorporate the survey design weights.

To better ascertain the difference in asthma incidence between the rural non-farming and farming environment groups among young children who would have spent a longer period in these environments, an analysis was conducted on the subsample of children aged 0-4 years of age. In this analysis, Cox PH regression was used to build a final model using the same variables included using the final model of the primary analysis.

This study was approved by the University of Alberta Health Research Ethics Board.

3.3 Results

Subjects with missing data on the living environment variable did not significantly differ in their sex or age distributions from those retained in the study at baseline. Variables which differed between the excluded subjects and those retained in the study sample included region of residence in Canada, SES index, parental smoking status, parental history of asthma, crowding index, and language first learned at home.

At baseline, the proportions of children living in a farming, rural non-farming or non-rural environment were 6.75%, 6.21% and 87.04%, respectively. The 14-year cumulative incidence of asthma in the entire cohort was 15.86%. The cumulative incidence of asthma among children living in farming environments was 10.18%. This was significantly lower than that which was observed for children living in rural non-farming (13.12%) or non-rural environments (16.50%).

Table 3.1 shows the distribution of independent variables among children living in the three living environment categories. There were no significant differences in the distributions of age group, sex, parental smoking, child's allergy status, and parental history of asthma variables between the three categories of the primary exposure variable. No statistically significant

differences were observed between the three living environment categories in any of the descriptive variables related with health utilization: PMK-rated health status, hospital stay in the past year, prescription drug use, and number of doctor visits in the past year. The Prairies had a higher proportion of farming children than other provinces while Ontario and Quebec had relatively more non-rural children. Children in the Maritimes were predominantly from rural non-farming households. Children living in a farming environment tended to be less likely to have a single parent, had lower SES levels, less daycare use, were less likely to live in rented dwellings than non-rural ones, and had a higher chance of living in a household in need of repair. On average, children living in a non-rural environment had resided at their current address at baseline for about two-thirds the time as those children living in a farming environment.

The cumulative incidence of asthma is shown in Table 3.2 for the categories of independent variables. There was no significant difference in the cumulative incidence of asthma between categories of sex, region, number of parents, daycare, parental smoking, dwelling type, traffic volume, and first language variables. Living environment was shown to be significantly associated with cumulative asthma incidence ($p = 0.0005$). Children who were younger at the baseline had a higher cumulative asthma incidence than those who were older. Those with no older siblings, one or more parents with asthma, or living in a dwelling that was rented or needed repairs tended to have a higher asthma incidence. Children with current non-food allergies had a significantly higher asthma incidence than those without any current allergies.

The results from univariate Cox proportional hazard models are also shown in Table 3.2. At the univariate level, living in a farming environment was found to have a strong protective effect against asthma incidence when compared to living in a non-rural environment (HR = 0.60; 95% CI: [0.44, 0.81]; $p = 0.001$). Residence in a rural non-farming environment was found to

have a marginally protective effect (HR = 0.78; 95% CI: [0.61, 1.00]; p = 0.053). Figure 3.1 shows the probabilities of remaining asthma-free along the levels of the primary exposure variable estimated from the unadjusted Cox PH model for living environment. Having two or more older siblings and being in an older age category at baseline were both associated with a reduced likelihood of developing asthma. The hazard ratio decreased significantly as the SES index increased. Other factors associated with asthma in the univariate analysis included parental history of asthma, child's history of allergy, residing in a dwelling in need of repairs, and living in a rented dwelling.

The results from the final multivariate model (Table 3.2) showed a significant decrease in the likelihood of developing incident asthma was associated with residing in a farming environment (HR = 0.56; 95% CI: [0.54, 0.76]; p < 0.001) and with living in a rural non-farming environment (HR = 0.76; 95% CI: [0.59, 0.99]; p = 0.040). The independent variables which remained in the final model were: living environment, age group, number of older siblings, child history of allergies, parental history of asthma, and living in a dwelling in need of repairs. The two plausible interactions tested (child age group with sex and living environment with parental asthma) were found to be non-significant and thus not included in the final model. Increasing number of older siblings was found to have a protective effect while child history of allergy and parental history of asthma were found to be risk factors for future asthma development. Living in a dwelling that was assessed as needing repairs at baseline was found to be a risk factor for future asthma development. The validity of the proportional hazards assumption for each variable in the final model was graphically assessed and no significant violations were observed (graphs not shown).

3.4 Discussion

This population-based longitudinal study found a significant reduction in 14-year asthma incidence associated with living in a farming environment during childhood compared to a non-rural environment. Living in a farming environment was associated with a greater decrease in asthma incidence than living in a rural non-farming environment. Further analysis restricted to children aged 0 to 4 years found a significantly lower asthma incidence in children living in a farming environment compared to those living in rural non-farming environment. Other factors found to be associated with incidence of asthma were number of older siblings, child's history of allergy, parental history of asthma, and residing in a dwelling in need of repairs.

This study found a weighted 14-year cumulative asthma incidence of 15.86% among children aged 0-11 who were free of asthma at baseline in 1994-95. A study conducted in the US found an asthma incidence rate of 10.1 cases per thousand person-years in 1990 (22). Assuming a roughly constant incidence rate in this group over time (the rate remained the same between 1990 and 1995, suggesting this assumption may hold), this translates to an estimated 14-year cumulative asthma incidence of 13.19%. The cumulative incidence of this study also broadly agrees with administrative population-based data collected in British Columbia, Ontario and Manitoba over the same time period (23).

At the baseline, there were no significant differences in the health status indicator variables between children living in rural-farming, rural non-farming and non-rural environments This suggests that the observed difference in asthma incidence between the farming and non-rural groups was most likely not related to the subject children's general health at baseline. The three groups were also similar in terms of number of doctor and hospital visits, suggesting that the groups had similar access to healthcare services. Other than dwelling repair need, which was more common in rural non-farming and farming environments than non-rural environment, none

of the independent variables included in the final model differed significantly between the three groups. The variable indicating dwelling needing repairs was retained in the final model.

The present study also found significantly lower asthma incidence among children with two or more siblings than those with no siblings. Strachan in his landmark paper on the hygiene hypothesis proposed that infections resulting from contact with older siblings both prenatally through the mother and postnatally were associated with reduced risk of allergy and atopic disease in later life (24). Other studies have similarly shown the number of siblings to be an important predictor of asthma as well (11). The current study found that child's history of allergy, as well as parental history of asthma, were strongly associated with future asthma diagnosis. This has been shown in other studies (10, 11). As the etiology of asthma has a strong genetic component and is related to atopy, asthma has been shown to be highly related to current allergy and parental history of asthma in other studies (2).

A combined analysis of two cross-sectional studies in Europe found that children living on farms were exposed to a larger range of microbes than non-farm children; this difference was said to explain a significant proportion of the observed farm effect on reduced asthma incidence (5). The present study found that residing in a farming environment during childhood may lead to a reduction in risk of future asthma diagnosis (HR = 0.58; 95% CI: [0.43, 0.80]). These findings support the hygiene hypothesis whereby reduced exposure to the infectious and microbial agents endemic to farming environments is associated with increased asthma risk.

The findings from this study agree with the other large-scale longitudinal studies on the farm effect conducted to date. A Canadian study using Cycles 1 and 2 of the NLSCY found a significant reduction in 2-year asthma incidence among children who lived in a farming

environment compared to those who lived in rural non-farming environment (OR = 0.47; 95% CI: [0.35, 0.64]) (10). In our study, a similar significant protective effect of living in a farming environment was observed only in children under 4 years when compared with rural non-farming environment (Appendix Table 1). The study also found an multiplicative effect between living environment and parental history of asthma; however, there was no evidence found for such an interaction in the present study. A longitudinal study using three years of follow-up conducted in Austria found that the children of full-time farming parents had significantly reduced asthma incidence than those whose parents were not farmers (OR = 0.34; 95% CI: [0.21, 0.98]) (7). This study found that the specific characteristics of the farms studied contributed to asthma development: farms with cows and cultivation showed a larger protective effect than farms that did not have these characteristics. A longitudinal school-based study conducted in Ulm, Germany found significantly reduced allergic sensitisation between children living in farming and non-farming environments after adjusting for potential confounders (HR = 0.58; 95% CI: [0.36, 0.92]) (18). This study followed subjects up for a maximum of 10 years. Both this study and the present one found that living in a farming environment in childhood was characterised by a significantly reduced risk of future asthma diagnosis compared to not living in one.

In this study, we reported a significant association between age at baseline and future asthma incidence. As children with prevalent asthma and/or wheeze were dropped from the analysis of this study, it was thought to be important to adjust for age at baseline. In this way, an attempt to adjust for the fact that certain children had lived longer than others without being diagnosed with asthma. Children aged 5 years old or older in Cycle 1 were found to have a significantly lower 14 year risk of asthma than those aged 0-1 years (HR = 0.73; 95% CI: [0.62,0.86]). This agrees with the notion that these children may have a reduced risk of future

asthma because they would have been free of asthma longer than children aged 0-1 at baseline. However, it is known that it may be difficult to diagnose asthma in younger children due to differences between certain wheezing phenotypes. It has been shown that some phenotypes of wheeze do not increase asthma risk in later life while others may do so (25). A premature diagnosis of asthma in young children or infants based on wheeze may ultimately lead to misdiagnosis. This potential effect may also contribute to the lower asthma risk that was observed in this study for children who were above five years of age at baseline.

This study did not find a significant difference in 14 year asthma incidence between children living in a farming environment and those living in a rural non-farming environment, although the children living in a farming environment had a (non-significantly) lower risk for asthma than those living in non-farming environments. This may suggest that rather than finding evidence for a farm effect this study found evidence for a rural effect as both of these environments are predominantly rural in nature. However, in an analysis conducted using rural non-farming rather than non-rural as a reference group on children aged 0-4, we found a significant difference between the farming and rural non-farming groups after adjusting for potential confounders (p-value = 0.044), thus providing evidence for a farm effect on childhood asthma rather than a "rural effect". Two large-scale cross-sectional studies investigating the relationship between farm living and asthma exclusively in rural children have been conducted in Canada. Both of these have shown similar findings to those of the present study. A study conducted in British Columbia found a nearly significant protective association between living in an environment with consistent livestock exposure before age 2 and future asthma incidence (OR = 0.62; 95% CI: [0.37, 1.06]) (9). This study also found a significant protective effect against asthma incidence of living in a farming environment during childhood when compared to a rural

non-farming environment (OR = 0.49; 95% CI: [0.27, 0.89]). A cross-sectional school-based study conducted in rural Québec using methacholine testing to diagnose asthma also found significantly reduced asthma incidence among adolescents who lived on a farm during childhood compared to ones who did not (12).

One of the strengths of our study was that it was the first population-based longitudinal study following children from youth into late adolescence and adulthood with the primary goal of investigating the farm effect on asthma. There has been no study conducted in Canada on this topic to date with such a long follow-up period. As the vast majority of research conducted on the topic has been cross-sectional in nature, a large-scale longitudinal cohort study was needed to confirm previous findings. As wheeze and asthma are often interchangeably diagnosed in young children, the potential bias which could have resulted from including prevalent asthmatics in the study cohort was diminished significantly by excluding children diagnosed with wheeze at baseline. Further, this study's large sample size allowed for accurate and precise estimation of population parameters. Issues with under-sampling of smaller subpopulations, which could have arisen from a simple random design, were mitigated through the complex survey methodology employed. The findings of this study are further strengthened by the measurement of and adjustment for significant recognised confounders for asthma in children. While the observational nature of this study does not lend itself to causal inference, the weight of evidence provided by prospective cohort studies such as this one are almost universally regarded to be stronger than that of cross-sectional or case-control studies.

While the present study uses data from a large, well-established cohort of children, it also has some limitations. The primary exposure variable was classified based on street-level frontage by Statistics Canada interviewers. The subjective manner of this variable may have resulted in

misclassification of the exposure status of subject children; however, there is no reason to believe that any potential misclassification was systematically different between levels of the other exposure variables. Further, this "on the ground" approach to classifying exposure may be more sensitive to each child's true living environment, and information may be more accurate than generalizations based on aggregated land use data. Loss to follow-up has the potential to be a problem in this study, as in most cohort studies, although we attempted to account for this through using Cox PH regression, which incorporated censoring.

The incidence of asthma was determined by diagnosis from a health professional which was reported either by the PMK for children under 16 years of age or by children themselves if they were 16 years of age or older. Previous studies have found a high agreement between childhood asthma as reported by the child's parent or guardian and a gold standard diagnosis. A Norwegian study found a sensitivity and specificity of 96% and 97%, respectively, between an affirmative response by the parent to a question about their child's asthma status and clinical diagnosis (26). A study conducted in Canada found a sensitivity of 83.6% and a specificity of 93.6% for parent-reported childhood asthma compared to diagnosis indicated in health claims data (27). Finally, a study conducted in the UK found similar sensitivity (88.5%) and specificity (95.7%) values for childhood asthma as reported by a parent compared to a gold standard clinical diagnosis before the age of 9 (28). Children excluded from this study for having missing data on the living environment variable had significantly different distributions of certain important independent variables than those retained in the sample; however, there were no differences between the distributions of age and sex between these two groups.

Evidence for a strong protective effect of living in a farming environment during childhood on asthma risk into late adolescence and beyond has been shown in this study. This

effect was found to persist after adjustment for potential confounding factors. The findings of cross-sectional and smaller longitudinal studies that assessed the farm effect on asthma are supported by this study using data from a large 14-year population-based cohort of Canadian children. This provides further evidence for the hygiene hypothesis in the development of asthma in childhood.

Table 3.1: Distribution of independent variables by living environment at the baseline (Cycle 1)

	Non-rural	Rural non-farm	Farming	Overall	p-value
Sex					
Female	50.8	48.5	47.3	50.4	0.20
Male	49.2	51.5	52.7	49.6	
Age					
0-1 years	16.4	11.6	15.5	16.0	
2-4 years	25.7	24.5	26.3	25.7	0.06
≥5 years	57.9	63.9	58.2	58.3	
Region					
Maritimes	7.3	20.0	5.0	7.9	
Quebec	25.5	12.7	13.9	24.0	
Ontario	36.3	39.1	33.5	36.3	<0.0001
Prairies	18.5	14.1	40.3	19.7	
BC	12.5	7.2	7.3	12.3	
Number of parents					
Two	85.7	92.6	96.0	86.8	<0.0001
One	14.3	7.4	4.0	13.2	
Number of older siblings					
None	44.2	38.7	31.1	42.9	
One	37.9	35.0	37.2	37.7	<0.0001
More than one	18.0	26.3	31.7	19.4	
SES index					
Mean (SE)	0.00 (0.02)	-0.17 (0.04)	-0.26 (0.04)	-0.03 (0.02)	0.009
Daycare use					
Yes	5.7	2.4	2.7	5.3	0.011
No	94.3	97.7	97.3	94.7	
Parental smoking					
Yes	44.4	46.2	40.0	44.2	0.31
No	55.6	53.8	60.0	55.8	
Allergies					
Yes	10.0	11.0	12.7	10.3	0.16
No	90.0	89.0	87.3	89.7	
Parent asthma history					
Yes	7.6	8.8	5.3	7.5	0.37
No	92.4	92.2	94.7	92.5	
Dwelling ownership					
Owned	73.0	88.1	84.3	74.7	<0.0001
Not owned	27.0	11.9	15.7	25.3	
Dwelling repair status					
Repairs needed	21.5	30.0	37.8	23.1	<0.0001
No repairs needed	78.5	70.0	62.2	76.9	
Crowding index					
Mean (SE)	1.39 (0.01)	1.39 (0.02)	1.47 (0.04)	1.39 (0.01)	0.10
Dwelling type					
Single detached	68.4	92.4	88.0	71.2	
Semi-detached	17.5	2.2	4.5	16.0	<0.0001
Other	14.1	5.4	8.7	8.7	
Years at current address					
Mean (SE)	5.21 (0.11)	6.65 (0.30)	8.11 (0.33)	5.49 (0.1)	<0.0001
Traffic volume					
Very light	48.5	57.8	61.7	50.0	
Light	23.3	18.5	14.7	22.4	0.0001
Moderate	18.9	17.3	13.8	18.4	
Heavy	9.3	6.5	9.8	9.2	
First language					
English or French	90.0	99.1	94.7	90.8	<0.0001
Other	10.0	0.1	5.3	9.2	
PMK-rated health status					
Excellent	68.12	69.00	66.60	68.07	
Very good	24.26	23.31	24.44	24.22	0.88
Good or less	7.62	7.69	8.96	7.71	

Hospital stay in past year					
Yes	4.2	3.5	4.0	4.1	0.78
No	95.8	96.5	96.0	95.9	
Number of doctor visits					
0	31.9	31.9	31.8	31.9	
1	22.1	26.8	23.5	22.5	0.27
≥2	46.0	41.2	44.7	45.6	
PMK relationship					
Biological mother	90.01	93.97	91.98	90.39	
Biological father	8.14	3.59	5.67	7.69	0.06
Other	1.85	2.44	2.35	1.92	

*Means and standard errors (SEs) are given for SES index, crowding index, and years at current address while column percentages are given for all other variables.

Table 3.2: Cumulative incidence and results from Cox's proportional hazards regression

		Univariate models		Final model	
	Incidence (%)	HR (95% CI)	p-value	HR (95% CI)	p-value
Living environment					
Non-rural	16.50	1.00		1.00	
Rural non-farming	13.12	0.78 (0.61,1.00)	0.053	0.76 (0.59,0.99)	0.04
Farming	10.18	0.60 (0.44,0.81)	0.001	0.56 (0.41,0.76)	<0.001
Sex					
Female	15.50	1.00		1.00	
Male	16.23	1.06 (0.92,1.24)	0.42	1.05 (0.91,1.22)	0.52
Age					
0-1 years	19.23	1.00		1.00	
2-4 years	16.36	0.85 (0.71,1.03)	0.09	0.84 (0.70,1.01)	0.07
>=5 years	14.72	0.77 (0.65,0.92)	0.004	0.73 (0.62,0.87)	<0.001
Region					
BC	14.92	1.00			
Maritimes	17.95	1.20 (0.93,1.56)	0.17		
Quebec	16.95	1.12 (0.82,1.52)	0.49		
Ontario	15.17	1.02 (0.77,1.35)	0.90		
Prairies	15.58	1.02 (0.79,1.33)	0.87		
Number of parents					
Two	15.56	1.00			
One	17.85	1.24 (1.00,1.53)	0.055		
Number of older siblings					
None	17.27	1.00			
One	16.22	0.94 (0.80,1.10)	0.42		
More than one	12.06	0.68 (0.53,0.86)	0.001		
SES index					
unit increase		0.90 (0.82,1.00)	0.047		
Daycare use					
No	15.95	1.00			
Yes	14.55	0.90 (0.57,1.41)	0.65		
Parental smoking					
No	14.66	1.00			
Yes	16.60	1.17 (1.00,1.38)	0.052		
Allergies					
No	14.91	1.00		1.00	
Yes	24.21	1.73 (1.38,2.18)	<0.001	1.81 (1.44,2.28)	<0.001
Parent asthma history					
No	14.96	1.00		1.00	
Yes	27.05	1.91 (1.47,2.49)	<0.001	1.85 (1.43,2.39)	<0.001
Dwelling ownership					
Owned	15.06	1.00			
Not owned	18.29	1.30 (1.09,1.55)	0.004		
Dwelling repair status					
No repairs needed	14.67	1.00			
Repairs needed	19.89	1.40 (1.16,1.69)	0.001	1.42 (1.18,1.72)	<0.001
Crowding index					
per unit increase		0.92 (0.76,1.11)	0.39		
Dwelling type					
Single detached	15.29	1.00			
Semi-detached	18.67	1.24 (0.98,1.58)	0.08		
Other	15.87	1.09 (0.84,1.41)	0.53		
Years at current address					
per year increase		0.97 (0.96,0.99)	0.001		
Traffic volume					
Very light	15.96	1.00			
Light	15.81	1.00 (0.80,1.26)	0.99		
Moderate	15.29	1.00 (0.81,1.22)	0.95		
Heavy	17.14	1.10 (0.82,1.46)	0.53		

First language			
English or French	16.16	1.00	
Other	13.13	0.85 (0.57,1.27)	0.43

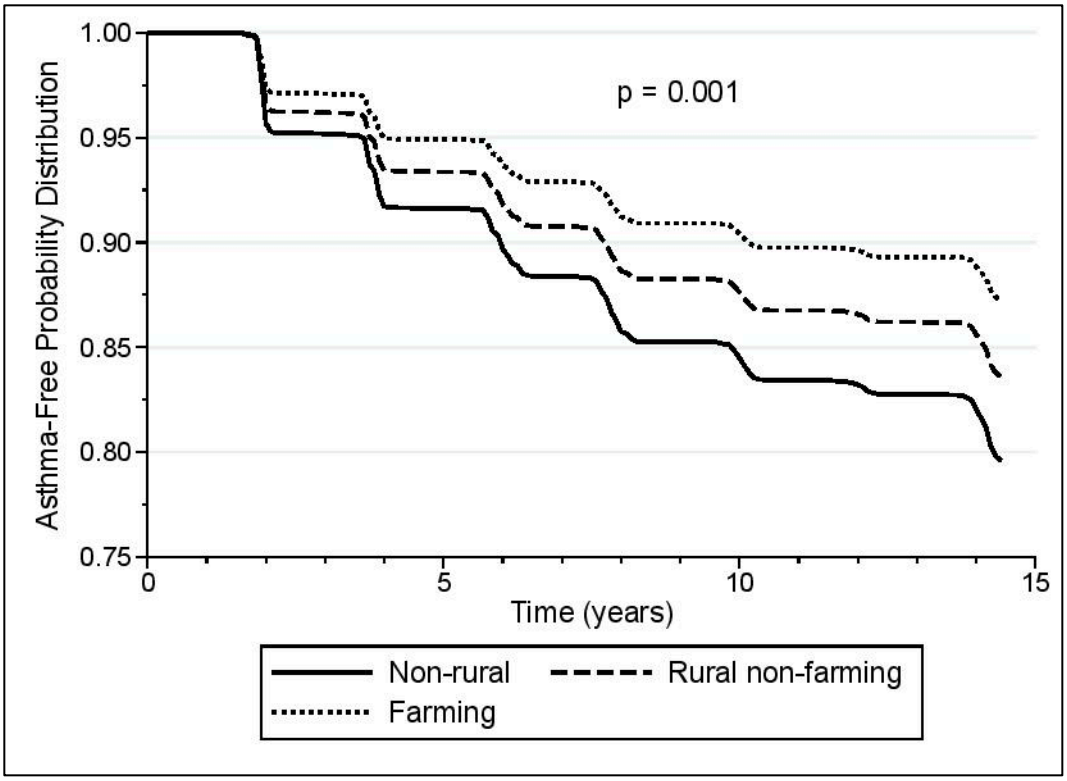

Figure 3.1: Asthma-free cumulative probability distribution plots for non-rural, rural non-farming and, farming environments were obtained after fitting a univariate Cox PH regression model for the exposure variable. The plots were truncated at 14.5 years to protect respondent privacy. The p-value indicates the overall significant differences between the three groups.

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Chapter 4

Effect of outdoor air pollution on asthma and asthma-like symptoms in Canadian children

4.1 Introduction

Asthma is a chronic respiratory condition primarily characterised by episodes of lower airway inflammation resulting in spontaneously reversible airflow obstruction (1). These symptoms are often brought upon by triggers such as physical activity or environmental stimuli (1). Wheezing is a very common early life condition and is associated with future asthma diagnosis (2). While non-severe asthma is generally manageable from a pharmacological perspective, the quality of life of those who are afflicted with it may be severely reduced (1). At a global scale, the economic costs associated with asthma are significantly larger than those of any other chronic condition (3).

The effects of air pollution on lung function and respiratory disease have been widely studied (4). Consistent exposure to outdoor air pollutants, even at low exposure levels, can lead to adverse respiratory and cardiovascular morbidity and mortality (5). Potentially harmful outdoor pollutants include nitrogen oxides such as nitrogen dioxide (NO_2), particulate matter (PM), and ozone (O_3). Nitrogen oxides are a significant source of smog pollution in urban areas. Motor vehicle emissions are the primary contributor to outdoor NO_2 pollution. Fine particulate matter ($PM_{2.5}$) consists of aerosols with an aerodynamic diameter less than 2.5μm. These particles, arising from both anthropogenic and natural sources, can deposit deep within the respiratory tract, as far as the alveoli (6). Ozone is a highly reactive substance formed by photochemical reactions with other particles. As the lower airways are generally responsive to inhaled pollutants and particulate matter, it has been hypothesised that asthma and air pollution

may be related, with children being more susceptible to pollutants than adults (1, 4, 7). Evidence from toxicological studies has shown that this relationship is biologically plausible (8).

It has been shown that poor air quality is related to an increased risk of asthma attacks (9-15) and wheezing symptoms (13, 16). Elevated pollutant levels have been shown to increase asthma-related hospitalisations and doctor visits (10, 12, 17-27). Ozone is considered a high-risk pollutant in triggering asthma attacks and hospitalisations due to its highly reactive nature (10). There is mixed evidence, however, to support poor air quality as a cause of *de novo* asthma in previously healthy subjects (28). A systematic review and meta-analysis conducted in 2013 (29) found no association between outdoor pollution and asthma prevalence; however, an earlier meta-analysis conducted in 2012 found evidence for such an association (8). Residential and school proximity to major roadways have been used as proxies for traffic-related air pollution exposure in children (30, 31); these studies have found potential associations between certain pollutants and asthma exacerbations (19), sensitisation (6, 8, 32, 33), and wheeze (33).

This cross-sectional study used data obtained from Cycle 7 of the Early Childhood Development (ECD) cohort of the National Longitudinal Study of Children and Youth (NLSCY) to ascertain the effect of ambient NO_2, $PM_{2.5}$, and ozone exposure with the prevalence of asthma-related outcomes in children. This study used individual-level data collected in interviews and long-term pollution exposure measurements combining satellite and ground-based data to ascertain the association between air quality and asthma-related outcomes.

4.2 Methods

The NLSCY was initiated by Statistics Canada in 1994 as an ongoing longitudinal panel study with the objective of investigating the factors associated with the well-being and general

health of children in Canada from early life into adolescence and adulthood (34). Cross-sectional samples of younger children and infants, particularly newborns aged 0-1, were collected as part of the Early Childhood Development (ECD) cohorts of the NLSCY. Children included in this study were sampled using a multi-stage design from respondent households to the population-based Labour Force Survey (LFS). There were several cycles of ECD cohorts sampled throughout the duration of the NLSCY from 1994-95 to 2008-09. The Cycle 7 cross-sectional ECD data collected in 2006-07 was used for this study in order to best match the collection dates of the air pollution data. Only children aged 0-5 years old were included. For all children participating in this study, interviews were completed by the person most knowledgeable (PMK) of the child. The PMK respondents primarily consisted of the biological mothers of the subject children (93.0%). The other PMKs predominantly consisted of biological fathers, but also included step-parents, foster parents, and more distant relations such as aunts, uncles, and grandparents.

The original Cycle 7 ECD cohort recruited n = 4,691 children. Of these children, n = 575 had missing data for the geographical identifier (first three digits of the postal code), that was required for linking with the air pollution data and were removed from the sample. This left n = 4,116 children for these analyses. The target population of this study was children aged 0-5 years as of December 31, 2006, resident in any Canadian province at the time of data collection in 2006-2007 (35).

The primary dependent variables included in this study were doctor-diagnosed ever asthma, 12 month asthma attack prevalence (current asthma), and 12 month wheeze prevalence (current wheeze). These outcomes were measured by PMK responses to questions posed by trained Statistics Canada interviewers during data collection at Cycle 7. Ever asthma was

ascertained by an affirmative answer to the following question: "Has this child ever had asthma that was diagnosed by a health professional?" Respondents who indicated "Yes" to this question were also asked the following: "Has he/she had an asthma attack in the past 12 months?" An affirmative answer to this question was considered as an indicator of current asthma. Children without doctor-diagnosed ever asthma were considered to have no risk of asthma attacks in the past 12 months and were not asked this question. Finally, wheezing symptoms in the previous 12 months was ascertained by an affirmative answer by the PMK to the following question: "Has he/she had wheezing or whistling in the chest at any time in the past 12 months?"

NO_2 measurements were estimated using data collected in 2006 from the National Air Pollution Surveillance (NAPS) program. (36) These ground-level measurements were supplemented with land-use regression (LUR) using geographic variables and satellite-based data on NO_2 sources from 2005-2011. Measurements of $PM_{2.5}$ were derived from remote sensing data from two previously conducted studies (37, 38). These represented average median annual concentrations from 1998-2006 (39). The average daily eight-hour maximum concentrations of ozone from May-October for 2002-2009 were estimated using Canadian air quality forecast models (40).

For all of the pollutants, measurements were assigned to postal codes based on pollution estimates at the postal code centroid. Each subject in the study, based on their residential postal code, was assigned a point estimate of each of the three pollutants. These data were then averaged over Forward Sortation Area (FSA) to account for unavailable data at the 6-digit postal code level for some children. FSAs are defined by the first three digits of a 6-digit postal code. Pollution data were categorized into quartiles for statistical analyses. These quartiles were based

on the unweighted sample in order to preserve similar raw sizes in each of the groups and prevent any of the air pollution groups being based on a small number of survey respondents.

The following independent variables were included in the analysis: child's age, sex, birth mother's age at the child's birth, region of residence in Canada, number of older siblings, breastfeeding status of the child during infancy, maternal smoking during pregnancy, dwelling ownership status, dwelling type, household income level, child history of allergy, parental history of asthma, urban-rural status, and years at current address. These variables were included based on their recognised and/or hypothesised potential as confounders in studies of childhood asthma and wheeze. A crowding index consisting of the number of bedrooms in the dwelling divided by the number of people resident there was used as a measure of crowded housing status. Number of doctor visits in the past year and PMK-rated child health status were considered as potential factors associated with asthma and wheeze and were used solely in descriptive analysis in order to establish the health status of children included in the study.

Proportions and means of the independent variables were estimated individually and for the quartiles of the air pollution variables. These tabulations were available for most independent variables, although for privacy reasons it was not possible to release the tabulation for region of residence by ozone quartile due to low unweighted cell counts. Chi-squared statistics for categorical variables and linear regression for continuous variables were used to identify significant differences between the air pollution quartiles at baseline. Descriptive Pearson's correlation coefficients were calculated to measure correlation between the air pollution variables. The means of the air pollution variables were calculated across the levels of certain independent variables for descriptive purposes. Kernel density estimation was used to graphically display the distribution of the air pollution variables. In order to explore the

relationship between geography and pollution in Canada the proportion of variance in the levels of each pollutant explained by region of residence was estimated using the coefficient of determination (R^2). Cross-sectional sample weights provided by Statistics Canada for the Cycle 7 ECD cohort were used to calculate descriptive statistics and to perform regression modelling. Adjusting for these weights reduces the potential bias induced by the complex sampling design employed in the NLSCY.

Linear regression was conducted to estimate the variance in the air pollution variables explained by differences between the geographic regions of Canada. Logistic regression models were built using each of the dependent variables as binary outcomes. Wald tests were used to test the overall significance of all independent variables included in each model. A final model was built for each of the three respiratory outcomes. These final models were fitted using the results from univariate models using purposeful model selection. Variables significant at the *a priori* significance level $p = 0.20$ when fitted into a full model including all of the independent variables were fitted into an interim model. Variables significant at $p = 0.05$ from this interim model were selected for the final model. Sex, age group and region were included in all final models in order to control for their hypothesised potential to confound the relationship between air pollutants and respiratory outcomes. All analyses for the present study were conducted using the svy set of commands included in STATA 13 (41).

4.3 Results

This study found overall prevalences of 2.93% for ever asthma, 1.47% for current asthma, and 23.03% for current wheeze. Mean ambient levels of NO_2, $PM_{2.5}$, and ozone were estimated to be 11.92 parts per billion (ppb), 8.33 $\mu g/m^3$, and 39.55 ppb, respectively (Table 4.1).

The distributions of each of the pollutants generally followed right-skewed distributions (Figures 4.1-4.3).

Appendix Tables 2-4 present the distribution of the independent variables along the quartiles of the air pollution variables. At baseline, the following variables were found to differ significantly at the 95% confidence level over the quartiles of at least one of the air pollution variables: child's age, sex, birth mother's age at the child's birth, region of residence in Canada, number of older siblings, breastfeeding status of the child during infancy, maternal smoking during pregnancy, dwelling ownership status, dwelling type, household income level, child history of allergy, and years at current address. Region of residence in Canada was found to be strongly associated with pollutant levels: children in Ontario and Quebec were found to generally live in areas with higher pollution levels than children resident in the Maritimes or British Columbia. For each of the three pollutants studied, region was found to be a strong determinant of a child's pollution quartile. Socio-economic variables such as household income, parental smoking, dwelling ownership, and dwelling type also showed strong associations with pollution levels. Children living in areas with high pollution levels were found to be more likely to be from higher income households than those resident in low pollution areas.

The general health status of children in the different air pollution groups was similar both in terms of PMK-rated health status and the number of doctor visits by the child in the past year. The only variable that differed significantly was number of doctor visits between the quartiles of $PM_{2.5}$, with children from areas with higher $PM_{2.5}$ levels showing generally more doctor visits than those from areas with lower $PM_{2.5}$ levels. The relationship of the PMK to the respondent children was found to vary significantly between the quartiles of NO_2 but not the quartiles of $PM_{2.5}$ or ozone.

All of the pollutants were found to be positively correlated with each other. The quartiles of $PM_{2.5}$ and ozone were found to be highly correlated ($\rho = 0.71$) while NO_2 and $PM_{2.5}$ ($\rho = 0.43$) and ozone and NO_2 ($\rho = 0.16$) were less correlated. Region of residence only explained 6.2% of the variance in NO_2 levels but did explain approximately 45.62% and 66.16% of the variance in ambient $PM_{2.5}$ and ozone levels, respectively. In each of these univariate models, region was a highly significant predictor of pollutant levels ($p < 0.0001$ for each).

Table 4.2 shows the incidence of ever asthma, current asthma, and current wheeze along the quartiles of the air pollution variables and the levels of important independent variables. There were significant differences in the prevalence of ever asthma between the quartiles of $PM_{2.5}$ and ozone while there were similar differences in current asthma prevalence for NO_2 and ozone. Prevalence of current wheeze was found to differ significantly between the quartiles of NO_2 and $PM_{2.5}$. The prevalences of ever asthma and current wheeze were found to differ between the regions of Canada at the univariate level. Child's sex was found to be predictive of current asthma only. Age was found to be a significant predictor of both ever asthma and current wheeze.

The results from fitting univariate logistic regression models for the potential confounders and air pollution variables for each of the three respiratory outcomes can be found in Table 4.3. These results were used in purposeful model building to determine which variables should be included in final models. The results from the final logistic regression models can be found in Table 4.4. Ever asthma prevalence was not found to be associated with any of the three pollutants after controlling for potential confounders. Ozone was retained as a significant predictor in the final model for current asthma and current wheeze. NO_2 was retained as a significant predictor in the final model for current asthma while $PM_{2.5}$ was retained in the final

model for current wheeze. Children resident in areas of higher NO_2 levels were found to be generally more at risk of having current asthma symptoms than those resident in the lowest quartile of NO_2. This association was statistically significant at the 95% confidence level. While the OR associated with the 3rd quartile of NO_2 was not found to be significant, the association with the 2nd and 4th quartiles were. For current wheeze, neither of the air pollution variables included in the final model were found to be statistically significant overall; although, the ORs associated with residence in the 3rd and 4th quartiles of $PM_{2.5}$ were significant. Statistical significance notwithstanding, the general trend in the ORs for current wheeze suggested a protective trend for $PM_{2.5}$ and a harmful one for NO_2.

In the final logistic regression model a number of other variables were associated with the outcomes of interest. Being aged 2-5 years old was strongly associated with the prevalence of both ever asthma (OR = 4.67; 95% CI: [2.42,9.01]; $p < 0.001$) and current asthma (OR = 4.62; 95% CI: [1.93,11.02]; $p = 0.001$) using children less than 1 year old as a reference. No association between age and wheeze symptoms was found. A significant relationship between sex and current or ever asthma was found, with males having higher odds of these outcomes than females. Evidence for a positive association between allergy and each of the three outcomes was found; this association was strongest for the prevalence of current asthma symptoms (OR = 3.20; 95% CI: [1.15,8.94]; $p = 0.026$), although it was highly significant for the other two outcomes as well. Parental history of asthma was also shown to be associated with higher prevalence of ever asthma and current wheeze at a statistically significant level; this variable was included in the final model for current asthma but was not found to be significant. Maternal smoking during pregnancy was found to be associated with ever asthma (OR = 3.02; 95% CI: [1.79,5.25]; $p = 0.014$) and current asthma (OR = 3.76; 95% CI: [1.74,8.11]; $p = 0.001$); children

who were exposed to smoking in this way were found to have significantly higher risk of these outcomes than children who were not. Region was found to be overall strongly significant at the 95% confidence level for current wheeze but not for either of the asthma outcomes. There was evidence for higher wheeze prevalence in the East region when compared to the West region (OR = 0.58; 95% CI: [0.44,0.77]; $p < 0.001$).

4.4 Discussion

This population-based cross-sectional study found that ambient NO_2 levels were be positively associated with the 12-month prevalence of asthma attacks in children aged less than five years old. This relationship has been previously shown to be biologically plausible (8). It has also been shown that ozone and $PM_{2.5}$ exposures may lead to increased risk of asthma attacks in a biologically plausible way as well (10, 11, 42, 43). None of the three air pollution variables were found to be associated with current wheeze or ever asthma at the 95% confidence level. While the mechanisms behind the air pollution effect on asthma and wheeze are far from clear, current research suggests that even low levels of ambient pollution can induce several components of classical asthma including airway inflammation and hyper-responsiveness (11, 28). At extremely high concentrations, pollutants can go as far as directly irritating respiratory epithelium and airway neuroreceptors and lead to inflammation (28, 44). Research also shows the potential for an epigenetic component in the relationship between asthma and air pollution (8). In genetically predisposed individuals and those with atopy, the oxidative stress and injury that pollutants may further increase asthma risk (11, 28, 44, 45). Specifically, nitrogen dioxide exposure has been shown to increase the risk of asthma exacerbations in other observational studies (11, 46).

Other factors found to be associated with current asthma symptoms in this study included child's age, gender, allergy status, and maternal smoking during pregnancy. Factors found to be associated with ever asthma include age, allergy status, parental history of asthma, and maternal smoking during pregnancy. Current wheeze symptoms were found to be associated with region of residence in Canada, number of older siblings, allergy status, and parental history of asthma.

The distributions of some of the independent variables differed significantly along the quartiles of the air pollution variables; however, there is no evidence that the general health status of the children in each of the air pollution quartiles differed significantly as none of the groups differed along the PMK-rated health status variable. $PM_{2.5}$ was the only pollutant that showed differences in potential access to health services between the children in each of its quartiles as the number of doctor visits in the past year variable differed significantly between them. This could have affected outcome ascertainment as the likelihood of presenting to the doctor to be assessed for potential asthma may have been different between the ozone quartiles. For NO_2, the relationship of the PMK to the child was found to differ significantly at the univariate level, with less biological mothers reporting to be PMKs at the highest pollution quartile. Some principal indicators of socio-economic status such as household income, maternal smoking while pregnant, parental smoking, and dwelling ownership status were found to be associated with one or more of the pollutants.

Region, sex, and age were included in all final models as potential confounders. Region of residence in Canada was found to explain a large proportion of the variance in pollution levels associated with ozone and $PM_{2.5}$, but not NO_2; regardless, it was still found to be significantly associated with each of the three pollutants. Region was also found to be associated with each of the three respiratory outcomes at the univariate level, suggesting that this variable may be a

potential confounder in the pollution-asthma relationship. This is plausible, as it is well known that pollution rates vary significantly between the different geographic regions of Canada.

Both sex and age are well known predictors of future asthma in children (1, 47). Males are considered to have higher risk of asthma among younger children than females (47). Higher prevalence of each of the three outcomes for males than females was observed; however, the final OR comparing males to females for current asthma was the only one found to be significant at the 95% confidence level. A strong association between age and asthma was found, with older children having higher risk of both ever and current asthma. This is consistent with the general understanding of asthma diagnosis in children, with diagnosis being more common in children older than four years old (1, 47).

The observed relationship between NO_2 exposure and asthma exacerbation in this study is biologically plausible. NO_2 exposure has been shown to cause airway inflammation and lung damage, particularly in children (7). The present study found an increase in the risk of asthma exacerbation for children aged 0-5 associated with living in a dwelling located in a higher NO_2 quartile compared to those resident in the lowest quartile. Several previously conducted studies have found an association between NO_2 levels and asthma attacks as measured by hospital admissions. A Danish study found a 10% increase in asthma hospital admissions associated with an inter-quartile range (IQR) increase in 5-day mean NO_2 levels (48). This association held equally for infants aged 0-1 and children aged 2-5. A 2007 study (20) conducted in Edmonton, Canada found an OR of 1.50 (95% CI: [1.31,1.71]) for asthma-related emergency department visits related to an IQR increase in 5-day mean NO_2 levels from April to September (20). This association was much stronger than that found for patients of all ages (OR = 1.14; 95% CI: [1.09,1.20]), suggesting that young children may be more susceptible to outdoor pollutants than

older children and adults. A multi-city North American study found an OR of 1.09 (95% CI: [1.03,1.15]) for asthma attacks associated with a 20 ppb increase in NO_2 levels over a 2-day lag (9). Increases in asthma attack risk were also found when considering other time lags. It has been suggested that pre-natal exposure to air pollutants may lead to an increase in asthma risk in later life (49). As the mothers of the children enrolled in this study may have been exposed to similar air pollution levels as their children were, there is the potential that some of the observed association between NO_2 exposure and asthma attack risk may be due to prenatal rather than postnatal exposure. While it is biologically plausible that NO_2 exposure may increase a child's risk of developing new-onset asthma, the present study found no evidence for such an association (28, 50).

The prevalence estimates of asthma and wheeze found in this study agree with those of previously published research. This study found an overall prevalence of ever asthma of 2.93% among children aged 0-5 years old in 2006-07. A study conducted in Minnesota found a similar prevalence (2.4%) among children aged 0-5 in 2006 (51). The current study also estimated the prevalence of both current asthma and current wheeze to be 1.47% and 23.03%, respectively. A Statistics Canada report showed that 39.3% of children aged 0-11 in 2000-01 with asthma had an asthma attack in the past year, translating to an overall prevalence of current asthma of 5.27% (52). Results from the International Study of Asthma and Allergies in Childhood (ISAAC) conducted between 1993 and 1994 found city-specific prevalences of current wheeze symptoms in Canada ranging from 14.1-20.1% among children aged 6-7 years old (53). A separate Canadian study found a wheeze prevalence of 18.7% among children aged 0-11 in 2000-01 (52). The air pollution estimates arising from this study generally agree with Environment Canada data derived from the NAPS program (54).

This study has strengths that differentiate it from previously conducted research. The long-term measurement of ambient air pollution used in this study allows the ascertainment of the effects of chronic rather than acute exposures. Many studies in the past have focused on short-term exposure timeframes for these exposures. Further, as the air pollution data used in this study is derived from multiple validated sources, the reliability of these measurements can be considered to be reasonably higher than if only ground-based measurements were used. This study has examined multiple endpoints and respiratory outcomes, allowing it to provide hypothesis-generating results on the relationship between respiratory conditions such as asthma and wheeze and ambient air pollution levels. The sample used in this study comes from the NLSCY. This cohort is population-based in nature and has been used and validated in many previous studies. Data from this cohort have been quality-controlled by Statistics Canada. In controlling for important confounders of asthma and wheeze, this study was able to better isolate and estimate the effect of air pollution and minimize the potential of bias. As asthma is widely regarded as having a strong hereditary and atopic component, the measurement of allergic disease and parental history of asthma, specifically, in this study allows for a better control of these potential confounders.

The present study has some limitations. While the sample size of this study was relatively large, there could have been a potential for the study to not be adequately powered to identify small associations. In most epidemiological studies of air pollutants, the estimated effect sizes associated with specific pollutants are generally quite small and require large sample sizes to effectively isolate (55). This analysis was conducted using a cross-sectional framework. This study design, in assessing exposure and outcome simultaneously, cannot establish temporality; however, the present study used pollutant exposure estimates which were measured generally

prior to the data collection interviews, thus placing time of exposure before potential asthma or wheeze diagnosis. The high correlation of the air pollution estimates may have reduced the power of this study to detect any true associations. As most air pollutants are positively correlated with each other, this has been a problem in past studies (12). While there are many air pollutants that may affect human health, only three were considered in this study. In addition, it was not possible to measure each subject's individual cumulative exposure to the pollutants included in this study. Pollution estimates were measured at postal code centroids. Further, it was possible that during the study period participants may have been exposed to different air pollution levels than those measured for their FSA of residence. This may lead to differences between actual and estimated pollution exposures. It has been shown, however, that both personal and ambient measures of pollution exposure may be highly correlated, thus allowing average outdoor measurements to be an acceptable proxy for personal exposure (56). Further, there were indications that the health status of children was significantly different between the levels of the some of the air pollution variables at baseline. As this study only found an association between NO_2 and current asthma, the potential bias resulting from this difference is most likely marginal.

Evidence for an association between chronic NO_2 exposure and the exacerbation of existing asthma has been shown in this study after controlling for age, sex, region of residence in Canada, and other important factors. This study found no evidence for an association between long-term exposure to $PM_{2.5}$ or ozone and the exacerbation or induction of asthma or wheeze. The associations between air pollution and asthma have been extensively studied in the past, with most research broadly coming to the conclusion that pollutants most likely cause exacerbations of existing asthma but may not necessarily induce the condition in non-asthmatics

(11, 28). This study provides an example of hypothesis generating research related to the effects of air pollution on childhood respiratory disease.

Table 4.1: Correlations, means, and quartile medians of the pollutants

	Correlation			Mean	Quartile medians			
	NO2	PM2.5	O3		1st	2nd	3rd	4th
NO2	1.00			11.92**	3.76	6.20	8.86	16.01
PM2.5	0.43	1.00		8.33 *	3.50	5.10	7.40	10.30
O3	0.16	0.71	1.00	39.55**	29.00	33.55	36.56	48.12

*$\mu g/m^3$; **parts per billion (ppb)

Table 4.2: Incidence of the respiratory outcomes along the levels of select independent variables

	Ever asthma (%)	p-value	Current asthma (%)	p-value	Current wheeze (%)	p-value
Sex						
Female	2.42		0.88		21.53	
Male	3.40	0.1697	2.03	0.0117	24.43	0.18
Age						
0 years	1.71		0.93		23.17	
1 year	3.71		1.82		22.67	
2-5 years	9.54	0.0001	4.47	0.0080	26.24	0.66
Region						
East	3.26		1.67		27.80	
Central	1.86		0.88		21.79	
West	3.93	0.0352	2.01	0.1452	20.16	0.014
NO2						
1st	4.08		0.70		28.84	
2nd	3.37		2.26		26.01	
3rd	1.87		0.79		23.75	
4th	2.97	0.1681	1.75	0.0422	19.67	0.012
PM2.5						
1st	4.52		1.63		31.94	
2nd	3.62		2.48		20.60	
3rd	4.05		1.55		24.41	
4th	1.87	0.0168	0.98	0.0904	21.73	0.009
O3						
1st	4.02		2.42		26.30	
2nd	2.88		0.89		18.70	
3rd	3.97		2.37		23.69	
4th	2.03	0.0488	0.85	0.0145	22.90	0.18
PMK relationship						
Biological mother	2.86		1.39		22.78	
Other	3.76	0.5069	2.60	0.2305	26.28	0.42

Table 4.3: ORs for the independent variables estimated in the univariate models of each of the respiratory outcomes

	Ever asthma		Current asthma		Current wheeze	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex						
Female	1.00		1.00		1.00	
Male	1.42 (0.86,2.35)	0.17	2.33 (1.18,4.60)	0.014	1.18 (0.93,1.50)	0.18
Age						
0 years	1.00		1.00		1.00	
1 year	2.22 (1.17,4.21)	0.015	1.98 (0.90,4.32)	0.09	0.97 (0.76,1.24)	0.82
2-5 years	6.07 (3.09,12.04)	<0.000	5.00 (2.07,12.02)	<0.001	1.18 (0.86,1.63)	0.31
Region						
East	1.00		1.00		1.00	
Central	0.72 (0.53,0.98)	0.039	0.52 (0.20,1.34)	0.18	0.72 (0.53,0.98)	0.039
West	0.66 (0.51,0.85)	0.001	1.21 (0.59,2.45)	0.61	0.66 (0.51,0.85)	0.001
NO2						
1st	1.00		1.00		1.00	
2nd	0.82 (0.43,1.56)	0.55	3.26 (1.27,8.38)	0.014	0.87 (0.63,1.20)	0.39
3rd	0.45 (0.23,0.87)	0.018	1.13 (0.41,3.09)	0.82	0.77 (0.55,1.08)	0.13
4th	0.72 (0.38,1.36)	0.31	2.51 (1.02,6.19)	0.045	0.60 (0.44,0.84)	0.003
PM2.5						
1st	1.00		1.00		1.00	
2nd	0.79 (0.44,1.44)	0.45	1.53 (0.60,3.90)	0.36	0.55 (0.41,0.74)	<0.001
3rd	0.89 (0.45,1.78)	0.75	0.95 (0.36,2.52)	0.92	0.69 (0.51,0.93)	0.017
4th	0.40 (0.22,0.75)	0.004	5.95 (0.21,1.66)	0.32	0.59 (0.44,0.79)	<0.001
O3						
1st	1.00		1.00		1.00	
2nd	0.71 (0.37,1.36)	0.30	0.36 (0.13,1.01)	0.053	0.64 (0.48,0.87)	0.005
3rd	0.99 (0.51,1.90)	0.97	0.98 (0.43,2.26)	0.97	0.87 (0.65,1.16)	0.35
4th	0.50 (0.26,0.93)	0.030	0.35 (0.13,0.92)	0.033	0.83 (0.62,1.12)	0.22
Number of older siblings						
None	1.00		1.00		1.00	
One or more	1.49 (0.93,2.39)	0.09	1.51 (0.77,2.96)	0.23	1.29 (1.02,1.63)	0.036
Birth mother age						
15-20	1.00		1.00		1.00	
21-30	2.25 (1.09,4.62)	0.027	1.84 (0.56,6.05)	0.32	1.12 (0.72,1.75)	0.61
>30	0.58 (0.32,1.05)	0.07	0.55 (0.27,1.14)	0.11	0.91 (0.71,1.18)	0.50
Household income						
1st	1.00		1.00		1.00	
2nd	0.75 (0.40,1.41)	0.37	0.61 (0.28,1.36)	0.23	0.72 (0.53,0.99)	0.045
3rd	0.46 (0.24,0.88)	0.019	0.63 (0.26,1.57)	0.33	0.85 (0.60,1.19)	0.35
4th	0.42 (0.21,0.82)	0.011	0.53 (0.20,1.41)	0.20	0.89 (0.64,1.25)	0.64
Maternal smoking						
No	1.00		1.00		1.00	
Yes	3.17 (1.87,5.39)	<0.001	3.60 (1.72,7.54)	0.001	1.91 (1.42,2.58)	<0.001
Breastfed child						
No	1.00		1.00		1.00	
Yes	0.85 (0.47,1.54)	0.59	1.17 (0.42,3.25)	0.77	1.02 (0.75,1.38)	0.90
Parental smoking						
No	1.00		1.00		1.00	
Yes	1.85 (1.15,2.95)	0.011	2.11 (1.10,4.04)	0.025	1.52 (0.18,1.95)	0.001
Allergies						
No	1.00		1.00		1.00	
Yes	4.81 (2.64,8.79)	<0.001	5.42 (2.36,12.43)	<0.001	2.14 (1.27,3.61)	0.004
Parent asthma history						
No	1.00		1.00		1.00	
Yes	3.60 (1.98,6.54)	<0.001	2.95 (1.38,6.33)	0.005	1.90 (0.38,2.62)	<0.001
Crowding index						
unit increase	0.86 (0.58,1.27)	0.44	0.83 (0.41,1.69)	0.61	0.86 (0.70,1.06)	0.15
Dwelling ownership						
Owned	1.00		1.00		1.00	
Not owned	2.06 (1.27,3.34)	0.003	2.10 (1..08,4.09)	0.029	1.08 (0.84,1.39)	0.56
Dwelling type						

Single detached	1.00		1.00		1.00	
Semi-detached	1.29 (0.73,2.29)	0.38	1.51 (0.69,3.33)	0.30	0.84 (0.61,1.15)	0.28
Other	1.13 (0.60,2.12)	0.70	1.47 (0.61,3.52)	0.39	0.90 (0.65,1.26)	0.55
Years at address						
>4 years	1.00		1.00		1.00	
3-4 years	0.52 (0.26,1.06)	0.07	0.67 (0.24,1.81)	0.43	1.02 (0.74,1.43)	0.89
1-2 years	1.44 (0.80,2.61)	0.22	1.33 (0.59,3.05)	0.49	0.90 (0.67,1.22)	0.49
<1 year	2.35 (1.21,4.57)	0.012	2.57 (0.94,7.01)	0.07	1.38 (0.94,2.01)	0.10

Table 4.4: ORs for the independent variables estimated in the final models of each of the respiratory outcomes

	Ever asthma	p	Current asthma	p	Current wheeze	p
Sex						
Female	1.00		1.00*		1.00	
Male	1.34 (0.78,2.30)	0.319	2.45 (1.18,5.11)	0.017	1.17 (0.92,1.48)	0.20
Age						
0 years	1.00***		1.00**		1.00	
1 year	2.01 (1.02,3.94)	0.043	1.90 (0.82,4.41)	0.137	0.96 (0.75,1.24)	0.68
2-5 years	4.67 (2.42,9.01)	<0.001	4.62 (1.93,11.02)	0.001	0.78 (0.55,1.11)	0.17
Region						
East	1.00		1.00		1.00***	
Central	0.75 (0.37,1.52)	0.422	1.22 (0.48,3.13)	0.680	0.69 (0.40,1.17)	0.17
West	1.28 (0.70,2.33)	0.577	0.79 (0.33,1.87)	0.590	0.58 (0.44,0.77)	<0.001
NO2						
1st			1.00*			
2nd			4.11 (1.43,11.80)	0.009		
3rd			1.78 (0.59,3.67)	0.285		
4th			4.01 (1.32,12.18)	0.014		
PM2.5						
1st					1.00	
2nd					0.83 (0.61,1.12)	0.28
3rd					0.59 (0.38,0.92)	0.021
4th					0.59 (0.36,0.99)	0.049
O3						
1st			1.00		1.00	
2nd			0.56 (0.18,1.75)	0.322	1.05 (0.61,1.39)	0.65
3rd			1.48 (0.59,3.67)	0.400	1.26 (0.83,1.91)	0.21
4th			0.47 (0.13,1.64)	0.234	1.51 (0.76,3.01)	0.23
Number of older siblings						
None	1.00				1.00*	
One or more	1.53 (0.92,2.54)	0.173			1.37 (1.07,1.75)	0.012
Allergies						
No	1.00***		1.00*		1.00**	
Yes	3.02 (1.53,5.94)	0.001	3.20 (1.15,8.94)	0.026	1.91 (1.17,3.12)	0.010
Parental asthma						
No	1.00**		1.00		1.00***	
Yes	3.01 (1.48,6.14)	0.002	2.46 (0.97,6.24)	0.058	1.88 (1.37,2.58)	<0.001
Maternal smoking						
No	1.00*		1.00***			
Yes	3.02 (1.79, 5.25)	0.014	3.76 (1.74,8.11)	0.001		
Crowding						
person/room					0.83 (0.65,1.05)	0.14

Variable significant overall at: 0.05*, 0.01**, 0.001***.

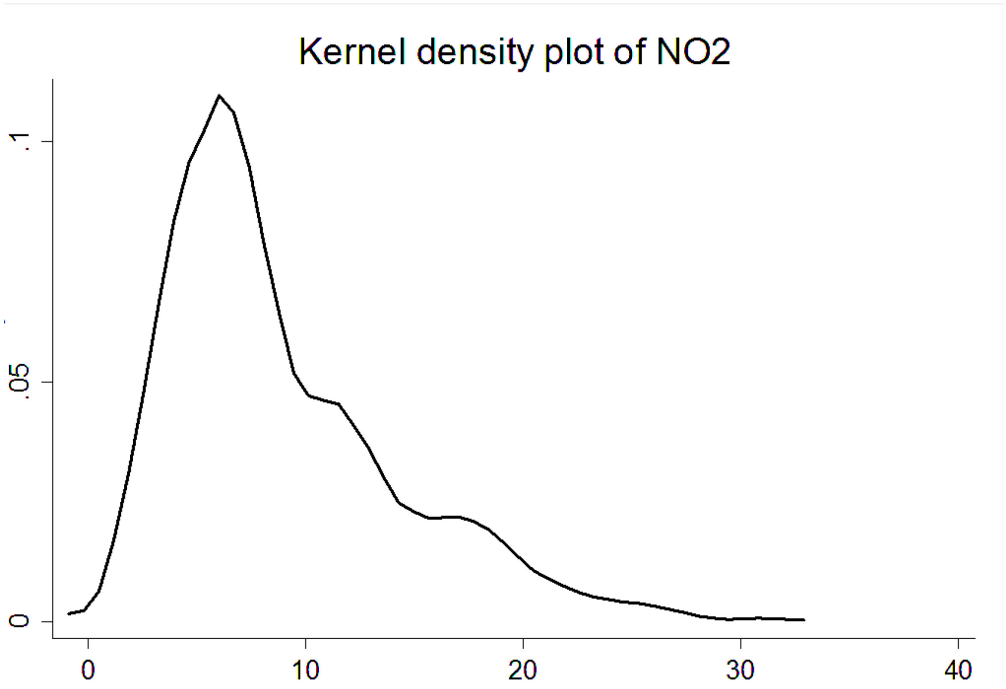

Figure 4.1: Kernel density plot of NO_2 (ppb)

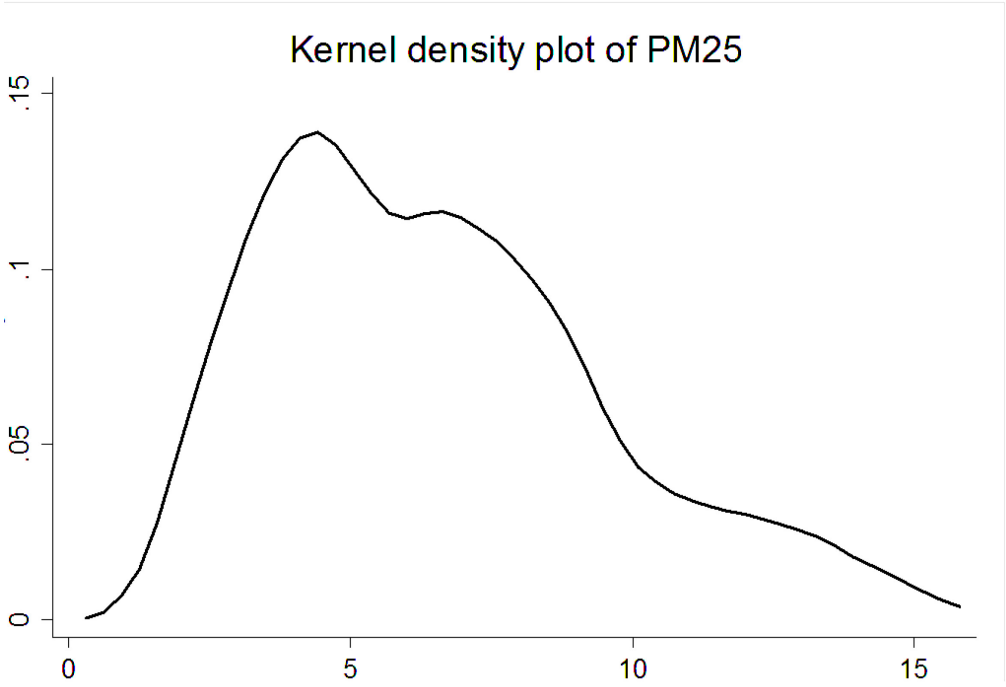

Figure 4.2: Kernel density plot of $PM_{2.5}$ ($\mu g/m^3$)

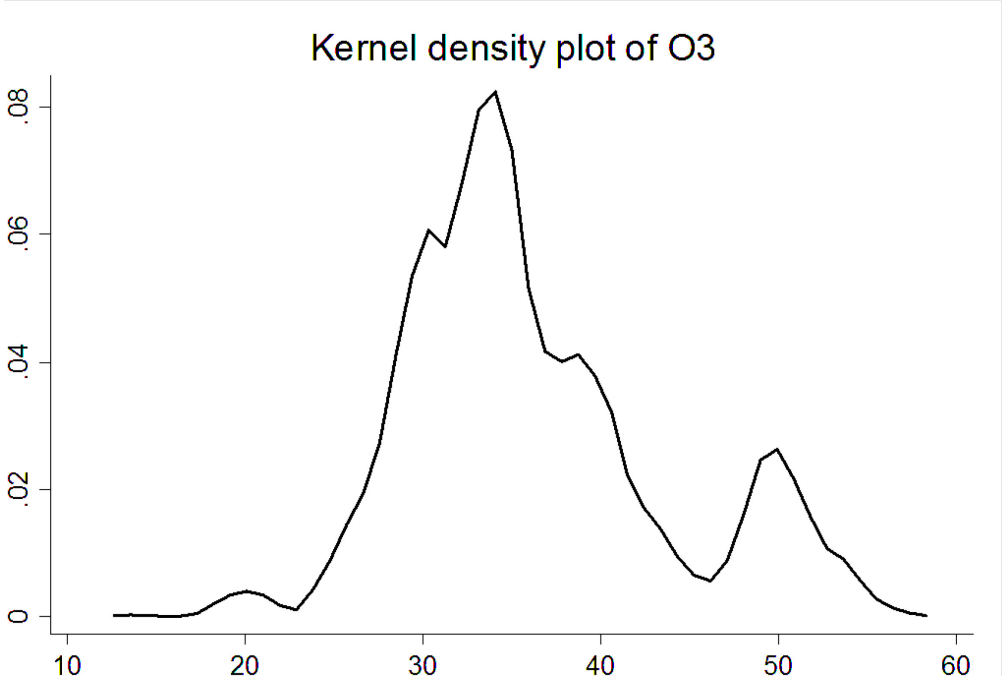

Figure 4.3: Kernel density plot of O_3 (ppb)

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Chapter 5

Discussion and conclusions

5.1 Summary of findings

In the studies included in this thesis, the environmental characteristics of the living environments of Canadian children were examined to assess their impact on the risk of asthma and asthma-like symptoms. The primary objectives of this thesis were examining the effects of farm living and ambient outdoor air pollution using data from the NLSCY.

Chapter 2 included a narrative review of the epidemiologic characteristics of asthma and asthma-like symptoms. The review focused on the effects of farm living and air pollution on these outcomes. In broad terms, the literature identified suggested that residing in a farming environment in early life may offer some protection against asthma incidence. Similarly, the literature on air pollution broadly concluded that while there is little evidence that airborne pollutants lead to incident asthma, they most likely act to exacerbate existing asthma.

The results of Chapter 3 outlined the findings from a longitudinal analysis of Cycles 1 through 8 of the NLSCY. These data, collected in biannual interviews, included information on the living environment, asthma status, demographics, and other characteristics of the respondents. The findings suggest that living in a farming environment is associated with a 44% decrease in 14-year asthma risk ($p<0.001$). In addition, age, allergy status, parental history of asthma, sex, and dwelling repair status were found to be important predictors of future asthma.

In Chapter 4, individual-level data from Cycle 7 of the NLSCY were supplemented by ground- and satellite-based air pollution measurements to ascertain the effect of ambient

pollution levels on the prevalence of ever asthma, current asthma symptoms, and current wheeze. The three pollutants studied were nitrogen dioxide, ozone, and fine particulate matter. This cross-sectional analysis suggested that children resident in the 2nd (p=0.009) and 4th (p=0.014) highest quartiles of nitrogen dioxide pollution had approximately four times the risk of current asthma symptoms than those living in the lowest quartile. Other factors found to be associated with either of the three respiratory symptoms included sex, age, region of residence in Canada, number of older siblings, allergy status, parental asthma status, maternal smoking status, and crowding in the household.

5.2 Importance of study

Globally, asthma is associated with a significant healthcare burden (1). It not only is implicated in economic costs through treatment and losses to productivity, it causes nearly two hundred thousand deaths worldwide each year (1). Although we do not have an exhaustive understanding of the root causes of asthma, known risk factors such as a parental history of asthma or atopy are important diagnostic indicators of the disease (2). In this way, research into the risk factors for asthma may lead to more effective asthma diagnosis and, thus, earlier management. This study has found evidence for several factors to be possibly implicated in the development of asthma such as residence in a farming environment during childhood; further, risk factors for the exacerbation of pre-existing asthma such as exposure to high levels of nitrogen dioxide pollution have also been identified by the analyses included in this thesis.

Many theories have been put forward to explain the root causes of the well-documented increase in asthma risk in affluent countries over the past few decades (2-6). The hygiene hypothesis is one such theory; although, debate continues to this day as to its validity and scope

(5). As children resident in farming environments are exposed to high bacterial diversity, the protective effect associated with farm living outlined in Chapter 3 lends itself towards supporting the hygiene hypothesis. Previous studies on farm exposures and asthma have come to a similar conclusion (7-17). It is worth noting, however, that this study was one of the largest conducted on the topic out of those identified in Chapter 2 in terms of sample size and follow-up time. This longitudinal study thus provides confirmation of what had been previously observed in primarily cross-sectional research.

The significant harmful effect of outdoor pollution on the risk of asthma exacerbations in Canadian children as reported in Chapter 4 provides new evidence for the negative effects of air pollution. Residing in an area of high NO_2 pollution was found to be a significant risk factor for reporting an asthma attack in the past year. The biological plausibility of this relationship has been shown in the past (18). In addition, other observational studies have concluded with similar findings (19, 20). The findings presented in this thesis can be used by policy makers as evidence supporting reductions in pollution levels, especially in residential areas, with the goal of preventing adverse outcomes. As NO_2 pollution is generated in part by heavy traffic, this may provide an argument for parents of asthmatic children to avoid living in close proximity to high-capacity roadways (21, 22).

5.3 Limitations

The limitations of the studies included in this thesis are similar to those of other non-randomised studies which rely on survey data. These include a reliance on self-reported outcome assessment, the potential for exposure misclassification due to human and/or measurement error, and the possibility of residual confounding. In the longitudinal component of the NLSCY there

was an overall response rate of 52.7% over the 14 years between Cycles 1 and 8; there is the possibility that non-differential loss-to-follow-up may have been present due to non-complete response over the study period. If the subjects who were lost to follow-up were significantly different along certain important risk factors for asthma than those who were not, the results of this study may be biased. In this study, longitudinal methods for statistical analysis such as Cox proportional hazards regression were used to account for the potential effect of lost or censored subjects. In addition, results derived from cross-sectional analyses cannot provide evidence to make any conclusions on the temporality of any association between exposures and outcomes. In fact, it is very difficult to infer causality from associations estimated using an observational framework. In the analysis of ecologic air pollution data, it is important to note that the measured exposures at a geographic level may not be representative of personal exposures. Additionally, in assessing the effects of multiple pollutants in the same model it must be noted that the power of the analysis may have been reduced due to the typical high levels of correlation between measurements of different air pollutants. In measuring air pollution levels using satellite- and ground-based monitoring supplemented with computer models, there may have been discrepancies induced between actual and estimated levels due to model error.

5.4 Conclusion

In this thesis, the relationship between childhood asthma and certain environmental exposures was explored. The studies presented above provide evidence for the farm effect on asthma and the potential for an increase in risk of asthma exacerbations in children due to poor air quality. The findings presented in this thesis are derived from population-based data sources and outline the effects of a child's living environment on the risk of developing asthma and/or experiencing an asthma exacerbation.

The studies presented in this thesis examined the effects of both biological (microbial exposures resulting from living on a farm) and chemical (ambient air pollutants) exposures on future asthma risk in Canadian children. Understanding the underlying context of exposure in both of these cases is important. The potential protective effects of living in a farming environment against asthma are most likely only realised during the first few years of life (13). Indeed, even prenatal farm exposures have been shown to affect future risk of asthma (13). In a similar fashion, the timing of air pollution exposure with asthma and asthmatic symptoms is also an important consideration. As the lungs continue to develop until approximately age 6, there may be a window in early life in which air pollution can have a significant effect (18).

Awareness of the potential risk factors for and signs of asthma and asthma-like symptoms in the general Canadian population is important. The studies presented in this thesis highlight certain risk factors for childhood asthma. Efforts on the part of government, non-governmental organisations, not-for-profits, agriculture and other industry groups, and public health agencies are crucial to raising the awareness of asthma and developing and funding targeted asthma management strategies. In including the studies presented in this thesis into the general literature on asthma and the environment, decision-makers and healthcare practitioners may be able to refer to them in order to improve asthma prevention and management.

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Appendix:

Appendix tables

Appendix Table 1: Results from Cox's proportional hazards regression models for children aged 4 years or less

	Univariate models		Final model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Living environment				
Non-rural	1.00		1.00	
Rural non-farm	1.06 (0.78,1.43)	0.72	1.06 (0.77,1.45)	0.72
Farming	0.64 (0.42,0.97)	0.036	0.62 (0.41,0.95)	0.026
Sex				
Female	1.00	0.20	1.00	
Male	1.14 (0.93,1.40)		1.14 (0.94,1.40)	0.19
Age				
0-1 years	1.00		1.00	
2-4 years	0.85 (0.71,1.03)	0.09	0.84 (0.70,1.01)	0.07
Region				
BC	1.00			
Maritimes	1.08 (0.77,1.52)	0.64		
Quebec	0.92 (0.63,1.33)	0.65		
Ontario	0.73 (0.52,1.03)	0.08		
Prairies	0.65 (0.46,0.92)	0.014		
Number of parents				
Two	1.00	0.65		
One	1.08 (0.78,1.48)			
Number of older siblings				
None	1.00			
One	0.91 (0.74,1.14)	0.42		
More than one	0.76 (0.55,1.05)	0.09		
SES index				
unit increase	0.93 (0.82,1.05)	0.248		
Daycare use				
No	1.00			
Yes	0.85 (0.56,1.31)	0.47		
Parental smoking				
No	1.00			
Yes	1.11 (0.90,1.38)	0.31		
Allergies				
No	1.00	0.003	1.00	0.004
Yes	1.71 (1.20,2.44)		1.70 (1.18,2.45)	
Parent asthma history				
No	1.00		1.00	0.003
Yes	1.65 (1.23,2.22)	0.001	1.58 (1.18,2.13)	
Dwelling ownership				
Owned	1.00			
Not owned	1.12 (0.89,1.41)	0.33		
Dwelling repair status				
No repairs needed	1.00		1.00	
Repairs needed	1.08 (0.85,1.37)	0.54	1.08 (0.85,1.37)	0.55
Crowding index				
unit increase	0.93 (0.75,1.15)	0.50		
Dwelling type				
Single detached	1.00			
Semi-detached	1.08 (0.81,1.45)	0.59		
Other	1.17 (0.86,1.58)	0.32		
Years at current address				
year increase	0.99 (0.97,1.01)	0.42		
Traffic volume				
Very light	1.00			

Light	1.02 (0.79,1.33)	0.85
Moderate	1.08 (0.82,1.43)	0.59
Heavy	1.48 (1.01,2.15)	0.042
First language		
English or French	1.00	
Other	1.02 (0.65,1.58)	0.94

Appendix Table 2: Distribution of NO_2 exposure for the independent variables

	1st	2nd	3rd	4th	Overall	p-value
Sex						
Female	47.42	44.02	45.60	52.08	48.44	
Male	52.58	55.98	54.40	47.92	51.56	0.033
Age						
0 years	41.94	50.72	49.98	49.03	48.61	
1 year	46.18	44.18	48.14	50.43	48.17	
2-5 years	11.95	5.10	1.88	0.54	3.22	<0.0001
Region						
West	64.96	36.43	25.03	17.70	31.79	
Central	26.55	27.69	36.83	48.55	39.02	
East	8.49	35.89	38.14	33.75	29.20	<0.0001
Number of older siblings						
None	40.49	46.06	43.70	47.95	45.58	
One or more	59.51	53.94	56.30	52.05	54.42	0.15
Birth mother age						
15-20	4.47	5.20	4.79	4.32	4.61	
21-30	63.49	58.67	53.63	47.97	53.35	
>30	32.04	36.13	41.59	47.71	42.04	<0.0001
Household income						
1st	27.56	21.28	21.44	28.07	25.19	
2nd	30.02	26.53	23.02	23.83	24.96	
3rd	26.19	32.36	26.83	21.06	25.17	
4rth	16.22	19.83	28.71	27.03	24.69	<0.0001
Maternal smoking						
Yes	18.27	16.75	11.50	8.34	12.05	
No	81.73	83.25	88.50	91.66	87.95	<0.0001
Breastfed child						
Yes	77.95	83.54	86.57	89.53	86.18	
No	22.05	16.46	13.43	10.47	13.82	<0.0001
Parental smoking						
Yes	35.93	34.56	27.81	24.83	28.79	
No	64.07	65.44	72.19	75.17	71.21	0.0005
Allergies						
Yes	3.75	5.50	2.73	2.46	3.25	
No	96.25	94.50	97.27	97.54	96.75	0.028
Parent asthma history						
Yes	11.34	13.16	9.52	9.52	10.42	
No	88.66	86.84	90.48	90.48	89.58	0.20
Dwelling ownership						
Owned	77.87	73.57	72.52	60.25	67.98	
Not owned	22.13	26.43	27.48	39.75	32.02	<0.0001
Dwelling type						
Single detached	82.55	75.61	71.52	51.98	65.07	
Semi-detached	8.46	11.45	15.17	23.31	17.21	
Other	8.99	12.93	13.32	24.72	17.73	<0.0001
Years at address						
<1 year	12.08	12.70	11.82	10.70	11.52	
1-2 years	29.02	32.42	33.52	40.23	35.69	
3-4 years	26.48	24.40	27.17	22.30	24.41	
>4 years	32.42	30.47	27.49	26.77	28.38	0.049
PMK-rated health status						
Excellent	69.43	71.54	66.92	67.52	68.35	
Very good	23.41	17.72	24.83	24.49	23.21	
Good or less	7.16	10.74	8.25	7.99	8.43	0.14
Number of doctor visits						
0	7.85	7.12	4.92	6.63	6.47	
1	11.09	9.21	7.49	8.02	8.52	
≥2	81.06	83.67	87.60	85.35	85.01	0.21
PMK relationship						
Biological mother	96.48	93.73	94.17	91.12	93.04	0.0031

Other	3.52	6.27	5.83	8.88	6.96

Appendix Table 3: Distribution of $PM_{2.5}$ exposure for the independent variables

	1st	2nd	3rd	4th	Overall	p-value
Sex						
Female	50.43	48.02	48.00	48.39	48.44	
Male	49.57	51.98	52.00	51.61	51.56	0.92
Age						
0 years	36.98	49.56	50.54	49.77	48.61	
1 year	44.22	46.68	47.09	50.02	48.17	
2-5 years	18.80	3.76	2.37	0.21	3.22	<0.0001
Region						
East	58.45	26.04	25.05	26.33	31.79	
Central	4.80	7.46	10.58	70.43	39.02	
West	36.75	66.50	64.37	3.24	29.20	<0.0001
Number of older siblings						
None	48.62	46.42	44.27	45.14	45.58	
One or more	51.38	53.58	55.73	54.86	54.42	0.69
Birth mother age						
15-20	7.14	4.02	5.09	4.17	4.61	
21-30	61.05	58.00	55.04	49.17	53.35	
>30	31.81	37.98	39.86	46.67	42.04	0.0002
Household income						
1st	27.60	24.53	25.27	24.95	25.19	
2nd	25.72	28.35	26.37	22.81	24.96	
3rd	24.85	25.52	27.83	24.04	25.17	
4rth	21.83	21.60	20.53	28.20	24.69	0.038
Maternal smoking						
Yes	19.14	10.95	13.84	10.31	12.05	
No	80.86	89.05	86.16	89.69	87.95	0.002
Breastfed child						
Yes	75.93	87.19	86.83	87.56	86.18	
No	24.07	12.81	13.17	12.44	13.82	<0.0001
Parental smoking						
Yes	37.91	25.41	29.46	28.14	28.79	
No	62.09	74.59	70.54	71.86	71.21	0.008
Allergies						
Yes	5.41	4.02	3.62	2.34	96.75	
No	94.59	95.98	96.38	97.66	3.25	0.057
Parent asthma history						
Yes	9.63	11.60	12.96	9.08	10.42	
No	90.37	88.40	87.04	90.92	89.58	0.094
Dwelling ownership						
Owned	68.95	67.42	70.73	66.93	67.98	
Not owned	31.05	32.58	29.27	33.07	32.02	0.53
Dwelling type						
Single detached	70.43	66.49	72.30	60.50	65.07	
Semi-detached	13.81	19.92	15.66	17.35	17.21	
Other	15.76	13.59	12.04	22.16	17.73	<0.0001
Years at address						
<1 year	12.58	12.42	12.66	10.46	11.52	
1-2 years	32.86	35.85	36.20	35.99	35.69	
3-4 years	23.99	24.52	23.74	24.72	24.41	
>4 years	30.57	27.21	27.40	28.83	28.38	0.92
PMK-rated health status						
Excellent	69.66	64.71	71.29	68.48	68.35	
Very good	20.94	25.99	20.64	23.51	23.21	
Good or less	9.40	9.30	8.07	8.02	8.43	0.40
Number of doctor visits						
0	8.49	4.31	5.64	7.32	6.47	
1	10.52	9.02	11.18	6.85	8.52	
≥2	80.99	86.67	83.18	85.83	85.01	0.006
PMK relationship						
Biological mother	95.95	92.04	93.45	92.73	93.04	0.20

Other	4.05	7.96	6.55	7.27	6.96

Appendix Table 4: Distribution of O_3 exposure for the independent variables

	1st	2nd	3rd	4th	Overall	p-value
Sex						
Female	50.68	49.46	47.35	48.08	48.44	
Male	49.32	50.54	52.65	51.92	51.56	0.78
Age						
0 years	45.96	44.62	48.69	50.50	48.61	
1 year	44.27	45.94	49.05	49.50	48.17	
2-5 years	9.77	9.44	2.26	0.00	3.22	<0.0001
Region						
East					31.79	
Central	-----	-----	-----	-----	39.02	-----
West					29.20	
Number of older siblings						
None	48.86	51.86	45.15	43.05	45.58	
One or more	51.14	48.14	54.85	56.95	54.42	0.049
Birth mother age						
15-20	7.27	4.73	3.41	4.43	4.61	
21-30	55.50	57.86	58.37	58.65	53.35	
>30	37.23	37.42	38.22	46.92	42.04	0.0002
Household income						
1st	31.41	24.90	24.06	24.01	25.19	
2nd	24.04	29.40	24.50	24.23	24.96	
3rd	21.96	29.50	26.62	24.11	25.17	
4rth	22.59	16.20	24.83	27.65	24.69	0.006
Maternal smoking						
Yes	17.99	13.12	11.53	10.23	12.05	
No	82.01	86.88	88.47	89.77	87.95	0.006
Breastfed child						
Yes	81.58	83.80	87.21	87.69	86.18	
No	18.42	16.20	12.79	12.31	13.82	0.035
Parental smoking						
Yes	35.92	28.31	26.29	28.15	28.79	
No	64.08	71.69	73.71	71.85	71.21	0.029
Allergies						
Yes	4.36	3.39	3.56	2.69	96.75	
No	95.64	96.61	96.44	97.31	3.25	0.44
Parent asthma history						
Yes	9.31	10.02	12.05	9.97	10.42	
No	90.69	89.98	87.95	90.03	89.58	0.45
Dwelling ownership						
Owned	61.68	66.48	65.57	71.64	67.98	
Not owned	38.32	33.52	34.43	28.36	32.02	0.012
Dwelling type						
Single detached	63.49	64.28	65.10	65.75	65.07	
Semi-detached	17.53	22.42	15.52	16.55	17.21	
Other	18.98	13.30	19.38	17.70	17.73	0.24
Years at address						
<1 year	14.34	10.10	13.01	10.25	11.52	
1-2 years	36.10	33.04	35.07	36.65	35.69	
3-4 years	22.31	26.81	22.39	25.47	24.41	
>4 years	27.26	30.05	29.52	27.63	28.38	0.42
PMK-rated health status						
Excellent	67.97	69.25	67.29	68.80	68.35	
Very good	23.03	23.20	22.31	23.77	23.21	
Good or less	9.00	7.55	10.40	7.43	8.43	0.59
Number of doctor visits						
0	6.48	5.44	8.03	5.90	6.47	
1	9.25	9.55	10.31	7.02	8.52	
≥2	84.26	85.01	81.66	87.08	85.01	0.10
PMK relationship						
Biological mother	91.85	93.20	94.07	92.80	93.04	0.63

Other	8.15	6.80	5.93	7.20	6.96

Ethics approval for the study from the University of Alberta

UNIVERSITY OF ALBERTA

Ethics Application has been Approved

ID:	Pro00052777
Title:	An analysis of the neighbourhood-level risk factors of childhood asthma and wheeze using a multi-level random effects proportional hazards model.
Study Investigator:	Ambikaipakan Senthilselvan
Description:	This is to inform you that the above study has been approved. Click on the link(s) above to navigate to the HERO workspace. **Note**: Please be reminded that the REMO system works best with Internet Explorer or Firefox. Please do not reply to this message. This is a system-generated email that cannot receive replies.

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