Examining Trends in the Incidence of Asthma in Children in Ontario

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science (Clinical Epidemiology)
Institute of Health Policy, Management and Evaluation
University of Toronto

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Abstract

**Background:** The causes of trends in asthma incidence are not fully understood. **Objectives:**

This study examined trends in age and severity at asthma diagnosis for Ontario children.

**Methods:** Multiple birth cohorts of Ontario children between 1992-2000 were created using health administrative data. Descriptive statistics and multivariable logistic regression examined changes in age and severity of asthma at diagnosis over time. **Results:** Age at asthma diagnosis decreased (p<0.0001) with a higher relative risk of asthma in children under age three (RR=1.5, 95% CI:1.47, 1.54). Predictors of asthma diagnosis before three included male sex, lower income quintile, and maternal asthma. ‘Severe onset asthma’ increased over time (p<0.0001), its predictors being male sex, lower income quintile, rural residence, comorbidity, low birth weight and age less than three. **Conclusions:** Observed trends in asthma incidence are not confined to mild disease and are secondary to variations in asthma rates in children under age three.
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1 Introduction

Asthma is the most common chronic disease of childhood. Starting in the 1950’s there was an ‘epidemic’ increase in the prevalence of asthma in both children and adults; however, in the last decade or more several studies have shown that the incidence of asthma in industrialized countries may be decreasing. Until now the factors that are responsible for changing trends in asthma incidence are not completely identified. Given there are numerous phenotypes of asthma in children which are predicted by the age of onset, it is possible that observed trends in asthma incidence have only been occurring among certain age groups.

The incidence of asthma over time has historically been measured using cross sectional observations of various populations at different ‘snap shots’ in time. However in this study a novel methodology, namely longitudinal observation of multiple consecutive birth cohorts of children from the same population using health administrative data is used to examine the change in age of onset of asthma in Ontario children over time. The reason for using such a technique is to ensure only incident cases of asthma are captured and to have a more full understanding of the change in asthma age of onset over time by longitudinally observing the entire life span of the study population for the entire study duration.

Many asthma epidemiologists suggest that earlier increases seen in asthma rates were simply due to an increased awareness of asthma and change toward labeling mild wheezing disorders in children as ‘asthma’ at younger ages. Hence, this study also explores changes over time in the severity of asthma at its onset, which may give a better overall representation of trends in asthma incidence without the confounding issue of varying definitions of asthma and thresholds for labeling over the decades.

A better understanding of changes over time in both the age of asthma onset and severity of asthma at its onset may shed light on the overall trends in asthma incidence, and provide direction for future study to identify etiologic factors driving these asthma trends. Studying the age of asthma onset and severity of asthma at its onset also has implications for health resource allocation since asthma is a disease associated with significant health care dollars spent in emergency room visits as well as hospital admissions, particularly in very young children.
2 Background

The following sections 2.1 to 2.5 are a discussion of relevant background material stating what has been studied previously in the literature to set the stage for the current study. Sections 2.6 to 2.8 highlight current ‘gaps’ in the literature, leading to the rationale for the current study.

2.1 The Changing Incidence of Asthma

There has been much study of the changes in asthma incidence over time. These previous studies have shown asthma incidence was initially increasing rapidly, but has more recently stabilized and even decreased in some industrialized countries.

Early in the second half of the 20th century, particularly in industrialized countries the prevalence of asthma was seen to increase at a rapid rate.(1-8) Many theories have attempted to explain this “asthma epidemic”, but no specific etiologic factors that fully explain these trends in prevalence have been identified. Although many reports suggest that the prevalence of asthma in children continues to increase globally, depending on the methods used to define asthma, many industrialized countries have seen stabilization and even a reduction in this trend.(1, 9-12)

Studies of children in Europe and Australia indicate that asthma diagnoses increased between 1991 to 2002, though these increases were confined to children with mild and infrequent symptoms.(13-15) Over the same time period, there was a reduction in primary care physician visits and hospitalizations for asthma as well as a reduction in the prevalence of current asthma symptoms.(16-18) These studies suggest that the paradoxical increase in the number of diagnosed asthma cases likely reflects a reduced threshold for labeling children with “asthma”.(19) Phase III of the ISAAC (International Study of Asthma and Allergies in Childhood), the largest global study examining trends in the prevalence of asthma and wheeze in children, has actually shown a modest reduction in the prevalence of wheezing symptoms in English-speaking populations over a similar time-frame.(9, 20) While increased use and advances in asthma controller medications might explain a reduction in healthcare visits and asthma severity, it less likely explains a reduction in mild asthma symptoms.(16) So, perhaps the incidence of new asthma cases is actually decreasing.(1)
With respect to Canada, a recent publication by Statistics Canada using data from the NLSCY (National Longitudinal Survey of Children and Youth) showed that the prevalence of asthma diagnoses among children zero to eleven years increased from 11% to 13% between 1994/95 to 2000/01 though there was no change in the rate of wheezing symptoms. (21) Among children aged two to seven, the number of children diagnosed with asthma then fell from 13% to 10% by 2008/2009. Within this same survey it was seen that in Ontario, there was similarly a significant increase in the prevalence of asthma from 12.1% in 1994/95 up to 13.7% in 2000/01 and down to 9.8% in 2008/09. (22, 23) The proportion of Canadian children with asthma with high-severity symptoms dropped from 41% to 36%, and the proportion of children who had experienced an asthma attack in the last year dropped from 53% to 36%. These findings were similar to those of a study using health administrative data in Ontario that showed a reduction in the sex-standardized prevalence of asthma in children four years of age or less from 1996 to 2005, and a stabilization in the incidence of asthma among children fourteen years of age or younger after the year 1999. (24) Other studies using Ontario health administrative data have also shown a reduction in the incidence of newly diagnosed asthma cases from 15.8 per 1000 children in 1996 to 11.3 per 1000 children in 2000. (25) Thus the prevalence of physician-diagnosed asthma and severe asthma symptoms in Canada and specifically in Ontario is certainly decreasing among children while the incidence of asthma has at least stabilized and may also be decreasing.

2.2 Defining Asthma

Some of the variability seen in different countries in asthma rates, and in asthma rates over time may be simply because asthma is difficult to define clinically, and thus difficult to measure.

2.2.1 Making a Diagnosis of Asthma

The definition and diagnosis of asthma is extremely controversial because it is an entity for which no specific underlying cause has yet been identified. The word ‘asthma’ has its origins from Greek and initially meant “short breath, a panting”. Over the centuries the definition of asthma has been refined primarily to exclude cardiac and infectious causes of dyspnea. (26, 27) In the early 1960’s JG Scadding proposed the specific definition of asthma to be ‘a disease characterized by wide variations over short periods of time in resistance to flow in intrapulmonary airways’. Restated, this is equivalent to the presence of reversible airflow
obstruction or airways hyperreactivity (AHR). (28) Now, more than 50 years later, the concept of asthma has not significantly changed, yet there still remains no gold standard diagnostic test to determine its presence. Thus defining and diagnosing asthma continues to be difficult. Diagnosis is often augmented through the use of objective measures of airflow limitation such as pulmonary function testing, and bronchoprovocation tests to determine airways hyperresponsiveness. Although abnormalities in these objective tests are not specific to the presence of asthma, some authors suggest that a diagnosis of asthma cannot be made without objective testing. (29)

Even in those for whom it is possible to test for AHR, and airflow obstruction, this may not be consistently present in a given individual and may require repeated testing to identify. Furthermore those individuals who develop airways remodeling may not have fully reversible airflow obstruction. Finally asthma, as defined above can coexist with other lung and airways diseases (eg. cystic fibrosis (CF)), which further complicates the picture. (28)

As an aid to health care practitioners in the identification of asthma, a number of clinical practice guidelines (30) have been developed in different countries around the world to further define this entity. (31, 32) The GINA (Global Initiative for Asthma) guidelines first developed by an international panel of experts in 1993 characterize asthma as a disease of “clinical, physiological, and pathological characteristics”, with its predominant clinical features being “episodic shortness of breath, particularly at night”, cough and wheeze, its main physiological feature being episodic airway obstruction characterized by expiratory airflow limitation and the dominant pathological feature being airway inflammation sometimes accompanied by structural changes. (33, 34)

Along these lines, the Canadian asthma consensus guidelines (updated in 2010 and 2012) (35, 36) define asthma as a disease of variable airflow limitation and airway hyperresponsiveness as a result of airways inflammation and highlight the most common clinical features. (37-39) However, in these guidelines it is duly acknowledged that since the pathogenesis of asthma is not clear, much of its characterization is descriptive. Diagnosis for the purpose of clinical identification and management is dependent on the individual health care practitioner’s interpretation of these and other guidelines, while also making note of the presence of atopy,
environmental triggers and genetic background that would make the diagnosis more or less likely.

2.2.2 Diagnosing Asthma in Young Children

Making a diagnosis of asthma in very young children is particularly difficult for a few additional reasons. Firstly, many different disorders can cause wheezing in childhood, and most of these ‘masqueraders’ are also difficult and laborious to diagnose definitively. Secondly, until recently, it has been nearly impossible to obtain any objective evidence of airflow limitation in children younger than six years of age. In the last decade there has been the development of infant pulmonary function testing as well as methods for pulmonary function testing in preschoolers. However, these tests have not been validated in the context of diagnosing asthma and are not widely available. Furthermore it remains extremely difficult to perform bronchoprovocation testing in this age group to determine the presence of AHR.

The Canadian pediatric asthma consensus guidelines do recognize these difficulties, and an updated review article pertaining just to children published in 2010(39) suggests that for these children “less than six years of age, for whom conventional pulmonary function testing is not feasible, the diagnosis of asthma is based on a typical pattern of symptoms (cough with wheezing or dyspnea that typically varies in severity over time), response to therapy”, and the careful exclusion of other explanations for the pattern of observed symptoms.

A third issue is that the phenotype of asthma can vary with age and age of onset. This idea is reflected in the most recent British Thoracic Society asthma guidelines which again highlight the difficulty of diagnosing asthma in children.(32) These guidelines also recognize that only a minority of those who wheeze with viral infections in early life will go on to develop wheezing with other triggers and more persistent symptoms similar to older children and adults with classical atopic asthma.

2.2.3 Asthma Phenotypes

It is well recognized that asthma is not a homogenous disease and that its many different phenotypes depend on age, gender, genetic background and environmental exposures. (40, 41)
In the past, two types of wheezing illnesses in young children were recognized: asthma and wheezing associated only with viruses. This second entity has been known by many different names including “wheezy bronchitis”, “asthmatic” and “spastic bronchitis”. However, over time it was felt by the general community of physicians treating children with breathing disorders, that these terms were responsible for under diagnosis of asthma in young children. (42) This resulted in a movement to call all recurrent wheezing in childhood, ‘asthma’. However, because of the clinical variability in what constitutes asthma, there still remains controversy as to whether all phenotypes should in fact be called “asthma” (43). If using the ‘nominalist’ approach to define disease, that is diseases may be comprised by a number of abnormal characteristics but a specific common characteristic is required to distinguish one disease from another, then asthma fits.(44) Asthma-like wheezing phenotypes though they are a heterogeneous group of conditions, all have a final common pathway represented by recurrent airway obstruction (40) and are in fact still called ‘asthma’ by most.

The most frequently cited studies to try to characterize the different wheezing or ‘asthma’ phenotypes in children were performed by Martinez through analysis of the Tucson Children’s Respiratory Study which is a birth cohort study including 826 children enrolled in the 1980’s. Among this group, Martinez and colleagues initially recognized three distinct wheezing phenotypes which have since been confirmed in other population-based longitudinal birth cohort studies (45, 46). These phenotypes are based on their different patterns of age of onset, and duration. In the Martinez studies it was shown that about half of children will never have wheeze in the first six years of life. However, about 20% of children will have ‘early transient wheezing’ which begins before age three and remits by age six, and 14-16% of children will begin wheezing before age three and continue to have ‘persistent wheezing’ that is still present at age six. In other words, less than 50% of those children with wheeze prior to three years of age will continue to have ongoing episodes of wheezing by the time they reach school age. Another 15%-20% of children will develop ‘late onset wheezing’ and begin to wheeze only after three years of age. It is of note in these early studies that the age of three seems to be an important distinguishing point between different asthma phenotypes and patterns of persistence and severity of symptoms over time.

In a follow up of the initial Tuscon Children’s Respiratory Study, the children had performance of peak flow variability testing and methacholine challenge responsiveness testing
(which both reflect AHR) at age six and eleven years in addition to serum measurements of immunoglobulin E (IgE) levels as a marker of atopy. Based on this, three relatively distinct asthma phenotypes were again identified as previously also proposed by Wilson(47) These phenotypes included ‘early transient wheezers’ who had virally-triggered wheeze prior to age three which had remitted by age six with no association to elevated serum IgE levels, or abnormalities in peak flow or methacholine challenge testing at six or eleven years. These children were found to have reduced lung function at birth as reflected in lower $V_{\text{max}}FRC$ which persisted into childhood. ‘Non-atopic wheezers’ were those children who had wheeze and abnormalities in peak flow variability persisting to age six, normal serum IgE levels, and normal methacholine challenge tests. These children also developed wheezing episodes in response to viral triggers. And finally ‘IgE associated wheezers’ or those with classical ‘asthma’ were those who had elevations of serum IgE and abnormalities in peak flow and methacholine testing that persisted by eleven years of age. Interestingly these children had normal range pulmonary function at birth but significant reduction in $V_{\text{max}}FRC$ compared to non-wheezing children by age 6.(46-48)

A recent Canadian review paper(39) in its interpretation of these studies state that there are really two clinically import types of asthma and these are a) early transient wheezing and b) persistent asthma.(39) Transient wheezing is described as being typically triggered by viral respiratory illnesses, and between episodic illnesses, there are no intervening symptoms. Often there is a history of maternal smoking which is known to be associated with the development of smaller airways in the infant.(49) Hence the hypothesis for this illness is that children with smaller airways due to genetic reasons, premature birth or as a result of certain maternal exposures, such as maternal tobacco smoking, tend to have wheezing with viral infections which typically resolves once the child reaches six years of age and the airway calibre has increased with normal growth of the child.(46) This type of wheezing is felt to represent the presence of anatomically small airways and thus, a mechanical cause for airflow obstruction, rather than obstruction due to hyperreactivity or lability of the airway calibre.(50) Many children with transient wheezing have no personal or family history of atopy. Within this category of ‘early transient wheeze’ there is still much clinical variability with respect to frequency, duration, and severity of episodes, but the majority of children demonstrate a mild condition.
The second clinically important asthma phenotype is called ‘persistent asthma’ and is more akin to the classic atopic asthma seen in older children and adults. This type of asthma can begin either before or after three years of age, though it is felt that 80% of cases likely start prior to age six. Young children in this category still have episodes of wheezing triggered by viral infections but they also have other manifestations of atopy, and have respiratory symptoms and wheeze even between viral exacerbations which often continue into adulthood. Many clinical indices have been developed to try to predict which of the children who wheeze prior to three years of age will continue to have a more persistent asthma phenotype. The validated Modified Asthma Predictive Index (mAPI) referenced in the Canadian Pediatric asthma guidelines suggests that children with more than three episodes of wheezing, wheezing between viral infections, a personal history of atopy (allergies or eczema), a first degree family history of asthma, and peripheral blood eosinophilia are more likely to have persistent asthma.

Many of the international asthma guidelines do comment on the variable phenotypes observed in children and emphasize that not all children who wheeze have asthma but, most children who develop wheezing after age five have asthma. And furthermore, the younger the child, the greater the likelihood that an alternative diagnosis may explain recurrent wheeze.

What is clear is that in children, the term ‘asthma’ in fact likely refers to a number of different disease entities which are variable in their pathology, natural history and clinical manifestations. Certainly in children there is controversy as to whether early transient wheeze should actually be called ‘asthma’ since it is an entity that typically resolves in early childhood and is not associated with atopy. In recent reviews, some authors actually advocate eliminating the concept and name ‘asthma’ altogether. However, because there are some children with early transient wheeze who can have a more severe course which may respond to typical asthma treatment, and more importantly, because it is difficult to distinguish at a very young age which children are likely to have persistent asthma, the Canadian asthma consensus guidelines (as well as others) continue to include this entity in their management guidelines as a phenotype of childhood asthma.

2.2.4 Defining Asthma in Research

When there is so much controversy and difficulty in clinically diagnosing asthma, it stands to reason that developing methods of accurately identifying children with asthma for the purposes
of clinical and epidemiologic studies can be very difficult. Hence asthma rates over time have been measured using various definitions and methodologies. What is particularly problematic (though not the scope of this thesis) is that in many cases, the definition of asthma used for epidemiologic studies is in fact different than the diagnosis used in clinical trials so what we are treating and what we are counting may not be the same entity. (55)

For defining asthma for the purposes of conducting research, several possible methods exist. Clinical trials often depend on characteristics that can be measured objectively such as atopy and AHR, with or without a physician’s clinical assessment. However, there can be significant variation between studies in asthma definition and even when using objective measures, there can be false positives or negatives in identifying children with asthma. Epidemiologic studies have traditionally used patient recall of a physician diagnosis of asthma or of typical asthma symptoms, such as wheeze, to identify relevant cases. For example, the validated ISAAC questionnaires were designed by a panel of experts in 1991 to assess the prevalence of asthma and allergic disorders in children between the ages of 6-7 or 13-14 years over time and across countries. These questionnaires ask questions such as “Have you/has your child ever had asthma”, and “have/has your or your child ever had wheezing or whistling in the chest?” (20) While it is fully expected that a child with asthma would have a positive response to these sorts of questions, thus allowing researchers to identify them as a case of asthma, this method of case detection is fraught with potential pitfalls. First of all, it is assumed that the respondent knows what asthma or wheeze is and that he/she has either received a formal physician diagnosis or has correctly self-diagnosed asthma. Secondly such questionnaires are always subject to recall bias and might result in milder cases not being detected/counted (i.e. false negatives). Finally, wheeze and nocturnal cough are not specific to asthma and could occur with other respiratory maladies, thus leading to over-identification of asthma cases (i.e. false positives), especially when no objective testing of AHR or airflow obstruction have been performed. Separate validation studies of the ISAAC have been performed within several different populations. The most frequently cited study by Jenkins in 1995 identified the ISAAC to have a 85% sensitivity and 81% specificity with a Youden’s index of 0.66 among Australian school children compared to a specialist diagnosis of asthma. (56)

In Canada, the NLSCY is a survey jointly conducted by Statistics Canada and Human Resources and Skills Development Canada since 1994. The survey is administered to a cross
sectional sample of 0-11 year old children and/or their parents. This survey includes questions to identify the prevalence and severity of asthma over time. The specific question used to assess asthma prevalence “Does this child have asthma that has been diagnosed by a health professional?” does eliminate the issue of wrong self-diagnosis of asthma. However, this questionnaire is still subject to recall bias and assumes that health care professionals who diagnosed the asthma were indeed correct in their assessment. Those who commonly treat and study adults with asthma have published that in many cases there is both over and under diagnosis of asthma, especially when the diagnosis is based only on symptoms without objective testing.(57-59) A Canadian study in 2008 showed that one third of adults with physician-diagnosed asthma in fact were ‘over-diagnosed’ and did not actually require ongoing asthma treatment.(60, 61) Part of this “over-diagnosis” may be due to an increased awareness of asthma over the last ten to twenty years as evidenced by the development of multiple new types of asthma treatments in the last decade. That is, what we call “asthma” today, may not have been called “asthma” twenty years ago.

However, other authors claim that in the past case detection studies have successfully used symptom questionnaires to screen for asthma in school-age children. It has previously been shown that a small number of questions about current symptoms, their relation to exercise and their occurrence at night have been sufficient to detect asthma relatively efficiently.(62, 63) In these studies, objective testing did not necessarily improve the specificity of these questionnaires in children. In fact it has been shown that clinical history alone has the ability to detect 85% of asthma cases.(64)

A recent Canadian study comparing what the authors termed a “questionnaire” diagnosis of asthma to a blinded clinical diagnosis of asthma in 204 children showed that the questionnaire diagnosis of asthma had a sensitivity of 82.6% but a specificity of only 70.7% compared to the ‘clinical diagnosis’, with a weak agreement between the questionnaire and clinical diagnosis, (kappa=0.48). Interestingly when “questionnaire diagnosis” was compared to physician assessment without objective testing the specificity improved to 92.3% with a sensitivity of 80.8% and kappa agreement of 0.73.(65) What is ultimately important to determine when performing an epidemiological study, is whether the sensitivity and specificity of the case-detection tool is sufficient for the needs of the study. Presumably a much more accurate diagnosis of asthma is required when performing clinical care and during clinical trials, though a
more inclusive (sensitive) and less specific study might suffice for epidemiologic studies aiming to assess trends in asthma rates over time.

### 2.3 Measuring Asthma Incidence

There are a few different ways to actually measure changes in asthma incidence over time. One option is to compare cross-sectional studies of asthma incidence at different time points, as long as the exact same methodology and sample population is used. The questions used in the NLSCY and ISAAC are in fact best suited for determining asthma prevalence and so are not suited to examining changes in asthma incidence. Other issues with this survey methodology include recall bias and changes in diagnostic threshold for labeling asthma over time.

#### 2.3.1 Using Health Administrative Data to Measure Asthma Incidence

As alluded to briefly in section 2.1, another way to define the prevalence of a disease is by using health administrative data. Health administrative data refers to that personal health information which is collected routinely by government or other organizations for the purposes of administering and monitoring health care delivery, enrolling members into health insurance plans and reimbursing physicians and other providers for services.\(^{(66)}\) It is important to note that this data is not collected with an aim for its use in research, though the use of health administrative data to answer population-based epidemiologic or health services research questions is becoming more and more popular. Since 1995, several research groups across Canada have developed algorithms using health administrative data to define the prevalence of asthma in the population. Specifically in Ontario, an algorithm was developed to identify asthma using health administrative data, for the purposes of asthma surveillance and determination of health resource utilization as part of OASIS (Ontario Asthma Surveillance Information System). The algorithm uses physician outpatient billing information through the Ontario Health Insurance Plan (OHIP), as well as data collected from hospital inpatient charts through the Canadian Institute for Health Information discharge abstract database (CIHI-DAD). In OASIS those children who develop asthma are defined as those who satisfied the following algorithm:

i) \( \geq \) one hospitalization for asthma OR

ii) \( \geq \) two outpatient claims for asthma within a two year period
The administrative diagnosis code of ‘asthma’ (ICD-9 diagnosis code 493) was previously case-verified in Ontario for children with asthma and found to have a sensitivity of 91% and specificity of 83%.(64) When evaluated within the youngest age groups of children only, the ‘asthma’ administrative diagnosis code continued to perform well with a sensitivity and specificity of 75.0% and 83.9% respectively among children aged zero to two years, and 96.0% and 84.2% respectively among children aged three to five years. This case verification was performed by chart abstraction from 630 charts of children zero to eighteen years of age from different primary care physician’s offices in Ontario in the years 2000-2001 by a panel of experts blinded to the child’s diagnosis. The expert chart-abstracted diagnosis of asthma was based on a standardized chart abstraction form and the recommendations of the Canadian Asthma consensus guidelines. When both expert reviewers (or two of three reviewers in cases of disagreement) independently agreed upon the child’s diagnosis of asthma, this was considered the gold standard (though there is no real gold-standard for the diagnosis of asthma) and was compared to the administrative diagnosis code of ‘asthma’ to determine its accuracy as stated above. The above-stated algorithm using this ICD-9 diagnostic code of ‘asthma’ from health administrative data to identify cases of asthma was found to have a sensitivity of 89% and specificity of 72%.(67)

The most similar Canadian algorithm for defining asthma in children developed by Kozyrskj et al. in the province of Manitoba in addition to two physician billing claims for asthma or one hospital admission, also includes children who have had at least two prescriptions for any asthma drug as ascertained through prescription drug records from the Manitoba Health Insurance plan. This algorithm was found to have a high positive predictive value of 94% and specificity of 92% when compared to an allergist diagnosis of asthma as the gold standard. (68, 69) Other Canadian algorithms for identifying asthma from administrative data simply include any child with even a single physician diagnosis of ‘asthma’ in billing claims data.(70) For example one asthma diagnosis in the Medical Services Database of Quebec was found to have a positive predictive value of 0.67-0.75 and a negative predictive value of 0.96-0.99 depending on whether the patient was assessed by a family physician or respiratory medicine specialist.(71, 72)

2.4 Causes of Asthma

Regardless of the methodology used to examine asthma rates over time, be it using repeatedly administered cross-sectional surveys, or health administrative data, the reasons for changing
trends in asthma incidence are not well understood. Though the underlying cause of asthma is still not known, it is felt that early exposures during a critical window period either in utero or in the first year of life are important for priming a child to the development of asthma. (46, 73) Then a ‘second hit’ or subsequent exposures to asthma triggering agents later in life are what bring on the manifestations of asthma symptoms. There has been significant previous study to understand which early exposures and later triggering exposures might be important for asthma development and it is believed that changes in asthma rates over time are partially attributed to changes in these environmental exposures.

2.4.1 Factors That Influence the Onset of Asthma

There has been much research to identify what factors trigger or protect against asthma. For example, it is well-known that asthma and atopic diseases are familial, and that asthma rates vary significantly among different ethnic populations with likely different genetic susceptibility to the disease. (74-76) Asthma rates are higher among Puerto Ricans and African Americans compared to Caucasians in the United States, even after adjusting for socioeconomic and demographic factors. (77-79) Children from a lower socioeconomic class have been identified consistently to have more severe asthma (80) and this is felt to be secondary to higher levels of asthma triggering agents in the environment such as environmental tobacco smoke (ETS). (81) mouse and cockroach antigen (82) and possibly traffic-related air pollution (83) However, in the United States research suggests that not just asthma severity, but asthma prevalence itself is highest among children in the lowest socioeconomic groups. This finding is not reproduced in most Canadian studies. In fact they show no significant difference in asthma prevalence among children from different income quintiles. (84) Another factor that plays a role in asthma susceptibility is sex. Studies consistently show a higher prevalence of asthma among boys at younger ages, but after puberty women tend to have higher rates of asthma. In this situation it is unknown whether the sex difference in asthma is due to hormonal factors, airway size or some other mechanism. (85)

However, when considering factors that may be driving changes in asthma incidence over time, it is probably important to focus on those exposures that may be changing in their prevalence over time. For example, external environmental exposures are felt to play an important role in asthma development and can vary over time. To illustrate this, a study in
Vancouver showed that Chinese adolescents born in Canada had higher prevalence of asthma diagnoses and wheezing symptoms than Chinese adolescents who had moved to Canada less than seven years earlier. A proposed mechanism for increased asthma rates in industrialized countries is that reduced exposure to bacterial infections or pets in the home, all of which likely reflect early exposure to bacterial lipopolysaccharide or endotoxin may actually prime the immune system to a more allergic or so-called T\textsubscript{H}-2 phenotype. This concept, called the ‘hygiene hypothesis’ originally proposed by Strachan in 1989 suggests that living in a less ‘sterile’ environment might protect an individual from developing asthma by allowing the adequate development of the T\textsubscript{H}-1 response, or cell-mediated immunity. Interestingly this observation has been supported by numerous studies showing reduced asthma rates among those children who grew up in a rural or farming environment.

There has been a trend for increasing maternal age in Canada over time. Older maternal age, particularly conception after thirty-five years of age is felt to be associated with an increased prevalence of chromosomal disorders, preterm births and smaller for gestational age babies, but there are few studies examining the relationship between maternal age and asthma. Those few that have been done suggest that younger maternal age is associated with increased asthma in children. Certainly there is a higher prevalence of asthma in those children who are born preterm and develop bronchopulmonary dysplasia (BPD) as well as in children with congenital heart disease (CHD). Interestingly, BPD rates have actually decreased over time so it is possible that this comorbidity along with advancing maternal age is an explanation for a small proportion of reduction of asthma rates in the last decade. While CHD rates may have increased over time, the contribution of this comorbidity to asthma rates along with preterm delivery and low birth weight is likely extremely small since the overall prevalence of these comorbid conditions in the population is still very low.

The above discussion is by no means an exhaustive list of all factors that may contribute to changes in asthma incidence over time. Furthermore, in studies measuring asthma incidence, depending on the study methodology, some factors can be adjusted for, and others not. For example, a study using health administrative data may be limited to only study potential demographic-type asthma-associated factors such as socioeconomic status, geography and a few others listed above. However a prospectively acquired longitudinal birth cohort study would be able to identify numerous additional exposures including ETS, nutrition, viruses, and allergen
sensitization, which may also contribute to asthma incidence and changes in asthma incidence over time.

Figure 2.1. Factors that can prevent or promote the development of asthma

![Diagram of asthma factors]

Figure 2.1 Legend: Yellow boxes represent possible asthma causing factors and pink boxes represent possible asthma protective factors. ETS = environmental tobacco smoke

2.5 Diagnostic Exchange

In any case, until now, all identified asthma-triggering factors (both those listed above and others not listed), are not felt to explain all the changes in asthma incidence over time. Thus as another explanation, some hypothesize that mis-labeling of mild wheezing and cough in young children as ‘asthma’ may in fact account for varying trends in asthma incidence, There has been an attempt in previous studies to see if this “diagnostic” exchange in fact explains changes in asthma rates. (95) For example, in a study by Manfreda et al. using health administrative data from Manitoba twenty years ago, the authors examined the rate of asthma-related outpatient physician visits and found only a slight decrease in some categories of non-asthma respiratory visits over time which was not felt to be a significant factor to explain increased asthma prevalence in the study population. Although this study and a few others have negated the likelihood that past increases in asthma rates were due entirely to “diagnostic exchange”,(96) many researchers continue to propose that changes in asthma incidence over time, particularly increases in asthma incidence seen in previous decades are due to mis-labeling of mild asthma-like disorders as ‘asthma’. (97) Thus studying changes in the rate of severe asthma over time might provide a more reliable picture of the overall trends in asthma incidence.
2.6 Asthma Severity

To date there have been few definitive studies examining changes in severe asthma rates over time, primarily because of difficulties in defining what constitutes ‘severe’ asthma, as well as the confounding effects of asthma medications which modify asthma severity. One method of defining asthma severity is through monitoring the types of health care used by individuals with asthma; for example, by monitoring the proportion of individuals who have been hospitalized or had intensive care unit admissions for asthma exacerbations. Using this definition, a study conducted out of New Jersey in 1992-2006 with data from the health administrative records of 28000 children with asthma showed that while the rate of hospital admission for status asthmaticus decreased by nearly 50%, the rate of pediatric intensive care unit admissions more than tripled during this timeframe.(98) Interestingly, during the same period the rates of children requiring ventilation did not change. The authors suggested that the study results were explained by a reduced threshold for admitting a child to an intensive care unit rather than an increase in the underlying severity of asthma.

Another way of determining asthma severity is by characterizing asthma symptoms. Analysis of data from the NLSCY showed in 1994/95 that as high as 53% of children zero to eleven years of age with asthma had experienced ‘severe asthma symptoms’ or an asthma attack in the previous year, but this proportion reduced to 36% by the year 2008/09.(22) This finding does suggest that the overall severity of asthma has reduced over time in Canada; however, what is not clear is whether the degree of inherent airways inflammation and AHR has reduced, or whether it is that available treatments, prescribing patterns and adherence to these treatments has improved over time. The GINA guidelines in 2006 address this issue of difficulty in classifying the severity of asthma, and suggest instead to classify ‘asthma control’ and the amount of anti-inflammatory asthma medication that is required to achieve it. Other factors important in determining asthma severity include measures of lung function and AHR as well as functional measures of morbidity such as days missed from school/work or asthma-related quality of life.

Thus to summarize, although there has been some attempt to study severity of asthma over time, these studies are limited by difficulties in defining the severity of asthma and confounding by variable thresholds for admission rates of children with acute asthma exacerbations, as well as treatment availability and adherence over time.
2.7 Age of Onset of Asthma

As explained in the above sections, until now varying trends in asthma rates over time remain largely unexplained. One proposed reason for this is that in previous studies of asthma incidence over time, all types of asthma have been lumped and measured together. However, there is much evidence that asthma is not just one disease and in fact there are many different phenotypes, which in children have different patterns of age of onset. Age of onset is felt to be an important variable in determining the persistence and severity of asthma and there has been some limited study of this factor in the literature previously.

Asthma is a condition that can manifest at any age and the incidence of asthma in different age groups is variable. In general, children have a higher incidence of the disease compared to adults. Furthermore, as indicated in section 2.2.3, the phenotype of asthma is correlated with the age of onset. Analysis of the Tucson birth cohort shows that children with “transient early wheezing” whose symptoms resolve by age three are unlikely to continue to have symptoms of asthma later in life. Nonetheless nearly half of all cases of persistent asthma with symptoms by age eleven had their onset prior to three years of age and 80% prior to age six. Those children with onset of symptoms prior to age three had increased severity of disease and worse airway hyperresponsiveness. Furthermore, the development of wheezing prior to age three that persisted until age six was a strong predictor of asthma at twenty-two years. Recent analysis of participants in a New Zealand population-based cohort study shows that the earlier the age at onset of asthma symptoms in childhood, the greater the risk of relapse in adulthood by age twenty-six for those individuals who had a period of remission during adolescence. But, another birth cohort study from the UK suggests that the wheezing phenotypes most strongly associated with atopy and airway responsiveness had their onset after eighteen months of age. Despite some contradiction in the exact age at which it happens, onset of symptoms sometime in the first three years of life is most likely to predict persistence or relapse and highest severity of the disease.

With respect to lung function and age of asthma onset, in the Tucson cohort study it was seen that for those children with asthma symptoms before three years of age, deficits in lung growth occurred by six years of age, and on continued follow-up, these same children experienced significant deficits in lung function at eleven to sixteen years of age compared to
children without asthma. In contrast, the group whose asthma symptoms began after three years of age did not experience deficits in lung function. Baseline data from the Childhood Asthma Management Program study further support the finding that age at the time of asthma onset influences declines in lung function growth. Specifically, when assessed at enrolment, for children who had mild or moderate persistent asthma at five to twelve years of age, there was an inverse association between lung function and duration of asthma and though not specifically studied, this data suggests that children with symptom onset prior to age three had the lowest lung function. Additionally, there was a subgroup of children identified in this study who experienced progressive (at least 1% a year) reductions in lung growth, regardless of treatment, and predictors of this progressive reduction, were male sex and younger age. Cumulatively, these studies suggest that most of the deficits in lung function growth observed in children is in those whose symptoms begin during the first three years of life, and the onset of symptoms after three years of age was usually not associated with significant deficits in lung function and growth.

One of the mechanisms for lung function deficits seen in the above-mentioned studies could include the development of irreversible airways remodeling. Airways remodeling involves activation of certain elements of the airways which cause “thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion”. Although airways remodeling is felt to occur most in those with longstanding uncontrolled airways inflammation, it has been reported to occur at very young ages in some children with asthma. Once established, it is thought that airways remodeling is an irreversible process and associated with poorer response to asthma therapy.

Despite the seeming importance of the age at which asthma develops in children, there has been no systematic study of the change in age of asthma onset over time.

2.8 Longitudinal Studies for Measuring Asthma

Another possible reason why the factors that are driving varying trends in the incidence of asthma have not been fully elucidated is because all previous measurements of asthma rates over time have been conducted in cross-sectional studies. That is, the methodology used to date to
measure asthma does not enable the reliable assessment of the temporal contribution of various factors to trends in asthma incidence.

There have been a number of population-based longitudinal birth cohort studies that have examined the incidence of asthma in different populations across the world. (107-109) These studies are advantageous for a valid determination of asthma incidence as they are not subject to recall bias and often identify cases of asthma by clinical criteria. Longitudinal studies can also better account for the fact that asthma is a disease with a variable age of onset.

**However, to best measure change in asthma incidence over time using population-based longitudinal birth cohorts, it would be necessary to compare multiple longitudinal birth cohorts taken from the sample population at different inception dates. This would be a tremendous, likely non-feasible undertaking if using traditional methods of longitudinal cohort assembly, and as such, it has so far not been done.**
3 Rationale

As discussed in the previous sections, asthma incidence has been seen in numerous previous studies to have significantly increased in the past but in the last decade or more there has been a stabilization and perhaps even a reduction in this trend. Measuring asthma both clinically and in research is difficult given there is no gold standard for diagnosing asthma and definitions of asthma have slightly varied over time. Asthma in children is particularly difficult to define due to lack of objective testing methods as well as the presence of various phenotypes. Numerous factors have been identified to contribute to the development of asthma, however the exact etiology of asthma, as well as a full explanation of varying rates of asthma over time remain unexplained.

Despite evidence to the contrary, many researchers continue to propose that changes in asthma incidence over time are due to mis-labeling of mild asthma-like disorders as asthma. Therefore, studying the rate of just severe asthma over time might provide better insight into overall trends in asthma incidence. In addition to eliminating the issue of ‘diagnostic exchange’, examining rates of severe asthma over time could have implications for health policy and health resource allocation given children with severe asthma have a higher risk of hospitalization and intensive care unit admissions.

One problem with previous studies of asthma rates and a possible reason why the cause of observed trends in asthma incidence remains unexplained is that all phenotypes of asthma have been studied simultaneously, but perhaps it is only certain phenotypes that have had a variable incidence over time. Although the age at which asthma develops is felt to be an important predictor of asthma severity and persistence over time as well as a marker of asthma phenotype, there have been no long term studies of the change in age of onset of asthma over time. Change in age of onset of asthma over time also has implications for health resource utilization, especially since young children with asthma are more frequently seen in the emergency room, compared with adults. Identifying a younger age of onset of asthma could imply that asthma severity overall is increasing and would suggest we should focus more efforts on this age group of children with asthma to identify and initiate better and earlier treatments that would not only reduce patient morbidity and health care utilization, but possibly prevent long term loss of lung function and the development of airways remodeling.
Finally, previous studies of trends in asthma incidence have been performed using cross-sectional methodology, some of which is subject to recall bias. Thus a more appropriate method for studying the incidence of a disease with a variable age of onset would be to examine multiple successive population-based birth cohorts of children, a study which has not yet been performed due to limitations of feasibility.

The following outlined thesis study aims to fill some of the above-identified gaps in the current literature with respect to explaining trends in asthma incidence over time. As such it will be the first study to longitudinally assess changes in the age of asthma onset over time as well as changes over time in the severity of asthma at its onset, to thereby overcome some issues of confounding caused by improved treatments available for asthma over time. This study will additionally employ a novel methodology, namely examination of multiple successive birth cohorts to assess these changes in age of asthma onset and severity of asthma. This is likely the best methodology for examining trends in asthma incidence and factors influencing asthma incidence over time because i) the entire life of the child is captured so one can be confident that only incident cases of asthma are being counted, ii) the current hypothesis for the development of asthma is that early exposures are important so this methodology speaks to the current understanding of the pathophysiology of asthma, iii) recall bias is not an issue in longitudinal assessments, and iv) given the incidence of asthma varies with age, this concept will be fully captured in the study.
4 Objectives and Hypotheses

4.1 Objective 1

Determine the change over time in the age of onset of asthma in multiple successive birth cohorts of Ontario children.

4.1.1 Hypothesis 1

The age of asthma onset has decreased over time for children born between 1992-2000 in Ontario.

4.2 Objective 2

Determine the change over time in the incidence of asthma in Ontario children stratified by age of onset.

4.2.1 Hypothesis 2

The majority of the increase in asthma incidence over time will be shown to occur in the group of children with asthma onset prior to age three.

4.3 Objective 3

Determine the change over time in the severity of asthma at its onset in multiple successive birth cohorts of Ontario children.

4.3.1 Hypothesis 3

The severity of asthma at onset has decreased over time for children born in Ontario between 1992-2000, as reflected by a decreasing proportion of children with hospitalization at asthma onset.

4.4 Objective 4

Determine the change over time in the incidence of asthma in Ontario children stratified by severity at the onset of asthma.
4.4.1 Hypothesis 4

The majority of the increase in asthma incidence over time will be shown to occur in the group of children who do not have ‘severe onset asthma’.
5 Methods

5.1 Setting and Participants

The study population included all children aged zero to eight years born in a hospital in the province of Ontario between April 1, 1992 and March 31, 2001, corresponding to fiscal years 1992 to 2000. Children were followed for the first eight years of life for the development of asthma. Study participants were identified using multiple Ontario health administrative databases as described further below.

5.2 Exclusions

Participants excluded from the study were as follows:
   a) Those children who were not born in Ontario.
   b) Those children with an invalid health card number (i.e. linkage not possible)
   c) Those children born in Ontario but not in a hospital (e.g. home births)
   d) Those children who did not have a “Date of Last Contact” (DOLC) recorded in the CIHI-DAD or OHIP (and likely representing children born in Ontario but residing in another province). DOLC is the last day an individual has been ‘seen’ in the encounter-based databases at ICES such as OHIP and CIHI-DAD
   e) Those children who died at less than six months of age.

5.3 Research Procedure

Nine consecutive birth cohorts of children born in Ontario from 1992 to 2000 were developed from which all those children who developed asthma within the first eight years of life were identified. Eight years was chosen as the observation period based on the availability of administrative data. However, it has been shown previously that 80% of childhood asthma has its onset within the first six years of life.(39) The crude cumulative eight-year incidence of asthma was plotted against birth year for each birth cohort (Figure 6.2) The eight-year incidence of asthma was obtained by taking the total number of children who developed asthma in the first eight years of life per birth year divided by the total population of children born in that year. This was then expressed for each birth cohort as a percent (i.e. mean cases of asthma/100 children). The algorithm to identify children with asthma is described below. Because longitudinal birth
cohorts were used in this study, asthma incidence was also expressed as cases per 1000 person years to adjust for the variable observation period before the development of asthma for each child, as incidence of asthma varies with age. The denominator for person years was calculated by taking the sum of a) the age of asthma incidence for all children who developed asthma and b) the number of children who did not develop asthma multiplied by the eight year observation period. A Cochrane Armitage trend test was performed simply to determine if the observed trend in crude eight-year asthma incidence seen was significant over time. The gamma distribution was used to estimate 95% confidence intervals for the calculated asthma incidence per cohort. (110)

Figure 5.1 Schematic representation of multiple asthma birth cohorts creation

5.4 Data Sources and Linkage

The data sources used in this study include the following:

a) The Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD) is a national database that includes information on inpatient hospitalizations.(96) It was used to identify all children born in hospital in Ontario and all patients hospitalized for asthma.

b) The Ontario Health Insurance Plan (OHIP) database includes information about all billable services provided by Ontario physicians who are paid on a fee-for-service
basis.\textsuperscript{(96)} It was used to identify all outpatient visits for asthma based on the diagnostic code associated with each visit.

c) The Ontario Registered People Database (RPDB) of the Ontario Ministry of Health and Long-Term Care contains information about all those individuals who are registered for OHIP. This database holds information such as date of birth, gender, address and date of death.\textsuperscript{(96)} It was used to identify any children who died during the study period.

These three databases were anonymously linked using each child’s Ontario health card number. That is, at ICES, each individual with a valid Ontario Health Card number is assigned a de-identified ICES key number (IKN) which is kept separately from the OHIP number, to maintain patient confidentiality and privacy. It is this IKN that is used as the patient identifier for all analysis and linkage. Furthermore, any analysis results yielding a very small output number of 5 or fewer study participants is reported as “<6” to ensure that privacy is maintained. The study sample was further linked to the Canadian Census 1991, 1996, 2001 and 2006 via the postal code listed in the RPDB on the date of birth of the child. Of note, previous studies have shown the CIHI-DAD to have >95\% agreement on demographic variables and 81\% agreement on the ‘most responsible diagnosis’ when compared to the original patient charts. \textsuperscript{(111-113)}

Figure 5.2 Merging ICES datasets to create the study sample.

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**Figure 5.2 Legend**: CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database, HCN = Health Card Number, OHIP = Ontario Health Insurance Plan
5.5 Defining Outcomes and Variables

The following are the definitions used for the various outcomes and variables analyzed in this thesis. Further explanations for choosing each of the listed variables is presented in section 2.4.1.

5.5.1 Asthma

Those children who developed asthma were defined as those who satisfied the following algorithm during the first eight years of life:

i) ≥ one hospitalization for asthma OR

ii) ≥ two outpatient claims for asthma within a two year period

As stated in Section 2.3.1, this validated algorithm for detecting asthma cases has been reported previously to have a sensitivity of 89% and specificity of 72%. Hospitalization for asthma was defined as ‘asthma’ being listed as one of the discharge diagnoses (‘most responsible’ or ‘comorbid’) on the CIHI discharge abstract, while outpatient claims for asthma included ‘asthma’ as being listed as the diagnosis for a particular physician office or emergency room visit as per the OHIP database. ‘Asthma’ was defined using ICD-9 diagnostic code 493 or ICD-10 diagnostic codes J45 or J46. Beginning in 2002/2003 fiscal year, hospitals switched from ICD-9 to ICD-10 disease classification coding system. Of note, the switch from ICD-9 to ICD-10 would have possibly influenced the classification of asthma in the 1995 to 2000 birth cohorts for those children who developed asthma in fiscal year 2002 and later, but there are no published studies to assess the impact of this possible misclassification.

Children within the entire study sample, or children from just within the asthma cohorts who died during the study period were identified from each birth cohort if a date of death prior to age eight was recorded in the Ontario Registered Persons Database. As noted above, children who died at less than six months of age were excluded from the study as they would likely include all still births as well as those children with lethal birth disorders. These children would not likely have the opportunity to develop asthma and thus would not really contribute to the study objectives. In any case, as these children with early demise constituted less than 0.5% (N=5126) of the overall study sample, it is likely that their exclusion would not significantly affect the overall study findings. However, children older than six months of age who died
within the study period were still included in the numerators and denominators when calculating the incidence of asthma. As their numbers were very small (N = 2009), and not too different between birth years, continuing to include these children was not expected to significantly affect overall study findings.

Children were excluded from the asthma cohort if they were diagnosed with asthma prior to six months of age, since it is clinically felt to be extremely difficult to accurately diagnose asthma at such a young age and there would potentially be a high rate of mis-diagnosis in this group. However these ‘excluded’ children were subsequently ‘re-included’ in the asthma cohort if they had a further outpatient health care visit or hospitalization for asthma after one year of age. (Figure 4.1)

5.5.2 Age at Asthma Diagnosis

This was defined either as the age at the first OHIP claim for asthma for children who subsequently met the study definition of asthma, or as the first hospitalization when asthma was listed as a most responsible or comorbid diagnosis in the CIHI-DAD. Specifically, the age of asthma diagnosis was calculated by subtracting the child’s delivery date (CIHI-DAD) from the incident date of asthma.

As stated above, those children who met the definition of asthma prior to six months of age were excluded from the asthma cohort. However they were ‘re-included’ in the asthma cohort if they had a subsequent OHIP visit or hospitalization for asthma after one year of age. In this case, their age of diagnosis was the original incident date (i.e. at less than six months of age). All observations with a calculated negative age of asthma diagnosis were set to ‘missing’ and were not included in the analysis for this variable. (N=10)

Of note, this study only identified the age at which children were diagnosed with asthma, and not the actual onset of asthma symptoms. Previous studies have identified that there is a delay between the actual onset of asthma symptoms and the subsequent ‘doctor diagnosis’ of asthma(114) of one year for children one to four years of age and 0.4 years for children five to nine years of age. For this reason, it is “age of diagnosis” that is referred to in this study, rather than “age of onset”.
5.5.3 Severe Asthma at Diagnosis

This was defined as the proportion of children with asthma who presented with hospitalization at asthma diagnosis (ie ‘asthma’ was listed as the most responsible or comorbid diagnosis on the CIHI-DAD and there was no previous hospitalization or OHIP claim with ‘asthma’ listed as the diagnosis).

Of note it is difficult to define ‘severity’ of asthma, particularly using health administrative data, as most definitions are confounded by issues of access to health care. One recognized method of defining asthma severity is to compare the amount of asthma medication required to achieve good asthma control,(31) however the ICES databases do not contain information on medication use for most children, only for those children on Ontario Disability Support Program and/or the Trillium Drug Program. Thus, the concept of severity of asthma at diagnosis was used in this study to avoid the confounding issues of medication use and adherence.

5.6 Analysis

Except where specifically indicated, all analyses for this thesis were conducted using SAS 9.2.(115)

5.6.1 Analysis for Objective 1

a) The age of onset of asthma was measured by determining the mean age of diagnosis of asthma for each birth year and plotting this as a function of time (i.e. year of birth).

b) The distribution of the age of diagnosis of asthma, by year of life, was also plotted for each birth cohort.

c) The proportion of children with asthma diagnosis at less than three years of age for each birth cohort was determined by dividing the number of children with asthma diagnosed at less than three years of age by the total number of children with asthma born in the same year. Then the change over time in the proportion of children diagnosed with asthma at less than three years of age was examined using the Cochrane Armitage test for trend at a significance level of p<0.0001. A very small individual α error of <0.0001 was chosen after applying the Bonferroni correction,(116) given such a large sample size as well as
multiple statistical comparisons within the same dataset. The Bonferroni correction method is known to err on the side of being overly conservative, however given the large sample size in this study, the risk of the study being underpowered to find important associations and trends was felt to be very small.

d) Similarly, the change over time in the proportion of children diagnosed with asthma at equal to/greater than three years of age was determined using the Cochrane Armitage test for trend. The age cut off of three years for dichotomizing the age of onset outcome was chosen based on previous cohort studies showing that this is a clinically important age for distinguishing between different asthma phenotypes and persistence and severity of disease.

5.6.2 Analysis for Objective 2

a) The incidence rate ratio or relative risk of asthma for children younger than three versus children equal to/older than three was calculated for each birth year and expressed with 95% confidence intervals using the StatCalc program. The gamma distribution was used to estimate 95% confidence intervals around each calculated incidence rate.

b) Changes over time in the incidence rate ratio for asthma stratified by age of onset was examined using the Cochrane Armitage test for trend. Of note, the denominator for calculating the incidence of asthma among children less than three consisted of ALL children born in a given birth year, however, the denominator for calculating the incidence of asthma among children equal to/older than age three consisted of ALL children born in a given birth year minus the total number of children who developed asthma prior to age three.

c) A multivariable logistic regression analysis adjusting for important baseline covariates such as sex, residence geography, income quintile, maternal asthma, maternal age, comorbid health conditions and birth weight was conducted to assess the independent effect of the primary exposure, year of birth, on the odds of developing the outcome, asthma at less than three years of age versus equal to/greater than three years of age.
5.6.3 Analysis for Objective 3

a) The proportion of ALL children with ‘severe onset asthma’ was plotted over time against the year of birth. The proportion of ALL children with ‘severe onset asthma’ was calculated by dividing the number of children with severe onset asthma by the total number of children with asthma born in the same year.

b) The change over time in the proportion of children with ‘severe onset asthma’ was examined using the Cochrane Armitage test for trend at a significance level of p<0.0001 after applying the Bonferroni correction, given the large sample size and multiple statistical comparisons within the same dataset.

c) The change over time in the proportion of children with ‘severe onset asthma’ at less than three years of age was examined using the Cochrane Armitage test for trend. This proportion was calculated by dividing the number of children in a given birth year who had severe onset asthma diagnosed at less than three years of age by the total number of children who were less than three years old at asthma diagnosis, and born in the same year.

d) Similarly, the change over time in the proportion of children equal to/greater than three years of age with ‘severe onset asthma’ was examined using the Cochrane Armitage test for trend. This proportion was calculated by dividing the number of children in a given birth year who had severe onset asthma but were equal to/greater than three years at diagnosis by the total number of children who were diagnosed with asthma at equal to/greater than three years of age and born in the same year.

5.6.4 Analysis for Objective 4

a) The incidence rate ratio or relative risk of ‘severe onset asthma’ versus non-‘severe onset asthma’ was calculated for each birth year and expressed with 95% confidence intervals using the StatCalc program. The incidence of ‘severe onset asthma’ for a particular birth year was calculated as the total cases of ‘severe onset asthma’ divided by the total number of children born in the same year. And, conversely, the incidence of non-‘severe onset asthma’ was calculated as the total cases of non-‘severe onset asthma’ divided by the total number of children born that year.
b) Changes over time in the incidence rate ratio for asthma stratified by severity at onset was examined using the Cochrane Armitage test for trend.

c) A multivariable logistic regression analysis, adjusting for important baseline covariates such as sex, residence geography, income quintile, maternal asthma, maternal age, comorbid health conditions, and birth weight was conducted to assess the independent effect of the primary exposure, year of birth, on the odds of developing the outcome, ‘severe onset asthma’ versus non-‘severe onset asthma’.

Of note, despite the longitudinal nature of the data collected in this study by using multiple consecutive birth cohorts, a longitudinal approach was not taken for data analysis, other than to measure trends using the Cochrane Armitage trend test. Rather it was decided to perform binary, multivariable logistic regression analyses in this study, given the clinical importance of the dichotomous age outcome (i.e. less than three versus equal to/greater than three) identified in previous cohort studies. This is expanded upon further in the discussion section.

5.7 Baseline Covariates Used in Logistic Regression

Below is a description of how each covariate was defined and described. Of note, all proportions of a given variable being present in ALL children versus just among children with asthma were compared for each birth year using the equivalence test. However, equivalence tests were generally only conducted if the proportional difference between comparison groups appeared to be greater than 5%, as this is felt to represent a clinically significant difference. All trends over time for each of the variables in ALL children and in just the ASTHMA cohorts were examined using the Cochrane Armitage trend test and reported as significant for p values <0.0001.

5.7.1 Sex

This was used as a dichotomous variable, male or female, and was identified first by the information in the CIHI-DAD and if not available then by the RPDB. All those individuals with a nonsensical value for sex (e.g. “U”) listed in the CIHI-DAD were set to missing and not included in analysis for this variable (N=2).
5.7.2  Neighbourhood Income Quintile

The socioeconomic status of each child in this study was approximated at an ecological level using average neighbourhood household income per person equivalent as a proxy, as identified by the subject’s postal code and linked to the smallest unit of distribution available for that Census which would translate to the Census enumeration area for Census years 1991, 1996 or the Census dissemination area for Census years 2001, 2006. Each census dissemination area includes less than 700 households. The Census that was closest to year of birth was used to calculate the average neighbourhood income at birth. That is, for children born in the year 1997 Census year 1996 was used and for those born in the year 1999 Census year 2001 was used to determine the average neighbourhood income at birth. The calculated average neighbourhood income for each child was categorized into quintiles based on the average neighbourhood income for all persons in Ontario, and was used as a class variable, quintile 1 being the lowest income category.

The proportion of all children and proportion of children with asthma falling into each income quintile at birth was determined separately for each birth year. The ratio (Q1/Q5) and the numerical difference (Q1-Q5) in the proportion of children falling into the lowest income quintile (Q1) compared to the highest income quintile (Q5) was determined for each birth year, simply to compare this ‘gap’ over time.

5.7.3  Residence Geography (Urban versus Rural)

The geographic living environment of each subject represented by their postal code was dichotomized based on the following Statistics Canada definitions:

a) Rural = areas with a “community size” of < 10,000 persons.

b) Urban = all areas outside rural areas

Note, the nearest Canadian census information was used to most accurately define the child’s geography at birth. The proportion of all children and proportion of children with asthma who were born into a rural versus urban environment was determined separately for each birth year.
5.7.4 Comorbid Health Conditions (Comorbidity)

This was defined as the presence of any one of the following comorbid disease conditions listed as a diagnosis (either most responsible diagnosis or comorbid diagnosis) as ascertained through the CIHI-DAD for any hospitalization during the child’s entire first year of life: i) prematurity (gestational age <37 weeks), ii) congenital cardiac disease, or iii) chronic lung disease. Both ICD-9 and ICD-10 diagnostic codes were assimilated to define each of these types of comorbidity as seen below in Table 5.1.

The category of chronic lung disease included diagnoses such as bronchitis, chronic bronchiectasis, non-asthma chronic airway obstruction, respiratory distress syndrome (RDS) and likely bronchopulmonary dysplasia (i.e.“chronic respiratory disease arising from the perinatal period” (ICD-10) and “other respiratory conditions of the fetus and newborn” (ICD-9)). Transient tachypnea of the newborn (TTN) and meconium aspiration syndrome were both excluded where possible since an infant with each of these entities would not likely or necessarily progress to chronic lung disease that could influence the development of asthma after 6 months of age. However it was assumed that for children with both meconium aspiration/TTN AND respiratory distress syndrome, that respiratory distress syndrome would also be listed as a diagnosis in the CIHI-DAD, and thus this comorbidity would still be captured in this study.

The category of congenital heart disease included all right sided and left sided cardiac lesions as well as all cardiac and pulmonary vascular malformations (including pulmonary hypertension). The diagnosis of persistent ductus arteriosus was excluded as this entity is usually corrected within the first few months of life, and therefore would not likely influence the diagnosis of asthma.

Of note, only those comorbid conditions that were present in the first year of life were included in the study so it is possible that some important diagnoses that developed or were identified later in a child’s life and possibly influence the diagnosis of asthma could have been missed, though it was assumed that this number would be very small since the majority of the comorbid conditions of interest are usually diagnosed in the newborn period.
Table 5.1 Diagnostic codes used to define COMORBIDITY

<table>
<thead>
<tr>
<th>Type of Comorbidity</th>
<th>CIHI-DAD Diagnosis Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD-9 Diagnostic Code</td>
</tr>
<tr>
<td>Preterm</td>
<td>765</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>490, 491, 494, 496</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>770.7</td>
</tr>
<tr>
<td>RDS</td>
<td>769</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>745 – 747</td>
</tr>
<tr>
<td></td>
<td>Exclusions:</td>
</tr>
<tr>
<td></td>
<td>i) 747.6-AV malformation unspecified</td>
</tr>
<tr>
<td></td>
<td>ii) 747.81-747.82-cerebrovascular malformations</td>
</tr>
</tbody>
</table>

ICD = International Classification of Diseases, CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database, BPD = bronchopulmonary dysplasia, RDS = respiratory distress syndrome

*unable to exclude transient tachypnea of the newborn or persistent ductus arteriosus from ICD-9 codes

5.7.5 Birth Weight

Birth weight is a mandatory variable recorded during the birth admission of every child in the CIHI-DAD. It was analyzed in this study as per the categories below. Of note, birth weight categories were not mutually exclusive.

i) Low birth weight (LBW) was used as a dichotomous variable and as per the World Health Organization was defined as a birth weight of <2500 g.

ii) Very Low Birth weight (VLBW) was defined as a birth weight <1500 g.

iii) Extremely Low Birth weight (ELBW) was defined as a birth weight of <1000 g.

All negative, or nonsensical (eg. “ZZZZ”) values listed for birth weight were set to ‘missing’ and excluded from analysis of this variable (N=341). Similarly, birth weight values <350 g were set to missing (N=29). Of note the “limit of viability” birth weight below which resuscitation of an infant is not mandatory in Ontario is 400g. The proportion of children with a birth weight falling into the LBW, VLBW or ELBW as defined above was determined using the total number of children born in that year as the denominator.
5.7.6 Maternal Variables

For all children in the dataset, probabilistic linkage using the institution that the child was admitted to at the delivery, the postal code at birth and admission and discharge dates around the time of delivery was performed to identify the likely birth mother for each child. This linked dataset is held at ICES and called the MOM-BABY dataset. This dataset contains information for all Ontario births dating back to 1988 and was used to determine information on some ‘maternal variables’ that might influence the development or diagnosis of asthma in a child as detailed below. That is, by linking with this database, the maternal IKN, or ‘ICES Key Number’ could be identified for the majority of mothers (≥ 85 % Table 6.19) and linked back to the OHIP and CIHI-DAD and RPDB databases to acquire information on key maternal variables.

5.7.6.1 Maternal Age

This variable was used both as a dichotomous variable and represented the age of the mother on the date of delivery of the child. This variable was calculated by subtracting the mother’s birth date (RPDB) from the delivery date (CIHI-DAD) of the child. For dichotomous analysis, the variable was split as age at delivery less than/equal to thirty-five years or age greater than thirty-five years at delivery. The maternal age of thirty-five was chosen as a cut-off as it is well recognized that the risks of negative health effects both for the mother and the child rapidly increase from age thirty-five years and onward.(90, 91)

Negative values for maternal age likely resulted from an invalid maternal birthdate recorded in the RPDB. Thus all negative maternal ages were set to missing and these observations were not used in the analysis of this variable (N=108352, 9.2%). However in general it is extremely rare for girls younger than twelve years of age in Canada to deliver a child, thus all those linked mothers with age of delivery calculated as being less than twelve years were set to missing on the assumption that the date of birth listed in the RPDB for the mother may not have been accurate. (N=273) Similarly for all those mothers who were calculated as having an age at delivery greater than fifty years, age was reset to ‘missing’ as they were felt to represent invalid data. (N=55). An additional portion of mothers had a ‘missing’ birthdate in the RPDB and were also not used in the analysis of this variable (N=76874, 6.5%). Of note, determination of missing linkage between children and mothers in this dataset was only determined after ‘cleaning’ the age variable (as explained above), so the number of ‘negative’ or
‘missing’ maternal birthdates stated above is inflated. Table 6.18 better represents the proportion of missing maternal age data after also accounting for missing maternal IKNs.

The proportion of mothers with an age greater than thirty-five years at delivery for all children (asthma plus non-asthma) was determined by dividing the total number of mothers with age greater than thirty-five years by the total births in that year. Similarly, the proportion of mothers of children with asthma with an age greater than thirty-five years at delivery was determined by dividing the total number of mothers of children with asthma who were older than thirty-five years at delivery by the total number of children with asthma in that birth year.

5.7.6.2 Maternal Asthma

This was a dichotomous variable to indicate whether the child’s mother was ever diagnosed with asthma prior to the birth of the child. This data was available by linking the maternal IKN with the OASIS dataset housed at ICES which is a cumulative database that contains all asthma incident and prevalent cases since fiscal year 1993. Asthma in the mother was defined using the same algorithm as used for children in this study. Case verification studies have identified the sensitivity and specificity of this algorithm for identifying cases of asthma in adults aged eighteen years and older as 84% and 76% respectively. The proportion of all children (asthma plus non-asthma) with a mother with asthma was determined by dividing the total number of mothers with asthma by the total number of children born that year. Similarly, the proportion of children with asthma with a mother with asthma was determined by dividing the number of mothers of children with asthma who themselves had asthma by the total number of children with asthma born in that year.

5.8 Method for Building the Logistic Regression Models

In the logistic regression analyses, the year 1992 was used as the reference and was compared to all other birth years. For the variable, neighbourhood income quintile, quintile 5 (highest) was used as the reference and was individually compared to quintile 1, 2, 3, and 4. Birth weight was simply dichotomized to the presence or absence of LBW (<2500 g). Comorbidity was used as a dichotomous variable and was defined as the presence or absence of any one of the comorbid disease conditions identified in this study, including ‘preterm gestation’, chronic lung disease, and congenital heart disease.
Initially an attempt was made to construct the multivariable models using the method of Harrel, that is, by manually, sequentially adding variables to the model only if they were to change parameter estimates by more than 10%. However none of the explanatory variables other than year of birth changed the parameter estimates by more than 10%. Thus the multivariable models were simply developed by including all variables of clinical interest in this study. Only those variables for which information was present for children with and without asthma were included.

Table 5.2 Description of multivariable logistic regression models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incidence of Asthma</th>
<th>Reference Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Exposure Variable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of Birth</td>
<td>1992</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Neighbourhood Income Quintile</td>
<td>Quintile 5 (highest)</td>
<td></td>
</tr>
<tr>
<td>Residence Geography</td>
<td>Urban</td>
<td></td>
</tr>
<tr>
<td>Birth Weight</td>
<td>&gt;2500 g</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Maternal Asthma</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Maternal Age</td>
<td>&lt; 35 years old</td>
<td></td>
</tr>
</tbody>
</table>

5.8.1 Checking for Multicollinearity

Multicollinearity of the independent variables was determined by calculating the ‘variance inflation factor (VIF) and examining the collinearity statistics for the model, including the ‘condition index’ and ensuring that neither was too large (i.e. greater than 2.5 or 10 respectively). The ordinal variables, neighbourhood income quintile and year of birth were also included in this assessment after reprogramming them as dummy variables for each categorical level of the ordinal variable.

5.8.2 Assessing Model Fit

To assess model fit, both the Hosmer Lemeshow statistic as well as the ‘c-statistic’ which represents the ‘area under the receiver-operator curve’ were determined.
5.9 Asthma Related Health Care Visits

Though not a specific objective of this study, the total proportion of children both in the first three years of life and in the first eight years of life with other ‘asthma-related’ respiratory health care visits was also determined for the first five birth cohorts (birth years 1992 – 1996). This was done to differentiate whether observed changes in the age of onset of asthma over time were due simply to differences over time in labeling respiratory symptoms/diseases as asthma, otherwise referred to in previous literature as “diagnostic exchange”. (95) This was done only for the first five birth cohorts as this was the period when the incidence of asthma increased most rapidly.

5.9.1 Defining Asthma Related Conditions

There have been a few previous studies examining trends in asthma rates over time using health administrative data which have concurrently examined the rate of asthma-related visits to health care over time. The definition of asthma-related conditions in a study by Manfreda et al. in 1993 (95) included only the following diagnoses in Table 5.3.

Table 5.3 Asthma related diagnoses by Manfreda et al., 1993.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD 9 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>486, 490,</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>491, 492, 496</td>
</tr>
</tbody>
</table>

Another ongoing ICES study by Teresa To et al. used the following slightly expanded definition of “asthma-related” conditions (Table 5.4)

Table 5.4 Definition of asthma-related diagnoses in children, by ICES reports (96, 122)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD 9 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pharyngitis</td>
<td>462</td>
</tr>
<tr>
<td>Acute laryngitis tracheitis</td>
<td>464</td>
</tr>
<tr>
<td>Acute upper respiratory infection</td>
<td>465</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>466</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>480-486</td>
</tr>
<tr>
<td>Bronchitis unspecified</td>
<td>490</td>
</tr>
<tr>
<td>Wheeze</td>
<td>786.07</td>
</tr>
</tbody>
</table>
From a clinical perspective, since asthma is a lower airways disease, the most relevant asthma-related diagnoses would include the following non-asthma acute (or chronic) lower respiratory diagnoses: influenza, pneumonia, bronchitis and bronchiolitis and unspecified lower respiratory infection. As such, these are the diagnostic categories included in the current study definition of ‘asthma-related’ visits. However, in order to allow comparison with the previous ICES studies of asthma rates in Ontario, some of the acute upper respiratory diagnoses were also included in this thesis for the definition of ‘asthma-related’ diagnoses as shown below in Table 5.5. The symptom-diagnoses of “wheeze” and “cough” were also included, so the definition of asthma-related diagnoses is in fact more inclusive in this thesis than in definitions used in previous studies. Of note, the frequently referred to entity called “reactive airways disease” actually does not have a specific ICD-9 or ICD-10 designation.

Table 5.5 Defining ‘asthma related’ diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9 Codes</th>
<th>ICD-10 Codes</th>
<th>OHIP Diagnosis Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute URTI</td>
<td>460, 461, 462, 464, 465</td>
<td>J00, J01, J02, J04, J06</td>
<td>460, 461, 464</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>466, 490</td>
<td>J20-J22, J40, J42</td>
<td>466</td>
</tr>
<tr>
<td>Chronic rhinitis</td>
<td>472.0, 473, 477</td>
<td>J30, J31.0-J31.1, J32</td>
<td>473</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>480-486</td>
<td>J12-J18</td>
<td>486</td>
</tr>
<tr>
<td>Flu</td>
<td>487-488</td>
<td>J09-J11</td>
<td>487</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>491, 496</td>
<td>J41</td>
<td>491, 496</td>
</tr>
<tr>
<td>Wheeze</td>
<td>786.07</td>
<td>R06.2</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>786.2</td>
<td>R05</td>
<td>786</td>
</tr>
</tbody>
</table>

Table 5.5 Legend: URTI=upper respiratory tract infection

5.10 Research Ethics Approval

Research ethics approval for this study was obtained from the Hospital for Sick Children, Toronto research ethics board as well as by the University of Toronto research ethics board, and additionally from the Toronto Sunnybrook Hospital research ethics board.
6 Results

6.1 Study Cohort Assembly

Of all children born in Ontario between the years 1992 through 2000, as shown below in Figure 4.1, 1177888 of them met inclusion criteria for this study and a total of 210336 were identified as having asthma.

Figure 6.1 Study sample after meeting inclusion and exclusion criteria.

![Flowchart of study cohort assembly]

Figure 6.1 Legend: DOLC = Date of last contact with administrative databases

6.2 Asthma Incidence

The eight-year incidence of asthma increased overall (p<0.0001) from 1992 with a period of stabilization from birth year 1996 onwards. Asthma incidence as expressed as cases per 1000 person years followed the same trend. There was no missing data for the variable birth year.
Table 6.1. Study population divided into birth cohorts

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Total Sample (N)</th>
<th>Deaths (N)</th>
<th>Asthma Sample (N)</th>
<th>Deaths (N)</th>
<th>Asthma Incidence(^a) (%)</th>
<th>95% Confidence Intervals(^c)</th>
<th>Asthma Incidence (cases/1000 person yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>118365</td>
<td>230</td>
<td>8367</td>
<td>15</td>
<td>7.1(^b)</td>
<td>6.9, 7.2</td>
<td>8.9</td>
</tr>
<tr>
<td>1993</td>
<td>141455</td>
<td>246</td>
<td>13847</td>
<td>33</td>
<td>9.8</td>
<td>9.6, 10.0</td>
<td>12.6</td>
</tr>
<tr>
<td>1994</td>
<td>141975</td>
<td>239</td>
<td>18672</td>
<td>28</td>
<td>13.2</td>
<td>13.0, 13.3</td>
<td>17.6</td>
</tr>
<tr>
<td>1995</td>
<td>136015</td>
<td>244</td>
<td>26124</td>
<td>49</td>
<td>19.2</td>
<td>19.0, 19.4</td>
<td>27.5</td>
</tr>
<tr>
<td>1996</td>
<td>131147</td>
<td>238</td>
<td>29695</td>
<td>74</td>
<td>22.6</td>
<td>22.3, 22.9</td>
<td>33.7</td>
</tr>
<tr>
<td>1997</td>
<td>129820</td>
<td>224</td>
<td>29376</td>
<td>50</td>
<td>22.6</td>
<td>22.4, 22.9</td>
<td>33.7</td>
</tr>
<tr>
<td>1998</td>
<td>127607</td>
<td>189</td>
<td>28981</td>
<td>51</td>
<td>22.7</td>
<td>22.4, 23.0</td>
<td>33.9</td>
</tr>
<tr>
<td>1999</td>
<td>126759</td>
<td>215</td>
<td>28379</td>
<td>36</td>
<td>22.4</td>
<td>22.1, 22.7</td>
<td>33.3</td>
</tr>
<tr>
<td>2000</td>
<td>124745</td>
<td>184</td>
<td>26895</td>
<td>42</td>
<td>21.6</td>
<td>21.3, 21.8</td>
<td>31.8</td>
</tr>
</tbody>
</table>

\(^a\)Deaths' in table represent for entire 8 year observation period, after first 6 months of life. \(^b\) Asthma incidence expressed cumulatively for first 8 years of life with total birth cohort population as denominator
\(^c\) \(p<0.0001, Z=142.7\), for increased asthma incidence over time, by Cochrane Armitage test for trend
\(^c\) Confidence intervals calculated using the Gamma distribution

Figure 6.2. Cumulative crude eight-year incidence of asthma by birth year

* Error bars represent 95% confidence intervals as approximated using the Gamma distribution
6.3 Age at Asthma Diagnosis

As represented in Figure 6.4, the mean age of asthma diagnosis appeared to decrease between birth years 1992 until 1996 then stabilize for the remainder of the cohort years, however there was significant overlap in the standard deviation for mean age of asthma diagnosis between birth years.

Table 6.2 Mean age of asthma diagnosis by birth cohort year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (Yrs ± SD&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>5.4 (1.3)</td>
<td>4.7 (1.5)</td>
<td>3.9 (1.8)</td>
<td>2.9 (2.0)</td>
<td>2.5 (2.1)</td>
<td>2.5 (0.1)</td>
<td>2.6 (2.1)</td>
<td>2.6 (2.1)</td>
<td>2.6 (2.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> SD = standard deviation, referring to numbers in parentheses. Age of asthma incidence variable ‘missing’: N=7

Figure 6.4 Mean age of asthma diagnosis by birth year

*Vertical error bars represent the standard deviation of the mean
The overall age distribution for asthma diagnoses skewed younger over time by birth year, yielding an overall increase in the proportion of children with asthma diagnosed at less than three years of age (p<0.0001).

Table 6.3 Number and proportion of children with asthma diagnosis before or after age 3

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>&lt;3 yrs old (N)</th>
<th>&lt;3 yrs old (%)</th>
<th>&gt;3 yrs old (N)</th>
<th>&gt;3 yrs old (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>0</td>
<td>0.0</td>
<td>8367</td>
<td>100.0</td>
</tr>
<tr>
<td>1993</td>
<td>1816</td>
<td>13.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12031</td>
<td>87.9</td>
</tr>
<tr>
<td>1994</td>
<td>7035</td>
<td>37.7</td>
<td>11673</td>
<td>62.3</td>
</tr>
<tr>
<td>1995</td>
<td>15182</td>
<td>58.1</td>
<td>10942</td>
<td>41.9</td>
</tr>
<tr>
<td>1996</td>
<td>19532</td>
<td>65.8</td>
<td>10163</td>
<td>34.2</td>
</tr>
<tr>
<td>1997</td>
<td>19093</td>
<td>65.0</td>
<td>10283</td>
<td>35.0</td>
</tr>
<tr>
<td>1998</td>
<td>19049</td>
<td>65.7</td>
<td>9932</td>
<td>34.3</td>
</tr>
<tr>
<td>1999</td>
<td>18434</td>
<td>65.0</td>
<td>9945</td>
<td>35.0</td>
</tr>
<tr>
<td>2000</td>
<td>17077</td>
<td>63.5</td>
<td>9818</td>
<td>36.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>p<0.0001, Z=129.3 for increase in proportion of children diagnosed with asthma at < 3 years old, by Cochrane Armitage trend test
6.4 Incidence of Asthma by Age

Table 6.4 Incidence of asthma in under three years or over three years age groups

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Incidence at &lt; 3 years old (%; 95% CI)</th>
<th>Incidence at &gt; 3 years old (%; 95% CI)</th>
<th>Incidence Rate Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>0.0&lt;sub&gt;a&lt;/sub&gt;</td>
<td>7.1 (6.9, 7.2)&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>1993</td>
<td>1.3 (1.2, 1.3)</td>
<td>8.6 (8.5, 8.8)</td>
<td>0.15</td>
<td>0.14, 0.16</td>
</tr>
<tr>
<td>1994</td>
<td>5.0 (4.8, 5.1)</td>
<td>8.7 (8.5, 8.8)</td>
<td>0.57</td>
<td>0.56, 0.59</td>
</tr>
<tr>
<td>1995</td>
<td>11.2 (11.0, 11.3)</td>
<td>9.1 (8.9, 9.2)</td>
<td>1.23</td>
<td>1.20, 1.26</td>
</tr>
<tr>
<td>1996</td>
<td>14.9 (14.7, 15.1)</td>
<td>9.1 (8.9, 9.3)</td>
<td>1.64</td>
<td>1.60, 1.67</td>
</tr>
<tr>
<td>1997</td>
<td>14.7 (14.5, 14.9)</td>
<td>9.3 (9.1, 9.5)</td>
<td>1.58</td>
<td>1.55, 1.62</td>
</tr>
<tr>
<td>1998</td>
<td>14.9 (14.7, 15.1)</td>
<td>9.1 (9.0, 9.3)</td>
<td>1.63</td>
<td>1.59, 1.67</td>
</tr>
<tr>
<td>1999</td>
<td>14.5 (14.3, 14.8)</td>
<td>9.2 (9.0, 9.4)</td>
<td>1.58</td>
<td>1.55, 1.62</td>
</tr>
<tr>
<td>2000</td>
<td>13.7 (13.5, 13.9)</td>
<td>9.1 (8.9, 9.3)</td>
<td>1.50</td>
<td>1.47, 1.54</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<0.0001, Z-statistic=129.3 for Cochrane Armitage trend test, <sup>b</sup> p<0.0001, Cochrane Armitage trend test

The incidence of asthma among children older than three increased gradually in successive birth cohorts from 7.1% to 9.1% through the birth years 1992 to 2000 (p<0.0001). However, the incidence of asthma among children younger than three increased much more quickly overall from birth year 1992 onwards (p<0.0001). The incidence rate ratio, or relative risk for asthma onset was initially higher for children greater than three years of age in birth
years 1993 and 1994, then flipped and became higher in children less than three years of age from the birth year 1995 and onward.

Figure 6.7 Incidence of asthma by age of diagnosis.

![Incidence of asthma by age of diagnosis](image)

Table 6.5 Logistic regression: odds of asthma diagnosis at <3 vs ≥ 3 years predicted by birth year

<table>
<thead>
<tr>
<th>Year (1993 = Ref)</th>
<th>Unadjusted Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>2000</td>
<td>11.52</td>
<td>10.90</td>
<td>12.17</td>
</tr>
<tr>
<td>1999</td>
<td>12.27</td>
<td>11.62</td>
<td>13.00</td>
</tr>
<tr>
<td>1998</td>
<td>12.70</td>
<td>12.02</td>
<td>13.42</td>
</tr>
<tr>
<td>1997</td>
<td>12.29</td>
<td>11.64</td>
<td>13.00</td>
</tr>
<tr>
<td>1996</td>
<td>12.72</td>
<td>12.05</td>
<td>13.44</td>
</tr>
<tr>
<td>1995</td>
<td>9.19</td>
<td>8.74</td>
<td>9.71</td>
</tr>
<tr>
<td>1994</td>
<td>4.00</td>
<td>3.78</td>
<td>4.24</td>
</tr>
</tbody>
</table>

C-statistic: 0.622,  HL test: p = 1.0

In a simple logistic regression comparing the outcome, odds of asthma onset at less than three years of age versus equal to/greater than three years of age, year of birth was a significant predictor, and as already shown in the Cochrane Armitage trend test results, demonstrates that the overall odds of asthma onset at less than three years of age increased over time. There was good model fit with a C-statistic of 0.622 and Hosmer and Lemeshow p-value of 1.0. As there were no asthma diagnoses at less than three years of age in the year 1992, it is possible that the
odds ratios for the association between year of birth and odds of asthma diagnosis at less than age three may be inflated when using even the year 1993 as the reference category. Thus a sensitivity analysis was performed by using the year 2000 as the reference category and this logistic regression model continued to show a significant relationship between year of birth and the odds of asthma diagnosis at less than three. (Appendix 2).

Table 6.6 Multivariable logistic regression: odds of asthma diagnosis at < 3 vs ≥ 3 years of age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Birth Year:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>11.20</td>
<td>10.58</td>
<td>11.86</td>
</tr>
<tr>
<td>1999</td>
<td>11.88</td>
<td>11.22</td>
<td>12.56</td>
</tr>
<tr>
<td>1998</td>
<td>12.25</td>
<td>11.57</td>
<td>12.97</td>
</tr>
<tr>
<td>1997</td>
<td>11.96</td>
<td>11.30</td>
<td>12.66</td>
</tr>
<tr>
<td>1996</td>
<td>12.36</td>
<td>11.67</td>
<td>13.08</td>
</tr>
<tr>
<td>1995</td>
<td>8.99</td>
<td>8.50</td>
<td>9.52</td>
</tr>
<tr>
<td>1994</td>
<td>3.93</td>
<td>3.71</td>
<td>4.18</td>
</tr>
<tr>
<td>(reference) 1993</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income Quintile:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.36</td>
<td>1.32</td>
<td>1.40</td>
</tr>
<tr>
<td>2</td>
<td>1.17</td>
<td>1.13</td>
<td>1.21</td>
</tr>
<tr>
<td>3</td>
<td>1.07</td>
<td>1.04</td>
<td>1.10</td>
</tr>
<tr>
<td>4</td>
<td>1.06</td>
<td>1.03</td>
<td>1.10</td>
</tr>
<tr>
<td>(reference) 5</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural birth residence</td>
<td>0.99</td>
<td>0.96</td>
<td>1.02</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.25</td>
<td>1.23</td>
<td>1.28</td>
</tr>
<tr>
<td>With comorbidity</td>
<td>0.77</td>
<td>0.74</td>
<td>0.81</td>
</tr>
<tr>
<td>With low birth weight</td>
<td>0.93</td>
<td>0.89</td>
<td>0.98</td>
</tr>
<tr>
<td>With maternal asthma</td>
<td>1.26</td>
<td>1.22</td>
<td>1.29</td>
</tr>
<tr>
<td>Maternal age &gt;35 years</td>
<td>0.93</td>
<td>0.91</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Model Fit statistics: C statistic = 0.648, Hosmer and Lemeshow: p = 0.002
Total ‘n’ used for analysis (asthma cases) = 190236

Significant independent predictors of asthma onset at less than three years of age in the multivariable logistic regression in addition to year of birth included, lower neighbourhood
income quintile, male sex, and maternal asthma. On the contrary low birth weight, comorbid health conditions and older maternal age were associated with later onset asthma. Rural residence at birth was not found to be a significant predictor of asthma onset at less than three but this covariate was still included in the model since it is considered of clinical significance in the incidence of asthma overall.

For the final logistic regression model, a total of 20100 observations were not included due to missing information for the response or explanatory variables which equaled to 9.5% of the total asthma sample. A large portion of this ‘missing data’ (N=8367 observations) was explained by the fact that there were no children with asthma onset prior to three years of age in birth year 1992. Hence the multivariable regression model was essentially run for cohort years 1993 to 2000. The remainder of the ‘missing data’ was due to maternal age being missing for a large number of children (N=11733). A sensitivity analysis performed by removing maternal age from the multivariable logistic regression model, showed a non-significant change in parameter estimates for all other predictors (<5%) (Section 6.7.6).

Although the Hosmer and Lemeshow test is traditionally used to test model fit in a logistic regression analysis and in this case suggests poor model fit, in fact the c-statistic, reflecting the area under the receiver-operator curve is a more relevant measure of model fit in the setting of very large sample sizes as in this population based study. Thus a c-statistic of 0.648 in fact suggests there was good model fit. There was no significant multicollinearity between any of the independent variables in the model as the VIF ranged from 1.0 to 1.9 and the condition index varied from 2.4 to 10.1.

### 6.5 Severity at Onset

Table 6.7. Proportion of children with ASTHMA, hospitalized at diagnosis (‘severe onset’)  

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Asthma at Diagnosis (%)</strong></td>
<td><strong>ALL Children</strong></td>
<td>4.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.7</td>
<td>6.1</td>
<td>6.7</td>
<td>6.3</td>
<td>6.2</td>
<td>6.4</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td><strong>&lt; 3 years old</strong></td>
<td>0.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.9</td>
<td>9.0</td>
<td>8.1</td>
<td>7.2</td>
<td>6.9</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td><strong>≥ 3 years old</strong></td>
<td>4.5&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>4.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.7</td>
<td>4.6</td>
<td>5.0</td>
<td>4.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>p < 0.0001, Z-statistic = -4.8 for increase in ‘severe onset asthma’ by Cochrane Armitage trend test  
<sup>b</sup>p<0.0001 for increase in proportion of children < 3 yrs with ‘severe onset asthma’, by Cochrane Armitage trend test,  
<sup>c</sup>p=0.02 for non-significant trend in proportion of children older than three with ‘severe onset asthma’,  
<sup>d</sup>p =0.2 indicating non-equality between proportions (null hypothesis), by equivalence test at 5% margin of difference
There was an overall increase in the proportion of children with asthma who were hospitalized at first diagnosis (p<0.0001). Children over age three in the first six birth cohorts demonstrated a small increase over time in the proportion hospitalized at diagnosis but this was not significant (p=0.02). As the trend in hospitalization over time for children less than three was not linear so Cochrane Armitage trend tests were not used to assess the change over time. However, just based on Figure 6.8, there did appear to be an initial increase (from 1992 to 1994) then gradual decrease in the proportion of children less than three who were hospitalized at diagnosis. There was a significantly larger proportion of children under age three with ‘severe onset asthma’ compared to children older than three, for cohort years 1992 to 1994 at a margin of difference of 5% (p=0.2) and for cohort years 1994-1996, 1998-2000 at a margin of difference of 2.5% (p=0.1-0.5) by the equivalence test.

Figure 6.8. Change over time in proportion of children with ‘severe onset’ asthma

6.6 Incidence of Severe Onset Asthma

The incidence of both severe onset asthma as well as non-severe onset asthma did increase over time by birth cohort year (p<0.0001), however the incident rate ratio, or relative risk of severe onset versus non-severe onset asthma did not change over time.
Table 6.8 Incidence of ‘severe onset asthma’ versus non-‘severe onset asthma’.

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Severe Onset Asthma (%; 95% CI)</th>
<th>Non-Severe Onset Asthma (%; 95% CI)</th>
<th>Incidence Rate Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>0.32(^a) (0.29, 0.35)</td>
<td>6.75(^a) (6.60, 6.90)</td>
<td>0.05</td>
<td>0.04, 0.05</td>
</tr>
<tr>
<td>1993</td>
<td>0.46 (0.42, 0.49)</td>
<td>9.33 (9.18, 9.49)</td>
<td>0.05</td>
<td>0.05, 0.05</td>
</tr>
<tr>
<td>1994</td>
<td>0.80 (0.76, 0.85)</td>
<td>12.35 (12.17, 12.53)</td>
<td>0.07</td>
<td>0.06, 0.07</td>
</tr>
<tr>
<td>1995</td>
<td>1.28 (1.22, 1.34)</td>
<td>17.93 (17.70, 18.16)</td>
<td>0.07</td>
<td>0.07, 0.07</td>
</tr>
<tr>
<td>1996</td>
<td>1.44 (1.37, 1.50)</td>
<td>21.21 (20.96, 21.45)</td>
<td>0.07</td>
<td>0.06, 0.07</td>
</tr>
<tr>
<td>1997</td>
<td>1.41 (1.34, 1.47)</td>
<td>21.22 (20.97, 21.47)</td>
<td>0.07</td>
<td>0.06, 0.07</td>
</tr>
<tr>
<td>1998</td>
<td>1.45 (1.38, 1.51)</td>
<td>21.27 (21.01, 21.52)</td>
<td>0.07</td>
<td>0.06, 0.07</td>
</tr>
<tr>
<td>1999</td>
<td>1.42 (1.36, 1.49)</td>
<td>20.97 (20.72, 21.22)</td>
<td>0.07</td>
<td>0.06, 0.07</td>
</tr>
<tr>
<td>2000</td>
<td>1.28 (1.22, 1.35)</td>
<td>20.28 (20.03, 20.53)</td>
<td>0.06</td>
<td>0.06, 0.07</td>
</tr>
</tbody>
</table>

\(^a\) p < 0.0001 for increase in asthma incidence, by Cochrane Armitage trend test

Table 6.9 Logistic regression: odds of ‘severe onset asthma’ predicted by year of birth

<table>
<thead>
<tr>
<th>Year (1992 = Ref)</th>
<th>Unadjusted Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>2000</td>
<td>1.33</td>
<td>1.19</td>
</tr>
<tr>
<td>1999</td>
<td>1.43</td>
<td>1.27</td>
</tr>
<tr>
<td>1998</td>
<td>1.43</td>
<td>1.28</td>
</tr>
<tr>
<td>1997</td>
<td>1.40</td>
<td>1.25</td>
</tr>
<tr>
<td>1996</td>
<td>1.43</td>
<td>1.27</td>
</tr>
<tr>
<td>1995</td>
<td>1.50</td>
<td>1.34</td>
</tr>
<tr>
<td>1994</td>
<td>1.37</td>
<td>1.22</td>
</tr>
<tr>
<td>1993</td>
<td>1.03</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Model Fit Statistics: C-statistic: 0.521, Hosmer and Lemeshow: p = 1.0

Birth year overall was found to be a significant predictor of odds of severe onset asthma in the unadjusted model, but was not a significant predictor in the multivariable regression model adjusting for additional baseline covariates.
Table 6.10 Multivariable logistic regression for odds of ‘severe onset asthma’

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Birth Year:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1.01</td>
<td>0.89</td>
</tr>
<tr>
<td>1999</td>
<td>1.06</td>
<td>0.94</td>
</tr>
<tr>
<td>1998</td>
<td>1.07</td>
<td>0.95</td>
</tr>
<tr>
<td>1997</td>
<td>1.04</td>
<td>0.92</td>
</tr>
<tr>
<td>1996</td>
<td>1.04</td>
<td>0.92</td>
</tr>
<tr>
<td>1995</td>
<td>1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>1994</td>
<td>1.14</td>
<td>1.00</td>
</tr>
<tr>
<td>1993</td>
<td>0.96</td>
<td>0.83</td>
</tr>
<tr>
<td>(reference) 1992</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Income Quintile:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.26</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>1.15</td>
<td>1.08</td>
</tr>
<tr>
<td>3</td>
<td>1.08</td>
<td>1.01</td>
</tr>
<tr>
<td>4</td>
<td>1.04</td>
<td>0.98</td>
</tr>
<tr>
<td>(reference) 5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Rural birth residence</td>
<td>1.66</td>
<td>1.57</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.14</td>
<td>1.10</td>
</tr>
<tr>
<td>With comorbidity</td>
<td>1.24</td>
<td>1.14</td>
</tr>
<tr>
<td>With low birth weight</td>
<td>1.16</td>
<td>1.07</td>
</tr>
<tr>
<td>With maternal asthma</td>
<td>0.98</td>
<td>0.93</td>
</tr>
<tr>
<td>Maternal age &gt; 35 years</td>
<td>0.81</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Model Fit statistics: C statistic = 0.589, Hosmer and Lemeshow: p = 0.15

Thus, the significant independent predictors of ‘severe onset asthma’ in the multivariable logistic regression included lower neighbourhood income quintile, rural birth residence, male sex, comorbid health conditions, and low birth weight, while older maternal age was associated with non-‘severe onset asthma’. Maternal history of asthma was also not found to be a significant predictor of ‘severe onset asthma’ but was still included in the model as this covariate is considered of clinical significance in the onset of asthma.
Both the Hosmer and Lemeshow and the c-statistic suggest there was good model fit for the multivariable logistic regression, and there was no significant multicollinearity between any of the dependent variables in the model as the VIF ranged from 1.0 to 1.9 and the condition index varied from 2.4 to 10.1.

6.7 Descriptive Analysis of Logistic Regression Covariates

The following is a descriptive analysis of the covariates that were included in both of the multivariable regression models. Reasons for adjusting for these baseline covariates is that they are known to influence the incidence of asthma (Section 2.4.1), but prior to this study, it was not known what their contribution to the two outcomes of interest, namely incidence of asthma in children less than three, or ‘severe onset asthma’ might be.

6.7.1 Sex

Table 6.11 Distribution of females in ASTHMA and TOTAL cohorts by birth year

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Total Females (N)</th>
<th>Total Females (%)</th>
<th>Asthma Cohort Females (N)</th>
<th>Asthma Cohort Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>57823</td>
<td>48.9</td>
<td>3736</td>
<td>44.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1993</td>
<td>69102</td>
<td>48.9</td>
<td>6174</td>
<td>44.6</td>
</tr>
<tr>
<td>1994</td>
<td>68926</td>
<td>48.6</td>
<td>8106</td>
<td>43.4</td>
</tr>
<tr>
<td>1995</td>
<td>66452</td>
<td>48.9</td>
<td>10954</td>
<td>41.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1996</td>
<td>63979</td>
<td>48.8</td>
<td>11928</td>
<td>40.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1997</td>
<td>63335</td>
<td>48.8</td>
<td>12012</td>
<td>40.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1998</td>
<td>62482</td>
<td>49.0</td>
<td>11557</td>
<td>39.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1999</td>
<td>61488</td>
<td>48.5</td>
<td>11367</td>
<td>40.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2000</td>
<td>60492</td>
<td>48.5</td>
<td>10720</td>
<td>39.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> p < 0.0001, Z = -13.2 for decrease in proportion of females over time, by Cochrane Armitage test for trend
<sup>b</sup> p = 0.9-1.0 indicating non-equality for comparison of proportion of females in total cohort vs. asthma cohort alone at 5% margin of difference; Sex variable ‘missing’: N=2

The total proportion of females in the total study sample was slightly less than the proportion of males and did not change by birth year. However, the proportion of females within the asthma cohorts decreased over time by nearly 5% overall, from birth year 1992 to 2000 (p<0.0001).
6.7.2 Neighbourhood Income Quintile

Table 6.12 Percent of children with ASTHMA in different income quintiles at birth

<table>
<thead>
<tr>
<th>Income Quintile</th>
<th>Birth Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (%)</td>
<td>24.2</td>
</tr>
<tr>
<td>Q2 (%)</td>
<td>21.7</td>
</tr>
<tr>
<td>Q3 (%)</td>
<td>19.3</td>
</tr>
<tr>
<td>Q4 (%)</td>
<td>19.9</td>
</tr>
<tr>
<td>Q5 (%)</td>
<td>14.7a</td>
</tr>
<tr>
<td>Missing (%)</td>
<td>2.9</td>
</tr>
<tr>
<td>Ratio Q1/Q5</td>
<td>1.6</td>
</tr>
<tr>
<td>Difference Q1-Q5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

\*p < .0001 for increase in proportion of children in highest income quintile, Cochrane Armitage trend test

‘N’ used for analysis = 209222

There were more children overall (with and without asthma) living in the lowest versus the highest neighbourhood income quintiles at birth, (p<0.0001, 5% M.D.) The difference between the proportion of children in the highest versus the lowest income quintile changed over time for children with asthma and for ALL children. The magnitude of this difference or ‘gap’ in income distribution increased from 9.5% in birth year 1992, up to 11.1% by birth year 1996 and
then fell down to 8.4% in birth year 2000. Of note, for the children with asthma the proportion of children in the highest income quintile did significantly increase over time (p<0.0001).

Figure 6.10 Income quintile at birth for children with ASTHMA.

Table 6.13 Percent of ALL children in different income quintiles at birth

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (%)</td>
<td>23.6</td>
<td>23.7</td>
<td>24.3</td>
<td>23.7</td>
<td>23.5</td>
<td>23.5</td>
<td>23.5</td>
<td>23.1</td>
<td>23.1</td>
</tr>
<tr>
<td>Q2 (%)</td>
<td>20.9</td>
<td>21.1</td>
<td>20.8</td>
<td>20.8</td>
<td>20.5</td>
<td>20.3</td>
<td>20.3</td>
<td>20.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Q3 (%)</td>
<td>20.0</td>
<td>19.8</td>
<td>19.9</td>
<td>19.9</td>
<td>20.0</td>
<td>19.5</td>
<td>19.8</td>
<td>20.1</td>
<td>20.3</td>
</tr>
<tr>
<td>Q4 (%)</td>
<td>19.5</td>
<td>19.3</td>
<td>19.2</td>
<td>19.6</td>
<td>19.8</td>
<td>20.1</td>
<td>19.9</td>
<td>19.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Q5 (%)</td>
<td>16.0</td>
<td>16.1</td>
<td>15.7</td>
<td>16.0</td>
<td>16.2</td>
<td>16.6</td>
<td>16.5</td>
<td>16.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Missing (%)</td>
<td>2.9</td>
<td>2.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Ratio Q1/Q5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Difference Q1-Q5</td>
<td>7.6</td>
<td>7.6</td>
<td>8.6</td>
<td>7.7</td>
<td>7.3</td>
<td>6.9</td>
<td>7.0</td>
<td>6.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*N* used for analysis = 1166400
Figure 6.11 Income quintile distribution for ALL children at birth.

6.7.3 Residence Geography

The proportion of all children (with and without asthma) living in a rural environment at birth decreased gradually over time by birth year (p<0.0001). There was a significantly higher proportion of children born into an urban versus rural environment (Table 6.14). Of note there was less than 1% missing data for the variable geography for any of the birth cohorts.

Table 6.14 Frequency and proportion of children living rural at birth

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>aALL: at Birth (N)</th>
<th>ALL: at Birth (%)</th>
<th>Asthma: at Birth (N)</th>
<th>Asthma: at Birth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>19701</td>
<td>16.8(^b)</td>
<td>1240</td>
<td>15.0(^c)</td>
</tr>
<tr>
<td>1993</td>
<td>21777</td>
<td>15.5</td>
<td>1758</td>
<td>12.8</td>
</tr>
<tr>
<td>1994</td>
<td>19151</td>
<td>13.5</td>
<td>1940</td>
<td>10.4</td>
</tr>
<tr>
<td>1995</td>
<td>18410</td>
<td>13.6</td>
<td>2763</td>
<td>10.6(^d)</td>
</tr>
<tr>
<td>1996</td>
<td>17188</td>
<td>13.1</td>
<td>3089</td>
<td>10.4(^d)</td>
</tr>
<tr>
<td>1997</td>
<td>16513</td>
<td>12.7</td>
<td>2807</td>
<td>9.6(^d)</td>
</tr>
<tr>
<td>1998</td>
<td>15748</td>
<td>12.4</td>
<td>2645</td>
<td>9.1(^d)</td>
</tr>
<tr>
<td>1999</td>
<td>14782</td>
<td>11.7</td>
<td>2562</td>
<td>9.0(^d)</td>
</tr>
<tr>
<td>2000</td>
<td>14301</td>
<td>11.5</td>
<td>2322</td>
<td>8.6(^d)</td>
</tr>
</tbody>
</table>

\(^a\)“ALL” refers to the total birth cohort, \(^b,c\) p<0.0001 for reduction over time for children living in rural at birth by Cochrane Armitage trend test, \(^d\)p=0.3-1.0, 5% M.D., indicating non-equality for proportion of children born rural vs urban, by equivalence test. ‘N’ used for analysis of total cohorts = 1174795 and for asthma cohorts = 210040.
6.7.4 Comorbidity

The proportion of ALL children (p=0.7) or children with asthma (p=0.2) with comorbid cardiorespiratory conditions or preterm gestation did not change significantly over time.

Table 6.15 Percent of ALL children and those with ASTHMA with comorbid health conditions

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Asthma Cohorts</th>
<th>Total Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aResp</td>
<td>bCHD</td>
</tr>
<tr>
<td>1992</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>1993</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>1994</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>1995</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>1996</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>1997</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>1998</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>1999</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>2000</td>
<td>1.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

aResp= bronchopulmonary dysplasia, bronchitis or neonatal respiratory distress syndrome, bCHD = congenital heart disease, cPrem = preterm gestation, dCom=any combination of Resp, CHD or Prem
Figure 6.13 Comorbid conditions among children born in 1992 and 2000

BPD = bronchopulmonary dysplasia, RDS = respiratory distress syndrome, Resp = combination of bronchopulmonary dysplasia or bronchitis or neonatal respiratory distress syndrome, Prem = premature (gestational age <37 weeks), CHD = congenital heart disease, Com = any of ‘Resp’, ‘Prem’ or ‘CHD’.

6.7.5 Birth Weight

Table 6.16 Low birth weight distribution for ALL children and children with ASTHMA

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Children with Asthma (%)</th>
<th>All Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LBW</td>
<td>VLBW</td>
</tr>
<tr>
<td>1992</td>
<td>5.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
<tr>
<td>1993</td>
<td>6.0</td>
<td>0.8</td>
</tr>
<tr>
<td>1994</td>
<td>6.6</td>
<td>1.1</td>
</tr>
<tr>
<td>1995</td>
<td>7.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td>1996</td>
<td>7.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td>1997</td>
<td>7.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4</td>
</tr>
<tr>
<td>1998</td>
<td>7.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td>1999</td>
<td>7.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td>2000</td>
<td>7.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
</tbody>
</table>

LBW = low birth weight, VLBW = very low birth weight, ELBW = extremely low birth weight
<sup>a</sup>p < 0.0001, Z = 6.9 for increase in proportion of children with LBW in asthma sample, Cochrane Armitage trend test,
<sup>b</sup>p = 1.0, 5% M.D. indicating non-equality for proportion of children with low birth weight in asthma vs. ALL cohorts, by equivalence test. ‘N’ used for analysis of total cohorts = 1177544 and asthma cohorts = 210300.
There was no change over time in the proportion of all children (asthma plus non-asthma) born with LBW, VLBW or ELBW. However within the asthma cohorts, compared to the total cohorts, there was a higher proportion of children born with LBW (p=1.0, 5% M.D.) for birth years 1995-2000 and an overall modest increase in the rate of LBW over time (p<0.0001), from 5.9% to 7.6% over the birth years 1992 to 1996 and subsequent stabilization. There was approximately 0.03% missing data for the birth weight variable for the entire study sample for all birth years combined.

6.7.6 Maternal Variables

Maternal age as reflected by the proportion of mothers with age greater than thirty-five at the time of delivery was seen to steadily increase by cohort year, for all mothers and mothers of those children with asthma (p<0.0001). The overall rate of maternal asthma also increased by birth cohort year, for all mothers and for mothers whose children developed asthma (p<0.0001). There was a higher proportion of asthma among those mothers whose children developed asthma compared to mothers of children who did not develop asthma for birth years 1994-2000 (p=0.9 – 1.0, 5% M.D.)

Table 6.17 Age and asthma history for mothers of children with ASTHMA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Birth Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal ever asthma (%)</td>
<td>3.5\textsuperscript{a}</td>
</tr>
<tr>
<td>Maternal age &gt;35 years (%)</td>
<td>10.6\textsuperscript{b}</td>
</tr>
<tr>
<td>Maternal age missing (%)</td>
<td>8.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a} p < 0.0001, Z = 41.6 for increase in maternal ever asthma, calculated using Cochrane Armitage trend test
\textsuperscript{b} p < 0.0001, Z = 24.9 for increase in proportion of maternal age > 35, calculated using Cochrane Armitage trend test
N for analysis of maternal age = 198601, representing a total of 5.6% missing data
Table 6.18 Age and asthma history for mothers of ALL children

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal ever asthma (%)</td>
<td>2.4</td>
<td>3.8</td>
<td>5.0</td>
<td>6.1</td>
<td>7.0</td>
<td>7.9</td>
<td>8.7</td>
<td>9.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Maternal age &gt;35 years (%)</td>
<td>10.1</td>
<td>11.3</td>
<td>12.0</td>
<td>13.2</td>
<td>14.6</td>
<td>15.3</td>
<td>16.3</td>
<td>16.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Maternal age missing (%)</td>
<td>9.5</td>
<td>8.3</td>
<td>6.5</td>
<td>6.4</td>
<td>5.9</td>
<td>5.6</td>
<td>5.3</td>
<td>5.9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

a \( p < 0.0001 \), Z-statistic = -98.4 for increase in maternal ever asthma, calculated using Cochrane Armitage trend test, c \( p < 0.0001 \), Z-statistic = -71.7 for increase in maternal age >35, calculated using Cochrane Armitage trend test
N for analysis of maternal age = 1088822, representing 7.6% missing data
N for analysis of maternal asthma = 1088305, representing 7.6% missing data

Figure 6.14 Proportion of mothers greater than 35 years old at delivery

Figure 6.15 Proportion of mothers with asthma
Table 6.19 Validity of data linkage between mothers and their children in this study

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Linkage Missing</td>
<td>N</td>
<td>11120</td>
<td>11604</td>
<td>9131</td>
<td>8670</td>
<td>7713</td>
<td>7213</td>
<td>6780</td>
<td>7476</td>
</tr>
<tr>
<td>(%)</td>
<td>9.4</td>
<td>8.2</td>
<td>6.4</td>
<td>6.4</td>
<td>5.9</td>
<td>5.6</td>
<td>5.3</td>
<td>5.9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

As indicated in tables 6.17 and 6.18 there was a considerable amount of missing data, partly due to between 5.3% - 9.4% missing linkage information for the different birth cohorts. This did make the validity of the maternal variables, namely ‘asthma’ in the mothers questionable as those mothers who did not have linkage with OHIP or CIHI databases due to a missing IKN (which links to the OHIP number) would be coded as ‘not’ having asthma. As such, a sensitivity analysis, performed by removing those mothers with missing linkage information from the logistic regression did not change the parameter estimates significantly in either model (< 5% change). Similarly for the variable maternal age, there was a significant amount of missing data (up to 9.5% in earlier cohorts), so a sensitivity analysis was performed by removing this variable from the multivariable logistic regression models, and showed there was a non-significant change in parameter estimates for all other predictors (<5%) with respect to both outcomes, asthma onset at less than three years, and ‘severe onset asthma’.

6.8 Asthma Related Visits

Table 6.20 Asthma-related visits for ALL children and those under 3 years old

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>First 3 years of life</th>
<th>First 8 years of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total visits (N)</td>
<td>Proportion with visit (%)</td>
</tr>
<tr>
<td>1992</td>
<td>500066</td>
<td>12.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1993</td>
<td>582549</td>
<td>19.9</td>
</tr>
<tr>
<td>1994</td>
<td>655444</td>
<td>23.3</td>
</tr>
<tr>
<td>1995</td>
<td>635979</td>
<td>22.8</td>
</tr>
<tr>
<td>1996</td>
<td>452756</td>
<td>21.4</td>
</tr>
</tbody>
</table>

All visits in above table represent asthma related visits as defined in this thesis. <sup>a</sup> Significant increase over time by Cochrane Armitage trend test, p<0.0001).
The total proportion of children with an asthma-related visits for the entire cohort did not appear to change over time. However, the total proportion of children with an asthma-related visit in the first three years of life increased over time by birth year. (p<0.0001)

Figure 6.16 Proportion of children with asthma related visits by birth year
Discussion and Limitations

While it is well known that the incidence of asthma varies with age, this is the first study to fully characterize the change over time in the age of asthma diagnosis in children. As such, one important finding in this study is that the mean age of asthma diagnosis has decreased significantly over time.

However, as indicated by the large standard deviation around the mean age of asthma onset identified in this study, (Fig. 6.4) this is not really the best way to measure this concept. Interestingly, by dichotomizing the age of asthma diagnosis to before and after the age of three, it was possible to further identify that the proportion of asthma diagnoses in young children, as well as the relative risk of incident asthma in children under three has significantly increased over time, even after adjusting for multiple potentially confounding baseline variables. In the same time period, the incidence of asthma in children older than three has not really changed much. These findings in combination suggest it is not just that the age of asthma onset has decreased over time, but that previously seen trends in asthma incidence are primarily due to changes in asthma incidence among children less than three, while the incidence of asthma in older children has largely remained stable.

There is one previous study by Weitzman that showed a younger age of asthma onset over time in African Americans who were less than five years old compared with the same aged Caucasian children. However, other than genetic differences in the two groups of children, the authors did not propose an explanation for the observed earlier onset of asthma. (123) Another previous study by Akinbami did also show that the highest increase in asthma prevalence occurred in the youngest age group of children zero to four years old between the years 1980 to 1996, (124) but again, no biologic explanation for this finding was offered.

It is currently not fully understood what factors are responsible for causing or triggering asthma onset in children. But based on the results in this thesis study, in the last few decades, whatever these environmental factors are, they seem to be preferentially promoting asthma onset in very young children. This is either because these unknown etiological factors only affect young children or because older children are already “saturated” in their exposure to these factors.
asthma inciting environmental factors, thereby explaining a stable rate of asthma in this older population.

The importance of finding a higher burden of asthma in children under three is that previous cohort studies showed more cases of childhood asthma that persisted into adulthood had their onset prior to age three. (46) So the finding of a significant reduction in age of asthma onset over time suggests that the rate of persistent asthma may in fact increase over time. However, the interesting question generated by these results is whether the ‘asthma’ that had its onset in children younger than age three in this study is in fact the same disease as in those children with onset of symptoms at less than three years of age in previous cohort studies. That is, has there simply been an increased burden of virally-triggered wheezers (which is currently felt to be the dominant phenotype of children under three with asthma) in recent decades, and the burden of atopically driven wheezers who are more likely to persist into adulthood hasn’t really changed. If this is the case, then the next question is what exposures were newly or increasingly present in the environment since the birth years 1993 onward that increased the rate of either smaller airway size at birth, or AHR and subsequent wheezing with virus exposure. Or alternatively, has something changed about the viruses that children are exposed to in that they are now more likely to cause wheezing in the first few years of life? It is of note, however, that in this study it is not possible to really discern asthma phenotype or the presence of atopy in children with an asthma diagnosis, so it is equally possible that for unknown reasons there has been an increased proportion of children with atopic asthma presenting at less than three years of age. In fact, other studies of anaphylaxis and IgE sensitization would suggest that the prevalence of atopy continues to increase in young children. (125, 126) Unfortunately these hypotheses are not testable in this present study and would be interesting areas for future research.

Previous studies have shown that increases in asthma rates over the last few decades have primarily been noted in children with milder phenotypes; that is, there have been fewer children requiring emergency room visits or hospitalization for asthma over time. Improvements in medications for childhood asthma have significantly reduced the severity of symptoms, health care utilization and hospitalization rates among those children requiring regular medication. However, another explanation for the changes in asthma incidence over time seen in children under three in this study may be that overall there has been a shift in what physicians today diagnose as asthma compared to 20 years ago. (97) In fact, it is suggested that milder phenotypes
of recurrent cough and wheezing in recent years are often ‘mis’-labeled as asthma, (61) whereas they may have been called some other diagnosis decades ago. (13) There are a number of studies that have aimed to determine whether in fact this proposed ‘diagnostic exchange’ adequately explains the changes in asthma rates seen over time. In these studies the concurrently examined rate of ‘asthma-related’ diagnoses did not drop during the study period, thus negating the contribution of ‘diagnostic exchange’ as an explanation for changes in asthma prevalence over time. (95, 122). In this thesis the change in the rate of asthma-related diagnoses was also examined. More specifically, the change over time in the proportion of children with an asthma-related (but ‘non-asthma) respiratory health care visit either in the first three or the first eight years of life was measured. In the setting of a significant diagnostic shift, one would expect the change over time in the proportion of children with ‘asthma-related visits’ to be in the opposite direction to the change over time in the proportion of children with an ‘asthma diagnosis’. Since the proportion of children over time with an asthma-related health care visit in the first three years of life was shown to have increased in this study (and remain stable overall for the first eight years of life), the overall increase in asthma incidence identified in children under three is not explained by ‘diagnostic shift’.

However, another way to determine if overall changes in asthma incidence, particularly in children under age three are due to ‘over-labeling’ of mild symptoms, would be to only examine more severe asthma phenotypes, as was done in this thesis. As explained in section 2.6 there is no consensus on how best to identify asthma severity, however, in this thesis an attempt was made to further avoid the confounding issue of changes in asthma treatments and treatment adherence over time by examining only the rate of ‘severe onset’ asthma over time. Reasons for an increase in admission to hospital at the first diagnosis of asthma, particularly in children under three, may relate either to a higher severity of disease at its onset or to a lower threshold for admission to hospital over time. But in any case, the increase in severe onset asthma over time in this study negates the likelihood that the increased asthma burden in children under three only reflects milder asthma phenotypes. In contrast, this study actually suggests that changes in asthma incidence seen in children under three are primarily reflecting changes in severe onset asthma over time, rather than milder phenotypes.
7.1 Limitations of Health Administrative Data

Although using health administrative data provided significant power and the feasibility for conducting a study of multiple birth cohorts that would have been prohibitive to undergo using traditional methods of patient recruitment, this type of research also has its limitations. For example identifying study participants using health administrative does not allow collection of all clinically relevant information, such as participant exposure to ETS, respiratory viruses or the presence of atopy, all of which could have contributed to the age of diagnosis and severity at onset of asthma. Furthermore, this particular birth cohort study goes only as far back as 1992 due to the availability of the health administrative data used, and thus the study is limited to approximately the last twenty years.

One of the most important limitations in the current study is in the validity of the identification of asthma. Since health administrative data is being used as the primary data source, it is necessary to rely on validated algorithms for identification of asthma in the study population. The sensitivity and specificity of the algorithm to identify children with asthma in the present study were found to be 89% and 72% respectively so the possibility of misclassification bias is real. However, given the large sample size and the fact that the goals of this study were to simply examine trends in asthma incidence by age and severity over time, even if there was some misclassification, the assumption is that the overall direction of change in asthma incidence over time would unlikely be affected. Of note, the trend in the crude eight-year cumulative incidence of asthma noted in this study mirrors trends in asthma incidence seen in several other studies using different populations and methods for identifying asthma both in Canada and across the world, thus lending concurrent validity to the current study findings.

With respect to age of asthma diagnosis, there is consensus among clinicians that diagnosing asthma in very young children is extremely difficult and thus asthma diagnosis in the youngest children in this study could be disproportionately affected by misclassification bias. It is to be noted that the original case-validation studies for the algorithm used in this thesis study to identify asthma did in fact include children less than one year old. However, to further improve diagnostic validity in this study, those children with asthma diagnosed at less than six months of age were excluded from the asthma sample, unless they had a subsequent health care visit for asthma after 1 year of age. It is also to be mentioned that in this study it was identified
that there were no children diagnosed with asthma at less than three years of age for children born in 1992 in Ontario. Though this thesis shows that age of asthma diagnosis decreased over time, it seems implausible that there were zero children with asthma under age three born in 1992 and calls into question data validity for the earlier cohort years. As such, a sensitivity analysis was performed by using the year 2000 as the reference (rather than 1992) and still showed an association between year of birth and asthma diagnosis at less than three years of age. (Appendix 2).

Another possibility is that there may have been a proportion of children less than three with asthma who were ‘missed’ by the algorithm used to identify asthma in this study which was validated in 2000 and may not be as sensitive when applied to the year 1992. Nonetheless, it is likely that the overall study finding of a trend for an increase in the proportion of asthma diagnoses at less than age three would still be valid.

Another limitation of using health administrative data and derived algorithms to identify asthma cases is that they rely on a ‘doctor-diagnosis’ of asthma. However, previous studies show there is a lag between onset of asthma symptoms and doctor-diagnosis of asthma. As such, it is possible that the lag or delay between asthma onset and asthma diagnosis may have changed over time, and would not be identified in this study but could contribute to an observed change in the age of asthma ‘diagnosis’ over time.

Additional general limitations of using administrative databases is that those physicians who are paid on salary (and this proportion among primary care providers has increased over time) as well as nurse practitioners who care for patients with asthma, may not have incentive to bill and submit claims to OHIP, thereby possibly resulting in ‘missed’ asthma cases in this study. However, as per a recent ICES report covering the period 2008 – 2010 in Ontario (outside the study period for this thesis), less than 1% of Ontarians were cared for by salaried physicians in the setting of community health centres with approximately 35% of patients seen in these centres falling into the lowest income quintile. (127) So while it is possible that this study disproportionately ‘missed’ cases of asthma within the lowest income quintiles, and perhaps more so over time, the actual number of asthma cases missed would have been very small and unlikely to affect overall trends seen in this study.
7.2 Limitations of the Definition of Asthma Severity

In order to eliminate the confounding issue of changes in asthma treatments over time, the definition of asthma severity used in this study focused only on a measure of asthma severity at the first diagnosis of asthma, namely, need for hospitalization. However, this definition has not been clinically validated and still has the confounding issues of access to health care and possible change in hospital admission criteria over time for children with asthma. Furthermore, there is a possibility that there was a bias toward over-identification of ‘severe-onset’ asthma in this study as those children who may have seen a physician with mild asthma symptoms and been diagnosed with ‘wheeze’ or ‘cough’ or other asthma-related diagnoses would have only met the definition of asthma upon hospitalization (though their asthma symptoms clearly developed earlier). This issue speaks to the known lag between onset of asthma symptoms and diagnosis as discussed earlier (Section 7.1). Of importance in this study however, is that there is no reason to expect that the lag between onset of asthma symptoms and diagnosis of asthma has increased over time. In fact current hypotheses suggesting a tendency to ‘over-diagnosis’ of asthma would imply that the lag between asthma onset and diagnosis has likely decreased over time.

7.3 Limitations of Analytic Methods Used

As mentioned in the methods (Section 5), despite the longitudinal nature of the data collected in this study by using multiple consecutive birth cohorts, a longitudinal approach was not taken for data analysis. For example, Cox Proportional Hazards modeling could have been performed with time to asthma onset as a continuous outcome. However, this type of analysis may not have so clearly shown the obvious demarcation in asthma incidence in the two age groups specified in this study (i.e. less than vs. equal to/greater than three). Another possibility would have been to conduct a formal time-series analysis of the data. However, given this study is limited to only an eight year observation period for each birth cohort, it was felt that significant trends over time might be missed with this methodology at this early stage.

In this thesis, other than graphing out the additional baseline covariates over time by birth cohort year, (as discussed further below) the potential time-dependent influence of each of these variables (e.g. sex, LBW, etc.) was not analyzed because there did not seem to be a biologic rationale for doing this for most variables. For example, there is no reason to expect that LBW would affect the risk of the onset of asthma in a time-dependent fashion. With respect to other
covariates such as comorbidity, residence geography or income quintile, it is possible that these would have a time dependent relationship with asthma onset, however, given the short observation period of only eight years, this was not explored in the current study.

7.4 Other Factors

In addition to crude asthma incidence, age of asthma onset and asthma severity at onset, this study also examined multiple other baseline factors that could be contributing to changes in age of asthma diagnosis and severity of asthma at its onset, over time.

7.4.1 Sex

As seen in multiple previous studies, it was noted that there was a higher proportion of males with asthma in this study as opposed to females. It is not yet entirely known why there is a sex difference in asthma onset at different ages. Research suggests there may be a difference in the actual lung and airway size in young boys compared to girls. That is, boys often have smaller lungs and airways at birth so if they are already primed to develop asthma, they would be more likely to manifest symptoms at an earlier age compared with females.(85) Interestingly in the current thesis study, the proportion of females within the asthma cohorts decreased over time by nearly 5% overall, from birth year 1992 to 2000. This reduction is likely a reflection of the concurrent finding of a reduction in age of asthma diagnosis over time as discussed above. Since a higher proportion of boys have asthma at younger ages, if the overall age of asthma onset has reduced over time, this may be the explanation for an overall increase in the proportion of boys relative to girls in the asthma cohorts over time.

7.4.2 Socioeconomic Status

This study found that children overall, both within the asthma and non-asthma cohorts were disproportionately represented in the lowest income quintiles compared to the highest, though the difference in the proportional distribution of children between the lowest versus the highest income quintiles decreased over time by birth cohort. In fact, it is well know that more children in Canada are born into lower income quintiles, likely because younger families on the whole are less affluent than older families. Previous Statistics Canada research in 2004 shows that low income is highly prevalent among children, with 13% of all Canadian children less than eighteen years old actually living below the low income after tax cut off (LICO-IAT) and children living
in families with several siblings being more likely to be in this low income category. (128) In Canada there is no real definition of poverty but the LICO-IAT is a marker of the most economic disadvantage.

There is a huge body of literature which explores the relationship of SES and asthma. It is well established from multiple studies that asthma morbidity is highest among those children living in the lowest socioeconomic circumstances. Even in Canadian studies, asthma symptom control, frequency of emergency room visits and hospitalizations are higher among children from lower SES. (129, 130) In this context, it is not surprising to have found increased odds of ‘severe onset asthma’ among children in the lowest income quintile in this study. While making it possible to eliminate the confounding influence of asthma treatments over time, the definition of asthma severity used in this study is confounded by access to health care. As mentioned above, asthma diagnosis lags behind the initial presentation of asthma symptoms. So it is very possible that children from higher income quintiles with better access to health care may have had earlier recognition of asthma symptoms by their health care providers and initiation of appropriate asthma treatments, thereby mitigating hospitalization as the first presentation of the disease.

Though asthma morbidity is well known to be highest among those of lower SES, what is not clear is whether asthma incidence actually varies by SES. Previous studies on this topic have shown inconsistent results, some showing higher asthma rates in lower socioeconomic groups (79, 131-133) and others showing the opposite, (134) and these relationships have also varied over time,(135) by the ethnic distribution within the population studied, and whether the study sampled from an inner city, urban or non-urban area. (84, 136, 137) In Canada, most studies have not shown a difference in asthma rates based on SES,(138) and this has been explained by the lesser degree of wealth separation between the higher and lower socioeconomic groups in this country compared to in the US, as well as the lack of true ‘inner-city’ populations where asthma rates are found to be the highest in US studies. However, the finding in this thesis study that being born into a lower income quintile was predictive of a younger age of asthma onset is interesting, as it suggests that some aspect of living in a neighbourhood with an average lower income actually promotes earlier manifestation of asthma symptoms and speaks to the underlying etiology of asthma.
7.4.2.1 Validity of Neighbourhood Income Quintile Variable

With respect to the findings of the relationship between neighbourhood income quintile and asthma incidence in this study, there are some limitations to be noted. First of all, the measure ‘neighbourhood income quintile’ is considered to be a reflection of the broader concept of ‘socioeconomic status’, which refers to “the placement of persons, families, households and census tracts or other aggregates with respect to the capacity to create or consume goods that are valued in our society”. (139) The mechanisms by which SES can influence health is through predicting i) an individual’s use of health care services, ii) their environmental exposures and iii) their health behaviour and lifestyle. (50) There is much controversy and numerous ways to ‘best’ assess SES such as measuring an individual’s or groups “current income”, “wealth”, “education”, “occupation” or by using composite indices. (139) Each marker of SES has its own benefits and disadvantages over the others, though most authorities in this area recommend the use of multiple methods to measure SES. When various markers of SES are used, it can be difficult to directly compare the results of different studies showing the impact of SES on health outcomes. (140) An added issue when using health administrative data for research studies, is that it is not possible to get individual SES-related information, thus ecological proxies are often used. In this study, neighbourhood income quintile was used as a proxy for the SES level of each individual child. In fact, neighbourhood income quintile is an average for all children living within a particular postal code area in Ontario and thus does not necessarily reflect the individual socioeconomic conditions of each child and how these may relate to asthma risk. However, the validity of using ecological measures of SES has been compared with and found to be a reasonable reflection of individual level measures when it comes to measuring health outcomes. (141) There is also evidence that neighbourhood effects are important independent determinants of health. So finding a difference in age of asthma diagnosis and severity at asthma onset by neighbourhood income quintile in this study suggests that there are differences in exposures encountered by individuals living in different postal code areas, be they SES-related or otherwise, that influence the development of asthma.

7.4.2.2 Limitation of Environmental Tobacco Smoke Exposure

Some possible environmental factors that could differ between postal code areas overall might include exposure to certain antigens such as cockroach, or traffic related air pollution or ETS. In fact, a major limitation of this study is that there is no adjustment for exposure to ETS. This is
particularly important as ETS exposure has been shown in previous studies to increase the risk of developing asthma, and trigger higher severity symptoms. Thus, finding younger age of asthma onset, and higher severity of asthma at onset among children in the lower neighbourhood income quintiles in this study could in fact be explained by higher ETS exposure. This is an interesting hypothesis as there has been a reduction in ETS exposure for all children over time (142) and perhaps this is some of the reason for a decreasing difference in asthma incidence among children in the highest versus the lowest income quintiles in this study in the last few birth cohort years.

7.4.3 Geography

This study found that there was a lower proportion of children with asthma who were born into a rural environment compared to the entire population of children and that the proportion of all children living in a rural environment (asthma and non-asthma) continues to drop overall by birth year. It is possible that an increase in the proportion of salaried physicians in rural areas, who have less incentive to submit OHIP billings, could explain an observed decrease over time in the proportion of children with asthma in these rural areas, due to missed asthma cases. However, finding less asthma in rural regions also follows current hypotheses suggesting that living in a rural, particularly a farming environment is protective against the development of asthma (143). One of the first explanations for the ‘asthma epidemic’ seen in the 1950’s and onwards was the ‘hygiene hypothesis’ proposed by Strachan (88). This hypothesis suggested that early childhood infections and exposure to bacteria in the environment are actually protective against the development of asthma but in westernized countries that were seeing a rapid increase in asthma rates the environment was ‘too clean’ and thus children were more susceptible to developing asthma. This hypothesis has since been supported in numerous studies that show reduced allergic sensitization and asthma rates in children born on farms, and with multiple siblings in the home. In fact many studies confirm at a cellular level, that exposure to bacterial lipopolysaccharide and other factors found particularly in a farming environment (144) primes the immune system to the T\text{H}1-phenotype or ‘cellular-mediated immunity, rather than a T\text{H}2-phenotype or ‘humoral mediated’ immunity where allergic sensitization and subsequent asthma are more likely. (145-148) It is also important to point out that not only does living in a rural environment protect against the development of asthma, but also that living in an urban
environment in fact increases the risk of developing asthma. (149) There are several studies showing increased rates of asthma and allergy in urban populations that are not due just to socioeconomic conditions or race. (150, 151)

There are a few Canadian studies showing a lower rate of asthma among children living on a farm, but it is interesting that in these studies, living in a rural, non-farming environment was not protective against asthma. (89, 152) In the current thesis study, there was no distinction between farming versus rural, non-farming place of residence and this may be why there was no association found between age of asthma onset and rural versus urban residence geography. In fact, a previous Canadian study in 1994/1995 using NLSCY data for children aged zero to fourteen years also did not show a difference in asthma prevalence by geography. (84)

The finding that rural residence was associated with a higher odds of severe onset asthma in this study is initially counter-intuitive to the discussion presented above suggesting that rural environments should reduce the risk of asthma (and possibly asthma morbidity). However, this may be explained as mentioned earlier, that the definition of ‘severe onset asthma’ used in this study is in fact confounded by access to health care. In other words, it is very likely that children living in a rural environment have less access to primary care providers and certainly asthma specialists who could initiate early asthma treatment, thereby preventing subsequent hospitalization.

### 7.4.3.1 Validity of Geography Variable

It is important to note that both income quintile and geography were based on the postal code reported in the RPDB. Thus the validity of these two variables is directly related to the data quality of the postal code variable in the RPDB. Postal code information in the RPDB is initially acquired at the time of birth of a child, and is then updated at least every time a child’s health card is renewed (at age two and then every five years subsequently). Thus geography and neighbourhood income quintile in this study would be most valid at the time of birth, as used in this study.

### 7.4.4 Low Birth Weight and Comorbidity

This study found a modest increase in the proportion of children with LBW represented within the asthma cohorts over time, compared to in children without asthma, as well as an increased
odds of severe onset asthma among children with LBW. Several studies around the world have shown that LBW contributes to asthma risk, even after accounting for gestational age.\(^{(153-155)}\) The proposed mechanisms for this relationship include poor organ development due to inadequate nutrition of the fetus in utero, or increased airway lability reflecting increased uterine smooth muscle irritability that prompted preterm labour in the first place. Another explanation for more asthma in the LBW cohorts, and higher severity at onset may be related to an increased risk of ETS exposure, particularly as maternal smoking is known to correlate both with LBW and asthma. However it was not possible to explore the relationship between maternal smoking and asthma or birth weight in this study given the limitations of health administrative data.

The rate of comorbid conditions did not differ between the asthma cohorts and the total study population, and did not change over time. However, the presence of comorbid health conditions was independently predictive of increased odds of severe onset asthma. It is certainly possible that children with comorbid health conditions have more severe asthma that may require hospitalization at first presentation, especially since the biggest contribution to the ‘comorbidity’ variable used in this study was preterm gestation (less than 37 weeks). Being born preterm is associated with lower birth weight and is a known independent risk factor for the development of asthma.\(^{(153, 156, 157)}\) Previous studies have shown an overall increase in preterm gestation over time\(^{(158-160)}\) but there was no appreciable change in the rate of preterm births over time by cohort year in this study. This may be explained by the fact that all children who died at less than six months of age were excluded from the analysis. It is likely that a large proportion of children who died within the first six months of life were born very preterm as there is a much higher mortality rate associated with preterm gestation than for children born after 37 weeks in Canada. It is of note that preterm gestation was identified only if ‘preterm’ was listed as a diagnosis (either comorbid diagnosis or primary diagnosis) in the CIHI-DAD. Thus if a child was born at a gestational age of less than 37 weeks but ‘preterm’ was not listed as a discharge diagnosis this information would not be included for that particular child in this study. The actual ‘gestational age’ variable did not become mandatory for reporting until the year 2003, and hence was not reliable to use as an indicator of preterm gestation in this study.

It should be mentioned that another possible explanation for finding increased odds of ‘severe onset asthma’ among children with comorbid health conditions may be related to diagnostic coding practices of physicians. That is, usually only one diagnostic code is listed per
ambulatory healthcare visit on the OHIP record. Thus a child with CF or CHD would likely be ‘billed’ with this diagnosis listed for the ambulatory visit, and a co-existing asthma diagnosis may not become apparent until that child had a hospitalization during which time asthma was then listed as a contributing diagnosis in the CIHI-DAD.

It was interesting to find in this study that both LBW and comorbidity were protective against a younger age of asthma diagnosis. There is no obvious reason why children with comorbid conditions would have an older age of asthma onset compared to the general population, so perhaps this study finding is explained by physician diagnostic coding practices, as explained above. While many children with CF, CHD, BPD and prematurity do have comorbid asthma, it is possible that physicians are less likely to formally diagnose asthma in them until a later age when it is possible to perform objective measures of lung function. Or it may simply be that the presence of the comorbid diseases adjusted for in this study in fact do not confer a higher risk of asthma above the general population.

7.4.5 Maternal Variables

This study found an overall increase in maternal age over time, which has been seen in previous Canadian studies. (92, 161) Although older maternal age in the literature is said to be associated with negative perinatal health consequences including increased rates of preterm births, stillbirths (91) and LBW infants, there is actually some evidence that there is less asthma risk among children born to older mothers. (93, 162) As such the finding in this study that older maternal age was protective against both severe onset asthma and younger age of asthma onset, aligns with previous research.

Having a first degree relative with asthma is a known risk factor for developing asthma in a child. Given this, the findings in this study that the proportion of maternal asthma was higher among mothers of children with asthma compared to the total study population, as well as the increased odds of asthma diagnosis at under age three among children of mothers with asthma were as expected. It is interesting, however, that maternal asthma history was not associated with severity of asthma onset in this study. This may be because mothers who themselves have asthma may be more likely to recognize asthma symptoms in their child and obtain appropriate therapy, thereby preventing early hospitalization.
7.4.5.1 Validity of Maternal Variables

It is to be noted that it was only possible to link information for 90% to 95% of mothers and children in this study as many maternal IKN’s were missing in the MOM-BABY dataset from where linkage information was taken. Furthermore a significant proportion of the mothers were further eliminated from analysis because of missing birthdate information, thereby making data quality and validity somewhat questionable for this particular variable overall. If the missing maternal IKN’s were randomly distributed through the population, this should not have significantly affected trends over time, and thus should not have changed the overall study findings. In fact, for large population datasets <10% missing data could be considered acceptable and generally not felt to significantly affect study results. (163) In any case, sensitivity analyses performed by removing the mothers without valid IKN’s from the logistic regression models in this study did not significantly change parameter estimates for the odds of younger age at asthma diagnosis or ‘severe onset asthma’ as predicted by the year of birth.

It is of note that another reason for finding an increasing rate of maternal asthma in this study over time is because the ‘OASIS’ dataset from which this information was captured contains information on cases of asthma in the province of Ontario only from the fiscal year 1993 and onward. Thus in the case of maternal asthma that was present prior to 1993 with no subsequent OHIP or CIHI record of asthma following March 1993, maternal history of asthma would not be ascertained. Furthermore, mothers who developed asthma as an adult but did not have any asthma health care visits, likely denoting less active asthma would not be identified as having asthma in this study. This limitation would affect children born in the earlier cohorts more so than in the later cohorts.

There was also a significant proportion of mothers with missing or invalid birth date data, making it impossible to determine their age at delivery, and calling into question the validity of making associations between maternal age at delivery and asthma incidence. Sensitivity analyses performed by removing the variable of maternal age from the logistic regression analyses entirely did not significantly change parameter estimates either for the outcome of age of asthma diagnosis or ‘severe onset asthma’ as predicted by year of birth.
7.4.6 Limitations on Generalizability of Study Findings

This study does not generalize to all children in Ontario because all those born outside Ontario (even if they moved to Ontario at a very young age) would be excluded. Furthermore, this study captures only births in Ontario which occurred in a hospital. However, it is known that 97.9% of all live births in Ontario occur in hospitals or clinics.(164) Furthermore, midwives did not become licensed in Ontario until 1994(165) so the rate of home births for the duration of this study would have been very small. For these reasons, the number of Ontario-born children that would not have been captured in this study is extremely small and would unlikely significantly affect the study results.
8 Conclusions

This is the first study to systematically measure the change in age of onset of asthma over time and uses a novel methodology of examining multiple consecutive birth cohorts so as to be able to reliably capture all incident cases of asthma. This study showed that the age of asthma diagnosis has significantly decreased over time and that the changes in asthma incidence seen over time are primarily occurring in just children under the age of three, while asthma incidence in children above age three has only marginally increased over time. The increase in asthma incidence in the youngest age group was not explained by a diagnostic shift as the proportion of children with an asthma-related health care visit increased over time for children in the first three years of life. Furthermore, the increase in asthma incidence in the earlier birth cohorts was not explained by increased labeling of mild wheezing phenotypes as asthma, since the proportion of children with severe asthma at diagnosis (i.e. hospitalization at diagnosis) increased over time. Changes over time in both age of asthma onset and severity at asthma onset remained even after adjusting for multiple additional baseline covariates. Other independent predictors of younger age of asthma onset included male sex, lower income quintile and maternal asthma, while additional independent predictors of ‘severe onset asthma’ included male sex, lower income quintile, comorbid health conditions, low birth weight and rural residence at birth.

Most studies aiming to establish causes of varying asthma rates over time have studied all age groups of children, however this study suggests that efforts should really be focused on the under three age category when trying to identify etiological factors in the pathogenesis of asthma.

8.1 Future Directions

There were a number of interesting findings in the current study that were hypothesis generating and would be interesting to study in more depth in future. For example given that birth cohorts were used in the current study and followed over time, it would be interesting in future to do a formal time-series analysis to assess trends in asthma incidence over time. Though this methodology could have been used immediately in the current study, because the data is limited to only eight years of follow up for all cohorts, it would be more informative to perform this type of analysis in future so as to have a longer follow up period to better assess trends. Furthermore,
it would be interesting to attempt to link the datasets used in the present study with the CTUMs surveys, at least for a portion of the population, to get a better sense of the influence of changing ETS exposure on trends in age and severity of asthma onset.

Again, given the longitudinal nature of this study, it would be informative in future to perform Cox-proportional hazards analysis to model the onset of asthma adjusted for age. In this type of more rigorous assessment of the changing age of asthma onset it would be interesting to examine the importance of other factors such as the type of ‘usual health care provider’ (i.e. family practitioner versus pediatrician) performing the majority of health care visits for a child and whether this may be impacting on the age of asthma diagnosis. Changes over time in the rate of hospitalization at the first diagnosis of asthma were studied in this thesis as a reflection of changes in asthma severity over time. It would be further illuminating to expand the definition of asthma severity and also examine the change over time in the rate of intensive care unit admissions for asthma.

Previous research has suggested that earlier onset of asthma predicts higher disease severity for those children who continue to persist with asthma symptoms into later childhood and adolescence. However in the current study it was not apparent whether the children with a younger age of asthma onset represent the same asthma phenotype as in the earlier Tucson birth cohort studies. That is, in the current study it was not possible to determine whether the higher incidence of asthma in the under three age group reflects atopic asthma or intermittent virally-triggered asthma that children are more likely to outgrow over time. Thus following the children with earlier age of onset in this study over time to identify predictors of persistence and later severity of asthma would be an additional interesting future direction.

8.2 Knowledge Translation Plan

The findings in this thesis study are important and many are not previously reported in the literature. In fact the finding that most of the change in asthma incidence over time is actually occurring just in children under the age of three is new information that may benefit other asthma epidemiologists as the search for the ‘root cause of asthma’ continues. Thus one important audience for the translation of these study findings is other asthma researchers, particularly epidemiologists.
Unfortunately current asthma treatments are not effective in a large proportion of preschool children with viral induced wheezing. However as this study confirms that the highest burden of asthma in fact falls within this age category, identifying better asthma treatments for this age group could have enormous impact on health care use and overall asthma morbidity. Thus another important audience for the translation of these study findings would be to asthma researchers and pharmaceutical companies who are currently developing new treatments for asthma. And a third important audience for the translation of these study findings, given the high rate of health care utilization among young children with asthma is to the Ontario Ministry of Health and those involved in setting health policy and allocating health resources in the province of Ontario.

Given these three key audiences, the knowledge translation plan for this thesis project would be to first present study findings at well-attended international conferences, and in fact the findings from this thesis have already been presented at three different international scientific meetings. The next step would be to publish these study findings in peer-reviewed journals with appropriate readership so as to reach the target populations of asthma researchers who are working on elucidating asthma etiology and developing new asthma treatments.

On a less ‘traditional’ knowledge translation platform, given the Ontario Thoracic Society provided funding toward this thesis study, it would be appropriate to publish an article highlighting the salient findings in the Ontario Thoracic Reviews. This publication reaches a target population of physicians and scientists involved in the care of individuals with asthma in Ontario. It specifically reaches individuals associated with the Ontario Lung Association, an organization that has a mandate for promoting respiratory health in Ontarians in partnership with the Ontario Ministry of Health.
9 References


5. Omran M, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. BMJ. 1996;312(7022):34.


## Appendix 1. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AHR</td>
<td>airways hyperreactivity</td>
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<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
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<tr>
<td>CF</td>
<td>cystic fibrosis</td>
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<td>CHD</td>
<td>congenital heart disease</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CIHI-DAD</td>
<td>Canadian Institute for Health Information-Discharge Abstract Database</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CTUMs</td>
<td>Canadian tobacco use monitoring survey</td>
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<tr>
<td>DOLC</td>
<td>date of last contact</td>
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<tr>
<td>ELBW</td>
<td>extremely low birth weight</td>
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<td>ETS</td>
<td>environmental tobacco smoke</td>
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<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>HCN:</td>
<td>health card number</td>
</tr>
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<td>ICES</td>
<td>Institute for Clinical and Evaluative Sciences</td>
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<td>IgE:</td>
<td>immunoglobulin E</td>
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<td>ICES key number</td>
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<tr>
<td>ISAAC</td>
<td>International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>LBW</td>
<td>low birth weight</td>
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mAPI: modified asthma predictive index
M.D.: margin of difference
NLSCY: National Longitudinal Survey of Children and Youth
OASIS: Ontario Asthma Surveillance Information System
OHIP: Ontario Health Insurance Plan
RDS: respiratory distress syndrome
RPDB: Registered Persons Database
RR: relative risk
SD: standard deviation
SES: socioeconomic status
T\text{H}_1: T helper cell type 1
T\text{H}_2: T helper cell type 2
TTN: transient tachypnea of the newborn
URTI: upper respiratory tract infection
US: United States of America
VIF: variance inflation factor
V\text{LBW}: very low birth weight
\text{V}_{\text{max}}\text{FRC}: maximal expiratory flow at functional residual capacity
Appendix 2. Logistic regression: odds of asthma diagnosis at < 3 years, reference year 2000.

<table>
<thead>
<tr>
<th>Year (2000 = Ref)</th>
<th>Unadjusted Odds Ratio</th>
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<tr>
<td></td>
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<td>Lower</td>
</tr>
<tr>
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<td>0.082</td>
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<td>1994</td>
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<td>1995</td>
<td>0.763</td>
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<td>1.064</td>
<td>1.031</td>
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<tr>
<td>1998</td>
<td>1.099</td>
<td>1.064</td>
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<tr>
<td>1999</td>
<td>1.064</td>
<td>1.031</td>
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</tbody>
</table>

C-statistic: 0.659, HL test; p = 1.0

Type 3 Analysis of Effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>Degrees of Freedom</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>8</td>
<td>14386.98</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

This logistic regression with the predictor being year of birth for the outcome, odds of asthma diagnosis at less than three years of age with the reference birth year being 2000 shows a significant relationship between year of birth and age of asthma diagnosis. This table shows that the odds of asthma diagnosis at less than three years of age was higher in the birth years 1996 – 1999 compared to the birth year 2000. However the odds of asthma diagnosis at less than three years of age was lower in the birth years 1993, 1994 and 1995 relative to birth year 2000.